NOVARTIS

Clinical Development

SEG101, crizanlizumab

Clinical Protocol CSEG101B2201 / NCT03474965

A phase 2, Multicenter, Open-Label Study to Assess Appropriate Dosing and to Evaluate Safety of Crizanlizumab, with or without Hydroxyurea/Hydroxycarbamide, in Sequential, Descending Age Groups of Pediatric Sickle Cell Disease Patients with Vaso-Occlusive Crisis

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List of abbreviations

ACS	Acute Chest Syndrome
ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area Under the Curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CFR	Code of Federal Regulations
CMO&PS	Chief Medical Office and Patient Safety
COVID-19	Coronavirus disease 2019
CRD	Chronic Renal Disease
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation
DCO	Data cutoff
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of Treatment
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FMI	Final Market Image
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
Hb	Hemoglobin
HbA	Hemoglobin A
HbE	Hemoglobin E
HbF	Fetal hemoglobin
HbS	Human hemoglobin S (sickle cell hemoglobin)
HbS β	one copy of the HbS gene plus a β-thalassemia variant (β^0 or β^+)

HbSC	Heterozygous sickle Hemoglobin C disease (hemoglobin SC disease)
HbSD	one copy of the HbS gene plus an abnormal hemoglobin gene “D”
HbSS	homozygous sickle cell disease (hemoglobin SS disease)
HIV	Human immunodeficiency virus
hr	Hour
HU/HC	Hydroxyurea/Hydroxycarbamide
i.v.	intravenous(ly)
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IG	Immunogenicity
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related reaction
IRT	Interactive Response Technology
ITT	Intent-to-treat
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LPLV	Last patient last visit
mAbs	Monoclonal antibodies
MCA	Middle cerebral artery
MCH	Mean cell hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD-GFR	Modification of Diet in Renal Disease-Glomerular Filtration Rate
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
MHRA	Medicines & Healthcare products Regulatory Agency
min	Minute
mL	Milliliter(s)
mPAP	Mean pulmonary arterial pressure
NSAIDs	Non-steroidal anti-inflammatory drugs
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics
[redacted]	[redacted]
PDS	Pharmacodynamics Analysis Set
PHI	Protected Health Information
PK	Pharmacokinetics
PKPDS	Pharmacokinetic-Pharmacodynamics Analysis Set
PopPK	Population PK
PSDS	Post-study drug supply
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothrombin time
PTA	Post Trial Access
QTcF	QT interval corrected by Fridericia’s formula

R Value	ALT/ALP x ULN
RBC	Red blood cell(s)
REB	Research Ethics Board
RoW	Rest of the World
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCD	Sickle Cell Disease
SCPC	Sickle Cell-related Pain Crises (also known as VOC leading to a healthcare visit in this document)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TCD	Transcranial Doppler
TRV	Tricuspid regurgitation jet velocity
UK	United Kingdom
US	United States
ULN	Upper Limit Normal
VES	Visit Evaluation Schedule
VOC	Vaso-Occlusive Crisis
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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). 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
Dose level	The dose of drug given to the participant (total daily or weekly etc.)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study treatment whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Multiple dose	Time point (at Week 15 or later) when presumed steady state is reached following at least 3 full consecutive infusions following Week 3 Day 1 (loading dose). If dose is interrupted, partially administered or delayed prior to Week 15, then 3 full consecutive infusions (administered within allowed visit window) are required to reach the steady state after the dose has been resumed
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
Participant	A trial participant (can be a healthy volunteer or a patient). “Participant” terminology is used in the protocol whereas term “Subject” is used in data collection
Participant Number (Patient No.)	A unique identifying 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.
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
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited for a new Screening visit after medical judgment and as specified by the protocol
Remotely	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
SEG101	Novartis supply of crizanlizumab
SelG1	Reprixys Pharmaceuticals Corporation supply of crizanlizumab
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g., premedication of vitamin supplementation and corticosteroid for pemetrexed disodium
Study treatment interruption	Dose administration that cannot be made as per protocol and the infusion is fully skipped
Teleconsultation	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
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent / Opposition to use of data / biological samples	Withdrawal of consent 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 6 (14-Mar-2024)

Amendment Rationale

At the time of this amendment, 117 participants were enrolled (at least 100 participants were planned as per the original protocol) in the study. It includes 50 participants in Group 1 (12-<18 years), 53 participants in Group 2 (6-<12 years) and 14 participants in Group 3 (6 months – 6 years). The primary purpose of this protocol amendment is to amend the study plan by not extending it to the cohort of Group 3 Part B. Novartis does not intend to enroll patients in Group 3 Part B (6 months to 6 years) of the trial. The rationale for cancelling the Group 3 Part B is to focus on age groups where the manifestation of Sickle Cell Disease (SCD) and the feasibility of intervention assessment are more suitable. The original study plan required at least 8 patients aged 2-<6 years to evaluate and determine the age-appropriate dose. 14 patients have already been enrolled in Group 3 Part A (patients 2 to <6 years), that are expected to provide sufficient data to study the PK parameters for this age group. Study of the youngest age group (6 months to < 24 months) was initially planned [redacted] which has since been withdrawn in its entirety due to the revocation of the conditional marketing authorization of crizanlizumab in the EU and UK. Therefore, Novartis has decided not to study crizanlizumab for the reduction of VOCs in additional patients with SCD below the age of 6 years, as very young children with SCD are less likely to experience frequent vaso-occlusive crises (VOC) episodes compared to older children, adolescents, and adults.

In addition, this amendment updates the risks and benefits of treatment with crizanlizumab to reflect the most recent available clinical data as described in the latest edition of the Investigator's Brochure (Edition 13, released on 15-May-2023).

In this amendment, the dose and the rationale of the dose confirmed for Group 2 and Group 3, derived from Group 1 and Group 2 Part A pediatric data, are presented. These data were not available at the time of submission of the initial study.

Further, typographical, grammatical and formatting errors have been addressed as part of this document.

Changes to the protocol

- Protocol summary, Section 2.2, Table 3-1, Section 4.1, Figure 4-1, Section 5.1, Section 5.2, Section 7.1.4, Table 7-1, Section 7.2.2.3, Section 7.2.3.1, Table 7-7, Table 7-8 and Section 10, Section 10.1, Section 10.1.5, Section 10.4, Section 10.4.1, Section 10.5, Section 10.5.2, Section 10.8.
  - Text related to Group 3 Part B (6 to 24 months) cohort removed/updated.
- Section 1.2.1.2 and Section 2.3
  - Details about Phase III Clinical Study (STAND – CSEG101A2301) added.
- Section 2.6
  - Risks and Benefits updated.
- Section 6.1, Table 6-1, Section 6.6.1, Section 6.6.3.1
  - Standard text language added for alignment with protocol Version 8 template.

- Section 6.3.3.1
  - Hy's law and DILI language updated.

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.

Amendment 5 (31-Mar-2022)

Amendment Rationale

At the time of this amendment, 77 participants were enrolled in the study. It includes 50 participants in Group 1 (enrolled under SEG101 at 5 mg/kg dose) and 27 participants in Group 2 Part A (13 participants enrolled under SEG101 at 5 mg/kg dose and 14 participants enrolled under SEG101 at 8.5 mg/kg).

The primary purpose of this amendment is to:

- update the options of post-trial access for participants in this trial who continue to derive clinical benefit from the treatment based on the Investigator's evaluation. The post-trial access language was revised to reflect the options available to participants to continue treatment after completion of the study. This may include access to Novartis investigational product in a rollover protocol or provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate as per the country regulations.
- 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 11, released on 12-May-2021).
- align with the requirements of EU Clinical Trial Regulation (EU CTR) to accommodate the transfer of the study under this regulation.
- include changes based on Health Authorities feedback:
    - update the Serious Adverse Event reporting section as per Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM, Federal Institute for Drugs and Medical Devices in Germany) recommendations.
    - update of the wording used in Exclusion criterion #26 incorrectly considering bilateral tubal ligation as a female sterilization as per Medicines & Healthcare products Regulatory Agency (MHRA, United Kingdom (UK) health authority) feedback.
    - addition of the definition of childbearing potential in Section 7.2.7.6 Pregnancy and assessments of fertility as per MHRA (UK health authority) and FAMHP (Federal Agency for Medicines and Health Products, Belgium health authority) feedback.
- update the recommendations on use of vaccines, to consider withholding administration of any live or live attenuated vaccines 4 weeks prior to first dose and during the study duration. The change was performed to provide more clarity about use of live vaccines considering the adverse events including potential infections.

Further, typographical, grammatical and formatting errors have been addressed as part of this document. Some re-wording has been made to improve clarity in alignment with the latest Novartis Global Clinical Trial Protocol Template v 5.0 (released on 14-Jan-2022).

Changes to the protocol

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

The main changes made to the protocol are as follows:

- List of abbreviations
  - List updated with new terms and deletion of unused term.
- Section 1.1 Overview of disease Overview of disease pathogenesis, epidemiology and current treatment
  - Update to report accelerated approval received for Oxbryta™ (voxelotor) by US FDA on 17-Dec-2021 for treatment of sickle cell disease in patients aged 4 years to less than 12 years, and the approval by EMA on 16-Feb-2022 for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older.
- Section 2.6: Risks and benefits
  - Section aligned with Investigator's Brochure (Edition 11, Safety cut-off date 31-Mar-2021 and released on 12-May-2021) to reflect updated frequency of adverse drug reactions and adverse events of special interest.
  - Section clarified to mention that highly effective contraception method must be used.
- Section 4.1: Description of Study
  - Reference to new section 6.1.6 added.
  - Addition of non-trial setting as option for post-trial access to drug treatment
- Section 4.3: Definition of end of study
  - Rewording of definition of end of study for improved clarity.
  - Post-trial access language moved to new section 6.1.6
- Section 5.3: Exclusion criteria
  - Exclusion criterion #11 updated to clarify that silent infarcts are not excluding patients from the study participation.
  - Exclusion criterion #26
    - Text updated based on MHRA feedback to clarify that "bilateral tubal ligation" is not a form of female sterilization in alignment with the Clinical Trial Facilitation Group guidance document for clarification of effective contraception in clinical trials.
    - Text updated regarding feedback from MHRA for considering local regulations for appropriate methods of contraception if more stringent.
    - Text updated to specify oral hormonal method of contraception as estrogen and progesterone.
- Section 6.1.5: Treatment duration
  - Reference to new section 6.1.6 added.
- Section 6.1.6: Post trial access
  - New section added to reflect current post-trial access options to participants who continue to derive clinical benefit from the treatment based on the Investigator's

evaluation, including a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate as per the country regulations.

- Section 6.4: Concomitant medications
  - Clarification that details on administration of Erythropoietin Stimulating Agent should be collected until at least 6 months prior to screening as aligned with inclusion criterion #4.
- Section 6.4.1: Permitted concomitant therapy
  - Recommendation on vaccinations updated to consider withholding any live or live attenuated vaccines 4 weeks prior to first dose of the study treatment (Week 1 Day 1) and during study duration with decision to be taken on a case-by-case basis considering potential benefit/risk of vaccination.
- Section 6.4.4: Use of Bisphosphonates (or other concomitant agents)
  - Heading and section deleted as not applicable for the study.
- Section 6.5.1: Participant numbering
  - Update to limit re-screening to once in the study. Reconsent requirement in case of re-screening removed and added in Section 7.1.2.2.
- Section 6.6.4: Disposal and destruction
  - Clarification added that study drug supply and destruction must comply with site processes, monitoring process and as per local regulation/guidelines.
- Section 7.1: Study flow and visit schedule
  - Clarification made to allow replacements of certain protocol assessments (and not full visits on site) by telephone contacts and/or virtual contacts during a public Health emergency if allowed by local Health Authority, but also by national and local regulations.
- Table 7-1: Visit evaluation schedule
  - Prior/concomitant medications – Erythropoietin stimulating agent added to visit evaluation schedule in alignment with Section 6.4.1.
  - The option of post-trial access in a non-trial setting was added to footnote k.
- Section 7.1.2.2: Information to be collected on screening failures
  - Clarification added that data and samples collected from participants prior to screen failure may still be analyzed.
  - Clarification added that individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once.
  - Update to clarify requirement to reconsent the re-screened participant only in case re-screening is performed more than 28 days after initial consent, unless reconsent is required by local regulations.
- Section 7.1.2.3: Participant demographics and other baseline characteristics
  - Clarification added that country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

- Requirements for documentation of relevant and current medical history until date of informed consent specified.
- Section updated to specify that all prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented.

- Section 7.1.8: Post-treatment Follow-up
  - The option of post-trial access in a non-trial setting was added to this section.
- Section 7.1.9: Lost to follow-up
  - Section updated to clarify that a loss to follow-up could be considered if participant failed to respond to any site attempts to contact them, and not only if participant failed to appear for study visits.
- Section 7.2.2.1: Physical examination
  - Section updated to mention that information for all physical examination information must be included in the source documentation at the study site.
- Section 7.2.2.7.6: Pregnancy and assessments of fertility
  - Definition of female of childbearing potential added to comply with Novartis Pregnancy Guidelines and wider feedback on fertility from MHRA and FAMHP.
- Table 7-5, Table 7-6, Table 7-7, Table 7-8
  - The option of post-trial access in a non-trial setting was added to the footnotes.
- Section 7.2.4.1.1: Optional Additional Research
  - Headline and section updated to clarify the optional consent to the additional research on biological samples and data remaining after analysis and purpose of this additional research.
- Section 8.1.1: Definitions and reporting
  - The option of post-trial access in a non-trial setting was added to this section.
  - Section updated to specify the follow-up period of detected AEs.
- Section 8.2.1: Definitions
  - Section updated to include study treatment errors and uses outside of what is foreseen in the protocol in the AE/SAE reporting in alignment with EU CTR requirements.
- Section 8.2.2: Reporting
  - SAE reporting definition updated to meet the needs of BfArM (Federal Institute for Drugs and Medical Devices) in Germany.
  - Deleted duplicate details referring to follow up information for SAE in the same section.
  - Reference to EU CTR added.
- Section 8.3: Protocol Exempt AEs & SAEs
  - SAE reporting definition updated to meet the needs of BfArM (Federal Institute for Drugs and Medical Devices) in Germany.
- Section 8.6: Reporting of study treatment errors including misuse/abuse
  - Section updated to include study treatment errors and uses outside of what is foreseen in the protocol in the SAE reporting in alignment with EU CTR requirements.

  - Reference to Section 8.1.1 and Section 8.2 added which provide more information on AE and SAE definition and reporting requirements.
- Table 8-2 deleted and replaced by a reference to AE/SAE definition and reporting requirements detailed in respective sections of the protocol.
- Section 9.2: Site monitoring
  - Section updated to clarify that check on completeness of participant records will be completed by the field monitor via ongoing source data verification, not necessarily triggered by visit on sites.
- Section 9.4: Database management and quality control
  - Clarification added that for EDC studies the investigator will receive a CD-ROM or paper copies of the participant data for archiving after the final database lock.
- Section 10: Statistical methods and data analysis
  - Section updated to mention that additional cut-offs and analyses may be performed to support regulatory filings or potential Health Authority requests.
- Table 10-1: Noncompartmental pharmacokinetic and pharmacodynamic parameter
  - Table updated to consider dosing interval for the first dose in the definition of AUCd15.
- Section 11.1: Regulatory and ethical compliance
  - Reference to EU CTR added.
- Section 11.2: Responsibilities of the investigator and IRB/IEC/REB
  - Section updated to clarify the requirement to get protocol amendments approved by relevant authorities before implementation of changes, except in case of urgent safety measures.
  - Investigator responsibilities are refined in this section.
- Section 11.3: Informed consent procedures
  - Section updated to clarify Investigator (or representative) responsibilities in obtaining participants` informed consent.
  - Section updated to specify the medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
  - Section updated to mention that a copy of the ICF(s) must be provided to the participants or their legally authorized representative.
  - Section updated to add that Informed Consent Form (ICF) provided by Novartis complies with 21 CFR 50, local regulations, ICHE6 Good Clinical Practice (GCP) guidelines and privacy and data protection requirements, where applicable.
  - Section updated to add the consent to optional additional research.
  - Clarification added that information included in Investigator Brochure should be shared with the participant upon obtaining consent.
  - Clarification added that Main Study Consents include a subsection that requires a separate signature for ‘Optional consent for activities that may be done outside of the study site’.

- New Section 11.4: Data Protection
  - New section added to specify data protection procedures.
- Section 11.6: Publication of study protocol and results
  - Addition of publication of study results on CTIS public website (Clinical Trials Information System) upon transfer under EU CTR.
  - Statement added that any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.
  - Clarification added that summary of results will be disclosed upon global Last Participant Last visit date.
- Section 12: Protocol adherence
  - Section updated to clarify that no collection of additional data or conduct of additional procedure are allowed outside of protocol requirements or for reasons other than supporting the purpose of the study. In case additional data is collected accidentally, Investigator should notify Novartis immediately.
- Section 12.1: Amendments to the protocol
  - Section updated to specify that any change or addition to the protocol can only be made in a written protocol amendment that must be approved prior to implementation.
  - Section updated to specify if amendments are required for participant safety it may be implemented immediately but providing relevant Health Authorities and reviewing IRB/EC are notified, and the safety measure is subsequently included in a protocol amendment.

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.

Amendment 4 (30-Mar-2021)

At the time of this amendment, 77 participants were enrolled in the study. It includes 50 participants in Group 1 (enrolled under SEG101 at 5 mg/kg dose) and 27 participants in Group 2 Part A (13 participants enrolled under SEG101 at 5 mg/kg dose and 14 participants enrolled under SEG101 at 8.5 mg/kg).

The primary purpose of this amendment is to update the requirement for a 105 days post-treatment follow-up visit for all participants. The intention of the 105 day post-treatment follow-up period is to capture any potential adverse events including development of anti-drug antibodies following discontinuation from study treatment, taking into account the half-life of the drug. This amendment clarifies that participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g. enrollment in a Novartis roll-over protocol to provide continued drug treatment) will not have to perform the 105 days post-treatment follow-up visit in this study.

Regarding eligibility, inclusion criterion (#4) was clarified regarding L-glutamine and erythropoietin stimulating agent. Several drugs are being used to treat SCD, including HU/HC, L-glutamine, and erythropoietin stimulating agent. The downstream effects of these drugs might affect the PK/PD analyses that are the primary objective of this study. Given this possibility, participants taking those drugs at study entry are required, at least for Part A, to maintain the same dose of these drugs unless it has to be changed for safety reasons or due to growth and periodic weight changes. In addition, exclusion criterion (#31) has been adapted to exclude patients with prior use of other selectin targeting agents as newer P-selectins antagonists are currently being tested in SCD, therefore patients who are screened in CSEG101B2201 may have been exposed, and may confound study objectives.

Finally, the protocol has been updated to address ongoing or future public health emergency mitigation procedures such as for the current COVID-19 pandemic. No substantial additional risk for participants due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. The risk/benefit balance will be re-evaluated as and when required whilst the COVID-19 pandemic continues.

Further, typographical, grammatical and formatting errors have been addressed as part of this document.

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.
  - “safety follow-up” was replaced with “post-treatment follow-up visit” consistently through the protocol, because the follow-up includes safety as well as efficacy assessments. Accordingly, “follow-up” was replaced with “post-treatment follow-up”.
  - Updates to align with the latest Novartis Global Clinical Trial Protocol Template v4.0 (15-Feb-2021).

- Glossary of terms
  - List of terms updated.
- Section 2.6
  - “patient” was replaced by “participant”.
- Section 2.7
  - Addition of new protocol section 2.7 to address ongoing or future Public Health emergency mitigation procedures.
- Section 4.1
  - Update to the requirement to have a 105 days post-treatment follow-up visit for all participants, as exception is made to the participants continuing under crizanlizumab beyond their EOT visit.
- Section 5.2
  - Clarification of inclusion criterion 4 regarding L-glutamine and erythropoietin stimulating agent.
- Section 5.3
  - To update the exclusion criterion 31 to include selectin targeting agents.
  - For exclusion criterion 26 it was clarified that “bilateral” tubal ligation is considered a highly effective contraception methods.
- Section 6.1.4
  - Update to the requirement to have a 105 days post-treatment follow-up visit for all participants, as exception is made to the participants continuing under crizanlizumab beyond their EOT visit.
- Table 6-3
  - Clarification added for infusion-related reactions (grade 2) that infusion is recommended to be interrupted temporarily.
- Section 6.4
  - Clarification added regarding notification of any new concomitant medications taken until completion of last visit: EOT visit or post-treatment follow-up visit.
- Section 6.4.1
  - Clarification added regarding the dosing modification of the (HU/HC, L-glutamine and erythropoietin stimulating agent) permitted concomitant medication in the study.
  - Use of other anti-platelets agents or anticoagulants at therapeutic doses have been moved to Section 6.4.2 as concomitant medications to be used with caution.
- Section 6.4.2
  - Paragraph added regarding cautious use of anti-platelets agents or anticoagulants due to potential effect of P-selectin on hemostasis.

- Section 6.4.3
  - Paragraph added regarding prohibition of new SCD treatments and/or treatments to prevent/reduce VOCs during the study and the use of selectin agents prior or during the study.
- 6.6.3.2
  - Clarification added that drug accountability will be monitored by the field monitor also during remote monitoring visits.
- Section 7.1
  - Wording added to address ongoing or future public health emergency mitigation procedures.
  - Wording added for allowed visit windows of EOT visit and 105 day post-treatment follow-up visit.
- Table 7-1
  - IRR added under safety assessments.
  - Footnote added regarding allowed visit windows of EOT visit and 105 day post-treatment follow-up visit.
  - Footnote added regarding the requirement to get 105 days post-treatment follow-up visit.
  - Footnote added regarding Infusion Related Reactions (IRR) eCRF page to be completed in case certain AE are reported as IRR.
- Section 7.1.5
  - Section header was updated.
  - Clarification added regarding EOT visit, and the 105 days post-treatment follow-up visit.
  - Withdrawal description removed as provided in Section 7.1.7.
  - Clarification added regarding data that should be collected at clinic visits or via telephone/email contacts after discontinuation from study treatment.
- Section 7.1.6
  - This section “Discontinuation from study” was added as per latest Novartis Global Clinical Trial Protocol Template v4.0 (15-Feb-2021).
- Section 7.1.7
  - Section header was updated to also refer to Opposition to use data/biological samples.
  - Update to the requirement to have a 105 days post-treatment follow-up visit for all participants, as exception is made to the participants continuing under crizanlizumab beyond their EOT visit.
  - Update wording for withdrawal of consent and Opposition to use data/biological samples as per latest Novartis Global Clinical Trial Protocol Template v4.0 (15-Feb-2021).

- Section 7.1.8
  - Update to the requirement to have a 105 days post-treatment follow-up visit for all participants, as exception is made to the participants continuing under crizanlizumab beyond their EOT visit.
  - Clarification on the SAE collection for participants continuing in post-treatment follow-up.
- Section 7.1.9
  - Clarification added for participants failing to appear for study visits resulting in unclear status.
- Section 7.2.1.1
  - Clarification added for vaso-occlusion crisis/dactylitis/transfusion information to be collected until last protocol visit.
- Section 7.2.2.6
  - Clarification added that middle cerebral artery (MCA) velocity is included in cerebral blood flow velocity (CBF-V) measurements.
- Section 7.2.2.7
  - Clarification added that if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.
  - Clarification that clinically relevant abnormal laboratory parameters have to be collected until last protocol visit.
- Section 7.2.3.1
  - Table 7-5, Table 7-6, Table 7-7, Table 7-8
    - PK collection number/Dose reference ID was added for post-treatment follow-up visit (last infusion + 105 days).
    - Footnote added that participants continuing crizanlizumab after their EOT visit do not have to complete the 105 days post-treatment follow-up visit.
  - Table 7-7
    - Footnote added clarifying that Part B in Group 3 (2 to <6 years old) is only applicable in case of dose alteration of HU/HC, L-glutamine or erythropoietin stimulating agent in Part A participants.
- Section 8
  - Wording added to address ongoing or future public health emergency mitigation procedures.
- Section 8.1.1
  - Clarification added that monitoring of adverse events as part of this study will stop from the time the participant performed EOT visit for participants continuing under crizanlizumab beyond EOT visit.
  - Adverse events should be evaluated to determine action taken with respect to study treatment for which the possibility “dose reduced” was added for consistency with the eCRF.

- Section 8.3.1
  - The entire Section 8.3.1 was moved under Section 8.2 as new Section 8.2.2. The following additional changes were made:
    - Update made to the monitoring of AEs to mention that for participants continuing crizanlizumab after their EOT, via commercial drug or post-trial access, monitoring of AEs as part of this study will stop from the time the participant completed their EOT visit.
    - Update to the requirement to have a 105 days post-treatment follow-up visit for all participants, as exception is made to the participants continuing under crizanlizumab beyond their EOT visit.
- Section 8.5
  - Clarification added regarding pregnancy consent form process.
- Section 9.2
  - Clarification added that Novartis ensures protocol and GCP compliance and the quality/integrity of the sites' data.
  - Clarification added that Novartis monitoring standards require also full verification of data that will be used for all primary variables.
  - Clarification added that no information in source documents will disclose the identity of the participants.
- Section 10
  - Reference to Week 27 Day 1, which was in brackets, deleted for indicating the completed first 26-weeks of treatment period.
- Section 10.5.2
  - Clarification added regarding VOC events and Dactylitis.
- Section 10.5.3.1
  - Clarification added regarding the definition of the on-treatment and post-treatment periods.
- Section 11.3
  - Wording added to address ongoing or future public health emergency mitigation procedures.
  - Clarification about information given to participant added in case his/her representative gives consent.
- Section 11.5
  - Examples added for publicly accessible database of clinical study results.

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.

Amendment 3 (21-Jul-2020)

At the time of this amendment, 63 participants were enrolled in the study, under SEG101 at 5 mg/kg dose. It includes 50 participants in Group 1 (split between 11 participants in Group 1 Part A and 39 participants in Group 1 Part B) and 13 participants in Group 2 Part A. The dose of SEG101 at 5 mg/kg was confirmed following single and multiple dose analysis in Group 1 Part A. However, the dose of 5 mg/kg was not confirmed in Group 2 Part A based on the results from the single dose analysis. The Data Monitoring Committee (DMC) did not raise any particular safety concerns related to the 5 mg/kg dose tested. However, the PK results were at the lower end of the pre-set boundaries defined in the protocol and suggested that the dose of 5 mg/kg may not be efficacious in achieving adequate inhibition of P-selectin. In order to ensure an efficacious dose in patients <12 years, Novartis, in agreement with the DMC, proposed testing a new adjusted dose for patients in Group 2 based on revised SEG101 PopPK modeling. Group 2 Part B and Group 3 had not yet been initiated at the time of this protocol amendment.

The main reasons of this amendment are:

1. To update and clarify the criteria used for dose confirmation following single-dose analysis in Part A of each group. The decision is based on first dose PK results, key safety data, and Novartis's assessment in conjunction with Data Monitoring Committee (DMC) recommendations. Previous wording considered the dose confirmed if the PK results were found to be within the pre-set boundaries defined in the protocol which might not be sufficient to confirm the appropriate dose. Current protocol clarifies that all relevant data will be used to make a decision on the dose. This amendment will thus allow evaluation of the newly defined dose in a new cohort of patients enrolled into Group 2 Part A (see study status above).
2. To include language 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 were added.
3. To adjust weight from 6 to 7 kg in inclusion criterion 1 and increase minimum eGFR value from 45 to 75 mL/min/1.73m^2 in inclusion criterion 8, in light of the higher doses that will be used in younger age groups, in order to avoid potentially exceeding recommended endotoxin and sucrose limits, particularly in very young children.
4. To consider uptake of voxelotor within 30 days of screening or plan to start voxelotor during the course of the study as an exclusion criterion. At the time of this protocol amendment, voxelotor is a newly approved drug for Sickle Cell Disease in the U.S.; there is no combination of safety or PK data with SEG101 (Drug-Drug Interaction is always a possibility). In anticipation that some patients may have been on voxelotor prior to start in the study, the protocol is requesting that participant has permanently stopped voxelotor prior to screening and to allow a wash-out period of 30 days or 5 half-lives, which is the typical duration for a wash-out (of exposure and potential lagging adverse events).

1. To include the possibility of provisional study treatment to participants via post-trial access at time of study completion to reflect the current integrated development plan of the program.
2. To modify guidance given to manage infusion-related reactions and corresponding dose interruption and re-initiation, based on feedback received from Medicines & Healthcare products Regulatory Agency (MHRA) on SEG101A2301 protocol amendment 1, and ensure alignment between all program studies. Pre-medication prophylaxis against infusion related reactions (IRRs) has been revised and is now allowed.
3. To update the risks and benefits of treatment with crizanlizumab to reflect the most recent available clinical data described in the latest version of the investigator's brochure (Edition 10, released on 12-May-2020).
4. [redacted]
5. To correct that at the time of primary analysis for each group, it will be possible to also conduct an analysis of data from other groups, if needed to support regulatory filings or potential Health Authority requests.
6. To collect prior use of hydroxyurea/hydroxycarbamide (HU/HC) and reason for discontinuation as part of participant demographics as requested by the European Medicine Agency (EMA).

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.
- Throughout: reference to 'subject' or 'patient' replaced by 'participant' when referring to trial participant to align with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Throughout: references reviewed to align with Harvard style
- List of abbreviations: updated by adding new abbreviations used across the protocol
- Glossary of terms: updated to align with the 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
- Section 1.2.1: reporting the results of the reproductive toxicology study with SEG101 ongoing at time of initial protocol release and completed in March 2019
- Section 2.3: clarification that the dose of 5 mg/kg is the starting dose for participants in Group 1 Part A

- Section 2.6:
  - added language in line with the latest version of the investigator's brochure (Edition 10, released on 12-May-2020), including the potential risks of hemorrhages, infections, infusion related reactions and immunogenicity, as well as potential risks pertaining to laboratory text interference with automated platelet counts, QT prolongation and hepatic safety, and pregnancy and lactation
  - strategy to mitigate risk of interference with automated platelet counts was removed as this section is not appropriate for management instructions or guidance and instructions were given to the sites through a specific letter addressed to investigators
  - option to keep the participant in the hospital for 24 hours following first infusion extended to subsequent infusions after first dose
  - removed referenced articles of Descotes 2009, Sing JA 2011, and Qi X 2014
- Section 4.1:
  - addition of requirement of having permanently discontinued voxelotor at least 30 days prior to screening and to not plan initiation of the drug during the course of the study
  - 'should' has been updated by 'must' to clarify that participants receiving HU/HC, L-glutamine or erythropoietin stimulating agent at study entry **must** have been taking it for at least 6 months prior to study entry and plan to take the same dose at the same schedule during the course of the study
  - clarification that for dose confirmation decision, PK results obtained from Group 1 following single and multiple dose analysis will be compared to the exposure level observed in adults from the CSEG101A2202 study, yet PK results obtained from Group 2 and Group 3 following single and multiple dose analysis will be compared to the exposure level predicted using PopPK model
  - clarification that participants from Part A switching to the new dose will be considered as Part B participants from the time they will start the new dose, but will not be counted among the minimum 26 participants planned for the group
  - clarification on the process applied in each group to confirm the dose based on single and multiple dose analysis
  - addition of the possibility to get the study treatment provisioned via post-trial access upon study discontinuation
  - clarification that the 5 mg/kg dose is the starting dose in Group 1 Part A
- Figure 4-1:
  - updated to reflect the possibility to separate or combine the different primary analysis for each group,
  - reference to 'participants' instead of 'patients'
  - number of participants in each part included
  - 'wk 0' updated in 'wk 7'to indicate the cutoff date of the single dose analysis
- Section 4.3: addition of the possibility to get study treatment provisioned by Novartis following study completion by participant in case crizanlizumab is not available commercially at that time

- Section 5 and Section 5.1:
  - headings of Section 5 and Section 5.1 updated as 'Study population' to be aligned with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
  - clarification that at least one VOC having led to healthcare/medical facility visit within 12 months prior to screening has to be reported to make the patient eligible
- Section 5.2:
  - To update the lower bound weight from 6 to 7 kg in inclusion criterion 1
  - To replace 'should' by 'must' in inclusion criterion 3
  - To update minimum eGFR value required from 45 to 75 mL/min/1.73m^2 in inclusion criterion 8
  - To clarify that for TCD assessment in inclusion criterion 9, the age of the participant at screening is considered
- Section 5.3:
  - exclusion criteria 5 and 27 that were removed with protocol amendment 2 were deleted from exclusion criteria section, instead of retaining them and mentioning they are not applicable anymore, to follow Novartis standard guidance
  - wording added to mention that local regulations must be followed in case of deviation from the contraception methods listed in the protocol
  - exclusion criterion 32 added to mention that uptake of voxelotor within 30 days prior to screening or planned during the course of the study excludes the patient from study participation
- Section 6.1.5: addition of the possibility to provide study treatment via post-trial access after trial completion
- Section 6.3.1.1:
  - clarification of the process and criteria used to confirm the dose in each group following single dose PK analysis
  - clarification that the investigator cannot decide to modify the dose at their own discretion
- Section 6.3.1.2: recommendations added for handling of study treatment in case of active or suspected COVID-19 infection, and recommendation to get COVID-19 tested in case of VOC
- Table 6-3: To modify guidance given to manage infusion-related reactions and corresponding dose interruption and re-initiation
- Section 6.3.3.1:
  - wording added in regards to use of clinical information to assess a medical diagnosis of the cause of the observed liver laboratory abnormalities
  - reference to 'without evidence of cholestasis' removed to match with updates made with protocol amendment 2

- Section 6.4.2:
  - paragraph on the use of pre-medications in case of infusion-related reactions moved from Section 6.4.3 (prohibited concomitant therapy) to Section 6.4.2 (permitted concomitant therapy requiring caution and/or action)
  - addition of requirement to get study treatment discontinued in case of Grade 3 or Grade 4 IRRs
  - addition on uptake of steroids that is permitted but with caution
  - reference to Brandon et al 2020 added
- Section 6.4.3: addition of washout period for voxelotor
- Section 7.1: language added to request maintenance of virtual/phone contacts with the participants in case on-sites visits cannot be performed
- Table 7-1:
  - category corrected for informed consent from source ('S') to data capture in the clinical database ('D')
  - removal of optional pharmacogenetics informed consent
  - removal of buccal swab for pharmacogenetics analysis
  - footnote added for ECG assessment scheduled at Week 15 to request alignment with steady state for Part A participants
  - footnote added for school/work employment status and sick time absence at screening to highlight that information based on last month prior to screening will be asked to be recorded in the clinical database
  - addition of collection of Hospitalization details at screening
  - addition of head circumference measure
  - table updated to correct that VOCs and Dactylitis events occurring during screening and prior to the first dose will be recorded on the History CRFs in alignment with other sections
  - addition of Prior/concomitant medications – L-glutamine
  - referenced section for concomitant medications updated to Section 6.4
  - addition of collection of PK and IG samples at the 105 days safety follow-up visit
- Section 7.1.2.3:
  - language added in regards to reason to collect race and ethnicity as part of demographics information, aligned with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
  - clarification that 'diagnosis of SCD' is collected, as well as Dactylitis history in addition to VOC history
  - addition of the collection of prior use of HU/HC and reason for discontinuation as part of background medical information
- Section 7.1.5: circumstances for study treatment discontinuation updated to add decision based on applicable board(s) after review of safety data and discontinuation of study drug development

- Table 7-2: corrected to make collection of Hospitalizations details at Screening/Baseline as mandatory
- Section 7.2.1.1:
  - clarification that at least one VOC having led to healthcare/medical facility visit within 12 months prior to screening is required to make the patient eligible
  - clarification that VOCs or Dactylitis events occurring during screening period and prior to first dose have to be collected on the respective History CRFs
- Section 7.2.2.3: addition of Head Circumference measure for participants aged 6 months to 2.5 years old at time of enrollment, until participants turn 3 years old
- Section 7.2.2.5.1: note added to clarify that in case of Stage V is reached, Tanner stagingmay be discontinued
- Section 7.2.2.6: clarifications on which participants are expected to get TCD assessments
- Section 7.2.2.7.5: clarification that age of the participant refers to age at time of enrollment
- Section 7.2.2.7.6: correction in section referenced
- Section 7.2.2.8.1: correction of minimum QTcF value from 500 to 480 ms to request additional unscheduled ECG evaluation to align text with Table 7-4
- Table 7-4: footnote added to clarify that for participants in Part A the ECG assessment at Week 15 Day 1 has to be aligned with steady sate
- Section 7.2.31: change of collecting PK/IG samples until safety follow-up visit (previously until EOT)
- Tables 7-5, 7-6, 7-7, 7-8:
  - addition of the time window allowed for PK/PD samples collection
  - addition of PK and IG samples collection at safety follow-up visit
- Section 7.2.4: deletion of the paragraph related to optional buccal swab collection for pharmacogenetics analysis
- Table 7-9: removal of optional buccal swab for pharmacogenetics analysis
- Section 8: 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 8.2.1: text revised based on the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) to clarify the definition of serious adverse event (SAE)
- Section 8.3:
  - clarification on adverse events (AEs) and SAEs exempt from protocol
  - addition that VOCs suspected to be related to study treatment, as well as fatal VOCs will have to be reported as serious adverse events in addition to the VOC CRF
  - clarification that any follow-up for SAE needs to be reported within 24 hours from investigator's awareness

- Section 8.3.1:
  - removal of reference to blinding as not relevant on this trial
  - addition of EU guidance for reporting of SUSARs to relevant authorities and ethics committees
- Section 8.5:
  - text 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
  - addition of the duration of the follow-up period
- Section 8.6: added to clarify the reporting of study treatment errors including misuse/abuse in alignment with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Section 9.3: reference to buccal swab collection for optional PG deleted
- Section 9.4:
  - clarification of WHO as World Health Organization
  - addition of data collected in IRT in alignment with the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020)
- Section 10: correction to mention that at time of primary analysis of each group, available data from other groups may be included in the reporting, if deemed necessary
- Section 10.1.5 and Section 10.1.6: reference to 'other tested dose' added to 5 mg/kg dose which is the starting dose
- Section 10.3: definition of dose adjustment updated based on data actually collected in the clinical database on study treatment CRF
- Section 10.4.1:
  - correction of 'Week 3' into 'Week 1' to match with Table 3-1
  - language added to clarify that the endpoint pertaining to the frequency of any AEs during the on-treatment period is pertaining to the primary 'safety' endpoint for Part A and B 'of all age groups'
- Section 10.4.2:
  - clarification that dose is not considered as confirmed only based on PK results
  - clarification that for group 1 primary PK parameters will be compared against observed adult PK parameters of study CSEG101A2202; yet for the other groups these parameters will be compared to predicted PK parameters for these participants derived from adults from the population PK model.
  - mention of 'predicted' removed in comparison of geometric means between observed and reference primary PK parameters
  - paragraph headers updated to clarify that both PK and safety data are part of the analysis for dose confirmation and primary analyses
- Section 10.5.2:
  - clarification that only VOCs having led to healthcare visits will be considered at baseline for consistency with the other sections of the protocol

- Section 11.1 updated to align with latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) and update of the local regulations references
- Section 11.2 updated to align with latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) and addition that in case of clinical site inspection by a regulatory authority, the investigator must inform Novartis immediately
- Section 11.3:
  - text aligned on the latest Novartis Global Clinical Trial Protocol Template v3.0 (31-Jan-2020) and reference to IB added
  - informed consent included in the study listed
  - deletion of additional consent form for optional pharmacogenetics component
- Section 13:
  - referenced articles of Descotes 2009, Sing JA 2011, and Qi X 2014 removed
  - new reference to Brandon et al 2020 added
  - missing references to Miller et al (2000) [redacted] added

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.

Amendment 2 (29-Jan-2020)

At the time of the amendment, 59 patients were enrolled in the study.

The main changes of this amendment are:

1. To update and clarify inclusion/exclusion criteria based on feedback received from sites, Steering Committee input and on current revised program safety (please see details on next section)
2. To update study objectives in order to
   - Modify the wording of the PK/PD endpoint for Part A to account for potential patients having study treatment interruptions prior to Week 15, where multiple dose is defined as 3 consecutives doses (not including the loading dose at Week 3 Day 1) in the primary objective.
   - Change the wording "number of" to "annualized rate of" in the secondary objectives to account for patients who do not complete the full treatment period and standardize the outputs to one-year time-frame. This applies to all the secondary objectives to assess the long-term efficacy of crizanlizumab in 6 months to < 18 year old patients at the time of study entry [redacted]
3. Risk benefit section has been updated to include information on immunogenicity and interference with automated platelets counts in line with the current version of the IB.
4. Specify that some screening evaluations such as auditory/ocular testing, echocardiogram, chest X-ray can be performed within a larger window (i.e. beyond 28 days). Change the requirement to get a TCD assessment performed at screening.
5. QTcF prolongation section has been removed, based on the current safety profile of crizanlizumab showing no QT liability as supported by absence of clinically relevant effect on QTc in SCD patients treated with crizanlizumab based on PK-QT analysis and assessment of safety as listed in the current IB.
6. Dose interruptions/delay section (including Table 6-2) has been revised, allowing treatment infusion during VOC as discussed and agreed with the Steering Committee as there are no safety concerns based on current safety profile.
7. Reviewed the DILI criteria requiring follow-up for certain isolated ALT increases that persist for more than 2 weeks and removing mention of patients with bone metastasis as patient with metastatic malignancy are not allowed per exclusion criterion #21.
8. Some information related to the study drug preparation, dispensation and timing has been removed to refer to the Pharmacy Manual.
9. Laboratory section has been updated to clarify that analysis for the hematology panel is now done at local site instead of central lab due to the limitations on blood volume collection for pediatric population and to mitigate the interference with automated platelets counts at the central lab. In addition, glucose assessment is removed as crizanlizumab does not have any impact on glucose. Urine drug screen, as well as criteria on alcohol and drug abuse, removed as it is no longer required as part of the screening.

1. Update sample time collection for coagulation from visit W15D2 to W19D1 to avoid patients from Part B to have to come back at W15D2.
2. PK/PD/IG Tables have been updated to clarify which samples time points are collected in each Part of the study and the samples required for steady state.
3. Conduct of primary analyses have been separated in order to gain flexibility with making data available as soon as possible for Group 1 and Group 2 in order to avoid to run analyses only once both of them are completed.
4. Following scientific advice for study A2301 and further alignment on the estimand framework for SEG101 project, the secondary endpoint on annual rate of VOC will exclude data collected post initiation/discontinuation of HU/HC or L-glutamine on treatment (instead of including them). A sensitivity analysis will be done, including those data.
5. Correction of editorial and typographical errors.

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: clarifications added
- Glossary of terms: including definitions of “Study treatment interruption” and “Multiple dose” to be used in this study, removed definitions not used in the protocol
- Protocol Summary: updated in alignment with the protocol sections updated
- Section 1.1: including Oxbryta™ (voxelotor) as approved by US FDA on 25-Nov-2019 for SCD treatment
- Section 1.2.1: including crizanlizumab as approved by US FDA on 15-Nov-2019 for SCD treatment
- Section 1.2.1.2: clarified that SCPC are also known as VOC leading to healthcare visit, and updated information on anti-drug antibodies development.
- Section 2.3: removed SCPC to refer to ‘VOC leading to healthcare visit’ instead, and removed the infusion time to refer to Pharmacy Manual
- Section 2.6: removed SCPC to refer to ‘VOC leading to healthcare visit’ instead. Consideration that infusion-related reactions can be considered as an identified risk deleted. Updates based on new data available on immunogenicity and interference with automated platelets counts in line with the current version of the IB.
- Table 3-1: objectives endpoints clarified for Primary, Secondary [redacted]
- Section 4.1:
  - Clarifying full PK/PD sampling collection at single dose and multiple dose in Part A and possibility for the patient to remain at site for the full PK/PD sampling
  - Clarifying that a minimum of at least 8 patients is required in Part A of Group 1 and Group 2
  - Clarifying the reason for study treatment permanently discontinued.

  - Removed sentence mentioning that all the screening evaluations must be done within a 28 days period prior to dosing.
  - Reference to "eligibility checklist" embedded in IRT system removed as not used in this study
- Section 5.1: conditions on HU/HC, L-glutamine or erythropoietin stimulating agent uptake prior to screening clarified.
- Section 5.2:
  - Including recommendation on confirmation of local SCD diagnosis by two methods in criterion #2
  - Period of time to experience at least 1 VOC for eligibility clarified in inclusion criterion #3
  - Including L-glutamine in criterion #4 as approved by US FDA for SCD treatment. Update made to mention that patients off HU/HC, L-glutamine or erythropoietin stimulating agent must have stopped treatment for at least 6 months prior to screening
  - Update made to inclusion criterion #7 to refer to 'prior to Week 1 Day 1', instead of screening visit
  - Clarify inclusion criterion # 9 regarding screening TCD, including requiring TCD only for ages 2 to <16 yrs, for certain genotypes/hemoglobin phenotypes, based on SOC and proof of relevance of TCD in these populations.
- Section 5.3:
  - Exclusion criterion #5 is no longer required as it has been merged with exclusion criterion #3 and revised to clarify the episodic transfusion (simple or exchange).
  - Clarifying exclusion criterion #11 to not exclude patients with silent infarcts only present on imaging.
  - Revised exclusion criterion #12 to exclude abnormal TCD within the past 12 months.
  - Exclusion criterion #14 has been updated to clarify timelines of hospitalization prior to Week 1 Day 1.
  - Exclusion criterion #16 updated to include L-glutamine as approved by US FDA for SCD treatment
  - Exclusion criteria #25 regarding impacting the cardiac or cardiac repolarization abnormality has been revised based on current program safety profile to remove exclusion of the use of concomitant medication with "Known Risk of Torsade de Pointes.
  - Exclusion criterion #27 related to the current drug and alcohol abuse has been removed.
  - Adding a new exclusion criteria #31 for patients already exposed to crizanlizumab.
- Section 6.1: removing the infusion time and referring to Pharmacy Manual.
- Section 6.3.1.2: clarifying guidance to restart study drug as soon as possible following dose delay. Change made to allow dose administration during VOC. Clarify permanent treatment discontinuation as per Table 6-2 and for Grade 4 adverse events deemed related to study drug. Deletion of redundancy.

- Table 6-2 revised as per crizanlizumab safety profile and for bringing additional guidance on criteria for dose interruption and dose re-initiation:
  - Change the wording “May maintain dose level” to “Recommendation continue study treatment” throughout the table as no dose change is allowed
  - Language updated for consistency for permanent study treatment discontinuation in case of Grade 4 toxicity
  - Language updated for consistency for study treatment interruption in case of Grade 3 toxicity
  - Modified criteria for interruption and dose re-initiation for Neutropenia G3 and febrile neutropenia
  - Removed eGFR as redundant with criteria for serum creatinine, and no safety issue with renal toxicity
  - Clarified criteria for dose re-initiation in case of Grade 2 and Grade 3 isolated direct bilirubin elevation
  - Removed isolated AST from the table.
  - Clarified criteria for dose re-initiation in case of Grade 2 and Grade 3 isolated ALT elevation
  - Changed total bilirubin by direct bilirubin
  - Updated criteria for dose interruption, re-initiation and monitoring of LFTs in case of combined elevations of ALT and direct bilirubin
  - Clarified wording for serious and non-serious infections to refer to CTCAE grade. For infections with toxicity Grade 3 (or Serious) or Grade 4, change made to clarify the conditions for permanent discontinuation.
  - Diarrhea replaced by GI toxicity (including diarrhea, nausea, vomiting)
  - Removed fatigue as not applicable
- Table 6-3: management of drug-related reactions have been revised to align with the CTCAE grade definition.
- Section 6.3.2: removed based on the current safety profile of the compound showing no clinically significant events of QTcF prolongation in SCD patients receiving crizanlizumab.
- Section 6.3.3.1: Reviewed the DILI criteria requiring follow-up based on ALT and direct bilirubin results at baseline. Removed reference to bone metastasis.
- Section 6.4.1: clarifying the use of vaccines in this study
- Section 6.4.3: modified the required discontinuation period in case of use of antibody or immunoglobulin therapy and including voxelotor as prohibited medication during the study.
- Section 6.5.1: clarifying the re-screening conditions
- Section 6.6: removed information on study drug preparation and dispensation and refer to the Pharmacy Manual. Clarifying that monitoring of patient after 6 months will be done as per local medical practices.
- Section 6.6.1: removed sentence referring to 2 parts (base plus tear of label) as not in alignment with the study treatment label.

- Section 7.1:
  - Specified the screening period for the chest X-ray, echocardiogram, auditory and ocular assessments.
  - Modified the window period to +/- 7 days for all visits after Week 3 Day 1.
  - Specified that a period of at least 21 days is required between 2 doses after Week 3 Day 1.
  - Specified that the dose at Week 3 Day 1 has to be given within 14 days +/-3 days after Week 1 Day 1 dose
- Table 7-1:
  - Added screening time details period.
  - Added group information for assessments.
  - Added IRT/IWRS registration at EOT visit
  - Modified the second coagulation test to be done at Wk19D1.
  - Removed drug screen assessment, as well as alcohol and smoking history.
  - Modified the type of optional buccal swab samples and clarified the time to collect the sample.
  - Modified TCD assessment time points.
  - Adding footnotes to clarify when the assessments are done based on the group the patient is enrolled to.
  - Correct typos in the table
- Section 7.1.2: wording simplified.
- Section 7.1.2.1: reference to “eligibility checklist” embedded in IRT system removed as not used in this study
- Section 7.1.2.2: information collected for screening failures updated as per current Novartis protocol template wording
- Section 7.1.4: full PK/PD sample collection clarified and reference to “eligibility checklist” embedded in IRT system removed as not used in this study
- Section 7.1.5: revised wording for discontinuation of study treatment and including a window of 7 days for EOT visit after decision for treatment discontinuation.
- Section 7.1.6: Withdrawal section updated to be aligned with the last Novartis protocol template wording
- Section 7.1.7: update of the CRFs requiring data collection at the time of safety follow-up visit.
- Section 7.2.1.1:
  - Definition of VOC was updated with the requirement to receive therapy with oral/parenteral opioids or parenteral NSAIDs
  - Definition of resolved Acute Chest Syndrome was clarified
  - Information to be collected for VOC in the CRF was removed
  - Removed drug infusion restriction during VOC.
  - Information to be collected in regards to dactylitis was clarified

  - Information updated for the chest X-ray required at screening to assess patient's eligibility.
  - Information regarding collection of transfusion data was modified
- Section 7.2.2.1: removed reference to EOT visit within 7 days following last infusion.
- Section 7.2.2.6: clarified TCD requirements.
- Section 7.2.2.7:
  - Allow local testing for hematology panel
  - Added requirement to get safety laboratory analysis repeated prior to Week Day 1 in case of hospitalization at screening
  - Added non allowance to get two consecutive lab tests used to assess dose interruption/disconnection missing
- Table 7-3: revised lab assessments in alignment with changes in different protocol sections.
- Section 7.2.2.7.1: change in the hematology panel testing method from central to local. Added possibility to use blood smear for manual platelet estimation.
- Section 7.2.2.7.3: urine drug screen test removed
- Section 7.2.2.7.4: second coagulation sample time-point at Week 15 Day 2 has been modified to Week 19 Day 1.
- Section 7.2.2.7.5: extend the collection of fetal hemoglobin sample to patients above 2 years.
- Section 7.2.2.7.6: adding report of child bearing potential status change during the study in the source document
- Section 7.2.2.7.7: including wording for EOT visit in alignment with VES
- Section 7.2.2.8.1: clarified time to collect ECG as per Table 7-4. Range of QTcF to define cardiac AEs corrected.
- Section 7.2.2.8.2: clarified echocardiogram assessment collection.
- Section 7.2.2.9: clarified the time window period for the screening auditory examination.
- Section 7.2.2.10: clarified the time window period for the screening ocular and retinal examination.
- Section 7.2.2.11: clarifying PFT assessment at screening for patients with existing lung disease.
- Section 7.2.3: collection of IG samples added.
- Section 7.2.3.1: removed instructions for PK/PD/IG blood collection as already described in the central lab manual. Clarifications for the blood sampling at steady state for Part A patients.
- Tables 7-5, 7-6, 7-7 and 7-8:
  - Removed the Sample blood volume column.
  - Included clarification on sample collection for Part A and Part B.
  - Footnote updated to clarify PK/PD sampling at steady state and collection of 0.5 hr post-dose sample
  - Addition of Dose reference ID at EOT (for last infusion prior to EOT)

- Section 7.2.4: modified optional swab collection type to buccal.
- [redacted]
- Section 8.1.1: list of outcome removed
- Section 8.3: removed the sentence related to fatal VOCs.
- Table 8-1: removed the SCPC wording.
- Section 9.3: section wording revised in alignment with protocol.
- Section 10: definition of cut-off for formal analysis revised
- Section 10.1.5: Pharmacokinetic analysis set revised taking in account the multiple dose definition.
- Section 10.1.6: Pharmacodynamics analysis set revised taking in account the multiple dose definition. Clarification about evaluability of % inhibition value.
- Section 10.4: cut off for the primary analysis revised
- Section 10.4.1: reference to 'fifth dose' replaced by 'multiple dose'. Information updated on primary PK/PD parameters for Group 3
- Section 10.4.2: clarification on the statistical model used. List of studies removed.
- Section 10.5.2: the annual rate of VOC will exclude data post initiation/discontinuation of HU/HC or L-glutamine (instead of including them). A sensitivity analysis will evaluate results with inclusion of those data. The definition of end date is also updated accordingly until the initiation/discontinuation of HU/HC or L-glutamine.
- Table 10-1: clarified the T1/2 definition.
- [redacted].
- Table 10-2: update in the number of patients from 89 to 86.

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.

Amendment 1 (23-Oct-2018)

Amendment rationale

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

The purpose of this amendment is as followed:

1. To update inclusion exclusion criteria in order to :
   - Clarify criteria #4 for patients receiving HU/HC, as dose alterations of HU/HC performed during part A will be not allowed to avoid any potential influence with the study treatment and PK results.
   - Re-word and clarify criteria #17 to ensure that patients with active HIV will be excluded as immunological effects of crizanlizumab are not sufficiently explored so far.
   - Including 2 new exclusion criteria as per GCP guidance.
2. Addition of a DMC to be in charge of the review of the key safety and PK data review at each dosing confirmation in Part A including the recommendation to open the next age group and to open enrolment in Part B to ensure pediatric patient safety is monitored.
3. To clarify the minimum observation period after the administration of the drug to monitor the patient safety following drug infusion.
4. Pregnancy test was extended to all females of childbearing potential
5. To update the declaration of Helsinki directive to fit to the last directive version (Art. 3 Par. 2 of the Directive 2005/28/EC).
6. To include mandatory reasons to terminate study prematurely due to safety reasons.
7. Dose interruption due to Adverse Drug Reaction table 6-2 has been updated as following to clarify the requirements in case of ADR:
   - Addition of the mandatory study treatment discontinuation in case of any grade 4 ADR.
   - Clarification on the timelines required to permanently discontinue the study drug in case of persistent abnormality.
   - Updates performed to align the grades values with CTCAE version 5
   - Footnotes clarifications including removal of “*Note” and “**Note” as they are not applicable for the table.
8. Drug-induced liver injury (DILI) section has been updated as subjects with SCD tend to have elevated transaminases, especially AST, and indirect bilirubin due to the hemolytic nature of this condition. In order to reduce the number of false positives, AST will not be considered and only ALT and bilirubin will be required in this criteria. The criteria in table 6-2 has been adapted accordingly.
9. Addition of mandatory dose interruption in case of confirmed QTc prolongation.
10. Drug treatment details has been updated as only SEG101 FMI is used from the start of the study and the preparation of the individual doses of SEG101 for patients are defined in the Pharmacy Manual.

11. Clarification of concomitant medication permitted during the study:
    - Use of live and inactivated vaccines as permitted concomitant medication during the trial. Live vaccines to be given at least 4 weeks prior first dose in accordance with guidelines for monoclonal antibodies
    - Use of HU/HC and L-Glutamine as per local guidelines and standard of care
    - Use of HU/HC during the Part A as dose modifications are not allowed.
12. Clarification that urine pregnancy tests will be done for all female childbearing potential or for all female becoming of childbearing potential during the study.
13. Clarification of the pre-dose PK/PD/IG samples time points for patients enrolled in Part B
14. Optional pharmacogenetics sample will be collected using a saliva swab instead of blood sample to reduce the blood volume collection in the 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.

- List of Abbreviations: Added ADR (Adverse drug Reactions) and NSAIDs (Non-steroidal anti-inflammatory drugs)
- Protocol Summary: Made updates to align the changes in protocol sections.
- Section 1.1: Nietert 2002 publication has been included
- Section 1.2.1.2: Clarification of non-steroidal anti-inflammatory drugs (NSAIDs) included.
- Section 2.2: inclusion of key safety data for the single dosing confirmation
- Section 4.1: a inclusion of key safety data for the single dosing confirmation
- Section 5.2: Inclusion criteria #4 updated to do not allow alterations of HU/HC during Part A
- Section 5.3: Exclusion criteria #17 clarified to exclude patients with active HIV
- Section 5.3: Addition of exclusion criteria # 29 and # 30
- Section 6.1.1: Drug treatment details updated as only SEG101 Final Market Image (FMI) is used from the start of the study and the preparation of the individual doses of SEG101 for patients are defined in the Pharmacy Manual.
- Section 6.3.1.1: Addition of DMC recommendation to be considered on the dose confirmation.
- Section 6.3.1.2: Clarification added for the permanent treatment discontinuation and typo corrected.
- Table 6-2: Addition of the mandatory study treatment discontinuation in case of any grade 4 ADR, clarification made on the timelines required to permanently discontinue the study drug in case of persistent abnormality, alignment with CTCAE grade version 5 and footnotes clarifications have been performed in the table.
- Table 6-3: clarification of the management of the infusion-related reactions for Grade 2.
- Section 6.3.3.1: Drug-induced liver injury (DILI) cases section updated

- Section 6.3.2: Section title updated to be in alignment with the section and addition of mandatory dose interruption in case of confirmed QTc prolongation.
- Section 6.4.1: addition of the vaccines administration (live and inactivated) as permitted concomitant therapy, concomitant use of HU/HC and L-Glutamine as per local guidelines and standard of care and clarification on the use of HU/HC during the Part A.
- Section 6.6: clarification of the place where the drug infusion have to be performed and the patient monitoring timing after drug infusion.
- Table 7-1: updates performed in the table to be in alignment with protocol sections
- Section 7.2.1.1: addition of NSAIDs (Non-steroidal anti-inflammatory drugs) and typos corrected.
- Section 7.2.2.7.6: Clarification on the pregnancy analysis for females of child bearing potential.
- Section 7.2.2.7.7: typo corrected
- Section 7.2.3.1: correction of the pre-dose PK/PD/IG samples timelines collection for Part B
- Section 7.2.4 and Table 7-9: saliva swab will be used for the optional pharmacogenetics sample
- Section 8.1.1: CTCAE version updated and clarifications provided on the reporting of the AE in the CRF.
- Table 8-1 footnote: addition of NSAIDs (Non-steroidal anti-inflammatory drugs)
- Section 8.7: addition of the Data Monitoring Committee section
- Section 10: inclusion of key safety data for the single dosing confirmation
- Section 10.5.3.3: CTCAE version updated
- Section 11.1: Update of the European directive
- Section 11.4: Update of the study discontinuation section to include the mandatory reasons to terminate study prematurely due to safety reasons
- Section 13: duplicate reference removed
- In addition, clarifications were added to correct typographical errors and inconsistencies in different sections.

IRBs/IECs

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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.

Protocol summary

Title	A phase 2, multicenter, Open-Label Study to Assess Appropriate Dosing and to Evaluate Safety of Crizanlizumab, with or without Hydroxyurea/Hydroxycarbamide, in Sequential, Descending Age Groups of Pediatric Sickle Cell Disease Patients with Vaso-Occlusive Crisis.
Brief title	Study of dose confirmation and safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the Phase 2 CSEG101B2201 study is to confirm and to establish appropriate dosing and to evaluate the safety in pediatric participants ages 2 to <18 years with a history of VOC with or without HU/HC, receiving crizanlizumab for 2 years. The efficacy and safety of crizanlizumab was already demonstrated in adults with sickle cell disease. The approach is to extrapolate from the PK/ pharmacodynamics (PD) already established in the adult population. The study is designed as a Phase II, multicenter, open-label study.

Primary Objective(s) and Key Secondary Objective	• Primary Objective:
	  • To confirm and establish appropriate dosing in participants from 2 to less than 18 years of age (Parts A and B)
	  • To evaluate the safety of crizanlizumab in participants from 2 to less than 18 years of age (Parts A and B).
	• Key Secondary objectives: none

Secondary Objectives	• To assess the long-term efficacy of crizanlizumab in participants aged 2 to <18 year old, as measured by annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital, annualized rate of VOC events treated at home, annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism), annualized rate of Hospitalizations and ER visits (both overall and VOC-related), annualized rate of days of ER/hospitalization (both overall and VOC-related), annualized rate of Dactylitis events • To assess other safety measures in participants aged 2 to < 18 year old in terms of frequency, seriousness, severity and causality of treatment emergent AEs, absolute change from baseline in hemoglobin, measurement of anti-drug antibodies (ADA) to crizanlizumab, ECG measures at the time of PK, growth and sexual maturation assessments. • Characterize the long-term PK and PD of crizanlizumab in participants aged 2 to <18 years at the time of study entry as measured by pre-dose concentrations prior to each study drug dose and percentage of P-selectin inhibition prior to dosing.
Study design	Open-label, single arm study of crizanlizumab in SCD (sickle-cell disease) pediatric participants. In Part A of the study across the ages 2- to <18 years, the dose for each group will be first confirmed on the basis of single & multiple dose (steady state) PK data and key safety data from an initial subgroup of participants. In Part B of Groups 1 and 2, safety and efficacy data will be collected from additional participants from 6 to <18 years.

Study population	The study will include at least 100 pediatric participants, ages 2 years to less than 18 years, with confirmed diagnosis of SCD (all genotypes, as in Table 1-1), who have experienced at least 1 VOC within the preceding 12 months. Group 1 will include at least 26 participants ages 12 to <18 years, group 2 will include at least 26 participants ages 6 to <12 years, and group 3 will include at least 8 participants ages 2 to <6 years. Participants must not plan to initiate voxelotor, HU/HC, L-glutamine or erythropoietin stimulating agent during the study. For participants who are already treated with HU/HC, L-glutamine or erythropoietin stimulating agent, they must be taking such drugs for at least 6 months prior to study entry and accept to take the same dose at the same schedule during the trial. Voxelotor must have been permanently discontinued at least 30 days prior to study entry.

Inclusion criteria	• Male or female patients ages 2 to <18 years
	• Confirmed diagnosis of SCD (any genotype including HbSS, HbSC, HbSβ^0-thalassemia, HbSβ^+-thalassemia, and others) by hemoglobin electrophoresis and/or high-performance liquid chromatography (HPLC) performed locally. Confirmation of diagnosis by two accepted methods is recommended.
	• Experienced at least 1 VOC within the preceding 12 months prior to screening, as determined by medical history. Prior VOC must have resolved at least 7 days prior to the first dose in the study and must include all the following:
	  • the occurrence of appropriate symptoms (see VOC definition in Section 7.2.1.1)
	  • either a visit to a medical facility or healthcare professional
	  • receipt of oral/parenteral opioid or parenteral non-steroidal anti-inflammatory drugs (NSAID).
	• If receiving HU/HC, L-glutamine or erythropoietin stimulating agent, must have been receiving the drug consistently for at least 6 months prior to Screening and plan to continue taking it at the same dose and schedule during the trial. Patients not receiving such drugs must have been off them for at least 6 months prior to screening.
	• Received standard age-appropriate care for SCD, including penicillin prophylaxis, pneumococcal immunization, and parental education.
	• Transcranial Doppler (TCD) for patients aged 2 to < 16 years at the time of screening, with HbSS, HbSβ0-thalassemia, and HbSD disease, indicating low risk for stroke (per investigator) as outlined in Section 7.2.2.6

Exclusion criteria	• History of stem cell transplant • Received any blood products within 30 days prior to Week 1 Day 1 dosing • Plan to participate in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) or undergo exchange transfusions/plasmapheresis during the study. Patients requiring episodic transfusion (simple or exchange) in response to worsened anemia or VOC are permitted. • Patients with bleeding disorders • Contraindication or hypersensitivity to any drug from similar class as study drug or to any excipients of the study drug formulation. • Planning to initiate or terminate HU/HC or L-glutamine while on study, other than for safety reasons. • Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs) in the opinion of the investigator. • Patients under voxelotor within 30 days prior to screening or planning to initiate voxelotor while on study.
Investigational and reference therapy	SEG101 (crizanlizumab)
Efficacy assessments	• VOC events leading to healthcare visit in clinic/ER/hospital

	• VOC events treated at home (based on documentation by health care provider following phone contact with participant) • Each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) • Hospitalizations and ER visits (both overall and VOC-related) • Days of ER/hospitalization (both overall and VOC-related) • Dactylitis events • [redacted] • School/ Work employment status and sick time absence
Safety assessments	• Monitoring of AEs/SAEs • Physical exam and vital signs • Performance status • Hematology, blood chemistry, coagulation and urinalysis (additional laboratory tests will be performed at the investigator's discretion for safety measures in the event of an adverse event) • [redacted] • Echocardiography (At Screening, Week 51 and at End of Treatment (EOT)) • Ocular and retinal exam • Transcranial Doppler (for participants aged 2 to < 16 yrs at time of screening, with HbSS, HbSβ^0-thalassemia, and HbSD disease. For participants with other SCD types, performance of TCD is by investigator discretion) • Auditory assessment • Absolute change from baseline in hemoglobin • Pulmonary function testing if respiratory problems by history or clinical exam • ECGs at relevant PK time points • Growth and sexual maturation assessments (Tanner stage) • Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab
Other assessments	• PK parameters after the starting dose and multiple dose. • Pre-dose PK (drug concentration) prior to each dose. • PD Parameter (%P-selectin inhibition) after starting dose and multiple dose • %P-selectin inhibition prior to each study drug dose • [redacted]

Data analysis	There will be multiple cut-off dates and formal analyses. PK, dose, demography, baseline characteristics and key safety data after a single dose for part A in each group will occur when at least 6 participants with evaluable PK have been enrolled and have completed the Week 7 Day 1 visit. Analysis of PK, PD, dose, demography, baseline characteristics and key safety data for part A of each group after multiple doses will occur when there are at least 6 evaluable participants who completed the full PK/PD sampling following at least 3 full consecutive doses after Week 3 Day 1. The primary analyses for parts A+B of Group 1, Group 2, and part A of Group 3 will occur consecutively when all the participants enrolled in each of these groups have completed 26-weeks of the treatment or discontinued the study treatment. PK, PD, demography and other baseline characteristics, efficacy and safety data will be reported. Additional data for any participants continuing to receive study treatment, as allowed by the protocol, will be further summarized in a final study report once all participants from all groups have either completed or early discontinued from the study.
Key words	Sickle cell disease, crizanlizumab, pediatric, pharmacokinetic, P-selectin

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

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

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

SCD patients also suffer from cerebrovascular complications, ranging from clinically evident acute stroke to transient silent ischemic infarct (Platt et al 2006). Other chronic complications include functional asplenia, leaving patients more susceptible to infection, (Clinical Practice Guideline No. 6. April 1993), bone growth retardation and avascular necrosis renal dysfunction (Saborio and Scheinman1999), and issues of the biliary tree (gallstones, congestion), eyes (retinopathy) (Charache 1996), and soft tissue (leg ulcers) (Ashley-Koch et al 2000, Gladwin et al 2004, Gladwin and Kato 2005). Chronic pain and opioid use are also common (Smith et al 2008). As a result of the totality of these complications, there is an approximately 20 to 30 year reduction in life expectancy in SCD patients (Platt et al 1994).

Hemoglobin values for SCD patients vary, typically ranging from 6 to 10 g/dL, but some patients can live with baseline hemoglobin of 4 g/dL or lower. Chronic hemolysis results in other abnormal labs, including reticulocytosis, low haptoglobin, and increased free hemoglobin, lactate dehydrogenase (LDH), and indirect bilirubin (and, by extension, total bilirubin). In

young SCD patients, glomerular filtration rate (GFR) is substantially increased (hyperfiltration: MDRD-GFR >130 in females, >140 ml/min per 1.73 m^2 in males) but tends to decrease progressively with time, and 4-5% of these patients develop stage 5 chronic renal disease (CRD) (Hirschberg 2010). SCD patients are also more susceptible to parvovirus B19 infection which can arrest erythropoiesis and lead to aplastic crisis (Heegaard and Brown 2002).

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

While SCD is genetically determined, clinical symptoms generally do not occur until 6 months of age, as elevated fetal hemoglobin (HbF) levels retard the polymerization of deoxy sickle hemoglobin (Miller 2000).

There is considerable variability in disease severity (Gill et al 1995), likely due to a complex interaction of genetic, rheologic and hematologic factors, as well as microvascular and endothelial factors. Therefore, despite the capacity to determine genotype, the ability to predict disease course from birth is limited (Thomas et al 1997). A prospective study of SCD participants with HbSS in the U.S. reported 54% of 0-9 year olds (n=1093), 68% of 10-19 year olds (n=635), and 73% of 20-29 year olds (n=424) experienced pain crises. Similarly, the average pain rate for the first 3 years of the study was 0.40 per year for 272 participants who entered the study at age 0-4 years and 0.56 for the 223 participants who entered the study at age 5-9 years (Platt et al 1991). Moreover, a recent study (PiSCES) evaluating health related quality of life issues in SCD participants indicated that VOC might be significantly underreported among SCD participants (McClish et al 2005).

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

Preventative therapies for SCD include chronic red cell transfusion programs to reduce the incidence of stroke in high-risk patients and hydroxyurea/hydroxycarbamide (HU/HC, Droxia/Siklos), one drug approved for VOC. The mechanisms by which HU/HC produces its beneficial effects are uncertain, but likely involve increasing HbF levels in RBCs, thereby decreasing the amount of hemoglobin S polymerization. Hydroxyurea is cytotoxic, myelosuppressive and teratogenic (Charache et al 1995), and the long-term effects of hematologic toxicities, organ damage and carcinogenicity are currently unknown (NIH Consensus and State-of -the Science Statements, 2008). Additionally, many patients continue to experience acute painful episodes despite HU/HC. Unmet medical need is even more acute in the pediatric population, as HU/HC is not approved for pediatric use in the US. According to the Droxia US PI: "Section 8.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established". In the EU, Siklos (HU/HC) is approved in pediatric patients aged 2 years and above. L-glutamine (Endari™) is approved for oral administration by the US Food and Drug Administration (FDA) to reduce the acute complications of SCD in adult and pediatric patients 5 years and older (Endari label). Patients taking L-glutamine still experience pain crises and the treatment is not approved for patients under 5 years of age. Oxbryta™ (voxelotor) has been approved by US FDA on 25-Nov-2019 for the treatment of SCD in adults and pediatric patients 12 years of age and older, and received an accelerated approval on 17-Dec-2021 for patients aged 4 years to less than 12 years. Oxbryta™ (voxelotor) also received approval from the European Medicines Agency (EMA) for the treatment of hemolytic anemia due to SCD in adults and pediatric patients 12 years of age and older on 16-Feb-2022.

In summary, despite standard of care management, many children and adolescents with SCD still experience VOC.

In some patients, bone marrow transplantation may be considered and can be curative, but a limited number of patients are eligible, and this carries a high risk of morbidity and mortality (NHLBI, The Management of Sickle Cell Disease. NIH Publication No.022117). Thus, SCD is a life-threatening disease with severe morbidities and represents a major unmet medical need.

The recognition that adherence of leukocytes, platelets and sickle red cells to blood vessel endothelium and to each other to have a primary role in VOC led to further research into the selectins, which mediate the first steps in the recruitment of leukocytes to specific tissues. Under shear flow in the blood, leukocytes first tether and begin rolling on vascular endothelium, eventually adhering firmly and infiltrating into the underlying tissue (Springer 1995). Selectins interact with glycoconjugated ligands on leukocytes to initiate this process (McEver et al 1995, Vestweber and Blanks1999). Transient adhesion mediated by selectins is a prerequisite for firm adhesion mediated by integrin receptors and subsequent transendothelial migration of leukocytes. Three selectins have been identified: P-, E- and L-selectin. P-selectin is the best characterized of the selectins, and binding specificity and affinity to its physiological ligand P-selectin glycoprotein ligand-1 (PSGL-1) is well-documented (Mehta et al 1998, McEver 2004). P-selectin is stored in Weibel-Palade bodies in endothelial cells that line blood vessels and in α-granules in platelets.

Extensive data have been published over the last decades that suggests a pivotal role for P-selectin in the pathophysiology of SCD (Matsui et al 2001). Much of this work has been conducted in mice engineered or altered to express human hemoglobin S (sickle cell hemoglobin) but not mouse β hemoglobin. These mice have a remarkably similar disease

pathology and inflammatory profile to that observed in human SCD, including vaso-occlusion. Using these mice, investigators have demonstrated P-selectin interactions between the endothelium and sickled red blood cells, leukocytes, and platelets. Additional studies have demonstrated direct P-selectin-mediated binding of leukocytes with sickled red cells and platelets. Platelet and leucocyte activation was observed in pediatric SCD patients (Inwald et al 2000, Yip et al 2015), similar to what was described in adults (Ruf et al 1997, Majumdar et al 2013). Soluble P-selectin, a surrogate marker of protein expression in endothelium and platelets, was elevated and appeared to be similar in adult and pediatric SCD patients (Krishnan et al 2010, Setty et al 2012, Hatzipantelis et al 2013, Colombatti et al 2013). All of these cell-cell interactions have been implicated in SCD vaso-occlusion. Further, blockade or genetic absence of P-selectin decreases or eliminates these cell-cell interactions and vaso-occlusion. Taken together, these studies establish P-selectin as a key mediator of vaso-occlusion in SCD.

Table 1-1 Sickle Cell Disease genotypes

Severe sickle-cell disease	**Characteristics**
HbS/S (β6Glu>Val/β6Glu>Val); sickle-cell anemia	The most common form of sickle-cell disease
HbS/β^0 thalassaemia	Most prevalent in the eastern Mediterranean region and India
Severe HbS/β^+ thalassaemia	Most prevalent in the eastern Mediterranean region and India; 1–5% HbA present
HbS/O Arab (β6Glu>Val/β121Glu>Lys)	Reported in north Africa, the Middle East, and the Balkans; relatively rare
HbS/D Punjab (β6Glu>Val/β121Glu>Gln)	Predominant in northern India but occurs worldwide
HbS/C Harlem (β6Glu>Val/β6Glu>Val/β, β73Asp>Asn	Electrophoretically resembles HbSC, but clinically severe; double mutation in β-globin gene; very rare
HbC/S Antilles (β6Glu>Lys/β6Glu>Val, β23Val–Ile)	Double mutation in β-globin gene results in severe sickle-cell disease when co-inherited with HbC
HbS/Quebec-CHORI (β6Glu>Val/β87Thr>Ile)	Two cases described; resembles sickle-cell trait with standard analytical techniques
Moderate sickle-cell disease	
HbS/C (β6Glu>Val/β6Glu>Lys)	25–30% cases of sickle-cell disease in populations of African origin
Moderate HbS/β^+ thalassaemia	Most cases in the eastern Mediterranean region; 6–15% HbA present
HbA/S Oman (βA/β6Glu>Val, β121Glu>Lys)	Dominant form of sickle-cell disease caused by double mutation in β-globin gene; very rare
Mild sickle-cell disease	
Mild HbS/β^{++} thalassaemia	Mostly in populations of African origin; 16–30% HbA present
HbS/E (β6Glu>Val/β26Glu>Lys)	HbE predominates in southeast Asia and so HbSE uncommon, although frequency is increasing with population migration
HbA / Jamaica Plain (βA/β6Glu>Val, β68Leu/Phe)	Dominant form of sickle-cell disease; double mutation results in Hb with low oxygen affinity; one case described
Very mild sickle-cell disease HbS/HPFH	
HbS/HPFH	Group of disorders caused by large deletions of the β-globin gene complex; typically 30% HbF
HbS/other Hb variants	HbS is co-inherited with many other Hb variants, and symptoms develop only in extreme hypoxia

Severe sickle-cell disease	Characteristics
Sickle Cell Disease genotypes (Rees et al 2010)	

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

1.2.1 Overview of crizanlizumab (SEG101)

Crizanlizumab (SEG101) is a humanized monoclonal antibody that binds P-selectin in humans and nonhuman primates and blocks the interaction of P-selectin with its ligands including PSGL-1. SelG1 has negligible binding activities to human E-selectin or L-selectin in *in vitro* binding assays. 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 current drug developer and sponsor for crizanlizumab. First global approval for crizanlizumab for SCD treatment has been obtained from the US FDA on 15-Nov-2019.

1.2.1.1 Non-clinical experience

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

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

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

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

As crizanlizumab is specific to human and nonhuman primate P-selectin, and in accordance with the International Council for Harmonization (ICH) S6 Guidance, one reproductive toxicology study with SEG101 was conducted and completed in March 2019. In this study, administration of crizanlizumab to pregnant cynomolgus monkeys once every two weeks during gestation did not elicit maternal toxicity and there were no effects on infant growth and development through 6-months postpartum directly attributable to crizanlizumab. All drug treated monkeys and their offspring were exposed to crizanlizumab, indicating that crizanlizumab was able to cross the placental barrier. Serum analyses showed dose-dependent inhibition of P-selectin by crizanlizumab in an *ex vivo* assay. The amount of inhibition was similar in adult females and infants.

There was a numerical increase in the proportion of pregnant monkeys that aborted or experienced an infant death, the cause of which is unclear and likely multifactorial. Some of these were attributed to common non drug-related effects such as maternal neglect or breech positioning. There were no teratological findings (external or visceral) in the aborted fetuses, infant deaths or those otherwise born alive.

This reproductive study 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. The maternal and developmental NOAEL for crizanlizumab in this study, therefore, was 50 mg/kg once every 2 weeks.

1.2.1.2 Clinical experience

Phase I Clinical Study (CSEG101A2101)

The objectives of this study (Reprixys study code: Se1G1-00003; Novartis study code: CSEG101A2101) were to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity (IG) of i.v. administered crizanlizumab (SelG1) versus placebo in 27 healthy participants at ascending dose levels (0.2, 0.5, 1.0, 5.0 and 8.0 mg/kg). Throughout this description of CSEG101A2101, the study drug is denoted as crizanlizumab and refers to SelG1.

Crizanlizumab concentrations slowly declined, with mean half-life ranging from 75.6 (at dose of 0.2 mg/kg) to 500 (at 5.0 mg/kg) hours. Therefore, clearance decreased with the increase in dose level: 88.6 mL/hr (at 0.2 mg/kg) to 9.91 mL/hr (at 5.0 mg/kg). Following two i.v. infusions of crizanlizumab at 8.0 mg/kg, the mean half-life was 363 hours, and the clearance was 3.86 mL/hr. 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 generated during the Phase I clinical trial indicate that no specific antibody response to crizanlizumab occurred in any participants receiving up to 2 doses of drug.

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

Phase II Clinical Study (SUSTAIN – CSEG101A2201)

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

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

The primary efficacy parameter was the assessment of the annual rate of VOC leading to healthcare visit, defined as an acute episode of pain, for which there is no other medically determined explanation or cause other than a vaso-occlusive event, which required a medical facility (clinic, emergency room (ER), or hospital) visit and treatment with oral or parenteral narcotics, or parenteral NSAIDs. ACS, hepatic sequestration, splenic sequestration and priapism events requiring a visit to a medical facility were also considered VOC leading to healthcare visit for analysis purposes. It was observed that treatment with 5.0 mg/kg crizanlizumab resulted in an annual rate of VOC leading to healthcare visit that was 45.3% lower than the rate with placebo which was statistically significant ($p = 0.010$). The annual rate of VOC leading to healthcare visit in the 2.5 mg/kg crizanlizumab treatment arm was compared with that of placebo, and although favorable (32.6% reduction with active treatment), it was not statistically significant ($p = 0.180$). In addition, in the 5.0 mg/kg crizanlizumab arm, numerical and clinically significant reductions in the annual rate of VOC leading to healthcare visit were observed across important subgroups, including participants receiving concomitant HU/HC (32.1%) and not receiving concomitant HU/HC (50.0%), and in participants with the HbSS genotype (34.6%) and non-HbSS genotype (50.5%) (HbSC, $HbS\beta^0$-thalassemia, $HbS\beta^+$-thalassemia and others). The median annual rate of days hospitalized was numerically reduced in the 5.0 mg/kg arm versus the placebo arm (4.00 versus 6.87, respectively); however, this difference was not statistically significant. Treatment with crizanlizumab at 5.0 mg/kg was associated with longer median time to first VOC leading to healthcare visit compared with placebo (4.07 versus 1.38 months, $p = 0.001$) and median time to second VOC leading to healthcare visit compared to placebo (10.32 versus 5.09 months, $p = 0.022$).

Crizanlizumab was well-tolerated. Adverse events that occurred in ≥5% of participants in an active dose group (either 2.5 mg/kg or 5.0 mg/kg) and were more than 2 times higher than placebo were: arthralgia, pruritus, vomiting, chest pain, diarrhea, fatigue, myalgia, musculoskeletal chest pain, abdominal pain, influenza, oropharyngeal pain and traffic accident. Adverse events that occurred in 10% or more of the participants in either active treatment group and at a frequency that was at least twice as high as that in the placebo group were arthralgia

(5.0 mg/kg: 18.2% versus 2.5 mg/kg: 14.1% versus placebo: 8.1%), diarrhea (10.6% versus 7.8% versus 3.2%), pruritus (7.6% versus 10.9% versus 3.4%), vomiting (7.6% versus 10.9% versus 4.8%) and chest pain (1.5% versus 10.9% versus 1.6%). There were 5 deaths during the study (2 at 5.0 mg/kg, 1 at 2.5 mg/kg and 2 in the placebo group), and no deaths were deemed related to study drug. The proportion of participants experiencing serious adverse events (SAEs) was 25.8% at 5.0 mg/kg, 32.8% at 2.5 mg/kg and 27.4% in the placebo group.

Treatment-induced anti-crizanlizumab antibodies were transiently detected in 2 out of 175 (1.1%) participants.

There was no evidence for any increase in infections: the frequency across treatment arms in the SOC of Infections and Infestations were evenly distributed (51.5%, 45.3% and 53.2% in the 5.0 mg/kg, 2.5 mg/kg and placebo treatment arms, respectively).

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

Phase III Clinical Study (STAND – CSEG101A2301)

The purpose of the phase III, multicenter, randomized, double-blind study CSEG101A2301 was to compare the efficacy and safety of two doses of crizanlizumab versus placebo in adolescent and adult patients with SCD who had a history of VOCs (at least 2 in the 12 months prior to screening period) leading to healthcare visits. This study included patients aged 12 years and older with a confirmed diagnosis of SCD, where all genotypes were eligible. The primary objective of this study was to compare the efficacy of crizanlizumab at doses of 7.5 mg/kg and 5 mg/kg, respectively, versus placebo (in addition to standard of care) in preventing VOCs leading to healthcare visits over the first-year post-randomization.

A total of 252 participants were randomized in Study A2301. Of these, 85 participants were assigned to the placebo arm, 84 participants to the crizanlizumab 5 mg/kg arm, and 83 participants to the crizanlizumab 7.5 mg/kg arm. The primary analysis, with a data cutoff (DCO) date of 31-Aug-2022, was performed when all 252 participants completed at least one year (52 weeks) of investigational treatment or discontinued within one year.

Study CSEG101A2301 did not demonstrate the superiority of crizanlizumab over placebo on its primary endpoint, which is the annualized incidence rate of VOC (Vaso-Occlusive Crises) events leading to a healthcare visit. This conclusion is based on a negative binomial regression analysis. The adjusted annualized incidence rate ratio of the crizanlizumab 5 mg/kg arm, compared with the placebo arm, was 1.08 with a 95% confidence interval of 0.76 to 1.55. The adjusted p-value was greater than 0.999, indicating that there is no statistically significant difference between the two treatment groups. In post-hoc analyses for the subgroup of participants located in the United States (n=22) a trend toward a treatment benefit in rates of VOC leading to a healthcare visit in the crizanlizumab 5 mg/kg vs. placebo arm was apparent. This positive trend was less apparent in the crizanlizumab 7.5 mg/kg arm vs. placebo arm.

The proportion of patients experiencing at least one adverse event (AE) was similar across the treatment arms: 90.6% in the placebo arm, 88.1% in the crizanlizumab 5 mg/kg arm, and 92.8% in the crizanlizumab 7.5 mg/kg arm. Grade 3/4 AEs were reported for a higher percentage of

patients in the crizanlizumab 5 mg/kg arm (56.0%) compared to the crizanlizumab 7.5 mg/kg arm (38.6%) and the placebo arm (31.8%). AEs leading to discontinuation were reported with a similarly low incidence in each arm (2.4%). Serious adverse events (SAEs) were reported for a higher percentage of patients in the crizanlizumab 5 mg/kg arm (41.7%) compared to the crizanlizumab 7.5 mg/kg arm (26.5%) and the placebo arm (30.6%). The reported SAEs generally did not have a suspected relationship to the study treatment. No treatment-induced ADAs were noted at 5 mg/kg. One participant, in the 7.5 mg/kg arm, presented with treatment induced transient ADA and no safety issue had been associated to the positive ADA tests.

At the time of this amendment, the study is still ongoing. Overall, the safety profile in study CSEG101A2301 was comparable across treatment arms and consistent with the safety results from previous studies involving crizanlizumab, with no new safety concerns identified.

2 Rationale

2.1 Study rationale and purpose

Children and adults with SCD share the same etiology and genetic variability, leading to a similar range of clinical manifestations and prognostic factors. However, within the pediatric population, infants with SCD typically have milder and less frequent symptoms than older children and adults, due to higher levels of fetal hemoglobin (HbF), which results in less sickling (Akinsheye et al 2011). A prospective study of the natural history of SCD in the U.S. reported the increased incidence of pain crises with increasing age. Of those with HbSS, 46% of 0-9 year olds (n=1093) had a pain rate of 0 events per year, versus only 32% of 10-19 year olds (n=635), and 27% of 20-29 year olds (n=424). Similarly, the average pain rate for the first 3 years of the study was 0.40 per year for 272 participants who entered the study at age 0-4 years and 0.56 for the 223 participants who entered the study at age 5-9 years (Platt et al 1991).

In the Dallas Newborn Cohort, 168 children who presented within the first year of life were followed for a mean of 7.1 years, and only 4 (2.4%) had frequent pain crises requiring hospitalization (defined as an average of ≥ 2 painful events per year for the entire follow-up period, with ≥ 2 events per year for 3 consecutive years) (Quinn et al 2008).

In contrast to the pain crises experienced by adults, crises in infants and children more commonly manifest as hand-foot syndrome, a painful swelling of hands and/or feet due to dactylitis (Stuart and Nagel 2004).

The expression of P-selectin in endothelium was shown in both healthy and SCD children (Miura et al 2004, Pryce et al 2014) and adults (Kutlar and Embury 2014, Chai and Song 2014, Souza et al 2015). P-selectin expression on platelets is activated in response to a range of physiologically relevant platelet agonists (Ferroni et al 2012). Platelet and leucocyte activation was observed in pediatric patients (Inwald et al 2000, Yip et al 2015), similar to what was described in adults (Ruf et al 1997, Majumdar et al 2013). Soluble P-selectin, a surrogate marker of protein expression in endothelium and platelets, was detected in blood of both adult (Blann et al 2008, Kanavaki et al 2012, Al Najjar et al 2017) and pediatric SCD patients (Krishnan et al 2010, Setty et al 2012, Hatzipantelis et al 2013, Colombatti et al 2013). The identified range of concentrations of soluble P-selectin in adult patients ranged from 42.5 ng/ml

to 268 ng/ml. Similar concentrations of soluble P-selectin were identified in pediatric patients (29.7 ng/ml – 370 ng/ml).

Based on the above evidence, no difference in the mechanism of action of crizanlizumab is expected between adult and pediatric patients. Proper dosing will be investigated in this pediatric study and confirmed for each pediatric age group. To address the unmet need in pediatric patients, the current proposed study is designed to confirm and establish appropriate dosing and to evaluate safety of crizanlizumab in pediatric SCD patients with a history of VOC, with or without HU/HC, based on the favorable safety and efficacy profile of crizanlizumab in adults.

2.1.1 Current understanding of PK/PD properties of crizanlizumab

The PK of crizanlizumab is not dose-proportional. Following single i.v. infusion for 50 minutes of crizanlizumab at dose levels of 0.2, 0.5, 1.0, and 5.0 mg/kg and two i.v. infusions of 8.0 mg/kg in healthy volunteers from the CSEG101A2101 study, the drug is slowly cleared, with clearance values ranging from 3.86 to 88.6 mL/hr and half-life values from 75.6 to 500 hours. The drug is cleared more rapidly at lower doses than at higher doses, which indicates that the drug exhibits the characteristic target-mediated drug disposition. Even though the infusion was stopped after 50 minutes, the median time of maximum concentration ranged from 1.43 to 4.83 h, indicating that the drug has slow distribution. The concentration-time profiles of the drug suggest that its PK is multi-compartmental with an initial rapid decline in concentration during the first 6-8 hours followed by a slower decline, in addition to a saturable elimination that occurs when its concentration reaches approximately 10 µg/mL

In the Phase II SUSTAIN CSEG101A2201 study in SCD participants, only crizanlizumab pre-dose concentrations were collected every 4 weeks after multiple i.v. infusions of 2.5 mg/kg and 5.0 mg/kg (from Week 6 to Week 50). The dosing regimen of crizanlizumab in SUSTAIN was such that the first dose was administered on week 1 followed by every 4 week dosing starting on week 3. Mean trough concentrations of crizanlizumab ranged from 2.8 to 6.83 µg/mL at 2.5 mg/kg dose and from 10.50 to 14.96 µg/mL at 5.0 mg/kg dose. The PD marker was derived from P-selectin inhibition that was collected at the same time as the pre-dose drug concentrations. The mean trough percentage P-selectin inhibition obtained 4 weeks post-dose ranged from 24% to 40% following administration of the 2.5 mg/kg dose and from 64% to 76% following administration of the 5.0 mg/kg dose, whereas mean trough P-selectin inhibition following treatment with placebo ranged from 2.8% to 6.1%. Pre-dose drug concentration versus percentage P-selectin inhibition shows a positive relationship that can be characterized by a sigmoidal Emax model.

The preliminary population PK (PopPK) model of crizanlizumab was developed based on the available adult data from CSEG101A2101 and CSEG101A2201. [redacted]

2.1.2 Study design consideration

The posology of crizanlizumab in this study (CSEG101B2201) follows that of the SUSTAIN study: first dose is administered on week 1, second dose on week 3, and then every four weeks thereafter. The similarity evaluation will be performed using the PK and PD (%P-selectin inhibition) data from the 5.0 mg/kg dose in participants in the CSEG101A2202 study. The CSEG101A2202 study has rich sample collection to characterize the drug exposure as well as the time-course of P-selectin inhibition. Given that the PK of crizanlizumab is best characterized by a 2-compartment model and that the distribution of crizanlizumab is slow, the sample collection should be optimized to gather the delayed time of maximum drug concentration, which is 2-3 hours after the end of infusion, as well as the time that the initial rapid decline transitions to the slower decline in the drug concentration-time profile. In order to characterize well the PK of crizanlizumab, at least 5 samples are required to capture the concentration-time profile sufficient for similarity evaluation; these are pre-dose, end of infusion, 2 hours after end of infusion, time of the transition from rapid decline to slow decline, and 24 hour sample.

The strong positive relationship between trough drug concentration and the percentage of P-selectin inhibition indicates that the PD sampling for computing area under the curve should be optimized in a similar manner as that for the PK of SEG101. The PD-AUC (area under the curve) is assumed to have lesser variability than the pre-dose percentage of P-selectin inhibition. The sample size is calculated based on the assumption of a smaller variability using PD-AUC rather than the pre-dose P-selectin inhibition.

2.2 Rationale for the study design

The purpose of the proposed Phase 2 CSEG101B2201 study is to confirm and to establish appropriate dosing and to evaluate the safety in pediatric participants ages 2 years to <18 years receiving crizanlizumab for 2 years.

Study CSEG101B2201 is designed as a Phase II, multicenter, open-label study. Indeed, the efficacy and safety of crizanlizumab was already demonstrated in adults with SCD (already receiving or not receiving HU/HC as concomitant treatment), it would thus not be considered ethical to randomize pediatric patients in a placebo-controlled study. The approach instead will consist in extrapolating from the PK/PD established in the adult population.

At least 100 participants will be enrolled in this trial in 3 sequential groups: group 1 (ages 12 to <18 years), group 2 (ages 6 to <12 years), and group 3 (ages 2 to <6 years).

Within the age groups, Group 1 and 2 of the study consists of two parts*:

- Part A: To confirm and establish appropriate dosing sequentially for each age group. Sequential enrollment of descending age groups will be based on first dose PK data and key safety data. Steady-state PK/PD data will be used as well, at a later point, to further evaluate the dose selection. Both after first dose PK and multi-dose PK/PD, the evaluation will combine the data of the particular age group with an extrapolation from the data of the previous age group. The PD marker used is an *ex vivo* P-selectin inhibition assay.
- Part B: To evaluate safety in additional pediatric participants with the confirmed dose in each age group. Enrollment into Part B will be opened after the dose is confirmed in the particular age group via first dose PK and key safety data in Part A.

*In Group 3, single dose PK/PD, multiple dose PK/PD and safety will be evaluated in Part A and no patients will be enrolled in Part B.

The primary safety objective will be AE frequency in part A and B. In addition, the following data will be collected for all participants through both parts A and B: AE's, VOC events, dactylitis events and hospital/ER visits to evaluate efficacy, and immunogenicity and growth and sexual maturation assessments as further safety measures.

2.3 Rationale for dose and regimen selection

Participants enrolled in Group 1 Part A will receive crizanlizumab (SEG101) 5.0 mg/kg by i.v. infusion (refer to Pharmacy Manual) on Week 1 Day 1 followed by a second (loading) dose of 5.0 mg/kg 2 weeks after the first dose (Week 3 Day 1) to accelerate reaching steady-state serum concentrations. This is followed by dosing of 5.0 mg/kg every 4 weeks to ensure that steady-state serum concentrations of crizanlizumab (SEG101) are maintained to provide a consistent blockade of P-selectin.

The doses chosen for the SUSTAIN study were based on P-selectin inhibition of SelG1 in healthy participants, as well as the acceptable safety experience observed with 5.0 mg/kg and 8.0 mg/kg dosing regimens during the Phase I safety study. As mentioned in Section 1.2.1.2, the phase I study (CSEG101A2101) showed that a single dose of SelG1 at 5.0 mg/kg yielded at least 28 days of complete P-selectin inhibition.

The SUSTAIN trial tested either 5.0 mg/kg or 2.5 mg/kg of SelG1 on this same dosing schedule and showed a statistically significant and clinically relevant reduction in median annual rate of VOC leading to healthcare visit in the 5.0 mg/kg dose group versus placebo, while the 2.5 mg/kg group did not have a statistically significant reduction. The overall safety was well-balanced across treatment and placebo groups (5.0 mg/kg: 86% AE and 26% SAE – 2.5 mg/kg: 88% AE and 33% SAE – placebo: 89% AE and 27% SAE) (Ataga et al 2017).

In the STAND trial (CSEG101A2301), free and total soluble P-selectin biomarkers were assessed before and during treatment. During the on-treatment period, both biomarkers were reduced in the crizanlizumab 5 mg/kg and 7.5 mg/kg arms, while no reduction was observed in the placebo arm

[redacted] From the experience with palivizumab, the dose of 5.0 mg/kg crizanlizumab that was used in CSEG101A2201 is expected to generate similar crizanlizumab concentrations in pediatric patients as that in adults.

2.4 Rationale for choice of combination

Not Applicable.

2.5 Rationale for choice of comparators drugs

Not Applicable.

2.6 Risks and benefits

Crizanlizumab offers the potential advantage of reducing the occurrence of VOCs leading to healthcare visits. This benefit is evident in Study CSEG101A2201, where crizanlizumab demonstrated a decrease in the annual rate of VOC leading to healthcare visits (primary endpoint), an increase in the proportion of patients free from VOC leading to healthcare visits, and a longer time to the first VOC leading to a healthcare visit (secondary endpoint) compared to placebo. The evidence supporting the key benefits of crizanlizumab 5 mg/kg in patients aged 16 years and older with SCD is primarily based on the efficacy results from the randomized, placebo-controlled registration Study CSEG101A2201. These results are further supported by the efficacy outcomes from the open-label study CSEG101A2202 (SOLACE-adults). On the other hand, Study CSEG101A2301, a phase III randomized, placebo-controlled study, did

not demonstrate the superiority of crizanlizumab over placebo in terms of its primary endpoint, which evaluated the annualized incidence rate of VOC events leading to healthcare visits

The contrasting results between Study CSEG101A2201 and Study CSEG101A2301 (except for the subgroup of US patients) may be attributed to the impact of the global COVID-19 pandemic and variations in the geographic distribution of participating patients. Differences in healthcare access, practices, and reduced triggers during the pandemic could have led to a decrease in VOCs, thereby diluting the treatment effect. The 52-week treatment period of the trial coincided at least partially with the pandemic, and the sites were affected differently as waves of infection spread worldwide.

Pooled data from studies CSEG101A2201 (SUSTAIN), CSEG101A2202 (DCO: 01-Jun-2022), CSEG101A2301 (DCO: 31-Aug-2022) and CSEG101B2201 (DCO: 05-May-2022) in SCD patients show that crizanlizumab 5 mg/kg is associated with an acceptable safety profile. The most frequently reported adverse drug reactions (≥10% of patients) in the crizanlizumab 5 mg/kg group were nausea, pyrexia, pain, and vomiting. These adverse drug reactions, along with diarrhea, fatigue, dizziness, pruritus may be signs and symptoms of an IRR when observed during/within 24 hours of an infusion. The majority of the adverse drug reactions were mild to moderate (grade 1 to 2). Severe events (Grade 3 and above) were observed in 16 (6.5%) patients for pain (12 patients, [4.9%]), pyrexia (2 patients, [0.8%]), diarrhoea, fatigue and infusion related reaction (1 patient for each, [0.4%].

Crizanlizumab is generally well tolerated, with the only defined key risk being IRRs. However, the review of potential IRR events revealed very few cases that supported typical IRRs. Eighteen (7.3%) patients experienced severe IRR reported in 5 mg/kg pool (n=245). Events developed in >2% patients were Infusion related reaction (15, 6.1%). Most of the events were grade 1 or grade 2. Only 2 (0.8%) patients experienced grade 3 severe IRR (anaphylactic reaction, infusion related reaction; one each, 0.4%) In 7.5 mg/kg pool (n=95), five (5.3%) patients experienced severe IRR. Events developed in >2% patients were infusion related reaction and anaphylactic reaction (2 each; 2.1%). None of these adverse events suggested a severe allergic or anaphylactic reaction to crizanlizumab. The majority of IRR events were mild to moderate in severity and non-serious. Only a small percentage of patients (3/245, 1.2%) in

the overall 5 mg/kg group discontinued treatment due to an IRR: bradycardia, infusion related reaction, and pain (one patient each, 0.4%), and most events resolved on the day of onset or the following day. Cases of infusion-related reactions including severe pain events have been reported, with the majority occurring during the first and second infusions, sometimes indistinguishable from vaso-occlusive crisis.

Crizanlizumab is not known to be associated with myelosuppression, genotoxicity, or carcinogenicity, which are risks associated with other treatments like HU/HC.

There is no evidence to suggest an association between treatment with crizanlizumab and renal or hepatic toxicity. Therefore, no dose adjustment is recommended for patients with renal or hepatic impairment.

The available data indicate a low potential for immunogenicity with crizanlizumab. In conclusion, except for the results from Study A2301, all the data support the benefits of using crizanlizumab 5 mg/kg in patients with SCD.

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 18 (7.3%) participants treated with crizanlizumab 5 mg/kg in the pooled data set; Events occurring in >2% patients were Infusion related reaction (15, 6.1%). Most of the events were grade 1 or grade 2. Only 2 (0.8%) patients experienced grade 3 severe IRR (anaphylactic reaction, infusion related reaction; one each, 0.4%). One (0.4%) patient had SAE due to anaphylactic reaction. Fourteen (5.7%) patients experienced treatment related AEs -infusion related reaction (14; 5.7%). Crizanlizumab was discontinued due to severe infusion related reaction in 1 (0.4%) patient. Crizanlizumab dose was reduced in 2 (0.8%) patients due to severe infusion related reaction (2; 0.8%). Fifteen (6.1%) patients required medication/therapy for severe IRR. Severe IRR events resolved in all patients.

From the safety pool of 7.5 mg/kg crizanlizumab (CSEG101A2202 + CSEG101A2301; N=95), five (5.3%) patients experienced severe IRR reported in 7.5 mg/kg pool. Events occurring in >2% patients were infusion related reaction and anaphylactic reaction (2 each; 2.1%). Anaphylactic reaction was not related to crizanlizumab. Grade 3 severe IRRs were reported in 2 (2.1%) patients (PTs-anaphylactic reaction, hypersensitivity; one each, 1.1%). Crizanlizumab was discontinued due to hypersensitivity in 1 (1.1%) patient. Five (5.3%) patients required treatment and all patients recovered.

Additionally, a broad search for IRRs presenting with symptoms of severe pain in various locations occurring within 24 hours of the infusion, identified 58 participants (23.7%; n=245) in the safety pool with at least one event. Among these patients, reactions experienced by at least 2% patients were headache (19 patients, 7.8%), pain in extremity (13 patients, 5.3%), back pain (12 patients, 4.9%) and arthralgia (9 patients, 3.7%). Other events experienced by <2% patients were abdominal pain, abdominal pain upper, chest pain, musculoskeletal chest pain, myalgia, neck pain, pain and oropharyngeal pain. The median duration from the onset of the

event to resolution was 2 days. Crizanlizumab was permanently discontinued in 2 patients (0.8%) due to an infusion related reaction manifesting as pain.

Immunogenicity

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

In clinical studies of adult patients, treatment-emergent ADA were transiently detected in 1 patient among the 195 patients who received crizanlizumab 5 mg/kg (0.5%). 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.

Incidence of infection was 62.4% (n=245) in 5 mg/kg safety pool (CSEG101A2201+ CSEG101A2202+ CSEG101A2301+ CSEG101B2201). The higher incidence in 5 mg/kg pool was mainly driven by COVID-19 (39; 15.9%), upper respiratory tract infection (31; 12.7%), urinary tract infection (29; 11.8%), and pneumonia (23; 9.4%). Forty (16.3%) patients developed grade 3 AEs, pneumonia (12; 4.9%) and COVID-19 (7; 2.9%), being the most common grade 3 infections. Two patients had grade 4 AE-COVID-19 and wound sepsis (one each) and 3 patients had fatal outcomes due to infections. Twenty-three patients (9.4%) required treatment interruption due to infection. Most of the treatment interruption was due to COVID-19 (14; 5.7%).

Sixty-three (66.3%; n=95) patients experienced infection in the 7.5 mg/kg safety pool (CSEG101A2202+ CSEG101A2301). The higher incidence in the 7.5 mg/kg pool was mainly driven by COVID-19 (30; 31.6%), pneumonia (12; 12.6%), urinary tract infection (9; 9.5%), and upper respiratory tract infection (8; 8.4%). Fourteen (14.3%) patients developed grade 3 infections, and the most common grade 3 infection was pneumonia (6; 6.3%). Thirteen patients (13.7%) required treatment interruption due to infection. Most of the treatment interruption was due to COVID-19 (7; 7.4%).

The incidence of infection was 55.1% (n=147) in placebo safety pool (CSEG101A2201+ CSEG101A2301) with the higher incidence coming from COVID-19 (17, 11.6%) and urinary tract infection (16, 10.9%). Fourteen (9.5%) patients developed grade 3 AEs. One patient had grade 4 AE-COVID-19 and one patient had fatal outcome dure to infection. Eight patients (5.4%) required treatment interruption due to infection. Most of the treatment interruption was due to COVID-19 (7; 4.8%). 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.

Effect on hemostasis

Considering the mode of action of crizanlizumab and physiological role of P-selectin, a potential effect on the hemostatic system was evaluated by searching for AEs related to hemorrhage, abnormal laboratory parameters of the hemostatic system, or thrombosis.

Forty-one (16.7%) patients experienced hemorrhage related events in 5 mg/kg safety pool. Events occurring in more than 2% patients were: epistaxis (9; 3.7%) and hemoglobin decreased

(6; 2.4%). Grade 3 AEs due to hemostasis (hemorrhage) were developed in 4 (1.6%) patients. Eight (3.3%) patients experienced treatment related AEs. Two patients (0.8%) required treatment interruption due to heavy menstrual bleeding and postmenopausal hemorrhage one each, 0.4%). Most of the patients (40; 16.3%) recovered/resolved except two (0.8%) patients.

Nine (9.5%) patients experienced hemorrhagic events in the 7.5 mg/kg safety pool. The only event occurring in at least 2% of patients was epistaxis (3; 3.2%). Grade 3 AEs hemorrhagic events developed in 2 (2.1%) patients. One patient had a fatal outcome to event Intracranial hemorrhage. Treatment related AEs were experienced in none of the patients. None of the patients required crizanlizumab treatment discontinuation/interruption due to hemorrhagic events. Most of the patients (5; 5.3%) recovered/resolved from hemorrhagic events.

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

Laboratory test interference with automated platelet counts

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

QT prolongation and hepatic safety

Based on the data generated to date, crizanlizumab does not have a clinically relevant effect on QT interval, and there is no evidence of 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 participants with SCD at 5 mg/kg once every 4 weeks). There was a numerical increase in fetal losses, the cause of which is unclear and may be related to development of antibodies against crizanlizumab in monkeys. No maternal toxicity was observed.

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

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.4. 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.

2.7 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.

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To confirm and establish appropriate dosing of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Part A and B)	Participants aged 2 to <18 years (Part A): • PK parameters after the starting dose and at multiple dose • PD parameter (%P-selectin inhibition) after starting dose and at multiple dose	
To evaluate the safety of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Parts A and B)	• Frequency of any adverse events	
Secondary		Refer to Section 10.5
To assess the long-term efficacy of crizanlizumab in participants aged 2 to < 18 years at the time of study entry (Parts A and B)	• Annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital • Annualized rate of VOC events treated at home (based on documentation by health care provider following phone contact with participant) • Annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism) • Annualized rate of hospitalizations and ER visits (both overall and VOC-related) • Annualized rate of days of ER/hospitalization (both overall and VOC-related) • Annualized rate of dactylitis events	
To assess other safety measures in participants aged 2 to < 18 years at the time of study entry	• Number, seriousness, severity, and causality assessments of treatment emergent adverse events and other safety data as considered appropriate • Absolute change from baseline in hemoglobin • Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab • ECGs at relevant PK time points • Growth and sexual maturation assessments (Tanner stage)	

Objective	Endpoint	Analysis
Characterize long-term PK and PD of crizanlizumab in participants aged 2 to <18 years at the time of study entry.	• Pre-dose concentrations prior to each study drug dose. • % P-selectin inhibition prior to dosing	

4 Study design

4.1 Description of study design

This is a multicenter, single-arm, open-label study to confirm and to establish appropriate dosing and to collect safety data in pediatric participants aged 2 to <18 years receiving crizanlizumab for 2 years.

The study will include pediatric participants, aged 2 to <18 years, with confirmed diagnosis of SCD (all genotypes included, as in Table 1-1) who have experienced at least 1 VOC within the preceding 12 months. Participants not on voxelotor, HU/HC, L-glutamine or erythropoietin stimulating agent at screening must not plan to initiate such drugs during the study. Participants on voxelotor must have permanently stopped the treatment at least 30 days prior to study start. For participants who are already treated with HU/HC, L-glutamine or erythropoietin stimulating agent at screening, they must be taking such drugs for at least 6 months prior to study entry and plan to take the same dose at the same schedule during the trial.

In Part A of the study across the ages 2 to <18 years, the dose for each group will be first confirmed on the basis of single & multiple dose PK data and key safety data from an initial subgroup of participants. In Part B of Group 1 and Group 2, safety and efficacy data will be collected from additional participants from 6 to <18 years.

At least 100 participants are planned to be enrolled in the trial in total, split in 3 age groups:

- Group 1 (age 12 to <18 years): at least 26 participants (at least 8 in Part A and at least 18 in Part B),
- Group 2 (age 6 to <12 years): at least 26 participants (at least 8 in Part A and at least 18 in Part B),
- Group 3 (age 2 to <6 years): at least 8 participants (in Part A)
- The remaining participants needed to achieve a total of at least 100 are planned to be recruited via trial Part B in either Group 1 or 2 age groups defined above without restriction.

All participants will receive SEG101. The participants enrolled in Group 1 Part A will receive SEG101 at 5.0 mg/kg i.v. on Week 1 Day 1, Week 3 Day 1 and then every 4 weeks. Full PK/PD sampling will occur from Week 1 (single dose PK) and at presumed steady state (Week 15 or multiple dose PK). This group is expected to provide at least 6 evaluable participants for first dose PK evaluation (see Section 7.1.6 for replacement policy and Section 10 for criteria defining evaluable participants).

Dose confirmation decision for each group will be based on: i) comparability of first dose pediatric PK results of evaluable participants against observed adults PK data (for Group 1) or predicted pediatric exposure from adults data (Group 2 and Group 3), ii) key safety results up to the cut-off date of the single dose analysis, and iii) Novartis's assessment, in conjunction with Data Monitoring Committee (DMC) recommendations and in light of all available relevant data, to either confirm the test dose or to evaluate a potentially more appropriate dose. [redacted]

[redacted]

At the time of the single dose PK analysis for Group 1 Part A, PK results will be compared to the exposure level observed in adults from the CSEG101A2202 study (see Section 10.4.2). Key safety data collected till the time of the cut-off for all the participants enrolled in Group 1 Part A will be evaluated. These PK and safety results will be reviewed by Novartis and DMC, please refer to Section 8.8 and Section 10.

If the evaluated dose is not confirmed, then an appropriate dose adjustment will be defined based on the PopPK model or other methods, at least an additional 8 participants will be enrolled in Group 1 Part A, and the process will be restarted at this newly-defined dose. The previous participants enrolled in Group 1 Part A will then also begin receiving the newly-defined dose at the next scheduled treatment visit and will enter Part B at the time they will start under the new dose; for these participants, no additional full PK/PD sampling under the new dose will be collected. However, these participants will not count towards the 26 participants planned for the group (i.e., those who did not have a dose change), but will be treated as additional participants for Part B.

Once the dose is confirmed on the basis of the single dose PK and key safety data analysis in Group 1 Part A as described above, enrollment in Group 1 part B and Group 2 Part A will be initiated at the confirmed dose. At least 18 additional participants will be enrolled in Group 1 Part B to ensure at least 26 participants in total in that age group are enrolled under the confirmed dose.

Following the dose confirmation, an additional evaluation of PK and PD, together with key safety parameters, will be conducted within the same enrolled Group 1 Part A participants, when multiple dose PK and PD are available. Results of this second evaluation will further ensure the validity of the tested dose or inform if additional modifications are required to the already confirmed dose.

The same process of enrollment and dose confirmation will be applied for Part A of Group 2, where single dose PK results will be compared to the exposure level predicted, using the PopPK model developed in adult SCD patients (see Section 10.4.2). Upon confirmation of the dose in Group 2 Part A, recruitment in Group 2 Part B, as well as in Group 3 Part A, will open at the confirmed dose.

For Group 3, safety and efficacy data will be collected for the confirmed dose from participants enrolled in Part A, but Part B will not be initiated for this cohort. [redacted]

Participants will receive treatment for up to 2 years unless study treatment is permanently discontinued earlier due to any reason. For participants who complete participation in this trial and who in the opinion of the investigator are still deriving clinical benefit from SEG101, every effort will be made to continue provision of study treatment via post-trial access, as indicated in Section 6.1.6. All participants will remain in the study until completion of the 105 days post-treatment follow-up visit, except the ones continuing crizanlizumab after their EOT visit, via

commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over protocol or in a non-trial setting to provide continued drug treatment).

Screening phase

Written informed consent/assent, according to local guidelines, will be signed by the participants and / or by the parents or legal guardian prior to any study related screening procedures being performed, as shown in Table 7-1.

Treatment phase

Once eligibility criteria have been confirmed, the participant will be enrolled in the trial and will receive SEG101.

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

Participants may be admitted to the study site prior to dosing for baseline evaluations. Such an admission is to be recorded as administrative and must not be reported as a SAE. The participants enrolled in Part A will receive SEG101 at the test dose (starting dose in Group 1 Part A is 5.0 mg/kg) by i.v. infusion (refer to Pharmacy Manual) on Week 1 Day 1, Week 3 Day 1, and then on Day 1 of every 4-week cycle. Once at least 6 participants have evaluable PK data (single-dose analysis) and PK/PD data (multiple dose analysis) at the test dose, PK/PD and key safety analysis will be performed to confirm the appropriateness of this dose. No dose change or modification of the study defined dose by the investigator will be allowed in the study. Dose interruptions for safety reasons are described in the Section 6.3.

All enrolled participants will have PK/PD sampling performed in order to characterize the PK/PD of SEG101 (see Table 7-5, Table 7-6, Table 7-7). On Week 1 Day 1 (single dose) and at presumed steady state (multiple dose), the participants may be asked to remain at the study site for at least 24 hours post-dose in order to complete the full PK/PD sample collection. [redacted]

In case of VOC, the related medical and treatment information should be collected as detailed in Table 7-2.

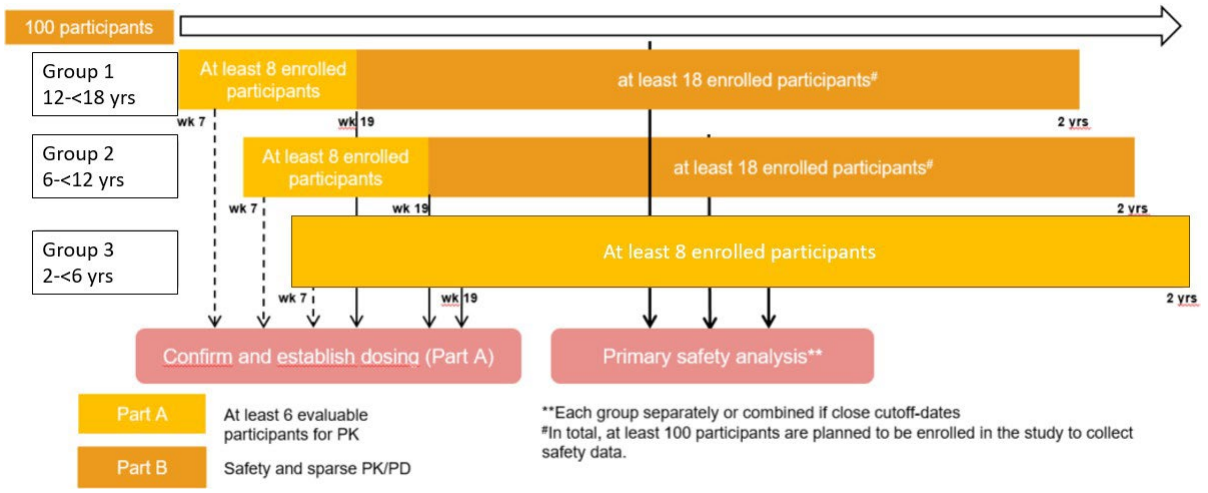
Safety will be monitored as outlined in Section 8. Participants will receive treatment for 2 years or until discontinued from study treatment for any reason.

All participants should perform an EOT visit following discontinuation from study treatment or completion of the 2 years of study treatment.

Post-treatment follow-up phase

After the EOT visit, all participants must be followed up for efficacy and safety up to 105 days (15 weeks) after the last infusion of study treatment, except the ones continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over protocol or in a non-trial setting to provide continued drug treatment).

Figure 4-1 Study Design



Note: In Group 3, single dose PK/PD, multiple dose PK/PD and safety will be evaluated in Part A and no patients will be enrolled in Part B.

4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned in this trial. However, statistical analyses for Part A of each group will be performed at two time points: when there are at least 6 participants with single dose evaluable PK profiles and key safety data for at least 6 weeks and when there are at least 6 evaluable participants with multiple dose PK and PD profiles.

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

Additional cut-off dates and analyses will also be performed during Part B conduct (refer to Section 10).

4.3 Definition of end of study

The end of the study is defined as the date of last visit of the last participant in the study and will occur when all the participants have either completed or discontinued the study treatment and/or have completed the last scheduled procedure as defined in Section 7.1 (105-days post-treatment follow-up visit when applicable).

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

5 Study Population

5.1 Study population

CSEG101B2201 will enroll at least 100 SCD participants (any genotype), ages 2 to <18 years who experienced at least 1 VOC leading to healthcare/medical facility visit within the preceding 12 months, and who are either

- not on HU/HC, L-glutamine or erythropoietin stimulating agent (for at least 6 months prior to screening) and not on voxelotor (since at least 30 days prior to screening) and are not planning to initiate such drugs during the trial,
- or who have been taking HU/HC, L-glutamine, erythropoietin stimulating agent consistently for at least 6 months and plan to continue at the same dose and schedule during the trial.

At least one hundred participants are planned to be enrolled in the trial in total, split into 3 age groups:

- Group 1 (age 12 to <18 years): at least 26 participants,
- Group 2 (age 6 to <12 years): at least 26 participants,
- Group 3 (age 2 to <6 years): at least 8 participants.
- The remaining participants needed to achieve a total of at least 100 are planned to be recruited via trial Part B in either Group 1 or 2 age groups defined above without restriction.

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

5.2 Inclusion criteria

1. Male or female patients aged 2 to <18 years
2. Confirmed diagnosis of SCD (any genotype including HbSS, HbSC, HbSβ^0-thalassemia, HbSβ^+-thalassemia patients, and others) by hemoglobin electrophoresis or/and high-performance liquid chromatography (HPLC) [performed locally]. Confirmation of diagnosis by two accepted methods is recommended.
3. Experienced at least 1 VOC within the preceding 12 months prior to screening, as determined by medical history. Prior VOC must have resolved at least 7 days prior to the first dose in the study and must include all the following:
   a. the occurrence of appropriate symptoms (see VOC definition in Section 7.2.1.1).
   b. either a visit to a medical facility or healthcare professional
   c. receipt of oral/parenteral opioid or parenteral NSAIDs
4. If receiving HU/HC, L-glutamine or erythropoietin stimulating agent, must have been receiving the drug consistently for at least 6 months prior to screening and plan to continue taking it at the same dose and schedule during the trial. Patients who have not been receiving such drugs must have been off them for at least 6 months prior to screening. Dose alterations of HU/HC, L-glutamine or erythropoietin stimulating agent during Part A are not allowed, and if this occurs, the participant will enter directly to Part B.

5. Received standard age-appropriate care for SCD, including penicillin prophylaxis, pneumococcal immunization, and parental education.
6. Performance status: Karnofsky ≥ 50% for patients >10 years of age, and Lansky ≥ 50 for patients ≤ 10 years of age.
7. Patient must meet the following laboratory values prior to Week 1 Day 1:
   - Absolute Neutrophil Count ≥1.0 x 10^9/L
   - Platelets ≥75 x 10^9/L
   - Hemoglobin (Hgb) > 5.5 g/dL
8. Patient must have adequate renal and hepatic function as defined:
   - Estimated Glomerular filtration rate (eGFR) ≥ 75 mL/min/1.73 m^2 using Schwartz formula
   - Direct (conjugated) bilirubin ≤ 2.0 x ULN
   - Alanine transaminase (ALT) ≤ 3.0 x ULN
9. Transcranial Doppler (TCD) for patients aged 2 to < 16 years at time of screening, with HbSS, HbSβ^0-thalassemia, and HbSD disease indicating low risk for stroke (per investigator). Please refer to Section 7.2.2.6 for details
10. Written informed consent/assent, according to local guidelines, signed by the patient and / or by the parents or legal guardian prior to any study related screening procedures are performed.
11. Female of non-childbearing potential or with negative serum pregnancy test on Screening and a negative urine pregnancy test (dipstick) prior to dosing on Day 1.

5.3 Exclusion criteria

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

1. History of stem cell transplant.
2. Received any blood products within 30 days prior to Week 1 Day 1 dosing.
3. Plan to participate in a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes) or undergo exchange transfusions/plasmapheresis during the study. Patients requiring episodic transfusion (simple or exchange) in response to worsened anemia or VOC are permitted.
4. Patients with bleeding disorders
6. Contraindication or hypersensitivity to any drug from similar class as study drug or to any excipients of the study drug formulation.
7. History of severe hypersensitivity reaction to other monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction
8. Received a monoclonal antibody or immunoglobulin-based therapy within 6 months of Screening, or has documented immunogenicity to a prior monoclonal antibody.
9. Received active treatment on another investigational trial within 30 days (or 5 half -lives of that agent, whichever is greater) prior to Screening or plans to participate in another investigational drug trial.
10. Pregnant females or females who have given birth within the past 90 days or who are breastfeeding.

11. Any documented history of a clinical stroke or intracranial hemorrhage, or an uninvestigated neurologic finding within the past 12 months. Silent infarcts (only present on imaging) are not excluding patients from study participation.
12. Any abnormal TCD within the past 12 months.
13. Use of therapeutic anticoagulation (prophylactic doses permitted) or antiplatelet therapy (other than aspirin) within the 10 days prior to Week 1 Day 1 dosing.
14. Hospitalized within 7 days prior to Week 1 Day 1 dosing.
15. Planning to undergo a major surgical procedure during the duration of the study.
16. Planning to initiate or terminate HU/HC or L-glutamine while on study (except if needed to terminate for safety reasons).
17. Patient with active human immunodeficiency virus (HIV) infection (detectable viral load).
18. Patients with known active Hepatitis B infection.
19. Patients with known Hepatitis C history.
20. Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs) in the opinion of the investigator.
21. Malignant disease. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; any completely resected carcinoma *in situ.*
22. Has a serious mental or physical illness, which, in the opinion of the Investigator would compromise participation in the study.
23. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study
24. Resting QTcF ≥450 msec at pretreatment (baseline) for patients under 12 years of age and ≥450 msec for males and ≥460 msec for female patients 12 years and older.
25. Cardiac or cardiac repolarization abnormality, including any of the following:
    a. History of myocardial infarction (MI), uncontrolled congestive heart failure, unstable angina, or coronary bypass graft (CABG) within 6 months prior to starting study treatment
    b. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (bifascicular block, Mobitz Type II, and third degree AV block)
    c. Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
        - Risk factors for Torsade de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/ symptomatic bradycardia
        - Inability to determine the QTcF
26. Sexually active females who are unwilling to comply with reliable method of birth control until 15 weeks following last dose of study drug.

    Females of childbearing potential, defined as 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 bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), or total hysterectomy 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 (estrogen and progesterone), 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, females should have been stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

28. Not able to understand and to comply with study instructions and requirements.
29. Patients who are an employee of the sponsor or investigator or otherwise dependent on them.
30. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
31. Patients who received prior crizanlizumab treatment and/or other selectin targeting agents are not allowed.
32. Patients having taken voxelotor less than 30 days prior to screening, or planning to take voxelotor while on study are not allowed.

6 Treatment

6.1 Study treatment

Novartis will supply crizanlizumab (SEG101) as an open label medication. The investigational drug will be the crizanlizumab administered every 4 weeks with a loading dose 2 weeks after the first dosing (i.e., by i.v. infusion (refer to Pharmacy Manual) on Week 1 Day 1, Week 3 Day 1, and then day 1 of every 4-week) for up to 2 years.

Table 6-1 Investigational and control drug

Treatment Title	Crizalizumab
Treatment Description	5.0 mg/kg and 8.5 mg/kg*
Type	biologic

Dose Formulation	Concentrate for solution for infusion
Unit Dose Strength(s)	Crizanlizumab (SEG101) concentrate for solution for infusion is supplied in single use 10 mL vials at a concentration of 10 mg/mL. One vial contains 100 mg of crizanlizumab (SEG101)
Dosage Level(s) and Regimen	5.0 mg/kg and 8.5 mg/kg Week 1 Day 1, Week 3 Day 1, and Day 1 of every 4-week cycle*
Route of Administration	IV infusion
Use	experimental
IMP	Yes
Sourcing	Novartis
Packaging and Labeling	Study treatment will be provided in vials. Each vial will be labeled as required per country requirement.

* dose was adjusted based on the dose confirmation step (refer to Section 6.3.1.1) as the initial dose was not confirmed for Group 2 and Group 3. Initial dose of 5 mg/kg dose for Group 1 participants was later adjusted to 8.5 mg/kg for Group 2 and 3 based on final dose confirmation and safety considerations as planned in the protocol.

6.1.1 Dosing regimen

SEG101 is supplied in single use 10 mL vials at a concentration of 10 mg/mL. One vial contains 100 mg of crizanlizumab.

On infusion day, the pharmacist or designated personnel will compound individual doses of SEG101 for participants by diluting it in accordance with the Pharmacy Manual.

6.1.2 Ancillary treatments

Not Applicable.

6.1.3 Rescue medication

Not Applicable.

6.1.4 Guidelines for continuation of treatment

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

Participants who permanently discontinue from the study drug for any reason, and will not continue crizanlizumab after their EOT visit (i.e., via commercial supply) should follow the protocol post-treatment assessments as scheduled for 105 days following the last dose. After discontinuing study treatment, further treatment is left to physician's discretion.

6.1.5 Treatment duration

The total planned duration of treatment in the study for each patient is planned to be up to 2 years.

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

For participants who complete participation in this trial and who in the opinion of the investigator are still deriving clinical benefit from SEG101, every effort will be made to continue provision of study treatment via post-trial access, as indicated in Section 6.1.6.

6.1.6 Post trial access

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the Investigator's evaluation, may receive post-trial access.

Post Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met:

- participant no longer derives clinical benefit,
- Investigator discontinues treatment,
- treatment receives regulatory approval, is commercially available and a reimbursement decision has been made in the patient's country (where applicable),
- treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include a rollover protocol, provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]) when no further safety or efficacy data are required, or any other mechanism appropriate as per the country regulations.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the development of the study treatment due to reasons which may include when study results are negative, Novartis will work with Investigators to transition participants onto locally available alternative treatment or standard of care.

6.2 Dose escalation guidelines

Not Applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

6.3.1.1 Dose modification

The investigator is not allowed to modify the study-defined dose at their own discretion. In case of unexpected emergent safety findings during the trial, the dosage of the corresponding age group will be reassessed at that time.

During Part A of each group, if the dose is not confirmed then an appropriate dose adjustment will be defined based on the PopPK model or other methods (see Section 4.1 and Section 10). At least an additional 8 participants will be enrolled in Part A of that group, and the process will be restarted at the newly defined dose. The decision on whether to confirm a test dose will be made internally at Novartis, in consideration of DMC recommendations, and will be documented. Investigators will be informed by Novartis of this decision promptly. If the decision is to adjust the dose, the previous cohort of participants enrolled in Part A of this particular group will then begin receiving the newly defined dose at the next scheduled treatment visit, and will enter Part B from the time they receive the new dose.

6.3.1.2 Dose interruptions/delay

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated in order to allow participants to continue the study treatment until the next dose scheduled. The criteria for interruption and re-initiation of SEG101 for Adverse Drug Reaction are provided in Table 6-2.

If drug-induced toxicities occur, participants will have to be closely monitored, and a decision to continue or discontinue the participant from the study treatment will have to be made at the next dose scheduled.

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

During COVID-19 pandemic, if a participant experiences a VOC and other subtypes of VOC event such as hepatic/splenic, priapism and especially acute chest syndrome, testing for COVID-19 is recommended as per local guidance/practice (refer to Section 7.2.1.1 for VOC definition).

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 infection has been ruled out.

Every effort should be made to maintain the participant on the protocol-defined dosing schedule. In the case of dose delay for any reason, the dose should be given as soon as possible but by keeping at least 21 days between 2 consecutive doses. 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), as planned per Table 7-1. If a participant misses 2 consecutive doses, the participant must be permanently discontinued from study treatment.

Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for grade 4 adverse events deemed related to study drug and for specific adverse events as indicated in Table 6-2 or listed in Section 7.1.5.

Dose interruptions must be recorded on the Dosage Administration Record CRF.

Table 6-2 Criteria for dose interruption and re-initiation of SEG101 treatment for adverse drug reactions

Dose interruptions for SEG101	
Worst toxicity [a] CTCAE Grade (value) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < lower limit of normal (LLN) - 1500/mm^3)	Recommendation: continue study treatment.
Grade 2 (ANC < 1500 - 1000/mm^3)	Recommendation: continue study treatment.
Grade 3 (ANC < 1000 - 500/mm^3)	Recommendation: interrupt study treatment until resolved to ≤ Grade 2. If abnormality persists beyond the next planned dose, permanently discontinue study treatment.
Grade 4 (ANC < 500/mm^3)	Mandatory: permanently discontinue study treatment.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C) A disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C	Mandatory: Interrupt study treatment until resolved. If abnormality persists more than 7 days, permanently discontinue study treatment.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Recommendation: continue study treatment.
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Recommendation: continue study treatment.
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Recommendation: interrupt dose until resolved to ≤ Grade 1. If abnormality persists more than 7 days, permanently discontinue study treatment.
Grade 3 (PLT < 50,000 – 25,000/mm^3) associated with bleeding	Mandatory: permanently discontinue study treatment.
Grade 4 (PLT < 25,000/mm^3)	Mandatory: permanently discontinue study treatment.
Investigations (Renal)	
Serum creatinine	
Grade 1 (>1.0 – 1.5 x baseline OR > ULN - 1.5 x ULN)	Recommendation: continue study treatment.
Grade 2 (> 1.5 – 3.0 x baseline OR > 1.5 - 3.0 x ULN)	Recommendation: interrupt study treatment until resolved to ≤ Grade 1 or baseline level. If abnormality persists beyond the next planned dose, permanently discontinue study treatment.
Grade 3 (> 3.0 x baseline OR > 3.0 - 6.0 x ULN)	Recommendation: interrupt study treatment until resolved to ≤ Grade 1 or baseline level. If abnormality persists more than 7 days, permanently discontinue study treatment.

Dose interruptions for SEG101	
Worst toxicity [a] CTCAE Grade (value) during a cycle of therapy	
Grade 4 (> 6.0 x ULN)	Mandatory: permanently discontinue study treatment.
Investigations (Hepatic)	
Isolated direct Bilirubin elevation	
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 liver function tests (LFTs)[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 1.5 x ULN or baseline. Monitor for hemolysis. If resolved 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. If abnormality persists >2 weeks, refer to Section 6.3.3.1 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 study treatment. 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[c] elevations of ALT and direct bilirubin	

Dose interruptions for SEG101	
Worst toxicity [a] CTCAE Grade (value) during a cycle of therapy	
For participants with normal baseline ALT and direct bilirubin value: ALT >3.0 x ULN combined with direct bilirubin >2.0 x ULN OR For participants with elevated baseline ALT or direct bilirubin value: ALT>2x baseline AND > 2.0 x baseline direct bilirubin	Mandatory: Interrupt study treatment. Repeat LFTs as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; follow-up for symptoms and initiate workup for competing etiologies. Monitor of LFTs [b] weekly, 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 6.3.3.1 for additional follow-up evaluations as applicable.
Gastro intestinal	
GI toxicity (diarrhea, nausea, vomiting)	
Grade 1	Recommendation: continue study treatment; initiate concomitant therapy as per institutional guidelines.
Grade 2 and Grade 3	Recommendation: interrupt study treatment until recovery to G1 or baseline.
Grade 4	Mandatory: permanently discontinue study treatment.
Infections	
Grade 1 and 2	Recommendation: continue study treatment.
Grade 3 or Serious (meeting definition for SAE)	Mandatory: Interrupt study treatment until recovery to ≤ Grade 1. If abnormality persists more than 7 days, permanently discontinue study treatment.
Grade 4	Mandatory: permanently discontinue study treatment.
a Common Toxicity Criteria for Adverse Events (CTCAE Version 5) b Core LFTs consist of ALT, AST, GGT, bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN.) c “Combined” defined as direct bilirubin increase to the defined threshold concurrently with ALT increase to the defined threshold If combined elevations of ALT and direct bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of direct bilirubin and isolated elevation of ALT, and take the most conservative action recommended (e.g., permanently discontinue treatment in the situation when interrupt dose is needed for one parameter and permanently discontinue treatment is required for another parameter).	

Table 6-3 Management for drug-related toxicities

Toxicity[a]	Management
Infusion-related reactions	
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Recommendation: • Continue study treatment and increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Consider slowing infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	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. • Steroids should be used with caution unless clinically indicated (e.g., management of hypersensitivity/anaphylaxis). • If symptoms resolve, restart infusion per investigator discretion at a slower rate (e.g., 50%) under continuous observation. Ensure a minimum of 1 hour observation period prior to restarting the infusion. • Before restarting, administer premedication (e.g., analgesics such as paracetamol/acetaminophen or NSAIDs and anti-histamines within 1 hour prior to dosing) as per local institutional guidelines, including subsequent infusions. • In case of recurring infusion reactions despite premedication and prolonged infusion, consider discontinuation from 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.
[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5)	

6.3.2 Recommended actions and dose adjustments for QTcF prolongation

Not Applicable.

6.3.3 Follow-up for toxicities

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

Transaminase increases combined with a total bilirubin (TBIL) increase may be indicative of potentially severe DILI, and should be considered as a clinically important event and assessed appropriately to establish the diagnosis. The required laboratory values, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

- Treatment-emergent elevations in ALT (>3x ULN for patients with normal baseline and >2x baseline for patient with elevated baseline) in combination with direct bilirubin >2x ULN for patients with normal baseline and >2 x baseline with elevated baseline or
- Elevations in ALT alone (>5x ULN for patients with normal baseline for more than 2 weeks and >3x baseline for patients with an elevated baseline for more than 2 weeks)

Patients with SCD tend to have elevated AST and indirect bilirubin due to the hemolytic nature of this condition. In order to reduce the number of false positives, AST will be considered for safety monitoring, but LFT monitoring/ follow-up will be conducted only if ALTand direct bilirubin criteria are met for DILI definition. 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 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, 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).

For this reason, a potential case meeting the above criteria requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded) using the term “potential drug-induced liver injury.” Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

In the absence of cholestasis or 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 obstructions/compressions, etc.

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

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as "medically significant", thus, meeting the definition of SAE (Section 8.2.1) and reported as SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.4 Concomitant medications

In general, the use of any concomitant medication/therapies deemed necessary for the care of the participant is permitted (see Section 6.4.1), except as specifically prohibited (see Section 6.4.3).

The participant/legal representative must be told to notify the investigational site about any new medications he/she takes within 30 days prior to initial dosing until the completion of the last protocol visit (EOT or post-treatment follow-up visit, 105 days after the last dose of study treatment as applicable); except for HU/HC, L-glutamine, and Erythropoietin Stimulating Agent medications for which information within 6 months prior to screening should be collected, and for analgesics within 12 months prior to screening. 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) taken or administered within the timeframe defined in the entry criteria until completion of the last protocol visit must be listed on the Prior and Concomitant medications, Surgical and Medical Procedures or Transfusion pages of the CRF.

6.4.1 Permitted concomitant therapy

Concomitant sickle cell therapy with HU, HC or L-glutamine (Endari™) is permitted as per local guidelines and standard of care, provided the participant has been prescribed HU/HC or L-glutamine consistently over at least the 6 months prior to screening, as stated in the Inclusion criteria. During the course of the study HU/HC or L-glutamine must not be initiated or terminated, except if termination is for safety reasons. Dose alterations, other than for safety reasons or for weight adjustments should not occur. Erythropoietin-stimulating agents are also permitted to manage chronic symptomatic anemia with the same requirement for 6 months prior therapy as HU/HC/L-glutamine. The dosing should not be altered or terminated, other than for safety reasons or to maintain hemoglobin level.

During Part A, HU/HC, L-glutamine or erythropoietin stimulating agent dose change other than for reasons mentioned above are not allowed. In case a dose modification (other than for weight adjustment) occurred, the participant will be moved to Part B. If a physician deems it medically necessary to terminate, or alter HU/HC treatment, L-glutamine or erythropoietin stimulating agent, changes should not lead by default to discontinuation from the study treatment; however, the Novartis medical monitor must be notified.

Aspirin, NSAIDs and prophylactic doses of anticoagulants are permitted.

All approved forms of analgesia for pain are permitted per standard of care. Other approved medications for supportive care (antiemetics, anxiolytics, hypnotics, antihistamines) are permitted, including marinol.

It is recommended to avoid any live or live-attenuated vaccines within 4 weeks prior to the first dose of study treatment (Week 1 Day 1) and during study duration. However, the decision to administer or withhold a vaccine should be done on a case-by-case basis considering the potential benefit/risk such as developing severe infection, adverse effects from the vaccination, or vaccination failure.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Although transfusion of blood products 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. It should also be considered that the administration of products containing immunoglobulins (plasma, intravenous immunoglobulin (IVIG), anti-globulins) may also impact the efficacy of crizanlizumab, and optional PK and PD testing may also be performed prior to and following administration of such therapies.

Although Endari™, the FDA-approved, version of L-glutamine, is permitted, other over- the counter forms of L-glutamine are discouraged, as are other natural and herbal remedies (e.g., EvenFlo and/or products containing dang gui, ligustrum root, ginseng root, white peony, corydalis, salvia, copodonosis, poria, jujbe, angelica sinensis, lovage) due the unproven efficacy and variable quality and composition of these products. Vitamin and mineral supplements (e.g., fish oil, folic acid, L-arginine, L-citrulline, magnesium, riboflavin, vitamin C, vitamin D, vitamin E, and Zinc) are also permitted, though caution is advised when taking amounts exceeding 100% of the recommended daily allowance.

Infusion related reactions have been observed with crizanlizumab administration. Pre-medication with analgesics (e.g., paracetamol/acetaminophen or NSAID) and anti-histamines (e.g., diphenhydramine or alternative, or in combination with H2 blocker) should be considered as per institutional standard of care, and at the discretion of the investigator (refer to Table 6-3 for further guidance on the management of crizanlizumab infusion reactions).

Steroids should be used with caution, and when clinically indicated (e.g., to manage hypersensitivity/anaphylactic reactions). There is no existing clinical data on concomitant use of crizanlizumab and corticosteroids. For patients presenting for acute pain related to sickle cell disease, the 2020 guideline from American Society of Hematology suggests against corticosteroids for acute pain management (Brandow et al 2020).

If a participant experiences a grade 3 or grade 4 infusion related reaction, study drug must be discontinued.

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

6.4.3 Prohibited concomitant therapy

The use of other investigational agents is prohibited during the study. In addition, the administration of monoclonal antibodies other than crizanlizumab is prohibited, due to the theoretical potential for cross-reactivity and/or overlapping toxicities with other monoclonal antibodies. If investigational agents have been used in the past, they must have been discontinued at least 30 days (or 5 half-lives of that agent, whichever is greater) prior to Screening. Monoclonal antibodies or immunoglobulin-based therapy must have been

discontinued at least 6 months prior to Screening. Patients who received prior crizanlizumab are not allowed. If voxelotor was taken in the past, it must have been permanently discontinued at least 30 days prior to Screening. The concomitant treatment with voxelotor is prohibited during the study.

Prior use of other selectin targeting agents and use during the entire study duration are prohibited. New treatments to treat SCD and/or to prevent/reduce VOCs are not permitted (except as outlined above) during the study.

6.5 Participant numbering, treatment assignment or randomization

6.5.1 Participant numbering

Each participant is identified in the study by a 7 Digit Participant Number (Participant No.) that is assigned when the participant starts screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (4 digits) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available to the investigator through the Rave EDC (Electronic Data Capture) interface.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the participant to register them into the IRT. Once assigned, the Participant No. must not be reused for any other patient.

It is permissible to re-screen a participant, one time, if she/he fails the initial screening.

If the participant is re-screened, a new unique Participant No. will be assigned to the re-screened participant and the original assigned number will be captured in the rescreening page. If the participant fails to start treatment for any reason, the reason should be recorded on the appropriate Case Report Form.

IRT must be notified within 2 days that the participant was not enrolled in the study.

6.5.2 Treatment assignment or randomization

No randomization will be performed in this study.

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

6.5.3 Treatment blinding

This is an open label study. Investigators, participants and Sponsor will have full knowledge of the treatment allocation.

6.6 Study drug preparation and dispensation

Crizanlizumab will be prepared by a pharmacist or study personnel appropriately trained in the preparation of solutions for parenteral administration (use aseptic techniques when preparing the study drug solution) in accordance with the Pharmacy Manual.

Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration.

Participants should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever, and vital signs monitored more frequently if clinically indicated, during and for at least 2 hours after the crizanlizumab infusion during the first 6 months of the study (after that monitoring would be based on local medical practice). The same may apply for the subsequent crizanlizumab infusions if medically indicated.

6.6.1 Study treatment packaging and labeling

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

Study treatment will be sourced as local commercial supply when available (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

Study treatment labels will comply with the legal requirements of each country and will include storage conditions, a unique medication number (corresponding to study treatment and strength). A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT system and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in the IRT system.

Table 6-4 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
Crizanlizumab (SEG101)	Vials containing 10 mL at a concentration of 10 mg/mL	Labeled as 'SEG101' (at Week 1 Day1, Week 3 Day 1, Week 7 Day 1 and at Day 1 of every 4-weeks).

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Refer to the Pharmacy Manual and labels for more details. Upon receipt, the study treatment should be stored according to the instructions specified in the Pharmacy Manual and in the Investigator's Brochure.

Table 6-5 Supply and storage of study treatments

Study treatments	Supply	Storage
Crizanlizumab (SEG101)	Centrally supplied by Novartis or local commercial supply when available.	Refer to study treatment label

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Infusions will be administered in the clinic. This information must be captured in the source document, the appropriate CRFs. Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of crizanlizumab in serum. All study treatment dispensed and returned must be recorded in the Drug Accountability and Returns Management functionality in the IRT system.

6.6.3.2 Study drug accountability

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

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.3.3 Handling of other study treatment

Not Applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate in compliance with site processes, monitoring process and as per local regulation/guidelines.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

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

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database or received electronically from a vendor (D) or remain in source documents only (S) (“Category” column)

As per Section 2.7, 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, national and local regulations and depending on operational capabilities, telephone contacts and/or virtual contacts (e.g., teleconsultation) with the participant, can replace certain protocol assessments, for the

duration of the disruption until it is safe for the participant to visit the site again. These telephone/virtual contacts should preferably be done according to the study visit schedule.

Screening assessments, apart from those listed below, must occur within 28 days prior to the enrolment as per Table 7-1.

- Auditory and Ocular assessments to be done at screening if not done within the last 24 weeks prior to Week 1 Day 1 dosing, refer to Section 7.2.2.9 and Section 7.2.2.10 for additional details.
- Chest-X ray and echocardiogram to be done at screening if not done within the last 12 weeks prior to Week 1 Day 1 dosing, refer to Section 7.2.1.1 and Section 7.2.2.8.2 for additional details.

Allowed visit windows are specified as follows:

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

For participants discontinuing from study treatment (prior to completion of the planned 2 years of study treatment, i.e. prior to completion of Week 103 Day 1 visit) and not continuing under crizanlizumab outside the study, the EOT visit is to be performed within 7 days from the decision to discontinue from the study treatment.

For participants discontinuing from study treatment (prior to completion of the planned 2 years of study treatment, i.e. prior to completion of Week 103 Day 1 visit) and continuing under crizanlizumab outside the study, and for all participants completing the 2 years of study treatment (completion of Week 103 Day 1 visit) whether they continue on crizanlizumab outside the study or not, the EOT visit should be completed 4 weeks (+/- 7 days) from last dose of study treatment.

In case of early discontinuation, TCD, echocardiogram, ocular and retinal exam, auditory exam, urine albumin/creatinine ratio, will need to be assessed at EOT visit if the latest available exams were not done within the last 12 weeks (denoted by X^b in the EOT column in Table 7-1).

There is a ± 7 day visit window permitted for the 105 day post-treatment follow-up visit.

Participants who discontinue from study should be scheduled for a final evaluation visit (EOT visit or post-treatment follow-up visit) if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, adverse events, VOCs, Dactylitis, transfusions and concomitant medications not previously reported must be recorded on the CRF.

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

Table 7-1 Visit evaluation schedule

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d,f]	Wk15D4 [e,f]	Wk16D1 [d,f]	Wk17D1 [d,f]	Wk18D1 [d,f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Screening																			
Obtain Study Informed Consent (and assent as per local guidelines)	D	7.1.2	X																
IRT/IWRS																			
IRT/IWRS registration	D		X															X	X
IRT/IWRS enrollment	D			X															
Disposition assessment																			
Disposition	D	7.1.2	X															X	X

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	1	2	4	8	15	43	71	99	100	102	106	113	120			
Participant history																			
Demography	D	7.1.2.3	X																
Inclusion/exclusion criteria	D	7.1.2.1	X																
Medical/Surgical history	D	7.1.2.3	X																
Karnofsky / Lansky performance status	D	7.1.2.3	X																
Sickle Cell – Vaso-Occlusive Crisis history	D	7.1.2.3	X (during the last year)																
Dactylitis history	D	7.1.2.3	X (during the last year)																

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Physical examination																			
Physical examination	S	7.2.2.1	X															X	
Abbreviated physical exam	S	7.2.2.1		X				X	X	X	X						X		X
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	D	7.2.2.3	X	X				X	X	X	X						X	X	X
Weight	D	7.2.2.3	X	X				X	X	X	X						X	X	X
Head Circumference (participants aged 2 – 2.5 years old at time of study entry until participants turn 3 years old)	D	7.2.2.3	X	X				X	X	X	X						X	X	X
Transcranial Doppler	D	7.2.2.6	X	Wk27D1, Wk51D1 and Wk103D1														X[b]	
Laboratory assessments																			

Visit Name	**Category**	**Protocol Section**	**Screening**	**Wk1 D1**	**Wk1D2 [d]**	**Wk1D4 [e]**	**Wk2D1 [d]**	**Wk3D1**	**Wk7D1**	**WK11D1**	**Wk15D1**	**Wk15D2 [d, f]**	**Wk15D4 [e, f]**	**Wk16D1 [d, f]**	**Wk17D1 [d, f]**	**Wk18D1 [d, f]**	**Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1**	**End of treatment (EOT) [j]**	**Post Treatment Follow up [k]**
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Hematology	D	7.2.2.7.1	X					X	X	X	X						X	X	X
Chemistry	D	7.2.2.7.2	X					X	X	X	X						X	X	X
Coagulation (Group 1 and 2 only)	D	7.2.2.7.4		X													Wk 19 D1, Wk 27 D1 and every 12 weeks	X	X
HbF	D	7.2.2.7.5		X													Wk 27D1, 51D1, 75D1, 103D1	X	
Urinalysis (microscopic +/- macroscopic)	D	7.2.2.7.3	X	X				X	X	X	X						X	X	X
Serum pregnancy test	S	7.2.2.7.6	X															X	X

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Urine pregnancy test	S	7.2.2.7.6		X				X	X	X	X						X		
Efficacy assessments																			
Sickle Cell – Vaso-Occlusive Crisis Event	D	7.2.1.1		Continuous															
Chest x-ray	D	7.2.1	X[a]	If clinically indicated															
Hospitalization	D	7.2.1	X	Continuous															
Prior/concomitant medications – Analgesic	D	6.4	X	Continuous															
Prior/concomitant medications – Hydroxyurea/ Hydroxycarbamide	D	6.4	X	Continuous															
Prior/concomitant medications – L-Glutamine	D	6.4	X	Continuous															

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Prior/concomitant medications – Erythropoietin stimulating agent	D	6.4	X	Continuous															
Transfusion	D	7.2.1	X	Continuous															
Dactylitis	D	7.2.1		Continuous															
School/ Work employment status and sick time absence	D	7.2.1	X[i]	X				X	X	X	X						X	X	X
Safety assessments																			
ECG	D	7.2.2.8.1	X						X	X	X[h]						Wk27D1 and Wk51D1 and Wk103D 1	X	
Cardiac imaging (Echo)	D	7.2.2.8.2	X[a]														Wk 51D1	X[b]	

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	**1**	**2**	**4**	**8**	**15**	**43**	**71**	**99**	**100**	**102**	**106**	**113**	**120**			
Pulmonary function test (in participants 6 years and older)	D	7.2.2.11	If clinically indicated[a]	If clinically indicated															
Ocular and retinal exam (only for Groups 1 and 2)	D	7.2.2.10	X[g]														Wk 51D1	X[b]	
Growth and sexual maturation assessment	D	7.2.2.5	X														Wk 51D1	X	
Auditory exam (only for Groups 1 and 2)	D	7.2.2.9	X[g]														Wk 51D1	X[b]	
[redacted]																			
Adverse Event/ Serious Adverse Event	D	8	X	Continuous															
IRR [l]	D			Continuous															

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			**-28 through Day -1**	1	2	4	8	15	43	71	99	100	102	106	113	120			
Prior/concomitant medications	D	6.4	X	Continuous															
[redacted]																			
Pharmacokinetics																			
PK sampling [c]	D	7.2.3		Please refer to Table 7-5, Table 7-6 and Table 7-7															X
Immunogenicity																			
Immunogenicity sampling	D	7.2.3		Please refer to Table 7-5, Table 7-6 and Table 7-7															X
Study Drug administration																			
SEG101 i.v.	D	6.1.1		X				X	X	X	X						X		

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			-28 through Day -1	1	2	4	8	15	43	71	99	100	102	106	113	120			

[a] [redacted]

[b] Assessment to be done at EOT if not done within the last 12 weeks prior to EOT

[c] [redacted]

[d] Only for participants enrolled in Part A of Groups 1, 2 or 3

[e] Only for participants enrolled in Part A of Groups 1 or 2

[f] For participants in Part A only: In case the dose is interrupted, partially administered and/or delayed prior to Week 15 Day 1, all the assessments planned between Week 15 Day 2 and Week 18 Day 1 (inclusive) will not be collected at these visits but will be performed on the same day of the full PK/PD collection after at least 3 full consecutive doses administered (following the loading dose at Week 3 Day 1).

[g] Assessment to be done at screening if not done up to 24 weeks prior to start of study drug

[h] For participants in Part A, 2hr post dose ECG measure planned at Week 15 Day 1 has to be aligned with 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. For participants in Part B, Week 15 Day 1 2hr post dose ECG should still be performed at the designated visit regardless of steady-state.

[i] [redacted]

[j] For participants discontinuing from study treatment (prior to completion of Week 103 Day 1 visit) and not continuing under crizanlizumab outside the study, the EOT visit is to be performed within 7 days from the decision to discontinue from the study treatment.

For participants discontinuing from study treatment (prior to completion of Week 103 Day 1 visit) and continuing under crizanlizumab outside the study, and for all participants completing the 2 years of study treatment (completion of Week 103 Day 1 visit) whether they continue on crizanlizumab outside the study or not, the EOT visit should be completed 4 weeks (+/- 7 days) from last dose of study treatment.

[k] Participants continuing under crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over protocol or in a non-trial setting to provide continued drug treatment) will not have to complete the post-treatment follow-up visit.

Visit Name	Category	Protocol Section	Screening	Wk1 D1	Wk1D2 [d]	Wk1D4 [e]	Wk2D1 [d]	Wk3D1	Wk7D1	WK11D1	Wk15D1	Wk15D2 [d, f]	Wk15D4 [e, f]	Wk16D1 [d, f]	Wk17D1 [d, f]	Wk18D1 [d, f]	Wk 19D1, 23D1, 27D1, 31D1, 4qWk till 103 D1	End of treatment (EOT) [j]	Post Treatment Follow up [k]
Visit Numbers			*1*	*110*	*120*	*130*	*140*	*150*	*160*	*170*	*180*	*190*	*200*	*210*	*220*	*230*	*240 …*	*1997*	*2000*
Visit Day			-28 through Day -1	1	2	4	8	15	43	71	99	100	102	106	113	120			

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

7.1.1 Molecular pre-screening

Not Applicable.

7.1.2 Screening

Prior to commencement of the screening examination, the patient / legal representative must have given full informed consent on the appropriate form. Investigators will also obtain consent/assent of patients according to local guidelines. Once this has been signed and dated by the patient and/or by the legal representative, the investigator can take the participant through the study inclusion and exclusion criteria to make sure that the participant is fully eligible.

Refer to Table 7-1 for the full screening assessment.

7.1.2.1 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.

Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

A participant who signs an informed consent/assent but fails to be enrolled for any reason will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details). Data and samples collected from participants prior to screen failure may still be analyzed.

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

If the participant fails to be assigned to study treatment, the IRT must be notified within 2 days of the screen fail.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date, unless re-consent is required by local regulations.

Participants who are enrolled and fail to start treatment, e.g., participants enrolled in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

7.1.2.3 Participant demographics and other baseline characteristics

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

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Participant race and ethnicity are collected as part of the Demographics characteristics, and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Background medical information, including diagnosis of SCD and dactylitis/VOC history, prior use of HU/HC and reason for discontinuation (as applicable), ECG, relevant and current medical history (until date of informed consent) will also be collected.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.4 Concomitant medications for further details on what information must be recorded on the appropriate page of the eCRF.

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

7.1.3 Run-in period

Not Applicable.

7.1.4 Treatment period

Once eligibility criteria have been confirmed, the participant will be enrolled to receive crizanlizumab on Week 1 Day 1, Week 3 Day 1, and then on Day 1 of every 4-week cycle (see Table 7-1). Participants may be admitted to the study site prior to dosing for baseline evaluations.

Initiation of treatment in the three study groups will occur sequentially. The first participants in the study will be enrolled in Group 1 and will receive crizanlizumab 5.0 mg/kg by i.v. infusion on Week 1 Day 1, Week 3 Day 1, and then on Day 1 of every 4-week cycle. The first participants of each study group will be enrolled in Part A of the study to confirm and establish appropriate dosing, before treatment is initiated in Part B and in Part A of the next study group (refer to Section 4.1).

No dose change or modification by the investigator of the study defined dose will be allowed in the study. Dose interruptions for safety reasons are described in the Section 6.3.

All enrolled participants will have PK/PD sampling performed in order to characterize the PK/PD of crizanlizumab (see Table 7-5, Table 7-6, and Table 7-7). On Week 1 Day 1 and Week 15 Day 1, the participants enrolled in Part A may be asked to remain at the study site for at least 24 hours post-dose in order to complete the full PK/PD sample collection. In case the

dose was interrupted, partially administered and/or delayed (out of allowed visit window, see Section 7.1) prior to Week 15 Day 1, the full PK/PD sample collection will not be collected at Week 15 but after 3 full consecutive infusions, see Section 7.2.3.1.

[redacted]

Safety will be monitored as outlined in Section 8. Participants will receive treatment for up to 2 years or until premature discontinuation from the study treatment for any reasons.

7.1.5 Discontinuation from study treatment

Discontinuation from study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of the 2 years of study treatment administration), and can be initiated by either the participant or the investigator.

Participant may voluntarily discontinue from the study treatment for any reason at any time. If a participant decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the participant's chart and on the appropriate CRF pages.

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.

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

In addition to mandatory discontinuation reasons for study treatment listed in Table 6-2 and Table 6-3, study treatment **must** also be discontinued under the following circumstances:

- Pregnancy
- Lactation
- Participant/Guardian decision
- Use of prohibited medication (see Section 6.4.3).
- Omission of two consecutive doses
- Grade 4 adverse events deemed related to study treatment (see Section 6.3)
- Emergence of the following AEs:
  1. Any severe or serious AE that requires treatment with an unacceptable co-medication
  2. Onset of lymphoproliferative disease or any other malignancies
  3. Life-threatening infection
- Severe hypersensitivity reaction or anaphylactic reaction
- Any other protocol deviation that results in a significant risk to the participant's safety
- Other reasons for earlier termination may include but are not limited to:
  - Decision based on recommendations from applicable board(s) after review of safety
  - Discontinuation of study drug development

Participants who prematurely discontinue from study treatment (prior to completion of Week 103 Day 1 visit) should NOT be considered discontinued from the study. The participants discontinuing from study treatment and not continuing under crizanlizumab outside of the study should return for the assessments indicated in Table 7-1 for an EOT visit within 7 days from the decision to permanently discontinue the study treatment, and the 105 day post-treatment follow-up visit (105 days after last dose of study treatment +/- 7 days). If the decision to discontinue the participant occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the participant return for an additional visit 7 days later.

The participants discontinuing from study treatment but continuing under crizanlizumab outside of the study (i.e. via commercial supply) should return for the assessments indicated in Table 7-1 for an EOT visit within 4 weeks (+/-7 days) from the last dose of study treatment. These participants will not have to complete the post-treatment follow-up visit.

Participants completing the 2 years of study treatment (Week 103 Day 1 visit) will perform the EOT visit as indicated in Table 7-1, within 4 weeks (+/-7 days) from last dose of study treatment.

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.

If the participants fail to return for these EOT assessments for unknown reasons, every effort (e.g., telephone, email, letter) should be made by the site staff to maintain regular telephone contact with them. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, the following data should be collected at clinic visits or via telephone/email contacts:

- New / concomitant treatments
- Adverse events / Serious Adverse Events

7.1.6 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation (EOT visit, or post-treatment follow-up visit) at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 7.1).

7.1.6.1 Replacement policy

If the initial number of at least 8 participants in Part A of each group treated at the initial dose for the group leads to less than 6 evaluable participants, enrollment in the group Part A will continue until 6 participants have successfully completed all study procedures and are evaluable for the first dose PK analysis (see Section 10).

7.1.7 Withdrawal of consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs only 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 his/her 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, all efforts should be made to complete a final evaluation prior to participant's withdrawal of consent/opposition to use data/biological samples (refer to Section 7).

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 to use data/biological samples.

7.1.8 Post-treatment Follow-up

All participants must have safety and efficacy evaluations for 5 half-lives (105 days) after the last dose of study treatment, except the ones continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over study or in a non-trial setting to provide continued drug treatment). The post-treatment follow-up visit should occur 105 days +/-7 days after the last dose of study treatment.

Once an AE is detected, investigators are required to follow this AE until its resolution or stabilization. Refer to Section 8.1.1 for definitions and reporting of AEs. Participants whose treatment is interrupted or discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event.

Data collected should be added to the Adverse Events, VOCs, Dactylitis, Transfusion and Concomitant Medications CRFs.

For participants followed until 105 days after last dose of study treatment, any SAEs experienced after the completion of the 105 day post-treatment follow-up visit should be reported to Novartis if the investigator suspects a causal relationship to the study treatment, unless otherwise specified by local law/regulations.

If participants refuse to return for a post-treatment follow-up visit or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the participant should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

7.1.9 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator should show "due diligence" by contacting the participant, family or family physician as agreed in the informed consent and 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 lost to follow-up until due diligence has been completed. Participants lost to follow-up should be recorded as such on the Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 VOC assessments

Definitions

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

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

1. Uncomplicated pain crisis is defined as an acute episode of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or parenteral NSAIDs; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism. The end of an uncomplicated pain crisis will be considered the resolution of acute pain, such that residual pain (or absence of any pain) is considered to be chronic, and the current pain medication regimen is considered to be for this chronic pain.
2. Acute Chest Syndrome (ACS) is defined on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with alveolar consolidation but excluding atelectasis (as indicated by chest X-ray). At least one of the following additional signs or symptoms needs to be present as well: chest pain, a

temperature of more than 38.5°C, tachypnea, wheezing or cough. ACS will be considered resolved when the participant is no longer hospitalized (unless for reason other than the ACS episode) and none of the additional signs or symptoms above are present (unless for reason other than the ACS) or have returned to pre-event baseline.

3. Priapism is defined as an unwanted or painful penile erection lasting at least 30 minutes. The end of an acute priapism event will be when the unwanted erection has resolved for at least 2 hours.
4. Hepatic sequestration is defined on the basis of findings of right upper quadrant pain, an enlarged liver, and an acute decrease in hemoglobin concentration (e.g., a decrease in hemoglobin of ~ 2 g/dL). Acute hepatic sequestration will be considered resolved when right upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.
5. Splenic sequestration if defined on the basis of findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in hemoglobin concentration (e.g., a decrease in hemoglobin of ~ 2 g/dL). Acute splenic sequestration will be considered resolved when left upper quadrant pain has returned to baseline (pre-event) levels and hemoglobin has been stable for 24 hrs.

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

Table 7-2 Vaso-Occlusion Crisis Assessment Collection Plan

Procedure / Assessment collection plan	**Screening/Baseline**	**During Treatment/Post-treatment Follow-up**
Chest X-ray	Mandated	If clinically indicated
Vaso-Occlusion Crisis information	Mandated	Mandated, when VOC crisis occurs
Dactylitis	Mandated	Mandated when dactylitis occurs
Concomitant medication – Analgesics	If clinically indicated	Mandated, when VOC crisis occurs
Hospitalization details	Mandated	Mandated, when VOC crisis occurs and hospitalization is done
Transfusion	If clinically indicated	If clinically indicated
School/ Employment status and sick time	If clinically indicated	If clinically indicated
Blood for PK/PD	Not Applicable	If possible

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Post-treatment Follow-up
Soluble P-selectin	Not Applicable	If possible

Vaso-Occlusion Crisis information

VOCs leading to healthcare visit in clinic/ER/hospital occurring within 12 months prior to screening and prior to first dose of study treatment will be collected at screening on the VOC history CRF. From administration of the first dose, throughout the treatment period and until the last protocol visit (EOT or post-treatment follow-up visit, as applicable), information for each VOC will be collected on the VOC event CRF.

Hospitalization

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. Participants will be issued an investigational study participation card that requests this information and can be presented at each medical facility visit.

Participants should be encouraged to call the Investigator (or surrogate from the site) when they believe they are experiencing a VOC that they believe they can manage at home, both for treatment guidance and for accurate information to be obtained for the VOC CRF page. VOCs treated at home but not documented by a telephone call within 24 hours of onset will not be counted as a VOC nor collected in the CRF, due to concern over the accuracy of participant recall of all relevant details. If a participant experiences a VOC surrounding a protocol-scheduled visit day, and the participant presents for this visit, it will be counted as a VOC that led to a healthcare visit (provided the event meets the criteria for VOC discussed above).

[redacted]

Participant must have experienced at least 1 VOC leading either to a visit to a medical facility or healthcare professional, within the preceding 12 months prior to screening to be eligible. However, participants who experienced a VOC ending within 7 days prior to Week 1 Day 1 are not eligible (refer to Section 5.2 Inclusion criteria).

Dactylitis

Dactylitis, also known as 'hand-foot syndrome', is a complication of acute vaso-occlusive disease characterized by pain and edema on the dorsum of the hands or feet, or both simultaneously, often accompanied by increased local temperature and erythema.

Dactylitis occurring within 12 months prior to screening and prior to first dose of study treatment will be collected at screening on the Dactylitis history CRF. From administration of the first dose, and throughout the treatment period and until the last protocol visit (EOT or post-treatment follow-up visit, as applicable), the investigators will collect information on dactylitis, including location, duration, presence and severity of pain, action taken with study treatment if any, outcome of the event, treatments administered, and need for hospitalization on the

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

If a single event meets criteria for both dactylitis and VOC, then both CRF forms should be completed.

Chest X-ray

Chest X-ray must be conducted at screening unless there is one available in the last 12 weeks prior to Week 1 Day 1, to establish the participant's baseline and confirm no significant new findings prior to enrolment. Chest X-ray must be repeated during the study in case of a VOC with suspected ACS and reported as unscheduled assessment in the CRF.

Transfusions

Transfusion data should be collected from 28 days prior to Week 1 Day 1 until the participant last protocol visit (EOT or post-treatment follow-up visit, as applicable). Participants planning to participate in a chronic transfusion program during study (pre-planned series of transfusions for prophylactic purposes) are not eligible. Episodic transfusion in response to worsened anemia or VOC is permitted and will be collected on the Transfusion CRF page.

7.2.2 Safety and tolerability assessments

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

7.2.2.1 Physical examination

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

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and 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 at the EOT visit.

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

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the participant's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the participant's CRF.

7.2.2.2 Vital signs

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

7.2.2.3 Height, weight and head circumference

Height and body weight (in indoor clothing, but without shoes) will be measured at screening and at all visits for which there is a scheduled study drug infusion (for dosing calculation), as specified in Table 7-1. Additionally, head circumference will be measured for participants aged 2 to 2.5 years old at time of enrollment, at all visits where weight and height are measured, until the participant turns 3 years old.

7.2.2.4 Performance status

The Karnofsky performance status scale (Appendix 1) will be used for children >10 years and the Lansky Play-Performance Status Scale Clinical Classification (Appendix 2) for children ≤ 10 years of age will be assessed as described in the Table 7-1.

7.2.2.5 Growth and sexual maturation

7.2.2.5.1 Pubertal stage

Pubertal stage according to Tanner staging will be scored at screening, at the end of the first year of treatment (Week 51 Day 1) and at the EOT visit. This assessment may be discontinued once Stage V is reached.

7.2.2.6 Transcranial Doppler

Transcranial Doppler (TCD) is a noninvasive ultrasound assessment used to measure cerebral blood flow velocity (CBF-V) including the middle cerebral artery (MCA) velocity in the major intracranial arteries.

It will be required for participants aged from 2 to <16 years old at the time of screening, with HbSS, HbSβ^0-thalassemia, and HbSD disease. For participants with other SCD types, performance of TCD is by investigator discretion.

In case TCD assessment during the screening period is not feasible, an acceptable TCD done within 12 weeks prior to Week 1 Day 1 can be used.

An acceptable TCD is defined as

- a TCD that was not performed within 60 days following a transfusion
- a TCD that was not impacted by change in treatment such as HU/HC or L-glutamine (e.g., stopped treatment or significant dose change) within 60 days prior to TCD assessment, or after TCD assessment and Week 1 Day 1

Only when screening TCD is unevaluable due to cranial ossification, a participant may be eligible based on investigator interpretation of “low risk” for the most recent, evaluable TCD within 12 months prior to enrollment (Week 1 Day 1). If all TCDs from the past 12 months are

unevaluable, intracranial flow MRI (if available) will be considered for enrollment. In case no evaluable TCD or MRI is available at screening visit the participant will not be eligible.

Subsequent TCDs will be required at Week 27 Day 1, Week 51 Day 1, Week 103 Day 1 and at the EOT visit, unless it was already done within 12 weeks prior to the EOT visit as outlined in Table 7-1, for participants aged from 2 to <16 years old at time of screening, with HbSS, HbSβ^0-thalassemia, and HbSD disease. For participants with other SCD types, performance of TCD is by investigator discretion.

During the study in case a transfusion was performed or in case of a change in HU/HC or L-glutamine (e.g., stopped treatment or significant dose change) within 60 days prior to the expected date of TCD, then the planned TCD will be skipped and an unscheduled TCD will need to be performed at least 60 days after.

7.2.2.7 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, urinalysis, coagulation) are to be performed at the central lab or locally at site according to the schedule of assessments and collection plan outlined in Table 7-1. As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster), if participants cannot visit the site for protocol specified safety lab assessments, an alternative certified local lab other than the study site may be used. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/Flowchart.

Screening assessments, apart from those identified in the visit evaluation schedule (VES) and in Section 7.1, must occur within 28 days prior to the enrolment as per Table 7-1 (see Section 7.1). If the participant was hospitalized at time of screening visit, safety laboratory analysis must be repeated prior to Week 1 Day 1 to verify participant's eligibility.

Novartis must be provided with a copy of the central and local laboratory's certifications and a tabulation of the normal ranges and units of each parameter collected in the CRF. 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, laboratory results from the central laboratory will be used, except for hematology (always performed locally), and other lab tests deemed for eligibility, in case of missing results from central lab.

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 (except for hematology which will be only performed locally at site).

The results of the local laboratory will be recorded in the CRF if any of 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.

Every effort should be made in order to perform local lab tests in case no concomitant central results are available (due to any reason). Missing of 2 consecutive lab tests deemed to assess dose interruption/discontinuation (as per Table 6-2) during the study is not permitted.

At any time during the study up to last protocol visit (EOT or post-treatment follow-up visit, as applicable), abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require 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 CRF 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 7-3 Central and Local Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	**Local (performed at site):** Hematocrit, Hemoglobin, Mean cell hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV), Reticulocytes (%), Platelets, Red blood cells, White blood cells, , Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other: absolute value preferred).
Chemistry	**Central:** Albumin, Alkaline phosphatase, ALT, AST, Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, , estimated Glomerular filtration rate (eGFR).
Urinalysis	**Local (performed at site):** Macroscopic Panel (Dipstick): Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen. **Central:** • Microscopic Panel: Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria and Epithelial cells performed if a positive dipstick. • [redacted]
Coagulation (only for Groups 1 and 2)	**Central:** Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Additional tests	**Central:** HbA, S, C, F, A2
Pregnancy Test (for female participants of childbearing potential)	**Central:** Serum pregnancy test (at Screening, EOT and post-treatment follow-up visit only). **Local (performed at site):** urine pregnancy test (before each infusion).

7.2.2.7.1 Hematology

Hematology tests [redacted] are to be performed locally at site according to the schedule of assessments and collection plan outlined in Table 7-1.

When needed, manual platelet estimation via blood smear to assess adequacy of the platelet count may be considered.

Detailed hematology panel is described on Table 7-3.

7.2.2.7.2 Chemistry

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

The estimated Glomerular Filtration Rate (eGFR) using Schwartz formula will be calculated centrally.

7.2.2.7.3 Urinalysis

Macroscopic urinalysis dipstick analysis will be performed locally at site according to the schedule of assessments and collection plan outlined in Table 7-1. Microscopic analysis will be performed centrally only in case of positive dipstick.

Detailed urinalysis panel is described on Table 7-3 .

7.2.2.7.4 Coagulation

Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) or activated partial thromboplastin time (APTT) will be assessed centrally according to the schedule of assessments samples outlined in Table 7-1 in Group 1 and 2 only. Samples will be collected at Week 1 Day 1, Week 19 Day 1, at Week 27 Day 1, and then every 12 weeks from Week 27 Day 1: at Week 39 Day 1, at Week 51 Day 1, at Week 63 Day 1, at Week 75 Day 1, at Week 87 Day 1, at Week 99 Day 1, at EOT and at the end of the post-treatment follow-up.

7.2.2.7.5 Fetal Hemoglobin

Fetal Hemoglobin by HPLC will be performed at the central lab in participants at time of enrollment 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, Week 51 Day 1, Week 75 Day 1, Week 103 Day 1 and EOT visits as outlined in Table 7-1.

7.2.2.7.6 Pregnancy and assessments of fertility

A female participant is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

All female participants of childbearing potential must perform a serum hCG pregnancy test at screening in order to confirm study eligibility, at EOT visit and at the end of the post treatment follow-up 105 days after the last infusion of the study treatment. In case the childbearing potential status changes during the course of the study compared to screening, site will record the childbearing status on source documents, as required.

At Week 1 Day 1 before the administration of the crizanlizumab dose and before all visits for which there is a scheduled study drug infusion, a urine pregnancy test will be performed locally in females of childbearing potential.

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

Each pregnancy in a participant on study drug must be reported to the sponsor within 24 hours of learning of its occurrence. See Section 8.5 for detailed reporting and follow-up procedures.

7.2.2.7.7 Urine albumin/creatinine ratio

At Screening, a urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary albumin/creatinine ratio. The assessment will be repeated at Week 27 Day 1, Week 51 Day 1 and EOT visits (if not done within 12 weeks prior EOT already) as outlined in Table 7-1. First morning void samples must not be used for this analysis.

7.2.2.8 Cardiac assessments

7.2.2.8.1 Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed (in the supine position) after the participant has been resting for 5-10 min prior to each time point indicated in Table 7-4. When triplicate ECG are required, the individual ECGs should be recorded approximately 2 minutes apart.

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

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

The mean QTcF value will be calculated from the triplicate ECGs for each participant. Unscheduled triplicate ECGs will be performed also in case QTcF >480 ms has been observed.

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

In the event that a QTcF value of > 480 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time

and date of the last study drug intake to determine the drug exposure (refer to Section 7.2.3). In case of QT prolongation, study drug must be discontinued (refer to Section 6.3.2).

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may also be performed at any time during the study at the discretion of the investigator. The local QTcB results must be captured in the source documents only.

All ECGs, including unscheduled safety triplicate ECGs with clinically relevant findings, collected during the study should be transmitted to the central core ECG laboratory for review. The results of the centrally assessed ECGs are automatically transferred into the clinical database. Any original ECG not transmitted to a central laboratory should be forwarded for central review and a copy kept in the source documents at the study site. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, participant number, date, and kept in the source documents at the study site.

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

Figure 7-1 Timing of study procedures:

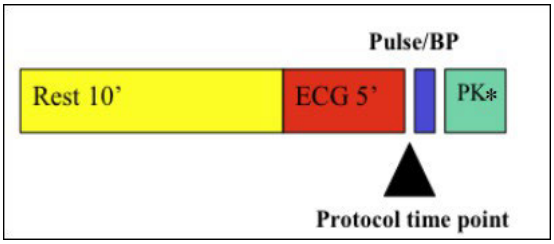


Table 7-4 ECG collection plan

Week	Day	Time	ECG Type	Type of reading
Screening	-28 to -1	Anytime	12 Lead, Triplicate	Central reading
W7	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Single	Central reading
W11	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Single	Central reading
W15[a]	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Triplicate	Central reading
W27	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Single	Central reading
W51	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Single	Central reading
W103	D1	Post-dose (within 2 hours post-infusion)	12 Lead, Single	Central reading
EOT		Anytime	12 Lead, Single	Central reading
Unscheduled ECG (triplicate) central reading		Anytime in response to cardiac AEs (arrhythmias,	12 Lead, Triplicate	Central reading

Week	Day	Time	ECG Type	Type of reading
		QTcF>480ms), additional ECGs are collected and submitted for central adjudication.		
[a] For participants in Part A, 2hr post dose ECG measure planned at Week 15 Day 1 has to be aligned with 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. For participants in Part B, Week 15 Day 1 2hr post dose ECG should still be performed at the designated visit regardless of steady-state.				

7.2.2.8.2 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 and interpreted by site personnel at screening (unless this was performed within the last 12 weeks prior to Week 1 Day 1), at Week 51 Day 1 and at the EOT visit (unless already done within 12 weeks before the EOT visit). Interpretation of the echocardiogram must be made by a qualified physician and documented on the CRF page.

Each echocardiogram report 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 CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study.

[redacted]

7.2.2.9 Auditory examination

Participants will undergo auditory examinations at Screening (if not already done within 24 weeks prior to Week 1 Day1), at Week 51 Day 1 and at EOT (unless it was done 12 weeks before the EOT visit) for Groups 1 and 2.

The auditory examination includes the following assessments:

- Comprehensive audiometry threshold examination

Interpretation of the audiometry examinations must be made by a qualified physician and documented on the CRF page.

Information about the audiometry must be present in the source documentation at study site.

[redacted]

7.2.2.10 Ocular and retinal examination

Participants will undergo ophthalmologic examinations at Screening (if not already done within 24 weeks prior to Week 1 Day 1), at Week 51 Day 1 and at EOT (unless it was done 12 weeks before the EOT visit) for Groups 1 and 2.

The ophthalmologic examination includes the following assessments:

- Distance visual acuity test
- Slit lamp
- Dilated funduscopic

Interpretation of the ocular examinations must be made by a qualified physician and documented on the CRF page.

Information and results of the ocular examinations must be present in the source documentation at study site.

[redacted]

7.2.2.11 Pulmonary Function test

Participants older than 6 years may have standard spirometry evaluations when it is clinically indicated during the study. The measures to be collected for spirometry are Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC). For participants with existing lung disease, PFT should also be performed during screening (if not performed within 12 weeks prior to Week 1 Day 1).

7.2.2.12 Tolerability

Not Applicable.

7.2.3 Pharmacokinetics, pharmacodynamics, and immunogenicity

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

7.2.3.1 Pharmacokinetic, pharmacodynamic, and immunogenicity blood collection and handling

Blood samples should be collected at specified time points as described in Table 7-5, Table 7-6, and Table 7-7 .

The blood samples will be allowed to clot for approximately 30 minutes at room temperature and then centrifuged for 10 minutes at approximately 3000g. Each serum sample will be aliquoted, and transferred into freezer-proof polypropylene screw-cap tubes (2 tubes for PK, 2 tubes for PD and 3 tubes for IG at each specified time points). The serum tubes will be frozen within 90 minutes of venipuncture and kept below - 70°C in an upright position pending shipment and analysis. Each serum sample should be labeled with the appropriate study, center and participant numbers, as well as the sequential PK/PD/IG sample and PK/PD/IG collection number with a unique sample number. The actual collection date and time of each sample will be entered on the PK/PD/IG Blood Collection CRF pages.

Refer to the SEG101B2201 Laboratory Manual for detailed instructions for the collection, handling, and shipment of PK samples.

Participants enrolled in Part B, following dose confirmation, will have only pre-dose PK/PD/IG samples collected starting from Week 1 Day 1 until EOT (PD) or post-treatment follow-up visit (PK, IG), as described in Tables Table 7-5, Table 7-6, and Table 7-7.

Specific instructions for the blood sampling at steady state (on Week 15 Day 1 or later) – Part A only

The full blood sampling for PK and PD intended to describe the steady state (PK samples 11 to 20 and PD samples 109 to 116) will only be performed between Week 15 Day 1 and Week 19 Day 1 if 3 full consecutive doses of crizanlizumab following the loading dose at Week 3 Day 1 were received by the participant. Otherwise if dose is interrupted, partially administered or delayed prior to Week 15, 3 full consecutive infusions (administered within allowed visit window) are required to reach the steady state after the dose has been resumed. In the case the steady state is not reached at Week 15, only the pre-dose samples will be collected at Week 15 Day 1 (PK sample 11 and PD sample 109). The other samples (PK samples 12 to 19 and PD samples 110 to 115) should not be collected as the PK/PD profile will not reflect the PK/PD steady-state.

In case steady state is reached after Week 15, unscheduled laboratory kits provided by the central laboratory (labeled UNS PK/PD STEADY STATE) should be used for the corresponding blood collection for full PK/PD sampling.

Maximum allowed infusion time to allow PK/PD profile sampling at steady state is 2 hours, beyond which PK/PD sampling for profile purpose will not proceed, meaning full PK/PD sampling should not occur in case infusion lasts more than 2 hours at presumed steady state. However, if full dose is administered at the visit, then multiple dose PK/PD profile sampling may occur at the next dose instead.

Table 7-5 Pharmacokinetic, pharmacodynamics and immunogenicity blood collection log Group 1

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD sample [a] No	IG sample No	Study part sample collection	
1	1	Pre-dose	1	--	1	101	201	Part A	Part B
1	1	0.5[d] (± 10 min after end of infusion)	1	--	2	--	--	Part A	--
1	1	2 (± 30 min)	1	--	3	102	--	Part A	--
1	1	4 (± 30 min)	1	--	4	--	--	Part A	--
1	2	24 (± 2 hr)	1	--	5	103	--	Part A	--
1	4	72 (± 2 hr)	1	--	6	104	--	Part A	--
2	1	168 (± 24 h)	1	--	7	105	--	Part A	--
3	1	Pre-dose	2	101[b]	8	106	202	Part A	Part B
7	1	Pre-dose	3	201[b]	9	107	--	Part A	Part B
11	1	Pre-dose	4	301[b]	10	108	--	Part A	Part B
15[c]	1	Pre-dose	5	401[b]	11	109	203	Part A	Part B

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD sample [a] No	IG sample No	Study part sample collection	
15 [c]	1	0.5[d] (± 10 min after end of infusion)	5	--	12	--	--	Part A	--
15 [c]	1	2 (± 30 min)	5	--	13	110	--	Part A	--
15 [c]	1	4 (± 30 min)	5	--	14	--	--	Part A	--
15 [c]	2	24 (± 2 hr)	5	--	15	111	--	Part A	--
15 [c]	4	72 (± 2 hr)	5	--	16	112	--	Part A	--
16 [c]	1	168 (± 24 h)	5	--	17	113	--	Part A	--
17 [c]	1	336 (± 24 h)	5	--	18	114	--	Part A	--
18 [c]	1	504 (± 24 h)	5	--	19	115	--	Part A	--
19 [c]	1	Pre-dose	6	501[b]	20	116	--	Part A	Part B
23	1	Pre-dose	7	601[b]	21	117	--	Part A	Part B
27	1	Pre-dose	8	701[b]	22	118	204	Part A	Part B
31	1	Pre-dose	9	801[b]	23	119	--	Part A	Part B
35	1	Pre-dose	10	901[b]	24	120	--	Part A	Part B
39	1	Pre-dose	11	1001[b]	25	121	--	Part A	Part B
43	1	Pre-dose	12	1101[b]	26	122	--	Part A	Part B
47	1	Pre-dose	13	1201[b]	27	123	--	Part A	Part B
51	1	Pre-dose	14	1301[b]	28	124	--	Part A	Part B
EOT		--	--	1401	29	--	205	Part A	Part B
Post-treatment Follow-up (last infusion + 105 days) [e]		--	--	1501	30	--	206	Part A	Part B
Unscheduled Sample		---	---		1001+	2001+	3001+	Part A	Part B

[a] PD: P-selectin inhibition

[b] For the PK pre-dose samples (sample number 8-11 and 20-28), the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table.

[c] Sampling to occur at steady state (week 15) or later, if dose was interrupted, partially administered or delayed prior to Week 15.

[d] 0.5 hr sample is collected at end of typical 30 minutes infusion. In the rare instance that infusion time is prolonged beyond 30 minutes, for example for up to 1 hr, then 0.5 hr sample is not collected and end of infusion sample will be collected at 1 hr instead.

[e] Participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment into a Novartis roll-over protocol or in a non-trial setting), will not have to complete the 105 days post-treatment follow-up visit.

Table 7-6 Pharmacokinetic, pharmacodynamics and immunogenicity blood collection log Group 2

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD sample[a] No	IG sample No	Study part sample collection	
1	1	Pre-dose	1	--	1	101	201	Part A	Part B

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD sample[a] No	IG sample No	Study part sample collection	
1	1	0.5[d] (± 10 min after end of infusion)	1	--	2	--	--	Part A	--
1	1	2 (± 30 min)	1	--	3	102	--	Part A	--
1	1	4 (± 30 min)	1	--	4	--	--	Part A	--
1	2	24 (± 2 hr)	1	--	5	103	--	Part A	--
1	4	72 (± 2 hr)	1	--	6	104	--	Part A	--
2	1	168 (± 24 h)	1	--	7	105	--	Part A	--
3	1	Pre-dose	2	101[b]	8	106	202	Part A	Part B
7	1	Pre-dose	3	201[b]	9	107	--	Part A	Part B
11	1	Pre-dose	4	301[b]	10	108	--	Part A	Part B
15[c]	1	Pre-dose	5	401[b]	11	109	203	Part A	Part B
15[c]	1	0.5[d] (± 10 min after end of infusion)	5	--	12	--	--	Part A	--
15[c]	1	2 (± 30 min)	5	--	13	110	--	Part A	--
15[c]	1	4 (± 30 min)	5	--	14	--	--	Part A	--
15[c]	2	24 (± 2 hr)	5	--	15	111	--	Part A	--
15[c]	4	72 (± 2 hr)	5	--	16	112	--	Part A	--
16[c]	1	168 (± 24 h)	5	--	17	113	--	Part A	--
17[c]	1	336 (± 24 h)	5	--	18	114	--	Part A	--
18[c]	1	504 (± 24 h)	5	--	19	115	--	Part A	--
19[c]	1	Pre-dose	6	501[b]	20	116	--	Part A	Part B
23	1	Pre-dose	7	601[b]	21	117	--	Part A	Part B
27	1	Pre-dose	8	701[b]	22	118	204	Part A	Part B
31	1	Pre-dose	9	801[b]	23	119	--	Part A	Part B
35	1	Pre-dose	10	901[b]	24	120	--	Part A	Part B
39	1	Pre-dose	11	1001[b]	25	121	--	Part A	Part B
43	1	Pre-dose	12	1101[b]	26	122	--	Part A	Part B
47	1	Pre-dose	13	1201[b]	27	123	--	Part A	Part B
51	1	Pre-dose	14	1301[b]	28	124	--	Part A	Part B
EOT		--	--	1401	29	--	205	Part A	Part B
Post-treatment Follow-up (last infusion + 105 days)[e]		--	--	1501	30	--	206	Part A	Part B
Unscheduled Sample		---	---		1001+	2001+	3001+	Part A	Part B

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID	PK sample No	PD sample[a] No	IG sample No	Study part sample collection

[a] PD: P-selectin inhibition

[b] For the PK pre-dose samples (sample number 8-11 and 20-28), the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table.

[c] Sampling to occur at steady state (week 15) or later, if dose was interrupted, partially administered or delayed prior to Week 15.

[d] 0.5 hr sample is collected at end of typical 30 minutes infusion. In the rare instance that infusion time is prolonged beyond 30 minutes, for example for up to 1 hr, then 0.5 hr sample is not collected and end of infusion sample will be collected at 1 hr instead.

[e] Participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment into a Novartis roll-over protocol or in a non-trial setting), will not have to complete the 105 days post-treatment follow-up visit.

Table 7-7 Pharmacokinetic, pharmacodynamics and immunogenicity blood collection log Group 3 (2 to 6 years)

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD[a] sample No	IG sample No	Study part sample collection
1	1	Pre-dose	1	--	1	101	201	Part A
1	1	0.5[d] (± 10 min after end of infusion)	1	--	2	--	--	Part A
1	2	24 (± 2 hr)	1	--	5	--	--	Part A
2	1	168 (± 24 h)	1	--	7	105	--	Part A
3	1	Pre-dose	2	101[b]	8	106	202	Part A
7	1	Pre-dose	3	201[b]	9	107	--	Part A
11	1	Pre-dose	4	301[b]	10	108	--	Part A
15[c]	1	Pre-dose	5	401[b]	11	109	203	Part A
15[c]	1	0.5[d] (± 10 min after end of infusion)	5	--	12	--	--	Part A
15[c]	2	24 (± 2 hr)	5	--	15	--	--	Part A
16[c]	1	168 (± 24 h)	5	--	17	113	--	Part A
17[c]	1	336 (± 24 h)	5	--	18	114	--	Part A
18[c]	1	504 (± 24 h)	5	--	19	115	--	Part A
19[c]	1	Pre-dose	6	501[b]	20	116	--	Part A
23	1	Pre-dose	7	601[b]	21	117	--	Part A
27	1	Pre-dose	8	701[b]	22	118	204	Part A
31	1	Pre-dose	9	801[b]	23	119	--	Part A
35	1	Pre-dose	10	901[b]	24	120	--	Part A
39	1	Pre-dose	11	1001[b]	25	121	--	Part A
43	1	Pre-dose	12	1101[b]	26	122	--	Part A
47	1	Pre-dose	13	1201[b]	27	123	--	Part A
51	1	Pre-dose	14	1301[b]	28	124	--	Part A

Week	Day	Scheduled time point following the initiation of infusion (hr)	PK collection number/Dose reference ID		PK sample No	PD[a] sample No	IG sample No	Study part sample collection
EOT		--	--	1401	29	--	205	Part A
Post-treatment Follow-up (last infusion + 105 days)[e]		--	--	1501	30	--	206	Part A
Unscheduled Sample		---	---		1001+	2001+	3001+	Part A

[a] PD: P-selectin inhibition

[b] For the PK pre-dose samples (sample number 8-11 and 20-28), the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table.

[c] Sampling to occur at steady state (week 15) or later if dose was interrupted, partially administered or delayed prior to Week 15.

[d] 0.5 hr sample is collected at end of typical 30 minutes infusion. In the rare instance that infusion time is prolonged beyond 30 minutes, for example for up to 1 hr, then 0.5 hr sample is not collected and end of infusion sample will be collected at 1 hr instead.

[e] Participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment into a Novartis roll-over protocol or in a non-trial setting), will not have to complete the 105 days post-treatment follow-up visit.

In Group 3, single dose PK/PD, multiple dose PK/PD and safety will be evaluated in Part A and no patients will be enrolled in Part B.

7.2.3.2 Analytical method

The crizanlizumab PK assay is a target capture enzyme-linked immunosorbent assay (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 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 its binding to a PSGL1 peptide.

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

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Other assessments

No additional tests will be performed on participants entered into this study.

7.2.5 Resource utilization

Not Applicable.

7.2.6 Patient reported outcomes

Not Applicable.

8 Safety monitoring and reporting

As per Section 2.7, 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 for 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.

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the participant's CRF. Adverse event monitoring should be continued for 105 days (or 5 half-lives) following the last dose of study treatment, except for participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over protocol or in a non-trial setting to provide continued drug treatment). For these participants, monitoring of adverse events as part of this study will stop from the time the participant performed EOT visit. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening and death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected though a Death form.

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

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

7. Outcome

If an event worsens in severity, the same event should be reported a second time in the CRF noting the start date when the event worsened in severity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined, a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

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

Once an adverse event is detected, it should be followed-up until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) on any changes in severity, on suspected relationship to the study treatment, on the interventions required to treat it, and on the outcome.

Vaso-occlusive crisis (including fatal outcomes), if documented by use of appropriate method (for example, as per VOC Event page), should not be reported as a serious adverse event, please refer to Section 8.3.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

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

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

8.1.3 Adverse events of special interest

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

AESI are defined on the basis of an ongoing review of the safety data.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or 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
- Is medically significant, i.e., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

  Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - VOC or dactylitis event, as defined in the protocol (Section 7.2.1.1)
  - 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
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

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 study treatment errors and uses outside of what is foreseen in the protocol, intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

8.2.2 Reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until at least 105 days after the participant has stopped study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail), except for participants continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g., enrollment in a Novartis roll-over protocol or in a non-trial setting to provide continued drug treatment). For these participants, monitoring of adverse events as part of this study will stop from the time the participant performed EOT visit.

All follow-up information for the SAE including information on complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). Follow-up information is submitted in the same way as the original SAE Report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the participant continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

For participants followed until 105 days after last dose of study treatment, any SAEs experienced after completion of the 105-day post-treatment follow-up visit should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form immediately, without undue delay, but under no circumstances later than within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

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 Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01, EU Clinical Trial

Regulation (CTR) 536/2014 once transfer is completed or as per national regulatory requirements in participating countries.

8.3 Protocol Exempt AEs & SAEs

Protocol Exempt AEs & SAEs are implemented in the SEG101 program. As VOCs are considered secondary endpoints for the purpose of evaluation of efficacy, these events SHOULD NOT be reported as AEs or SAEs for the purpose of this study and will not be considered as SAEs in regard to reporting requirements. Instead, VOCs must be reported on the dedicated VOC CRF.

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 themselves will be reported as AE/SAEs. Details will be given in the eCRF completion guidelines.

In case that new information arises which changes the diagnosis of a VOC, i.e. gives another medically determined explanation than vaso-occlusion in the opinion of the investigator, the event has to be reported according to the rules of Section 8 and must be reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 hours of learning of the new information.

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

However in case a VOC event is suspected to be related to study treatment, and/or resulting in a fatal outcome, it will be reported as SAE in addition to the VOC CRF.

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

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

Dactylitis events will also be covered by the protocol exempt SAEs and AEs. The information of VOCs and/or dactylitis events should be placed in their respective CRF forms “Sickle Cell - Vaso-Occlusive Crisis (VOC) Event” and/or “Dactylitis” form.

8.4 Emergency unblinding of treatment assignment

Not Applicable.

8.5 Pregnancies

If a female trial participant becomes pregnant, the study treatment must be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. Once consent for pregnancy follow-up given, information about pregnancy and health of the baby will be collected at different times, and until 12 months after the date of delivery (for a live birth).

To ensure participant safety, each pregnancy occurring while the participant is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

8.6 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the Study treatment CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, 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. For more information on AE and SAE definition and reporting requirements, please see the respective sections Section 8.1.1 and Section 8.2.

8.7 Warnings and precautions

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

8.8 Data Monitoring Committee

This study will institute 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 be constituted prior to the first dosing confirmation for Group 1 in Part A. The DMC will be responsible to regularly review key safety and PK data prior to opening the next age group and enrolment in part B.

Specific details regarding composition, responsibilities, meeting frequency, documentation of DMC reports, minutes, and recommendations will be described in a separate DMC charter.

8.9 Steering Committee

The steering committee will be established comprising investigators participating in the 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 a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

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

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

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

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs 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 perform ongoing source data verification to check the completeness of participant records, the accuracy of entries on the CRFs, 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.

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 recorded on CRFs must be traceable to source documents in the participant's file. The investigator must also keep the original signed ICF (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

9.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (CRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulations (CFR) Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the CRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Blood/Urine samples for safety laboratory data, blood samples for [redacted], PK, PD and IG analysis, will be collected by sites and sent to the Novartis designated central laboratory for processing. The laboratory results will be sent electronically to Novartis.

ECG data will be collected at the sites and the data will be transmitted to a designated CRO for centralized analysis, as well as further processing.

Data entered into IRT will be transferred electronically to Novartis according to the specifications described in the Data Transfer Specifications for the designated IRT vendor.

9.4 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered in the CRFs 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Dates of screening, enrollment, screen failures and study completion, as well as data about all study treatments dispensed to the participant and all IRT assigned dosage changes/interruptions will be tracked using IRT. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after final database lock, the investigator will receive a CD-ROM or paper copies of the participant data for archiving at the investigational site.

10 Statistical methods and data analysis

There will be multiple cut-off dates and formal analysis during this trial.

- The cut-off for the first dose PK analysis for Part A of each group will occur when at least 6 participants with evaluable PK have been enrolled in Part A and have completed the Week 7 Day 1 visit. This evaluation would be based on PK, dose, demography, other baseline characteristics data and key safety data (mainly AEs). If for a given age group the dose is not confirmed, then another group of participants will be recruited and an additional cut-off will be defined.
- The cut-off for the multiple dose analysis for Part A of each group (participants > 24 months) will occur when at least 6 participants with evaluable PK and PD have been enrolled in Part A and have completed multiple dose PK/PD sampling. This evaluation would be based on PK, PD, dose, demography, other baseline characteristics and key safety data.
- The cut-off for the primary analysis for Part A+B of Group 1 and 2 will occur after the multiple dose analysis and when all the participants enrolled in that group have completed the first 26-weeks of treatment period or discontinued the study treatment in that group. The intent is to be able to evaluate data for participants from each group without having to wait for next group. However, should the cut-off dates for groups 1 and 2 be close to each other, the primary analyses time points will be grouped together. At the time of the primary analysis for Parts A+B of group 1 and 2, available data of the other groups up to the same cutoff date may be included in the reporting, if needed to support regulatory filings or potential Health Authority requests. For all analyses, demographics and other baseline

characteristics, safety, efficacy and PK, PD data will be reported. [redacted]

- The additional data for any participants continuing to receive study treatment, as allowed by the protocol, will be further summarized in a final study report once all participants from all groups included in the trial (aged 2 to <18 years), have completed or early discontinued from the study.
- Additional cut-offs and analyses may be performed in order to support regulatory filings or potential Health Authority requests.

10.1 Analysis sets

The different analysis sets are described in following sections. Whatever the analysis set, the analysis will be presented according to the 3 following age groups at the time of study entry:

- Group 1: 12 years to <18 years
- Group 2: 6 years to <12 years, and
- Group 3: 2 years to <6 years.

Details will be provided in the analysis plan.

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all participants (enrolled in Part A or in Part B) to whom study treatment has been assigned and who received one dose of study treatment.

10.1.2 Safety set

The Safety Set includes all participants (enrolled in Part A or in Part B) who received at least one dose of study treatment.

10.1.3 Per-Protocol set

Not Applicable.

10.1.4 Dose-determining analysis set

Not Applicable.

10.1.5 Pharmacokinetic analysis sets

The Pharmacokinetic Analysis Set 1 (PAS1) includes:

1) All participants of part A 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 other tested dose before single dose PK profile or before multiple dose PK profile
    - Participant provides at least one primary 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

2) Participant does not have a transfusion of blood product in the last 4 weeks before the pre-dose sample.

If the planned dose is newly defined, the new dose group will be added to the PAS1 accordingly.

The Pharmacokinetic Analysis Set 2 (PAS2) includes all participants of part A and part B who receive at least one dose of crizanlizumab and provide at least one corresponding evaluable PK concentration. A pre-dose concentration is considered evaluable if not flagged out by pharmacokineticist.

10.1.6 Other analysis sets

The Pharmacodynamics Analysis Set 1 (PDS1) includes all participants of part A 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 other tested dose before single dose PD profile or before multiple dose PD profile
- Participant 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

If the planned dose is newly defined, the new dose group will be added to the PDS1 accordingly.

The Pharmacodynamics Analysis Set 2 (PDS2) includes all participants of part A and B who receive at least one dose of crizanlizumab and provide at least one corresponding evaluable PD assessment. A % inhibition value is considered evaluable if not flagged out by pharmacokineticist.

The Pharmacokinetic-Pharmacodynamics Analysis Set (PKPDS) includes all participants of part A and B included in the Safety set who have at least one measured pre-dose concentration and one matching P-selectin % inhibition value.

10.1.6.1 Efficacy/evaluable set

Not Applicable.

10.2 Participant demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by age group for the Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum and maximum values will be presented.

Relevant medical history at baseline will be summarized by system organ class, preferred term and age group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

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

The duration of exposure to investigational drug 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 (interruptions i.e. fully skipped infusions, or reductions derived based on dose change records i.e. partially administrated doses or dosing error) and the reasons will be summarized by age 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 age group.

10.4 Primary objective

The primary objectives of this trial are to confirm and establish the appropriate dosing in participants ages 2 to <18 years (Part A) and to evaluate the safety of SEG101 in participants aged 2 to <18 years (Part A for group 3 and Parts A+B for group 1 and 2).

The cut-off for the analysis for Part A of each group will occur when at least 6 participants with evaluable PK and PD have been enrolled in Part A and have completed the multiple dose PK/PD sampling (at Week 15 or later). If for a given group the dose is not confirmed, then an additional cut-off will be defined.

The cut-off for the primary analysis for Parts A+B of group 1 will occur after the multiple dose analysis for Part A of group 1 and when all participants aged 12 years and above at the time of study entry have completed the first 26-week of the treatment period or discontinued the study treatment. The cut-off for the primary analysis for Parts A+B of group 2 will occur after the multiple dose analysis for Part A of group 2 and when all participants aged 6 years to <12 years at the time of study entry have completed the first 26-week of the treatment period or discontinued the study treatment.

However, in case the cut-off dates for groups 1 and 2 or groups 1, 2 and 3 will be close to each other, the analyses time points will be grouped together.

10.4.1 Variable

Part A:

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

Primary PK Parameters

AUCd15 (week 1) after first dose, AUCtau after multiple dose, Cmax

The remaining PK parameters will be analyzed as secondary variables.

Primary PD Parameters

PD-AUCd15 (week 1) after first dose, PD-AUCtau after multiple dose.

Parts A and B:

1) Pre-dose PK concentrations from week 1 to week 19.

Pre-dose PD % inhibition from week 3 to week 19 will be analyzed as secondary variables.

2) The primary safety endpoint for Part A and B of all age groups is the frequency of participants with any adverse events during the on-treatment period (as defined in Section 10.5.3.1).

10.4.2 Statistical hypothesis, model, and method of analysis

Primary PK/PD analysis

Part A (patients from 24 months to < 18 years):

In order to confirm and establish appropriate dosing, the following methods will be used for each group and the defined dose:

For each group and defined dose, geometric means of the primary PK parameters will be derived for participants included in the PAS1. For group 1 these PK parameters will be compared against observed adult PK parameters of study CSEG101A2202; for the other groups these parameters will be compared to predicted PK parameters for these participants derived from adult from the population PK model.

Geometric mean ratio of observed (test) versus reference primary PK parameters and its 90% confidence interval will be derived and compared against the boundaries of 2 and 0.5, respectively. If the 90% confidence intervals of both PK parameters are within the boundaries, it is considered that there is no meaningful change in exposure versus the reference.

For estimation, a linear model will be fitted to the log-transformed PK parameters, mean and 90% confidence intervals will be estimated, and, finally, back-transformed to retain the geometric means and ratios and their respective 90% confidence intervals.

The data to be used for developing the population PK model will come from pooled study data of the previous studies. PK parameter prediction will be based on the population PK model. Methods will be specified and detailed in a separate document.

For each group and defined dose, geometric means of the primary PD parameters will be derived for participants included in the PDS1. Theses parameters will be compared against predicted PD parameters for these participants. For group 1 PD parameters will be compared against adult PD parameters of study CSEG101A2202.

Geometric mean ratio of observed (test) versus predicted (reference) PD parameters and its 95% confidence interval will be derived.

For estimation a linear model will be fitted to the log-transformed PD parameters, mean and 95% confidence intervals will be estimated, and, finally, back-transformed to retain the geometric means and ratios and their respective 95% confidence intervals.

Primary safety analysis

Part A+B (all age groups):

Number and percentage of participants with any adverse events will be provided by age group, and by starting dose within each age group (if applicable).

10.4.3 Handling of missing values/censoring/discontinuations

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

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

Missing values for the P-selectin inhibition will not be imputed and will be treated as missing.

Details of the imputations rules for missing start and end dates or AE will be provided in the SAP.

10.4.4 Supportive and Sensitivity analyses

Part A:

Not Applicable.

Part A and B:

Not Applicable.

10.5 Secondary objectives

The secondary objectives are to assess the Long-term efficacy of crizanlizumab and to assess other safety measures in 2 to < 18 year old participants.

10.5.1 Key secondary objective(s)

Not Applicable.

10.5.2 Other secondary efficacy objectives

VOC

VOC includes pain crises (defined as an acute onset of pain for which there is no other medically determined explanation other than vaso-occlusion and which requires therapy with oral or

parenteral opioids or parenteral NSAID) as well as other complicated crises, such as ACS, priapism, and hepatic or splenic sequestration. The occurrence of VOC events will be recorded in the case report form.

The number of VOCs leading to healthcare visit in clinic/ER/hospital will be summarized descriptively by age group in the FAS. The number of participants with 0 events will be presented. Summaries will be provided for the corresponding annualized rate of VOC leading to healthcare visit in clinic/ER/hospital overall and per year.

$$Annualized\ rate\ of\ VOC = \frac{\text{Number of VOC reported until End date } \times 365.25}{\text{End date} - \text{date of first dose of study treatment} + 1}$$

where End date is defined as the minimum of (last dose date until treatment discontinuation + 27 days, date of 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, cut-off date).

The change from baseline of the annualized rate of VOC leading to healthcare visit in clinic/ER/hospital will be provided overall and per year and corresponding figures (e.g., spaghetti plot) may be proposed in the analysis plan. The baseline annualized rate of VOC will be defined as the number of VOCs leading to healthcare visit reported in the last 12 months in the eCRF.

Despite all attempt to ensure complete follow-up for all participants, some participants may not be followed for VOC for the whole planned study duration. The annualized rate of VOC calculation will account for early discontinuation by extrapolating the VOC rate of every participant to one year. All VOC occurring until the End date will be taken into account in the summaries. If a participant initiates or discontinues HU/HC or L-glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) during the study, VOC occurring after the initiation/discontinuation of such therapy will not be taken into account in the analyses. A sensitivity analysis will be performed, including the crises post initiation/discontinuation of HU/HC or L-glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) in the numerator and the corresponding duration of extra follow-up in the denominator

Subgroup analyses will be performed by HU/HC use at time of study entry and number of VOC leading to healthcare visit at baseline.

The same analyses will be repeated for the number of VOCs treated at home based on documentation by health care provider following phone contact with participant, for the number of VOCs leading to healthcare visit and treated at home combined and for each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism) leading to healthcare visit in clinic/ER/hospital and treated at home combined or separately.

Time to first occurrence of VOC will be summarized by age group using Kaplan-Meier methods. Median time, 25th and 75th percentiles will be summarized and Kaplan-Meier plots will be generated. The time to first occurrence of VOC will be defined as the time from the date of the first dose of study treatment to the date of the first occurrence of the VOC. In the absence of a VOC, participants will be censored.

Dactylitis

The number of dactylitis events will be summarized descriptively in the FAS for participants from 2 to < 6 years of age (Group 3). Summaries will be provided for the corresponding annualized rate of dactylitis events overall and per year, defined in the same way as the annualized rate of VOC. The change from baseline of the annualized rate of dactylitis events will be provided and corresponding figures may be proposed in the analysis plan.

Subgroup analyses will be performed by HU/HC use, number of dactylitis at baseline.

Hospitalization

The number of hospitalizations and ER visits (both overall and VOC-related) will be summarized descriptively by age group in the FAS. Summaries will be provided for the corresponding annualized rate of hospitalizations and ER visits overall and per year, defined in the same way as the annualized rate of VOC. The change from baseline of the annualized rate will be provided and corresponding figures may be proposed in the analysis plan.

Subgroup analyses will be performed by HU/HC use.

The number of days of ER/hospitalization (both total and VOC-related) will be summarized descriptively by age group in the FAS. Summaries will be provided for the corresponding annualized rate of days hospitalized overall and per year.

Chest X-ray

The data on the chest X-ray will be listed and notable findings will be flagged.

10.5.3 Other safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by age group. If the target dose is different within a given age group (dose not confirmed in Part A for the participants enrolled) then the safety analyses may be repeated by starting dose within each age group for key selected analyses

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

- pre-treatment period: from day of participant's informed consent to the day before first dose of study medication
- 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)
- 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 post-trial access).

10.5.3.2 Adverse events (AEs)

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

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

Serious adverse events, non-serious adverse events and 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.

10.5.3.3 Laboratory abnormalities

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

In addition to the above mentioned tables and listings, [redacted], 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 liver function tests will be performed and described in the analysis plan.

10.5.3.4 Other safety data

ECG

12-lead ECGs including PR, QRS, QT, QTcF, QTcB, RR 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.

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

Vital signs

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

Growth and sexual maturation

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

10.5.3.5 Tolerability

Refer to Section 10.5.3 and Section 10.5.8.

10.5.4 Pharmacokinetics and Pharmacodynamics

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters defined in Table 10-1 except Tmax. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter, where only n, median, minimum and maximum will be presented. Zero concentrations will not be included in the geometric mean calculation. This summary will be provided by weight-adjusted dose and by group for the PAS1 and by weight-adjusted dose and by age group for the PAS2.

PK 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.

Table 10-1 Noncompartmental pharmacokinetic and pharmacodynamic parameter

AUCd15	The AUC from time zero to the last measurable concentration sampling time (tlast) or dosing interval (mass x time x volume-1) following the first dose
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
PD-AUCd15	The AUC of %inhibition from time zero to the last measurable inhibition sampling time (tlast)following the first dose
PD-AUCtau	The AUC of %inhibition calculated to the end of a dosing interval (tau) after multiple dose
Cmax	The maximum (peak) observed, serum, drug concentration after single or multiple dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak), serum, drug concentration after single or multiple dose administration (time)

Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1)
T1/2	The half-life during a dosing interval (time).

The following analyses will be done by weight-adjusted dose and by age group.

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

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

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

Descriptive statistics for P-selectin inhibition will be presented at each scheduled time point.

All individual inhibition-time profiles with median will be displayed graphically on semi-log view after single and multiple doses respectively. 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.

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

10.5.4.1 Data handling principles

Refer to Section 10.4.3

[redacted]

10.5.6 Resource utilization

Refer to Section 10.5.2

10.5.7 Patient-reported outcomes

Not Applicable.

10.5.8 Immunogenicity

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

[redacted]

[redacted]

[redacted]

10.7 Interim analysis

No formal interim analysis is planned for this trial.

10.8 Sample size calculation

For sample size consideration, PK and PD data from Study SEG101A2101 were used. Estimated inter-patient geometric mean coefficient of variation (CV%) of AUCinf, AUClast and Cmax for the 5 mg/kg participants were 21.1%, 11.9% and 15.8%, respectively. For the following sample size considerations, a CV% of 21.1% will be assumed for the main PK criterion.

For the Part A PK objective, when the sample size for this dose group is 6, a two-sided 90% confidence interval for a single mean will extend 0.140 from the observed mean, ensuring a 15% precision of the 90% confidence interval, assuming that the standard deviation is known to be 0.209 and the confidence interval is based on the large sample z statistic. Assuming a drop-out rate of 15% to 25% for the intensive PK part, at least 8 participants will be enrolled to each group to ensure 6 evaluable participants for characterization of crizanlizumab PK.

Given the small sample size a sensitivity calculation based on the t-distribution reveals an acceptable precision of the two-sided 90% confidence interval for a single mean of 0.17 assuming that the standard deviation is known to be 0.209.

Currently, the inter-patient variation of the P-selectin inhibition at 5 mg/kg and the respective area under the inhibition curve is not known. However, approximations utilizing results from lower dose groups tested in Study SEG101A2101 suggest an inter-patient coefficient of variation of approximately 34.1%.

For the Part A+B PK/PD objective, when the sample size is 22, a two-sided 95.0% confidence interval for a single mean of log transformed PD-AUC will extend 0.140 from the observed mean, ensuring a 15% precision and assuming that the standard deviation is known to be 0.332 and the confidence interval is based on the large sample z statistic

Assuming a dropout rate of 15% for the sparse sampling part, at least 26 participants in Group 1 and 2 are needed to be enrolled.

For the Parts A+B safety objective of this study, no formal statistical power calculations to determine sample size were performed. For the primary analysis of the groups 1 (12-<18 years) and 2 (6-<12 years), statistical computations were performed to evaluate probabilities to detect at least one participant with an AE given the range from 52 to 86 participants. Table 10-2 provides probability with a reasonable chance to detect AEs occurring with different scenarios of AE incidence rates. With a range from 52 to 86 participants, there is a probability ranged from 80% to 93% of detecting adverse events with incidence rate of 3% or higher, which will allow assessment of the primary safety analysis for Parts A and B of groups 1 and 2 based on the Rule of Three (Hanley, Lippman-Hand 1983). For the primary safety analysis of group 3, no statistical computation was performed to assess the sample size. Based on the objective

of the Part A and feasibility of enrollment in this younger age group, at least 8 participants will be enrolled.

Table 10-2 Probability to observe at least one AE for different incidence rates

Incidence rate of an AE	Probability that at least one participant out of 52 experiences the AE	Probability that at least one participant out of 86 experiences the AE
1%	0.41	0.58
2%	0.65	0.82
3%	0.79	0.93
4%	0.88	0.97
5%	0.93	0.99

10.9 Power for analysis of key secondary variables

Not Applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, EU CTR 536/2014 once transfer is completed, US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

Before initiating a trial, the trial protocol, the proposed informed consent/assent forms, any participant recruitment procedures (e.g., advertisements) and any other written information provided to the participant, must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB).

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Protocols and any substantial amendments/modifications to the protocol may require Health Authority approval (as per local regulations) prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Informing Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

11.3 Informed consent procedures

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and/or their legally authorized representative and answer all questions regarding the study. Participants must be informed that their participation is voluntary.

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

In cases where the participant's representative(s) gives consent, the participant must be informed about the study to the extent possible given his/her level of understanding.

Informed consent / assent as per local regulations must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the participant source documents. The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. The date when a participant's Informed Consent was actually obtained will also be captured in their CRFs. A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

Novartis will provide to investigators, in a separate document, a proposed ICF that is considered appropriate for this study and complies with the requirements of 21 CFR 50, local regulations, ICHE6 Good Clinical Practice (GCP) guidelines, privacy and data protection requirements, where applicable and regulatory requirements and is considered appropriate for this study. Any changes to this ICF suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

The main ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will have this documented.

As per Section 2.7, during a Public Health emergency as declared by Local or Regional authorities (i.e. pandemic, epidemic or natural disaster) that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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 for parents / legal guardians to give consent for their child
- Main Study Consent for participants entering adulthood

Both Main Study Consents include 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 and an 'Optional consent for activities that may be done outside of the study site'.

- Model Participant Information and Adolescent Assent 12-17 years old
- Model Participant Information and Adolescent Assent 7-11 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 pregnant participants

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

11.4 Data Protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

11.5 Discontinuation of the study

The study can be terminated by Novartis at any time.

Reasons for earlier termination may include but not limited to:

- Major safety reasons: unexpected, significant, or unacceptable safety risk to participants enrolled in the study.
- Decision based on recommendations from applicable board(s) after review of safety
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be decided, participants must be seen as soon as possible (please refer to Section 7.1) and treated as a participant who discontinued from study treatment The investigator will be informed of any additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

11.6 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g., clinicaltrials.gov and as required in EudraCT before study start. In addition, results of this interventional clinical trial will be submitted for publication and posted on a publicly accessible database of clinical study results such as the Novartis clinical trial results website (novartisclinicaltrials.com) and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT or CTIS (Clinical Trials Information System) public website once transfer to EU CTR 536/2014 is completed, etc.) after study completion (i.e., Last Participant Last Visit (LPLV)) and finalization of the study report.

Novartis follows the International Committee of Medical Journal Editors (ICMJE) authorship guidelines (icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

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

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and

potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

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

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

Summary results of primary and secondary endpoints will be disclosed based on the global LPLV date, since multinational studies are locked and reported based upon the global LPLV.

11.7 Study documentation, record keeping and retention of documents

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

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

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

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

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

11.8 Confidentiality of study documents and participants records

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

11.9 Audits and inspections

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

11.10 Financial disclosures

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

12 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 the study treatment 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. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

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

Only amendments that are required for participant safety may be implemented immediately, without prior approval by relevant authorities, provided the Health Authorities and reviewing

IRB/EC are notified and the safety measure is implemented subsequently in a protocol amendment.

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.

13 References (available upon request)

Akinsheye I, Alsultan A, Solovieff N, et al (2011) Fetal hemoglobin in sickle cell anemia. Blood; 118(1): 19-27.

Al Najjar S, Adam S, Ahmed N, et al. (2017) Ann Hematol 96:141–146.

Ashley-Koch A, Yang Q, Olney RS (2000) Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. Am J Epidemiol; 151(9):839-45.

Ataga KI, Kutlar A, Kanter J (2017) Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med; 376 (5): 429-439.

Blann AD, Mohan JS, Bareford D, et al (2008) Soluble P-selectin and vascular endothelial growth factor in steady state sickle cell disease: relationship to genotype. J Thromb Thrombolysis; 25(2):185-9.

Bookchin RM, Lew VL (1996) Pathophysiology of sickle cell anemia. Hematol Oncol Clin North Am; 10(6):1241-53.

Brandow AM, Carroll CP, Creary S, et al. (2020) American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Advances; 4(12): 2656-701.

Chai J, Song Q. (2014) Quantitative and multiplexed study of endothelial cell inflammation. Cell Biochem Biophys; 70(3):1783-90.

Charache S (1996) Eye disease in sickling disorders. Hematol Oncol Clin North Am; 10(6):1357-62.

Charache S, Terrin ML, Moore RD, et al (1995) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Eng J Med; 332(20):1317-22.

Chiang EY,Frenette PS (2005) Sickle cell vaso-occlusion. Hematol Oncol Clin North Am; 19(5):771-84 v.

Colombatti R, De Bon E, Bertomoro A, et al (2013) Coagulation activation in children with sickle cell disease is associated with cerebral small vessel vasculopathy. PLoS One; 25; 8(10):e78801.

Embury SH (2004) The not-so-simple process of sickle cell vaso-occlusion. Microcirculation; 11(2):101-13.

Ferroni P, Riondino S, Vazzana N, et al (2012) Biomarkers of platelet activation in acute coronary syndromes. Thromb Haemost; 108(6):1109-23.

Frenette PS (2004) Sickle Cell Vaso-occlusion: Heterotypic, Multicellular Aggregations Driven by Leukocyte Adhesion. Microcirculation; 11(2): 167-177.

Geng JG, Bevilacqua MP, Moore KL, et al (1990) Rapid neutrophil adhesion to activated endothelium mediated by GMP-140. Nature; 343(6260):757-60.

Gill FM, Sleeper LA, Weiner SJ, et al (1995) Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. Blood; 86 (2): 776-83.

Gladwin MT, Kato GJ (2005) Cardiopulmonary complications of sickle cell disease: role of nitric oxide and hemolytic anemia. Hematology Am Soc Hematol Educ Program: 51-7.

Gladwin MT, Sachdev V, Jison ML, et al (2004) Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med; 350(9): 886-95.

Hamburger SA, McEver RP (1990) GMP-140 mediates adhesion of stimulated platelets to neutrophils. Blood. 75(3): p. 550-4.

Hanley JA, Lippman-Hand A (1983), If Nothing goes wrong, is everything all right? JAMA; 249 (13): 1743-1745.

Hatzipantelis ES, Pana ZD, Gombakis N et al, (2013) Endothelial activation and inflammation biomarkers in children and adolescents with sickle cell disease, Int J Hematol 98:158–163

Heegaard ED, Brown KE (2002) Human parvovirus 819. Clin Microbial Rev; 15(3):485-505.

Hirschberg R (2010) Glomerular Hyperfiltration in Sickle Cell Disease. Clin J Am Soc Nephrol; 5:748-9.

Inwald DP, Kirkham FJ, Peters MJ, et al (2000) Platelet and leucocyte activation in childhood sickle cell disease: association with nocturnal hypoxaemia. Br J Haematol; 111(2):474-81.

Jones DA, Abbassi O, McIntire LV, et al (1993) P-selectin mediates neutrophil rolling on histamine- stimulated endothelial cells. Biophys J; 65(4): p. 1560-9.

Kanavaki I, Makrythanasis P, Lazaropoulou C, et al. (2012) Adhesion molecules and high-sensitivity C-reactive protein levels in patients with sickle cell beta-thalassaemia. Eur J Clin Invest; 42(1):27-33.

Kaul DK,Hebbel RP (2000) Hypoxia/reoxygenation causes inflammatory response in transgenic sickle mice but not in normal mice. J Clin Invest; 106(3):411-20.

Krishnan S, Setty Y, Betal SG, et al. (2010) Increased levels of the inflammatory biomarker C-reactive protein at baseline are associated with childhood sickle cell vasocclusive crises. Br J Haematol; 148(5):797-804.

Kutlar A, Embury SH (2014) Cellular adhesion and the endothelium: P-selectin. Hematol Oncol Clin North Am; 28(2):323-39.

Liu Z, Miner JJ, Yago T, et al (2010) Differential regulation of human and murine P-selectin expression and function in vivo. J Exp Med; 207(13): p. 2975-87.

Maitre B, Habibi A, Roudot-Thoraval F, et al (2000) Acute chest syndrome in adults with sickle cell disease. Chest; 117(5):1386-92.

Majumdar S, Webb S, Norcross E, et al. (2013) Stroke with intracranial stenosis is associated with increased platelet activation in sickle cell anemia. Pediatr Blood Cancer; 60(7):1192-7.

Matsui NM, Borsig L, Rosen SD, et al (2001) P-selectin mediates the adhesion of sickle erythrocytes to the endothelium. Blood; 98(6):1955-62.

McClish DK, Penberthy LT, Bovbjerg VE, et al. (2005) Health related quality of life in sickle cell patients: The PiSCES project. Health and Quality of Life Outcomes; 3: 50.

McEver RP, Moore KL, Cummings RD (1995) Leukocyte trafficking mediated by selectincarbohydrate interactions. J Biol Chem; 270(19): 11025-8.

McEver RP (2004) Interactions of selectins with PSGL-1 and other ligands. Ernst Schering Res Found Workshop; (44): 137-47.

Mehta P, Cummings RD, McEver RP (1998) Affinity and kinetic analysis of P- selectin binding to P-selectin glycoprotein ligand-1. J Biol Chem; 273(49): 32506-13.

Miller et al (2000) Prediction of adverse outcomes in children with sickle cell disease. N Eng J Med; 342(2):83-89.Miura M, Garcia FL, Crawford SE, et al. (2004) Cell adhesion molecule expression in coronary artery aneurysms in acute Kawasaki disease. Pediatr Infect Dis J; 23(10):931-6.

NHLBI (2002) The Management of Sickle Cell Disease. NIH Publication No.022117

Nietert PJ, Silverstein MD, Abboud MR (2002) Sickle cell anaemia: epidemiology and cost of illness. Pharmacoeconomics; 20(6):357-66.

NIH (2008) NIH State-of-the-Science Conference Statement on Hydroxyurea Treatment for Sickle Cell Disease. NIH Consensus and State-of–the-Science Statements; February 25-27, 2008. Vol. 25.

Okpala I (2006) Leukocyte adhesion and the pathophysiology of sickle cell disease. Curr Opin Hematol; 13(1):40-4.

Platt OS, Thorington BD, Brambilla DJ, et al. (1991) Pain in sickle cell disease. Rates and risk factors. N Engl J Med; 325:11–16

Platt OS (2006) Prevention and management of stroke in sickle cell anemia. Hematology Am Soc Hematol Educ Program; 2006:54-7.

Platt OS, Brambilla DJ, Rosse WF, et al (1994) Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med; 330(23):1639-44.

Pryce JW, Bamber AR, Ashworth MT, et al. (2014) Immunohistochemical expression of inflammatory markers in sudden infant death; ancillary tests for identification of infection. J Clin Pathol; 67(12):1044-51.

Quinn CT, Lee NJ, Shull EP, et al (2008) Prediction of adverse outcomes in children with sickle cell anemia: a study of the Dallas Newborn Cohort. Blood; 111:544–548.

Rees DC, Williams TN, Gladwin MT (2010) Sickle-cell disease. Lancet; 376: 2018-31.

[redacted]

Ruf A, Pick M, Deutsch V, et al. (1997) In-vivo platelet activation correlates with red cell anionic phospholipid exposure in patients with beta-thalassaemia major. Br J Haematol; 98(1):51-6.

Saborio P, Scheinman JI (1999) Sickle cell nephropathy. J Am Soc Nephrol; 10(1):187-92.

Setty BN, Key NS, Rao AK, et al. (2012) Tissue factor-positive monocytes in children with sickle cell disease: correlation with biomarkers of haemolysis. Br J Haematol; 157(3):370-80.

Sickle Cell Disease Guideline Panel. Sickle Cell Disease: Screening, Diagnosis, Management and Counseling in Newborns and Infants. Clinical Practice Guideline No. 6. AHCPR Pub. No. 93 0562. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U. S. Department of Health and Human Services. April 1993.

Smith WR, Penberthy LT, Bovbjerg VE et al. (2008) Daily assessment of pain in adults with sickle cell disease. Ann Int Med; 148: 94-102.

Souza Jd, Sousa JR, Hirai KE, et al. (2015) E selectin and P-selectin expression in endothelium of leprosy skin lesions. Acta Trop; 149:227-31.

Springer TA (1995) Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. Annu Rev Physiol; 57: 827-72.

Stuart MJ, Nagel RL (2004) Sickle-cell disease. Lancet; 364 (9442): 1343-60.

Thomas PW, Higgs DR, Serjeant GR (1997) Benign clinical course in homozygous sickle cell disease: a search for predictors. J Clin Epidemiol; 50(2):121-6.

Vestweber D, Blanks JE (1999) Mechanisms that regulate the function of the selectins and their ligands. Physiol Rev; 79(1): 181-213.

Vichinsky EP, Neumayr LD, Earles AN, et al (2000) Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Eng J Med; 342(25):1855-65.

Wagner MC, Eckman JR, ick TM (2006) Histamine increases sickle erythrocyte adherence to endothelium. Br J Haematol. 132(4): p. 512-22.

Wethers, DL (2000) Sickle cell disease in childhood: Part II. Diagnosis and treatment of major complications and recent advances in treatment. Am Fam Physician; 62(6):1309-14.

Wood, K., Russell J, Hebbel RP, et al (2004) Differential expression of E- and P-selectin in the microvasculature of sickle cell transgenic mice. Microcirculation. 11(4): p. 377-85.

Yale SH, Nagib N, Guthrie T (2000) Approach to the vaso-occlusive crisis in adults with sickle cell disease. Am Fam Physician; 61(5):1349-56, 1363-4. aafp.org/afp/2000/0301/p1349.html.

Yip C, Linden MD, Attard C, et al. (2015) Platelets from children are hyper-responsive to activation by thrombin receptor activator peptide and adenosine diphosphate compared to platelets from adults. Br J Haematol; 168(4):526-32.

14 Appendices

14.1 Appendix 1 - Karnofsky performance Status

Table 14-1 Karnofsky performance status scale rating (10%) criteria

Condition	Percentage	Comments
Able to carry on normal activity and to work; no special care needed.	100	Normal, no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death not imminent.
	20	Very sick; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

14.2 Appendix 2 – The Lansky Play-Performance Status Scale Clinical Classification

Table 14-2 The Lansky Play-Performance Status Scale Clinical Classification rating (10%) criteria

Rating	Description
100	fully active, normal
90	minor restrictions with strenuous physical activity
80	active, but gets tired more quickly
70	both greater restriction of, and less time spent in, active play
60	up and around, but minimal active play; keeps busy with quieter activities
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	mostly in bed; participates in quiet activities
30	stuck in bed; needs help even for quiet play
20	often sleeping; play is entirely limited to very passive activities
10	does not play nor get out of bed
0	unresponsive