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[SEG101/Crizanlizumab]

Clinical Trial Protocol CSEG101AUS05 / NCT03938454

A Prospective Phase II, Open-Label, Single-arm, Multicenter, Study to Assess Efficacy and Safety of SEG101 (crizanlizumab), in Sickle Cell Disease Patients with Priapism (SPARTAN)

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List of abbreviations

ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
CI	Confidence interval
CK	Creatinine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse events
CV	coefficient of variation
DDE	Direct Data Entry
DILI	Drug Induced Liver Injury
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EOI	End of Infusion
EOT	End of treatment
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
[redacted]	[redacted]
HSV	Herpes simplex virus
HU/HC	Hydroxyurea/hydroxycarbamide
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-related Reaction
IRT	Interactive Response Technology
IV	Intravenous
LFT	Liver function test
LPT	Low Platelet Count
LLN	Lower Limit of Normal
LVEF	Left ventricular ejection fraction

[redacted]

MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
NOAEL	No observed adverse effect level
PAP	Pulmonary Arterial Pressure
PD	Pharmacodynamic(s)
[redacted]	[redacted]
PLT	Platelet
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PSGL-1	P-selectin glycoprotein ligand 1
PT	Prothrombin time
QTcF	QT interval corrected by Fridericia's formula
RAP/SAP	The Report and Analysis Plan (RAP) is a regulatory document which documents preplanned statistical analyses
RBC	Red blood cell(s)
RVSP	Right ventricular systolic pressure
SAE	Serious Adverse Event
SCD	Sickle cell disease
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBIL	Total bilirubin
TEAEs	Treatment emergent adverse events
TRV	Tricuspid Regurgitant Jet Velocity
ULN	Upper limit of normal
USAN	United States Adopted Name
VOC	Vaso-occlusive crisis
WBC	White blood cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. screening, treatment, follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

[redacted]

Run-in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's intervention or treatment)
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures.
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 3 (16-Dec-2022)

At the time of this amendment, the required number of 36 patients for the study has been reached. The study is closed to further enrollment.

The primary purpose of this amendment is to clarify some statistical elements used to evaluate the study. In particular, the following points were addressed in the current protocol:

1. Section 2.1 was added to describe the primary estimand by the following attributes:
    a. Population: Sickle Cell Disease patients with priapism.
    b. Endpoint: Percent reduction from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks.
    c. Treatment of interest: investigational drug will be a crizanlizumab solution provided every 4 weeks with an additional loading dose 2 weeks after the first dosing.

[redacted]

d. List of intercurrent events:

i. Treatment discontinuation

ii. 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) or of prophylactic treatment

iii. Intake of analgesic (including opioids) or ad hoc transfusions administered temporarily.

e. The summary measure: Median percentage change from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks.

2. It was clarified that a formal interim analysis for this study is not planned, shall not be performed and that for publication purposes, only descriptive data will be reported, as needed.
3. It was clarified that the FAS include all enrolled subjects to whom the study treatment has been assigned regardless of whether or not they have received at least 1 dose of study treatment or have at least 1 post-baseline assessment.
4. Lower quartile (Q1) and upper quartile (Q3) were included in the summary statistics
5. The handling of missing values was described. It will be imputed using Poisson distribution, assuming the same effect as observed data. Imputed datasets will be created, and each dataset will be analyzed using the method described for primary endpoint. The results will be combined using Rubin's rule (Barnard J and Rubin DB 1999)
6. Sensitivity analyses were modified to include the following:
    a. To explore the robustness of analysis, sensitivity analysis as a 'tipping point approach will be performed for the primary endpoint to evaluate the impact of a deviation from the missing at random (MAR).
    b. As part of the sensitivity analysis, treatment policy strategy (that is, data after the intercurrent events will be included) will also be applied for the intercurrent events 4a and 4b, described in Section 12.4.2.
    c. As part of the sensitivity analysis, the primary analysis will be analyzed on all subjects in FAS without missing data.
7. It was clarified that the assumption that the relative risk reduction of 25% (approved for VOC events) observed with L-glutamine (Endari™) would be similar for priapism was used for the purpose of study sample size calculation.

Other minor corrections are also applied throughout the protocol.

Changes to the Protocol

- Throughout: typographical and grammatical errors addressed.

[redacted]

- **List of abbreviations:** AUC, AUCinf, AUCt, C_{max}, $t_{1/2}$ are not required and were removed. IV was added.
- **Glossary of terms:** The definitions of estimand and Intercurrent events were added. "Randomization number" is not required as this is a single-arm study and was removed.
- Section 2.1:
    - Section added to define what an estimand is. Language was added to describe the attributes of the primary estimand for this study: population, endpoint, treatment of interest, list of intercurrent events and the summary measure. Correspondingly similar changes were made in Section 12.4.2.
- Section 4.4:
    - Language was added to clarify that for publication purposes, descriptive data will be reported and that any decision on study continuation will not be based on the reports. Correspondingly similar changes were made in Section 12.8.
    - Changed the word patient to subject when the term refers to a participant of this study. Correspondingly similar changes were made throughout the protocol as appropriate.
- Section 6.3.2:
    - Language was added to clarify that the trial is a single arm study.
- Section 9.2:
    - Language was added to specify that the recommendation applies to "subjects who will receive commercially approved crizanlizumab".
- Section 12:
    - Included lower quartile (Q1) and upper quartile (Q3) in the summary statistics. Correspondingly similar changes were made in Sections 12.2, 12.3, 12.4.2 and 12.5.2.
    - Definition of the baseline period was clarified by removing the minus sign before 12 weeks and correcting "from" with "prior to".
- Section 12.1:
    - The definition of the FAS was corrected to: The FAS include all enrolled subjects to whom the study treatment has been assigned regardless of whether or not they have received at least 1 dose of study treatment or have at least 1 post-baseline assessment.
- Section 12.3:
    - Duration of exposure will be assessed in weeks rather than days to align with other Novartis SEG101 studies.
- Section 12.4.1:

[redacted]

- The sentence "The primary time point is week 26" was deleted as it was redundant given the previous sentence.

- Section 12.4.2:
  - The <7 category was included as a new number of priapic events category in a subgroup analysis of the primary endpoint.
  - The approach of accounting for the intercurrent events 4a, 4b and 4c was defined.
- Section 12.4.3:
  - This section was modified to specify that missing values will be imputed using Poisson distribution and imputed datasets will be created with each dataset analyzed using the method described for primary endpoint. The results will be combined using Rubin's rule.
- Section 12.4.4:
  - This section was re-written to outline a new sensitivity analysis as a 'tipping point approach will be performed for the primary endpoint to evaluate the impact of a deviation from the MAR assumption.
  - The titles of the two subsections were removed. The paragraph related to the Annualized Priapic Event Rate was kept under "Supportive Analyses" and the paragraphs on the COVID-19 sensitivity analyses were moved in the upper part of Section 12.4.4.
- Sections 12.5.1 and 12.5.2:
  - The words "(i.e. evaluation at Week 27, Day 1)" and "(i.e. evaluation at Week 53, Day 1)" were deleted after "by week 26" and "by week 52" respectively.
- Section 12.6.1:
  - The words "or not" were removed.

[redacted]

- Section 12.8:
  - Sentence was added to specify that no decision on study continuation will be based on these descriptive reports, and as such, no alpha adjustment will be needed.
  - The paragraph on the primary analysis was removed for clarity. Similar information was already detailed in Section 12.4.
- Section 12.9:

[redacted]

- The paragraph related to the basis of the calculations was moved earlier on in the section.
- Two sentences , referring the risk reduction of Endari™ were added

- Section 15:
  - References from Barnard and co; Edmond and co, Ratich and co as well as the ICH E9(R1) guideline were added.

Amendment 2 (16-Dec-2021)

At the time of this amendment, 25 patients have been enrolled in the study.

The primary purpose of this amendment is described below:

1. Modify selected Exclusion Criteria including:

- Exclusion Criteria #8: Use of therapeutic anticoagulants or antiplatelet therapy (other than aspirin or NSAIDs) within 10 days prior to Week 1 Day 1. Prophylactic anticoagulant dose is now permitted, as per local guidelines.
- Exclusion Criteria #10: Patients who have received crizanlizumab and/or other selectin inhibitor or plan to receive it during the duration of the study will be excluded.
- Exclusion Criteria #22: It was changed timing of "malignancies that were treated curatively and have not recurred within... " from 2 years to 3 years, to align with program guidelines.

2. The study design was changed to lower the age of inclusion to 12 years old. A large review of published literature cases reported that approximately half of all reported events of priapism in patients with sickle cell disease had their first episode before 18 years of age (Rogers et al 2005; Hamre et al 1991). An interview survey of male patients with sickle cell disease reported that there was a prevalence of priapism of 27.5% by 15 years of age and reported literature calculated actuarial probability of 50.5% of experiencing priapism by the age of 15 years. (Mantadakis et al 1999; Rogers et al 2005). The safety and the PK analysis of crizanlizumab was evaluated as part of the CSEG101B2201 trial in 50 participants aged 12 to <18 years of age. The dose of 5 mg/kg was confirmed in this group based on the results of the first dose PK analysis and the CSEG101B2201 data monitoring committee did not raise any particular safety concerns with this dose in this age group.
3. Due to challenges identifying and recruiting adequate population at sites, the statistical power of the study will be changed from 90% to 80% in Section 12.9, which reduces the number of evaluable patients from 44 to 34. The anticipated drop-out rate for the study is also revised from 20% to 5% based on the current status of the trial, which reduces the targeted number of enrolled patients from 56 to 36 (Section 12.9).
4. The baseline for the primary analysis will be changed from a combination of the 14-weeks pre-screening period plus the 12-weeks screening period to only the 12 weeks of the screening period. The change is prompted by the observed difficulties for patients and site to accurately recall and collect all the required information on the

[redacted]

priapic events during the pre-screening period resulting in inconsistent data quality between patients and sites. The number of pre-screening priapic events to qualify for the study (4) will remain the same. The change will also ensure consistency between the priapic event reporting methods for the baseline period and the treatment period (Section 12).

5. Specify that the subjects who will receive commercially approved crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up.
6. The recommendations for handling of study treatment in case of active or suspected COVID-19 infection were added in Section 6.5.
7. In the laboratory assessments, the word "albumin" was deleted from Table 8.4 to clarify the panel.

Other minor corrections are also applied throughout the protocol.

Changes to the Protocol

- Throughout: typographical and grammatical errors addressed.
- Protocol Summary: updated in alignment to the protocol sections updated.
- Section 1.1.1:
  - Updated list of treatments to include voxelotor.
- Section 1.2.1:
  - Updated approval information language and deleted "non-clinical experience" to reflect the fact that the information can be found in the IB.
- Section 1.2.2:
  - Deleted the "clinical experience" related to CSEG101A2101, CSEG101A2102 and CSEG101A2202 and CSEGB2201 to reflect the fact that the most updated information can be found in the IB.
- Section 1.3:
  - Updated baseline duration from 26 weeks to 12 weeks. Correspondingly, similar language was added in Section 3 and Section 12.
- Section 3:
  - The total number of patients to be eligible for the study was updated from 56 to 36 patients. Correspondingly this number was also changed in Figure 3-1 Study Design, Section 5, and 12.9 Sample size calculation.
  - Study duration language changed from 'will be 79 weeks' to 'will be up to 79 weeks' - in parentheses, '15 weeks of follow-up period' was changed to '15 weeks of follow-up period if applicable': Correspondingly, the study duration was changed in Follow-up phase and Figure 3-1 Study Design.

[redacted]

- Removed the phrase 'Mandatory safety follow-up period' and replaced with 'followed for safety for up to...'.
- Added a paragraph to clarify the follow-up period for subjects who receive commercially approved crizanlizumab after study treatment. Correspondingly, a footnote was added in Table 8.1 to clarify "as applicable".
- Pre-screening: The date, number, and duration of the priapic events in a 14-week period required prior to consenting was added to clarify the purpose of the form. Correspondingly, a footnote was added in the visit evaluation schedule (Table 8.1).

- Section 4.2:
  - Added reference to study CSEG101B2201 to support dosage of 5 mg/kg.
- Section 4.5:
  - Updated section on infusion-related reactions (IRRs) according to IBv11: percentages of certain events changed, events 'hypertension' and 'dizziness' were added.
  - Infections percentages updated based on IBv11.
  - Effect on hemostasis updated: 'decreased hemoglobin, and epistaxis' added; reference to eligibility criteria and permitted/prohibited concomitant medications removed.
  - Laboratory test interference with automated platelet counts: deleted language on mitigation of the laboratory test interference.
  - Changed the world participant to subject for language harmonization. Correspondingly similar changes were made in Section 6.2.1.3, Table 6.2, Section 12.4.4 and Section 14.
  - Statement added on how Novartis finds risk-benefit ratio favorable.
  - Small paragraph on risk for patients due to COVID-19 vaccine added.
- Section 5.1:
  - Inclusion criteria #2: Age of inclusion language changed from 16 to 12 years old. Correspondingly, the minimum age was changed to 12 in Section 3, Figure 3.1 and Section 5.
- Section 5.2:
  - Exclusion Criteria # 3 – added '(Lupron) or any other gonadotropin-releasing hormone receptor (GnRHR) agonist agents'.
  - Exclusion Criteria # 8 original – deleted use of therapeutic anticoagulants.
  - New Exclusion Criteria # 8is 'received crizanlizumab' to reflect already existing language in Section 6.2.2.

[redacted]

- Exclusion Criteria #10 – deleted original criteria and changed to 'received other selectin inhibitor or plans to receive it during the duration of study. To reflect the fact that another experimental selectin inhibitor is being developed.
- Exclusion Criteria #22 – revision in timeline for exception to malignant disease: 'malignancies that were treated curatively and have not recurred within 2 years' changed to 'malignancies that were treated curatively and have not recurred within 3 years to align with other SEG101 clinical trial protocols.

- Section 6.2.1.1:
  - Change in timeline for notifying investigational site about any new medications taken with 30 days prior to initial dosing from 'until the completion of (EOS)' to 'until the safety follow-up or EOT-visit as applicable' throughout the section. Correspondingly, similar changes were also made in Section 6.5.1, Section 9.1.1, Section 9.2, Section 10.1.1, Section 10.1.4 and Section 12.6.
  - Language on 105-day follow-up timeline removed.
  - Sentence starting with 'Aspirin, NSAIDs and prophylactic doses...' changed: 'should be used with caution (refer to Section 6.2.1.3)' added at the end to reflect the fact that anticoagulants at doses targeting therapeutic levels are no longer prohibited. Correspondingly, a new sentence was added in Section 6.2.1.3.
- Section 6.2.1.3:
  - Clarification that the decision to administer or withhold a vaccine should be done on case-by-case basis.
- Section 6.2.2:
  - Corrected that patients who have received a monoclonal antibody or an immunomodulatory agent within 1 year of screening or have documented immunogenicity to a prior biologic are not allowed to participate as per Exclusion criteria #9.
- Section 6.5:
  - The discontinuation rules for patients missing 2 consecutive doses were clarified: initially said patient should be discontinued; changed to 'if a subject misses two consecutive doses of crizanlizumab due to ADR (i.e., an AE attributable to study drug), the subject should be discontinued from crizanlizumab. In addition, the criteria for subjects experiencing IRR already present in Table 6-2 was inserted in the text: A subject with Grade 3 or 4 IRR will be permanently discontinued from crizanlizumab.'
  - Added crizanlizumab program language on course of treatment for patients with confirmed active COVID-19 or presenting symptoms of COVID-19.
- Table 6-2:
  - Infusion-related reactions: clarified first recommendation in grade 2 AE from "interrupt infusion and increase monitoring …" to "temporarily interrupt infusion and increase monitoring…"

[redacted]

- Section 6.7.1:
    - Clarified the monitoring visits related to drug accountability – will be performed by field monitors during onsite / remote visits and at completion of trial.
    - Clarified the language on end of study drug disposition - "at the conclusion of the study... the investigator or delegate will destroy all unused crizanlizumab, packaging, drug labels, as appropriate in compliance with site processes, monitoring processes, and as per local regulations/guidelines."
- Section 8:
    - In allowed visit windows specified, 'a + 7-day visit window for end of post-treatment phase' changed to 'a + 7-day visit window for the end of the safety follow-up phase.'
- Table 8-1:
    - Removed the Category column.
    - Last column, 'follow up phase' changed to 'follow up phase (as applicable)'.
    - For Priapism History, added an explicative footnote stating that: The date, number, and duration of the priapic events in the 14-week period prior to consenting will be captured in a separate CRF.
    - For laboratory assessments, a row is added for 'platelets (local)' with an explicative footnote reference also inserted at the end of the table.

[redacted]

    - In safety assessments, a row was added for 'IRR' with an explicative footnote reference also inserted at the end of the table.
- Section 8.2.3:
    - The word 'physician' was changed to 'health care professional.'
- Section 8.3.2:
    - Paragraph starting with 'for assessment of subject's eligibility to the study...', parentheses section revised to correct grammatical errors.
    - Following sentence added after bullet points on criteria for lab results being recorded in the eCRF: 'laboratory assessments can be repeated during the screening period as deemed appropriate by the investigator.'
    - Paragraph added before Table 8-4 on platelet counts and local sampling.
- Table 8-4:
    - In the chemistry assessment, the word 'albumin' was removed (subsequently removed from urinalysis as well); transferase typo corrected; 'glucose (fasting)' changed to 'glucose (non-fasting)'.
- Section 9.2:

[redacted]

- Study Completion visit definition was defined as last patient last visit.

- Section 10.1.2:
  - "In regards to" was corrected to "in regard to".
- Section 10.2.1:
  - Revised language on composition of steering committee: "investigators participating in the clinical trial..." changed to "SCD and priapism medical experts..."
- Section 12.4.2:
  - Added language on the uniformity in the occurrence of priapic events before exposure to crizanlizumab treatment.
  - Added text to specify that the baseline will be adjusted for 26 weeks for analysis purpose.
- Section 12.4.4:
  - Added language to specify that the number of priapic events will be summarized in the screening period (12 weeks baseline), in first 12 weeks on treatment (0-12 weeks), and in the last 12 weeks on treatment (15-26 weeks) and percent reduction from baseline will also be summarized in supportive analyses.
  - Paragraph related to the methods of analyzes using a mixed regression model was removed and will be instead included separately in the statistical analysis plan.
- Section 12.6:
  - The on-treatment and post-treatment period segments of the overall observation period were edited to reflect that some patients might receive commercial crizanlizumab after their study EOT.
- Section 12.6.2:
  - Clarification that an ECG will also be conducted at end of treatment: "... at screening and end of treatment visit."
- Section 12.8:
  - It was clarified that the primary analysis of the study will be performed after the last subject has completed Week 26 visit or discontinued earlier. Also, it was clarified that the analysis will be carried out on all visit-based safety assessments.
- Section 12.9:
  - Sample size calculation: The power of the study was changed from 90% to 80%. The drop-out rate was reduced to from 20 to 5% to reflect the higher-than-expected retention rate observed for the study. Based on the modification of these two parameters, the sample size calculation was revised to 34 evaluable subjects and approximately 36 subjects enrolled in the study.

[redacted]

- Section 15:
    - Two new references (Rogers et al 2005; Hamre et al 1991) were 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 1 (31-July-2020)

At the time of this amendment, 7 patients have been enrolled in the study.

The primary purpose of this amendment is described below:

1. Modify selected Inclusion/Exclusion Criteria including:
    - Inclusion criteria 6: Oxbryta™ (hereafter referred to as voxelotor) to be allowed on stable dose. The therapy was approved by the US FDA on 25-Nov-2019 for SCD treatment in adults and pediatric patients 12 years of age and older. Voxelotor has no reported beneficial effect on priapism.
    - Exclusion criteria 1: The timeframe for penile shunts was clarified. Instances of SCD patients suffering from priapism after having undergone penile shunt surgeries were reported to the team indicating that such procedures may not always prevent future occurrence of the complication.
    - Exclusion criteria 14: The drug or alcohol tests were replaced with a criterion based on a history of drug or alcohol abuse.

[redacted]

3. The visit windows were clarified throughout the protocol to remove any discrepancies and align with the other Novartis crizanlizumab clinical studies.
4. Following a literature review of antidepressants and antipsychotic drugs reported to cause priapism, the list of prohibited drugs was revised. These classes of drugs are now separately listed in Table 16-2 in Appendix 5. Ten drugs were added. Lithium was removed from the list as no literature reference was uncovered.
5. The guidelines for the management of infusion-related reactions (IRRs) were clarified with regards to the rules for interrupting and restarting infusions. It was also added that steroids should be used with caution unless clinically indicated (e.g. management of hypersensitivity/anaphylaxis). Sections related to IRRs were modified accordingly

[redacted]

throughout the protocol for consistency with other Novartis crizanlizumab clinical studies.

Other minor corrections are also applied throughout the protocol.

Changes to the Protocol

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

- Throughout: typographical and grammatical errors addressed.
- List of abbreviations: Anti-Drug Antibody (ADA), Adverse-Drug Reaction (ADR), Clinical Research Associate (CRA) and United States Adopted Name (USAN) were added. Ultrasonography (USG) was removed.
- Protocol Summary: updated in alignment to the protocol sections updated.
- Section 1.1:
  - Including Oxbryta™ (voxelotor) as approved by US FDA on 25-Nov-2019 for SCD treatment in adults and pediatric patients 12 years of age and older.
- Section 1.2.1:
  - Including first global approval for crizanlizumab obtained from the US FDA on 15-Nov-2019.
- Section 1.3 and Table 2-1:
  - Replaced “greater than” and “more than” by “at least” for clarity.
- Table 2-1:
  - Added the word “or” to align the definition of acute priapic events to that of priapism as defined in Section 8.2.1. Correspondingly the Protocol Summary and Section 8.2.2.2 were updated.
  - [redacted] Correspondingly, Table 8-1 was updated and the relevant sub-section in Section 8.2. was deleted.
- Section 3:
  - Pre-screening: Corrected that information to determine key eligibility criteria may be collected using an optional pre-screening form.
  - Screening Phase: Deleted the words “electronic” and “from Day 84 to Day 1” and referred to Section for schedule.
- Section 4.5:
  - Expanded risk and benefit section to align with IBv10 and included additional information on IRRs.
  - Added language to risk and benefit section regarding the important potential risks of hemorrhages, infections, infusion related reactions and immunogenicity in line with phase III crizanlizumab clinical trial.

[redacted]

- Added language to risk and benefit section regarding lack of evidence on mAb transmission in seminal fluid.

- Section 5.1:
  - Inclusion Criteria #6: Included voxelotor as a permitted concomitant therapy. Correspondingly, voxelotor was added in the Protocol Summary and four times in Section 6.2.1.1.
  - Inclusion Criteria #8: Clarified that the renal and hepatic function should be assessed prior to Week 1 Day 1.
  - Inclusion Criteria #9: Clarified that laboratory values should be assessed prior to Week 1 Day 1.
- Section 5.2:
  - Exclusion Criteria #1: Clarified that only patients who had a shunt surgical procedure on the penis performed within 12 months prior to consenting are not allowed. Correspondingly, the clarification was added in the Protocol Summary.
  - Exclusion Criteria #12 was modified to exclude patients on the basis of their family history of long QT syndrome or Torsades rather than a QTcF equal or superior to 470 msec.
  - Exclusion Criteria #13 was modified to remove History of myocardial infarction, angina pectoris, coronary artery bypass graft, or uncontrolled congestive heart failure within 6 months prior to starting study treatment as an exclusion factor. Specified the criteria indicating a significant risk of safety as "Concomitant clinically significant cardiac arrhythmias (e.g ventricular tachycardia), and clinically significant second- or third-degree AV block without a pacemaker".
  - Exclusion Criterion #14: current drug or alcohol abuse was replaced with a criterion to exclude patients with current drug or alcohol abuse as per investigator discretion. Correspondingly, drug and alcohol screens were deleted or changed to drug and/or alcohol history in Table 8-1 (row and Footnote b), Section 8.1.3, Section 8.3.2 and Table 8-4.
  - Exclusion Criterion #15: Language edited for clarity.
- Section 6.1.1:
  - Removed some irrelevant instruction related to the tear-off label on the medication package.
  - Deleted the composition of the formulation for the infusion solution. All allowed formulation are listed in the Pharmacy Manual.
- Section 6.2.1.1:
  - Added information on pre-medication in case of Infusion Related Reactions and a recommendation to use steroids with caution to treat IRR. Correspondingly, similar language was added in Section 6.2.1.3.
- Section 6.2.1.3.

[redacted]

- Text related to PK/PD was deleted because such procedures are not implemented in the protocol.
- Clarified the text by adding "as outlined above".
- Clarified the data collection method if other forms of L-Glutamine are used.
- Clarified the restrictions for administration of vaccines.
- Added text related to the use of pre-medication in case of infusion-related reactions. Clarified that there is no clinical data on the concomitant use of crizanlizumab and corticosteroids. Added a reference to Table 6-2 for further information on the management of infusion-related reactions.
- Added a recommendation to hold drug administration 4 weeks prior to a major surgery.

- Section 6.2.2:
  - Clarified that subjects that prior use of crizanlizumab, other selectin targeting agents or new treatment to treat SCD and/or to prevent/reduce VOCs are not permitted.
- Section 6.5:
  - Deleted that dose changes must recorded in the CRF.
- Table 6-2:
  - Clarified that version 5 of the CTCAE dictionary is used a reference.
  - Updated the units for Neutropenia and Thrombocytopenia to International System units.
  - Criteria for body temperature in febrile neutropenia changed from ≥38.5 °C to ≥ 38.3 °C.
  - Range for Grade 1 to Grade 4 isolated direct bilirubin has been clarified.
  - Clarified the recommendations for dose interruptions for Grades 1-4.
  - Range for Grade 1 to Grade 4 Infusion-related reactions has been clarified.
  - Updated recommendation to continue study treatment for Grade 1 infusion related reactions.
  - For Grade 2 infusion-related reaction, recommendation is updated to clarify the conditions to interrupt, administer pre-medication and res-start infusion.
  - Updated recommendation to discontinue study treatment for Grade 3 and 4 infusion related reactions.
  - Foot note has been deleted regarding recommendation to continue study treatment at Investigator's discretion if total bilirubin > 3.0 × ULN is only due to indirect component.
- Section 6.5.1.1:

[redacted]

- Modified definition of potential DILI to include normal ALP along with elevation of transaminases and increase in TBIL.
- Deleted the mention that AST will not be considered.
- Criteria for subjects with normal ALT and Direct BIL value at baseline modified to include that the subjects should be without evidence of cholestasis.
- Text modified to reflect that LFTs will be repeated for certain defined criteria preferably within 48-72 hours.

- Section 6.7.1:
  - Reference to the Pharmacy Manual has been added.
  - The language related to the management of IRRs was deleted as it was not relevant to this section. Management of IRRs is described in Table 6-2
- Section 8: Updating and clarifying the permitted visit windows:
  - Screening assessments must occur within 84 days (12 weeks) ± 7 days prior to the enrollment.
  - For all screening visits a general ± 7 day visit window is allowed.
  - A ± 7 day visit window is allowed at Week 1 Day 1 (calculated from day of consent).
  - A ± 3 day visit window is permitted on assessments at Week 3 Day 1.
  - For all other dosing visits a general ± 7 day visit window is permitted on assessments.
  - Deleted "to take into account scheduling over public holidays".
  - Corresponding text was updated in Section 8.3.2.
- Table 8-1:
  - Deleted "microscopic or macroscopic" as a microscopic panel is not always done. The conditions for urinalysis with a microscopic panel are detailed in Section 8.3.3.
  - Prior/concomitant medications-"Hydroxyurea" row was reformatted to highlight the continuous need to be recorded. The rows for "Transfusion, [redacted] Adverse Event/Serious Adverse Event and Prior/concomitant medications" were similarly modified.
  - ECG assessment was moved from Screening Visit 1 to Screening Visit 3 as it needs to be done closer to start of dosing. Corresponding language was clarified in Section 12.6.2.
  - Footnote "a" was updated to clarify that if the dose is delayed for more than 7 days, every effort should be made to bring the subject's infusions back onto the protocol-defined schedule (Section 6.5).
  - Footnote "c" became Footnote "b".
- Section 8.1:
  - Text modified in line with the modification of the screening windows in Section 8.

[redacted]

  - Deleted "use the electronic device(s) require" and added "as described in Section 8.2.4" to reflect the possibility of using a paper diary to record the priapic episodes. Correspondingly, text was deleted in Section 8.2.1 and modified in Section 8.2.4.
  - Added text to clarify the conditions for local testing when the results from the central laboratory are partial unavailable. Corresponding text was modified in Section 8.3.2.
  - Added text to clarify that re-screening of subjects is allowed under certain conditions and the steps that need to be undergone.

- Section 8.2.1:
  - Added text to clarify that In order to be treated as independent priapic events, two events will have to be separated by at least 2 hours, and the event would have to return to baseline during those 2 hours.
- Section 8.2.2.1:
  - Added "efficacy" to clarify that priapism was the primary efficacy endpoint as specified in Section 8.2.1.
- Section 8.3.2:
  - Deleted Flowchart as no central laboratory document other than the laboratory manual has been developed.
- Section 8.3.3:
  - Added text to clarify that a microscopic panel will be performed centrally if dipstick is positive.
- Section 8.3.5.1:
  - Removed two portions of text related ECG evaluation with a central laboratory. ECG are only done and interpreted locally.
- Section 8.3.5.2:
  - Parameters to be assessed by Echocardiogram are re-defined: PAP replaced with mPAP.
- Section 8.3.7:
  - Timeframe for the repeat assessment was removed at EOT to align with EOT being conducted with 2 weeks of the last infusion.
- Section 8.4.1:
  - Text modified as PROs will not administered electronically but via paper.
- Section 9.1.1:
  - Clarification that an EOT visit should be performed within 14 days of the last dose of the discontinued study treatment.
- Section 10.1.1:

[redacted]

  - Updated the list of outcomes to be recorded in the eCRF to include recovering/resolving AEs.

- Section 10.1.5:
  - Deleted the redundant word “Pregnancies”.
- Section 11.1:
  - Text of the Section was simplified by removing unnecessary or redundant language related to data capture in CRF, data storage and transfer, methods of monitoring and data verification.
- Section 11.3:
  - Clarified that continuous remote monitoring of each site’s data may be performed by a centralized Novartis-affiliated Clinical Research Associate (CRA) organization.
- Section 12.4.2:
  - Added that additional analyses will also be performed for the subgroups of subjects who have experienced priapic episodes lasting less than one hour and not for stuttering priapism. Corrected that these analyses are not for the primary endpoint.
- Section 12.4.3 and Section 12.4.4:
  - Added additional analyses to assess the impact of the COVID-19 crisis.
- Section 15:
  - Added the following additional references: Banholzer et al., Brandow et al., Scialli et al. and and Vichinsky et al.. The same changes were made wherever applicable in the protocol summary.
- Appendix 5:
  - Table 16-1 was modified to exclude the antipsychotics and anti-depressant drugs. The title was revised accordingly.
  - Table 16-2 was created to emphasize the list of anti-depressants and Antipsychotics that may induce priapism form other substances. Additional drugs uncovered from a systemic literature search were added. Tradenames were added for easier identification by the investigator. References were also included.
- **IRBs/IECs**

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

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

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

[redacted]

Protocol summary

Protocol number	CSEG101AUS05
Full Title	A Prospective Phase II, Open-Label, Single-arm, Multicenter, Study to Assess Efficacy and Safety of SEG101 (crizanlizumab), in Sickle Cell Disease Patients with Priapism (SPARTAN)
Brief title	Study of efficacy and safety SEG101 (crizanlizumab) in Sickle Cell Disease (SCD) Patients with Priapism (SPARTAN)
Sponsor and Clinical Phase	Novartis Phase of the trial: II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the effect of crizanlizumab on priapic events in sickle cell disease patients with a history of priapism. During screening, we will be collecting data for 12 weeks prior to the treatment phase to create a baseline for priapic events (defined as an event of an unwanted painful erection lasting at least 60 minutes), acute priapic events (which is defined as an event of an unwanted or painful erection lasting at least 4 hours), uncomplicated and complicated vaso-occlusive crisis (VOC). Our hypothesis is that crizanlizumab treatment will reduce priapic events by at least 25% in SCD patients with priapism.
Primary Objective	To evaluate the clinical efficacy *(*percent reduction from baseline) of crizanlizumab in SCD-related priapism
Secondary Objectives	• To evaluate the clinical efficacy (rate of priapic events) of crizanlizumab in SCD--related priapism • To evaluate the clinical efficacy of crizanlizumab in SCD-related acute priapism • To evaluate the clinical efficacy of crizanlizumab for uncomplicated VOC (defined as an acute event of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism and these events will not be adjudicated) • To evaluate the clinical efficacy of crizanlizumab in complicated VOCs (acute chest syndrome, hepatic sequestration, splenic sequestration, and acute priapism) • To assess the safety and tolerability of crizanlizumab
Study design	This is a multicenter, prospective, phase II, single-arm, open-label study to assess the efficacy and safety of crizanlizumab in SCD patients with priapism. A total of approximately 36 male subjects aged ≥ 12 years, who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study. The baseline period is defined as the 12 weeks screening period. Eligible subjects will be treated with crizanlizumab at a dose of 5.0 mg/kg. From the first screening visit until the end of follow-up, the total study duration will be up to 79 weeks (including 12 weeks of screening, 52 weeks of treatment and 15 weeks of follow-up period if applicable). The primary analysis of the study will be conducted by 26 weeks to assess efficacy of crizanlizumab in

[redacted]

	this patient population. The secondary [redacted] endpoints will be assessed by 26 weeks and/or 52 weeks. Subjects will be followed in the safety follow-up period until 105 days (15 weeks) after the last dosing. Subjects who will receive commercially approved crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up.
Population	A total of approximately 36 male patients with SCD-related priapism aged ≥ 12 years will be recruited across the United States. To be considered for this study, patients must have had ≥ 4 priapic events during the 14 weeks prior to screening and having at least 3 priapic events during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment.
Key Inclusion criteria	Subjects eligible for inclusion in this study must meet all of the following criteria: 1. Signed informed consent and applicable adolescent assent and/or parental consent for adolescent subjects, must be obtained prior to participation in the study 2. Male patients aged 12 years and above 3. Confirmed diagnosis of SCD by hemoglobin electrophoresis or high performance liquid chromatography. All SCD genotypes are eligible (HbSS, HbSβ^0, HbSC, HbSβ^+, and others) 4. Patients who have experienced ≥ 4 priapic events (unwanted erection lasting at least 60 minutes) over 14 week pre-screening 5. Patients who have experienced at least 3 priapic events (unwanted erection lasting at least 60 minutes) during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment. 6. If receiving hydroxyurea/hydroxycarbamide, L-glutamine, erythropoietin stimulating agent or voxelotor, must have been receiving the drug for at least 14 weeks prior to screening and plan to continue taking the drug at the same dose and schedule during the trial 7. If receiving prophylactic treatment for priapism, must have been receiving the drug for at least 14 weeks prior to screening and plan to continue taking the drug at the same dose and schedule during the trial
Key Exclusion criteria	Following are the key exclusion criteria: 1. Patients who have penile prosthetic implants. Shunts or any other surgical procedure on the penis performed within 12 months prior to consenting are not allowed. 2. Patients who have taken drugs/medications that may induce priapism (as per Appendix 5) over the 14 weeks pre-screening period 3. Patients who have received leuprolide acetate (Lupron) or any other gonadotropin-releasing hormone receptor (GnRHR) agonist agents within 3 months before pre-screening. 4. Patients who had an erection lasting more than 12 hours over the 14 week pre-screening period 5. Patients who had an erection lasting more than 12 hours during the 12 weeks of the screening period
Study treatment	Crizanlizumab (SEG101) at 5.0 mg/kg

[redacted]

Efficacy assessments	Following are the key primary and secondary planned efficacy assessments: • Percent reduction in priapic events by 26 weeks of treatment • The rate of priapic events by 26 and 52 weeks of treatment • Percent reduction in acute priapic events by 26 and 52 weeks of treatment • The rate of complicated/uncomplicated VOCs by 26 and 52 weeks of treatment
Key safety assessments	Following are the key safety assessment planned for this study: • Monitoring of AEs/SAEs • Vital signs, Physical assessments • Hematology, chemistry, coagulation, urinalysis, Hepatitis markers • Presence of HIV Antibody (at screening only) • Cardiac assessments: ECGs and echocardiogram
Other assessments	[redacted]
Data analysis	The primary endpoint of the study is the percent reduction from baseline in priapic events by 26 weeks (i.e. up to pre-infusion Week 27, Day 1). Efficacy endpoints will be analyzed using all FAS subjects who have completed treatment. It is hypothesized that crizanlizumab treatment will reduce the priapic events by at least 25% in SCD subjects with priapism. Assuming uniformity of the events occurrence before exposure to crizanlizumab treatment, baseline will be adjusted for 26 weeks for primary analysis purpose. Percent reduction from baseline in priapic events will be tested using a nonparametric test (i.e. Wilcoxon's Sign Rank test) along with Hodges-Lehmann estimate of median percent reduction Number of priapic events and percent reduction from baseline by Week 26 will be summarized descriptively. As part of the supportive analysis the primary analysis will be repeated on all subjects in FAS. In addition the annualized rate of priapic events will be summarized for all subjects in FAS that have completed treatment. Three additional supportive analyses will also be performed, the total number of priapic episodes in the screening period (12 weeks baseline) will be compared to the total number of priapic episodes occurring in the first 12 weeks on treatment (0-12 weeks) using a nonparametric test (i.e. Wilcoxon's Sign Rank test). A similar analysis will be performed to compare to the total number of priapic episodes occurring in the last 12 weeks on treatment (15-26 weeks). Finally an analysis using a mixed effects regression model will be performed using median event counts within pre-specified time windows. Similar analyses on percent reduction in acute priapic events for subjects will be conducted, as was completed for primary endpoint. Descriptive summary statistics will be presented for the rate of events and number of priapic events at Baseline, by Week 26 and by Week 52. In addition, the rate of uncomplicated VOC events and VOC events will be summarized. Safety analyses will be based on the safety analysis set. Adverse events

[redacted]

	will be summarized by system organ class and or preferred term, seriousness, CTCAE grade based severity, type of adverse event, relation to study treatment. Other safety assessments (e.g. ECG, vital signs) will be summarized by treatment group.
Key words	Priapism, sickle cell disease, crizanlizumab, P-selectin, vaso-occlusive crisis

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of Sickle Cell Disease pathogenesis, epidemiology and current treatment

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

Sickle cell disease is the most common single gene disorder in African Americans, affecting approximately 1 in 375-600 people of African ancestry (Nietert et al 2002). Sickle cell conditions are also common among people of Mediterranean countries, Africa, Middle East, India, Caribbean, and parts of South and Central America (Clinical Practice Guideline No. 6. 1993, Nietert et al 2002). The most frequent and typically most severe form is homozygous HbSS (sickle cell anemia) ($\alpha_2 \beta^s_2$, HbS). Other forms of SCD include compound heterozygous conditions, such as hemoglobin C (HbC) with HbS (HbSC), HbS with β-thalassemia (HbS/β^0-thalassemia or HbS/β^+-thalassemia), and HbS with other variants (Ware et al 2017). Clinical signs appear within the first 6 months of life, but there is considerable variability in severity (Gill et al 1995) resulting from genetic and environmental factors. Patients describe acute pain crises and chronic pain clearly as the most debilitating effects on their lives, affecting them physically and emotionally. Fatigue and cognitive effects also emerge as other debilitating effects. In addition, organ-damage and long-term complications have also a severe effect on them. As a result of these complications, patients often have reduced quality of life, significant anxiety, depression, and short life expectancy (Piel et al 2017, Kanter and Kruse-Jarres 2013).

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

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

Vaso-occlusive crises are typically treated symptomatically with pain management and with other supportive care (Bender 2003, Rees et al 2010). Severe pain is often treated with opioids, but their use is controversial due to the risk of opioid-related adverse events (AEs).

[redacted]

Preventive treatments to reduce the number of VOCs are limited. Hydroxyurea/hydroxycarbamide (HU/HC) is approved to reduce the frequency of painful crises and the need for transfusions in SCD patients aged 2 years and older with a history of recurrent, moderate-to-severe painful crises. Treatment with HU/HC presents several limitations, including significant toxicities and need for blood monitoring leading to poor patient compliance. It is cytotoxic, myelosuppressive and teratogenic, potentially carcinogenic, impacts fertility and has a number of contraindications or special warnings and precautions for use (Charache et al 1995, Pászty et al 1997, Hydrea-USPI 2016, Droxia-USPI 2017).

L-glutamine (Endari™), is approved in the United States to reduce the acute complications of SCD in adult and pediatric patients 5 years and older (Niihara et al 2018) and voxelotor (Oxbryta™) has been approved by FDA since 25 Nov 2019 for the treatment of SCD in adult and pediatric patients 12 years of age and older (Vichinski et al 2019).

Despite the use of HU/HC, transfusions, L-glutamine and/or voxelotor, patients with SCD may still experience VOCs. In particular, complicated VOCs such as priapism represent a major unmet medical need.

1.1.2 Overview of SCD-related priapism, epidemiology and current treatment

Priapism is an involuntary, painful, and persistent erection, in the absence of sexual activity or desire (Furtado et al 2012). It was found that 29% of male children and adolescents with SCD reported priapism, and projected that up to 89% of men with SCD would experience priapism by the age of 20 (Mantadakis et al 1999). The vast majority of cases are ischemic, in which increased pressure, compromises the vascular circulation (i.e. a type of compartment syndrome). Its ischemic form, presenting as a single, major event, or recurrence, is associated with penile pain, erectile tissue destruction and loss, and permanent erectile inability (Montague et al 2003, El-Bahnasawy et al 2002). The sickled erythrocytes predispose to venous stasis, which therefore perpetuates the priapism. Cavernosography shows that this stasis results in obstruction of the deep dorsal penile vein (Adeyoju et al 2002). The stagnation of blood within the sinusoids of the corpora cavernosa during a physiological erection increases erythrocyte rigidity and impairs the venous outflow from the corporeal bodies. Prolongation of the erection and pain induced by ischemia of the corporeal tissues are potential consequences of these events. (Fowler Jr et al 1991). Most of the affected patients had repeated events that lasted for less than 3 hours and a majority of the attacks occurred during sleep, which could be due to the physiological dehydration and metabolic acidosis that accompany sleep and that increase the rigidity of erythrocytes in patients with sickle cell anemia (Fowler Jr et al 1991). Priapism may be one reflection of the vasculopathy of SCD. (Kato et al 2017).

Apart from anecdotal experiences, there is no clear evidence-based guidelines in management or medical prevention strategies. The goal of priapism treatment is to achieve detumescence and preserve erective dysfunction (Montague et al 2003). Treatment for SCD-related priapism are lacking due to the clinical misunderstanding and the ideal medical interventions have not been developed. In recent years, major scientific progress has advanced the understanding of pathophysiology especially in molecular effector pathways mediating penile erection. The medical management of recurrent or stuttering SCD-related priapism is difficult and frustrating,

[redacted]

often involving sequential attempts with several different drugs, and clearly, more rigorous clinical research is needed in this area.

1.1.3 Role of P-Selectin in VOC

Extensive data have been published over the last decade that suggests a pivotal role for P-selectin in the pathophysiology of SCD. Adhesion of leukocytes to the endothelium during inflammation can involve multiple molecules and the process is initiated by P-selectin (Lawrence and Springer 1991). P-selectin expression increases the specificity of endothelial cell interactions with platelets and leucocytes during inflammation, coagulation and atherosclerosis. P-selectin expressed on endothelial cells also increases sickle erythrocyte adhesion, although the precise ligand interaction involved is not known. P-selectin is found in storage granules of resting endothelial cells and platelets and is rapidly transferred to the cell membrane on activation of the cell during processes such as inflammation. It is expressed on the surface of endothelium that mediates abnormal rolling and static adhesion of sickle erythrocytes to the vessel surface in vitro (Matsui et al 2001, Matsui et al 2002). Translocation of endothelial P-selectin to the cell surface results in the prompt adhesion of sickle erythrocytes to vessels and the development of vascular occlusion in transgenic mice with SCD (Embury et al 2004).

The role of P-selectin in SCD is further substantiated by the fact that transgenic mice with SCD that are deficient in P-selectin and E-selectin have defective leukocyte recruitment to the vessel wall and are protected from vaso-occlusion (Turhan et al 2012). The adherence of sickle erythrocytes and leukocytes to the endothelium is substantially reduced when P-selectin is blocked in transgenic mice expressing human HbS (Embury et al 2004, Gutsaeva et al 2011). These data support the concept that blockade of P-selectin could reduce the risk of vaso-occlusion, inflammation, and sickle cell–related pain crises (Ataga et al 2017).

In addition to the studies done in animals, human sickle red cells frequently interacted and adhered directly to the vascular endothelium (Matsui et al 2001). Platelets also respond to inflammation with the upregulation of P-selectin and are known to bind to leukocytes and endothelium, thereby contributing to vaso-occlusion in SCD (Wood et al 2004, Inwald et al 2000, Lee et al 2007). The adhesion of sickled human erythrocytes to activated endothelium in SCD is also an important contributor to vaso-occlusion and pain crisis (Wagner et al 2006, Hebbel et al 1980, Stuart and Johnson 1987).

1.1.4 Role of P-Selectin in SCD-related priapism

Preclinical studies in transgenic mice have shown that SCD promotes an increased P-selectin expression in several vascular beds of various organs (e.g. lung, heart, small bowel, large bowel, penis etc.). The penis is the only organ where the vascular bed exhibited an increased expression of both P- and E-selectin, which may be relevant to a SCD-related priapism. Although, priapism has been attributed to both ischemic and non-ischemic causes, vaso-occlusion-induced ischemia is generally thought to account for the priapism associated with SCD. This raises the possibility of an inflammatory process in priapism (Wood et al 2004).

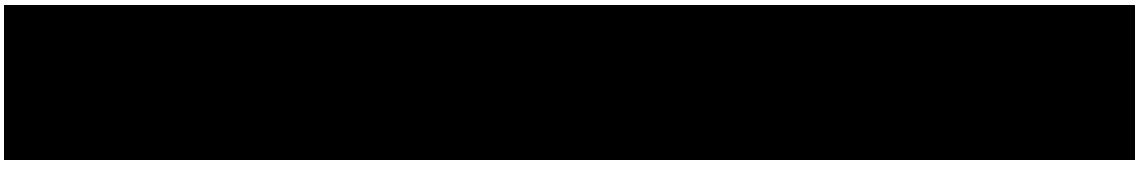
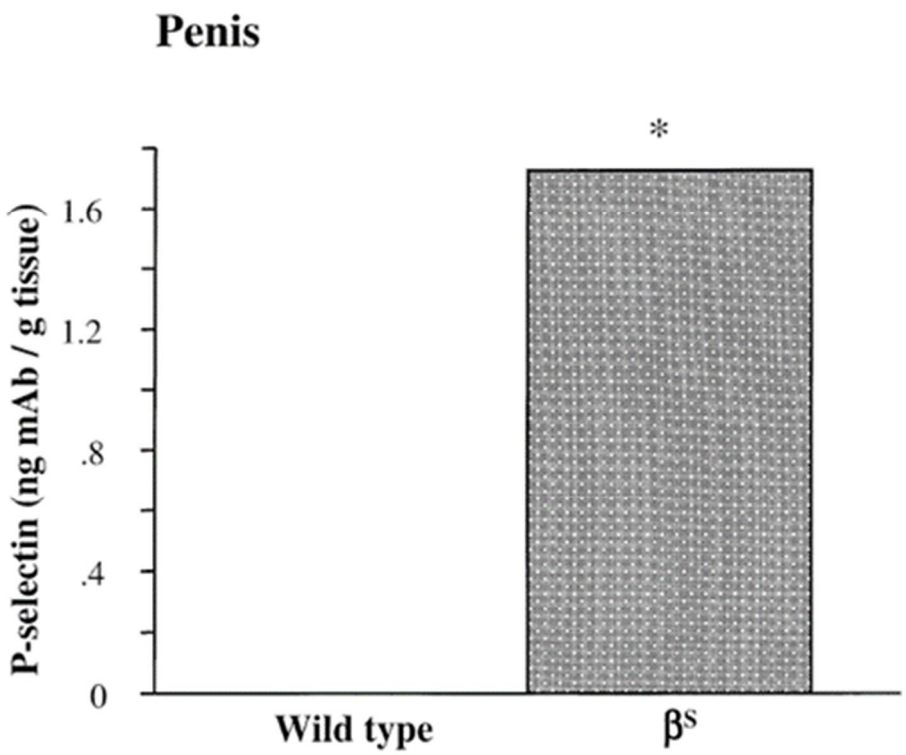


Figure 1-1 P-selectin expression in penis of wild-type (WT) and sickle cell transgenic (βS) mice



Constitutive expression of P-selectin in the penis of wild-type (WT) and sickle cell (βS) mice. While significant P-selectin expression is detected in the penis of βS mice, it was not be detected in the WT penis (P < .0005).

As P-selectin expression is increased in the penis and vaso-occlusion induced ischemia is thought to account for the priapic events, a study evaluating the effects of P-selectin inhibition on priapism associated with SCD is warranted.

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

1.2.1 Overview of crizanlizumab (SEG101)

Crizanlizumab is a selective IgG2 kappa humanized monoclonal antibody that binds to P-selectin with high affinity by blocking its interaction with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1). Extensive pre-clinical data have established P-selectin as a key mediator of VOC in SCD (Matsui et al 2001) and suggest that blockade of P-selectin could eliminate or reduce VOC.

The compound, crizanlizumab was initially developed by Reprixys Pharmaceuticals Corporation under the investigational drug code, SelG1. Novartis acquired the company on 18-Nov-2016, and is now the drug developer and sponsor for crizanlizumab, under the investigational drug code, SEG101. On 15-November-2019, the US FDA approved

ADAKVEO® (crizanlizumab-tmca), for the reduction of the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease.

The approval was based on safety and efficacy data from the Phase II SUSTAIN study (Ataga et al 2017; see Section 1.2.2) below.

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

1.2.2 Clinical experience

Phase II Clinical Study (SUSTAIN – CSEG101A2201)

Throughout this description of SUSTAIN, the study drug is denoted as crizanlizumab and refers to SelG1. The objective of this pivotal, randomized, placebo-controlled SUSTAIN study (Reprixys study code: [Se1G1-00005]; Novartis study code: [CSEG101A2201]) was to assess the safety and efficacy of crizanlizumab with or without HU/HC therapy in SCD patients with a history of VOC leading to a healthcare visit. A total of 198 SCD patients aged 16-65 years (inclusive), with any SCD genotype, a history of crisis within the previous 12 months, and either with a steady dose of HU/HC or not taking HU/HC, were randomized 1:1:1 to crizanlizumab 5.0 mg/kg, crizanlizumab 2.5 mg/kg or placebo.

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

Crizanlizumab was generally well tolerated with similar incidence of treatment emergent adverse events (TEAEs) across the 3 groups, and overall there were low incidence of discontinuations due to TEAEs (< 5%). The proportion of subjects 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. There were 5 deaths during the study (2 at 5.0 mg/kg, 1 at 2.5 mg/kg and 2 in the placebo group), and none was deemed to be treatment related. Please refer to Investigator's Brochure for further information.

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

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

[redacted]

1.3 Purpose

The purpose of this study is to evaluate the effect of crizanlizumab on priapic events in sickle cell patients with a history of priapism. We will be collecting data for 12 weeks prior to the treatment phase to create a baseline for priapic events (defined as an event of an unwanted painful erection lasting at least 60 minutes), acute priapic events (which is defined as an event of an unwanted or painful erection lasting at least 4 hours), uncomplicated and complicated VOCs. Our hypothesis is that crizanlizumab treatment will reduce priapic events by at least 25% in SCD patients with priapism.

[redacted]

[redacted]

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Primary Objective	Endpoint for primary objective
To evaluate the clinical efficacy of crizanlizumab in SCD-related priapism	Percent reduction from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks
Secondary Objectives	**Endpoints for secondary objectives**
To evaluate the clinical efficacy of crizanlizumab in SCD-related priapism	Rate of priapic events by 26 and 52 weeks
To evaluate the clinical efficacy of crizanlizumab in SCD-related acute priapism	Percent reduction from baseline in acute priapic events (defined as an unwanted or painful erection lasting at least 4 hours and mandates a visit to ER) by 26 weeks and 52 weeks
To evaluate the clinical efficacy of crizanlizumab for uncomplicated vaso-occlusive crisis (VOC) (defined as an acute event of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism and these events will not be adjudicated)	Rate of uncomplicated VOC events (including both healthcare visit and self-reported) by 26 and 52 weeks
To evaluate the clinical efficacy of crizanlizumab in complicated VOCs (acute chest syndrome, hepatic sequestration, splenic sequestration, and acute priapism)	Rate of complicated crisis (recorded by healthcare visit) by 26 and 52 weeks
To assess the safety and tolerability of crizanlizumab	Number, seriousness, severity, and causality assessments of treatment emergent adverse events and other safety data as considered appropriate by 52 weeks (Safety assessments will consist of monitoring and recording all adverse events, based on Common Terminology Criteria for Adverse events (CTCAE) V5.0. It will also include regular monitoring of laboratory testing of hematology, serum chemistry, and urinalysis, measurement of vital signs, and physical examination.)
[redacted]	[redacted]

2.1 Primary estimands

[redacted]

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

The primary clinical question of interest is: What is the effect of crizanlizumab on reduction from baseline period in priapic events, by week 26?

The primary estimand is described by the following attributes:

1. Population: Sickle Cell Disease patients with priapism. Further details about the population are provided in Section 5.
2. Endpoint: Percent reduction from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks.
3. Treatment of interest: investigational drug will be a crizanlizumab solution provided every 4 weeks with an additional loading dose 2 weeks after the first dosing. Further details about the investigational treatment are provided in Section 6.
4. List of intercurrent events:
    a) Treatment discontinuation
    b) 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) or of prophylactic treatment for priapism as described in the Sections 6.2.1, 6.2.2, 6.2.3
    c) Intake of analgesic (including opioids) or ad hoc transfusions administered temporarily as described in the Section 6.5.
5. The summary measure: Median percentage change from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks

Handling of intercurrent events is discussed in Section 12.4.2.

3 Study design

This is a multicenter, prospective, phase II, single-arm, open-label study to assess the efficacy and safety of crizanlizumab in SCD patients with priapism.

A total of approximately 36 male subjects aged ≥ 12 years, who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study. Subjects with ≥ 4 priapic events during the 14 week pre-screening period and having at least 3 priapic events during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment, will be included in the study.

The baseline period is defined as the 12 weeks screening period. Eligible subjects will be treated with crizanlizumab at a dose of 5.0 mg/kg. From the first screening visit until the end of follow-up, the total study duration will be up to 79 weeks (including 12 weeks of screening, 52 weeks of treatment and 15 weeks of follow-up as applicable). The primary analysis of the study will be conducted by 26 weeks to assess efficacy of crizanlizumab in those patient population, who have completed 26 weeks of treatment. The secondary [redacted] endpoints will be assessed by 26 weeks and/or 52 weeks. Subjects will be followed for safety for up to 105 days (15 weeks) after the last dosing if applicable. Subjects who will receive commercially approved

[redacted]

crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. The safety follow-up of these subjects will be at the End of Treatment (EOT) visit. All other subjects are required to complete the 105-day follow-up visit.

Pre-screening

Before participating in the study, information to determine key eligibility criteria may be collected as a part of a pre-screening form. In particular, the date, number and duration of the priapic events in a 14-week period required prior to consenting may be captured on this form. The use of this form is optional.

Screening phase

Eighty-four days (12 weeks) before start of treatment, written informed consent, according to local guidelines, will be signed by the subjects and prior to any study related screening procedures are performed.

During this period, subjects will have 3 visits and be monitored for priapic events to determine their eligibility to the trial using a reporting system. All screening evaluations must be performed during the screening period (see Section 8 for schedule).

Treatment phase

Once eligibility criteria have been confirmed by Novartis via the eligibility checklist, the subject will receive investigational treatment.

Subjects will receive investigational treatment by IV infusion over 30 min on Week 1 Day 1, Week 3 Day 1, and then on Day 1 of every 4-week cycle.

Safety will be monitored as outlined in Section 8. Subjects will receive investigational treatment for a maximum of 1 year (52 weeks) or until unacceptable toxicity, death, lost to follow-up or discontinued from the study treatment for any other reasons prior to 52 weeks.

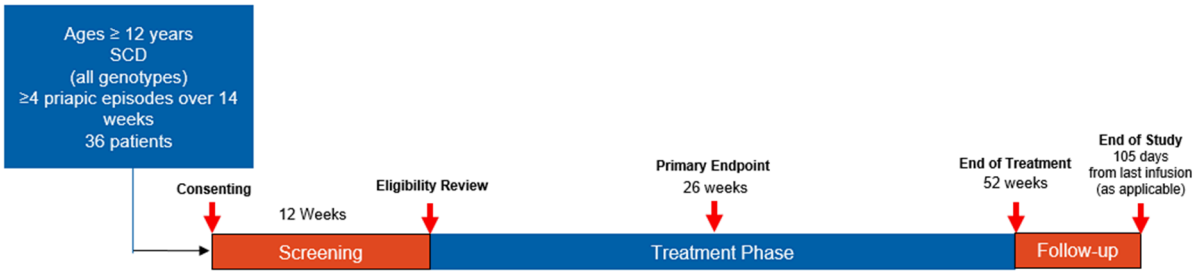
Following the treatment discontinuation, subjects will perform an end of treatment (EOT) visit.

Follow-up phase

After the end of treatment visit, all subjects will be followed up for safety up to 105 days (15 weeks) after the last infusion of study treatment if applicable (see Section 9.2).

[redacted]

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

The efficacy of crizanlizumab in SCD for the treatment of VOCs was established in the SUSTAIN study but was not fully investigated in priapism due to the limited number of cases observed during the study. The primary aim of this study is to demonstrate the clinical benefit of crizanlizumab in SCD-related priapism. A duration of 26 weeks was set to evaluate the primary efficacy of crizanlizumab on SCD-related priapism. This was based on studies conducted by Burnett and Olujohungbe, where recurrent ischemic priapic patients were evaluated over 16 and 26 weeks, respectively (Burnett et al 2014, Olujohungbe et al 2011). In addition, steady state concentrations for crizanlizumab were considered achieved by 15 weeks in the SEG101A2202 study.

The total duration of 52 weeks of treatment will enable evaluation of additional secondary [redacted] endpoints for the study.

4.2 Rationale for dose/regimen and duration of treatment

In this study, subjects will receive crizanlizumab 5.0 mg/kg every 4 weeks by IV infusion. A loading dose of 5.0 mg/kg will be administered 2 weeks after the first dose to rapidly achieve the steady-state serum concentration. This will be followed by dosing of 5.0 mg/kg every 4 weeks to ensure that steady-state serum concentration of crizanlizumab are maintained to provide a consistent blockade of P-selectin throughout the study.

In the SUSTAIN trial (SEG101A2201), both 5.0 mg/kg and 2.5 mg/kg of crizanlizumab on this same dosing schedule was tested and showed a statistically significant reduction in median annual rate of SCPC 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 addition, further PK modeling of 5.0 mg/kg and 2.5 mg/kg every 4 weeks demonstrates that the 5.0 mg/kg dose will provide trough PK levels of crizanlizumab above that necessary to achieve consistent blockade of P-selectin during the 12-month Phase II study.

[redacted]

Crizanlizumab 5 mg/kg dose is further supported by the data from healthy subjects in the Phase I Study CESG101A2102, and by data from SCD patients in the Phase II Study CSEG101A2202 and the 1st cohort of CSEG101B2201.

4.3 Rationale for choice of control drugs

This is a single arm study. Therefore, no control group will be assigned.

4.4 Purpose and timing of interim analyses

A formal interim analysis for this study is not planned and shall not be performed. For publication purposes, only descriptive data will be reported, as needed. Any decision on study continuation will not be based on these reports, as such no alpha adjustment will be needed.

4.5 Risks and benefits

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

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

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

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

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

Infusion-related reactions (IRRs)

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

[redacted]

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

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

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

Immunogenicity

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

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

Infections

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

Infection-related AEs (based on all preferred terms included in the system organ class "Infections") were reported in 55 (49.5%) patients in the safety pool. The most frequently reported infections were urinary tract infection (13 patients, 11.7%), upper respiratory tract infections (11 patients, 9.9%), pneumonia (5 patients, 4.5%) and sinusitis (4 patients, 3.6%). Most infections were low in severity (Grade 1 or 2). In the randomized SUSTAIN study, infection-related AEs were similar across the arms: 53.0% in the crizanlizumab 5 mg/kg and 53.2% in the placebo arm. In addition, there was no difference between the arms in the incidence of neutropenia or white blood cell counts.

In summary, no increased frequency or severity of infections has been observed in clinical studies with crizanlizumab so far, suggesting that crizanlizumab has no clinically relevant effect to induce or complicate infections in SCD patients. However, investigators are advised to monitor patients for signs/symptoms of infections.

[redacted]

Effect on hemostasis

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

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

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

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

Laboratory test interference with automated platelet counts

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

QT prolongation and hepatic safety

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

Monoclonal antibodies and male fertility

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

[redacted]

drug delivery to the vagina would be approximately 10,000 to 30,000 fold lower than by intravenous dosing. Thus the potential of fetal harm from semen delivery of a monoclonal antibody is currently considered to be biologically implausible (Breslin et al 2014).

Appropriate eligibility criteria and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.5. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring. If deemed clinically necessary, subjects 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.

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

COVID-19 pandemic
No substantial additional risk for patients due to the SARS-CoV-2 virus and the COVID-19 pandemic has been identified at this time and therefore the benefit risk remains unchanged. In case of active COVID-19 infection, please refer to Section 6.5. The risk/benefit balance will be re-evaluated as and when required whilst the COVID-19 pandemic continues.

5 Population

A total of approximately 36 male patients with SCD-related priapism aged ≥ 12 years will be recruited across the United States. To be considered for this study, subjects must have had ≥ 4 priapic events during the 14 weeks prior to screening and having at least 3 priapic events during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment.

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

5.1 Inclusion criteria

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

1. Signed informed consent and applicable adolescent assent and/or parental consent for adolescent subjects, must be obtained prior to participation in the study
2. Male patients aged 12 years and above
3. Confirmed diagnosis of SCD by hemoglobin electrophoresis or high performance liquid chromatography. All SCD genotypes are eligible (HbSS, HbSβ^0, HbSC, HbSβ^+, and others)
4. Patients who have experienced ≥ 4 priapic events (unwanted erection lasting at least 60 minutes) over 14 week pre-screening
5. Patients who have experienced at least 3 priapic events (unwanted erection lasting at least 60 minutes) during the 12 week screening period with at least 1 event occurring within 4 weeks prior to the first treatment.

[redacted]

6. If receiving HU/HC or L-glutamine or erythropoietin stimulating agent or voxelotor, must have been receiving the drug for at least 14 weeks prior to screening and plan to continue taking the drug at the same dose and schedule during the trial
7. If receiving prophylactic treatment for priapism, must have been receiving the drug for at least 14 weeks prior to screening and plan to continue taking the drug at the same dose and schedule during the trial
8. Adequate renal and hepatic function as defined prior to Week 1 Day 1:
   - Glomerular filtration rate ≥ 45 mL/min/1.73 m^2 calculated by CKD-EPI
   - Alanine aminotransferase (ALT) ≤ 3 × ULN
   - Direct (conjugated) bilirubin ≤ 2 × ULN
9. Patient must meet the following laboratory values prior to Week 1 Day 1:
   - Absolute Neutrophil Count ≥ 1.0 × 10^9/L
   - Hemoglobin > 4.0 g/dL
   - Platelets ≥ 75 × 10^9/L

5.2 Exclusion criteria

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

1. Patients who have penile prosthetic implants. Shunts or any other surgical procedure on the penis performed within 12 months prior to consenting are not allowed.
2. Patients who have taken drugs/medications that may induce priapism (as per Appendix 5) over the 14 weeks pre-screening period
3. Patients who have received leuprolide acetate (Lupron) or any other gonadotropin-releasing hormone receptor (GnRHR) agonist agents within 3 months before pre-screening.
4. Patients who had an erection lasting more than 12 hours over the 14 week pre-screening period
5. Patients who had an erection lasting more than 12 hours during the 12 weeks of the screening period
6. 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
7. Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of the study drug formulation
8. Received crizanlizumab
9. Received a monoclonal antibody or immunomodulatory agent within 1 year of screening, or has documented immunogenicity to a prior biologic
10. Received other selectin inhibitor or plans to receive it during the duration of the study
11. Patients should not be receiving 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
12. History of familial long QT syndrome or know family history of Torsades de Pointes
13. History or current diagnosis of ECG abnormalities indicating significant risk of safety such as:

[redacted]

- Concomitant clinically significant cardiac arrhythmias (e.g ventricular tachycardia), and clinically significant second or third degree AV block without a pacemaker

14. Subjects with evidence of current alcohol/drug abuse:
15. Any documented history of a clinical stroke or intracranial hemorrhage, or an uninvestigated neurologic finding within the past 12 months before screening. Silent infarct only present on imaging is not excluded
16. Clinically significant bleeding disorder
17. Planning to undergo a major surgical procedure during the duration of the study
18. Patient with active HIV infection (detectable viral load)
19. Patients with active Hepatitis B infection (HBsAg positive)
    Note: Patients with antecedent but no active Hepatitis B (i.e. anti-HBc positive, HBsAg and HBV-DNA negative) are eligible
20. Patients with positive test for hepatitis C ribonucleic acid (HCV RNA)
    Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥ 6 months (with the use of IFN-free regimes) or ≥ 12 months (with the use of IFN-based regimes) after cessation of antiviral treatment are eligible
21. Significant active infection or immune deficiency (including chronic use of immunosuppressive drugs)
22. Malignant disease. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 3 years prior to study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma *in situ*
23. Not able to understand or comply with study instructions and requirements
24. Any condition which, in the opinion of the investigator, is likely to interfere with the successful collection of the measurements required for the study

6 Treatment

6.1 Study treatment

Novartis will supply crizanlizumab (SEG101) as an open-label medication. The investigational drug will be a crizanlizumab solution provided every 4 weeks with an additional loading dose 2 weeks after the first dosing (i.e. dosing on first day of Week 1, Week 3, Week 7, and then every 4 weeks until Week 51).

6.1.1 Investigational and control drugs

Crizanlizumab will be supplied in single use vials containing 10 mL at a concentration of 10 mg/mL for administration by IV infusion. Each study site will be supplied with study drug in packaging as described under investigational drugs section.

A unique medication number is printed on the study medication label.

[redacted]

On infusion day, the pharmacist or designated personnel will prepare individual doses of crizanlizumab for subjects on a milligram per kilogram basis in a 100 mL infusion bag in accordance with the Pharmacy Manual. Study drug will be administered over 30 minutes by IV infusion. Please refer to Table 6-1 for dose and treatment schedule.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Crizanlizumab	Intravenous infusion	5.0 mg/kg	Week 1 Day 1, Week 3 Day 1, Week 7 Day 1 and Day 1 of every 4-week cycle until Week 51

6.1.2 Additional study treatments

No additional treatments beyond investigational drug are included in this trial.

6.1.3 Treatment arm/group

This is single arm study, all the subjects enrolled in this study will receive crizanlizumab (5.0 mg/kg).

6.1.4 Treatment duration

The total duration of treatment in the study for each subject is planned to be up to 52 weeks.

Subjects may be permanently discontinued due to unacceptable toxicity, death, lost to -follow-up or discontinued from the investigational treatment for any other reasons at the discretion of the investigator or the subject, prior to 52 weeks.

6.2 Other treatments

6.2.1 Concomitant therapy

6.2.1.1 Permitted concomitant therapy for the management of SCD

In general, the use of any concomitant medication/therapies deemed necessary for the care of the subject is permitted, except prohibited treatments (Section 6.2.2). The subject 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 safety follow-up or EOT visit as applicable). All medications (including prescription drugs, herbal medications/supplements, over the counter (OTC) medication, dietary and vitamin supplements) and significant non-drug therapies (including physical therapy and blood transfusions) taken or administered within the timeframe defined in the entry criteria until completion of the safety follow-up or EOT visit as applicable must be listed on the Prior and Concomitant medications, Surgical and Medical Procedures, or Transfusion page of the Case Report/Record Form (CRF). Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before allowing a new medication to

[redacted]

be started. If the subject is already enrolled, contact Novartis/sponsor to determine if the subject should continue participation in the study. Concomitant sickle cell therapy with HU/HC, L-glutamine or voxelotor is permitted, provided the subject has been prescribed HU/HC, L-glutamine or voxelotor consistently over at least the 14 weeks prior to screening, as stated in the Inclusion criteria. The dosing should not be altered or terminated, other than for safety reasons until the subject has completed 1-year of investigational treatment. In subjects not on HU/HC,L-glutamine or voxelotor, treatment should not be initiated during the first year of investigational treatment. If a physician deems it is medically necessary to terminate or alter HU/HC treatment, L-glutamine or voxelotor during the first year of crizanlizumab treatment, changes should not lead by default to discontinuation of the trial; however, the medical monitor must be notified. Erythropoietin-stimulating agents are also permitted to manage chronic symptomatic anemia with the same requirement for 6 months prior therapy. Aspirin, nonsteroidal -anti-inflammatory drug (NSAIDs) and prophylactic doses (as per local guidelines) of anticoagulants are permitted, while other anti-platelets agents or anticoagulants at doses targeting therapeutic levels should be used with caution (refer to Section 6.2.1.3). All approved forms of analgesia for pain are permitted per standard of care. Other approved medications for supportive care (antiemetics, anxiolytics, hypnotics, antihistamines) are permitted, including marinol (dronabinol).

6.2.1.2 Permitted concomitant therapy for the management of SCD-related priapism

Concomitant prophylactic treatment for SCD-related priapism is permitted provided the subject has been prescribed the same medication consistently for at least 14 weeks prior to screening as per inclusion criterion 7. Dosing should not be altered or terminated other than for safety during the duration of the study. In subjects not on prophylactic medications, treatment should not be initiated during the study. If a physician deems it necessary to terminate or alter treatment during the study, the monitor must be notified immediately to determine whether the subject may continue the study.

6.2.1.3 Permitted concomitant therapy requiring caution and/or action

Although transfusion of cellular blood products is permitted, it is unclear how such transfusions will impact crizanlizumab. It should also be considered that the administration of products containing immunoglobulins (plasma, IVIG, anti-globulins) may also impact the efficacy of crizanlizumab.

Although Endari™, the FDA-approved version of L-glutamine, is permitted as outlined above, other over-the counter forms of L-glutamine are discouraged, as are other natural and herbal remedies (e.g. EvenFlo and/or products containing dang gui, *Ligustrum* root, ginseng root, white peony, *corydalis*, salvia, copodonosis, poria, jujube, *angelica sinensis*, lovage) due the unproven efficacy and variable quality and composition of these products. If other forms of L-glutamine not approved by the FDA are used, the treatment information will be collected in the eCRF. Vitamin and mineral supplements (e.g. fish oil, folic acid, L-arginine, L-citrulline, magnesium, riboflavin, vitamin C, vitamin D, vitamin E, and zinc) are also permitted, though caution is advised when taking amounts exceeding 100% of the recommended daily allowance. It is recommended to avoid any live vaccines within 4 weeks prior to the first dose of investigational treatment and during study duration. However, the decision to administer or

[redacted]

withhold a vaccine should be done on case-by-case basis considering the potential benefits/risks such as developing severe infection, adverse effects from the vaccination, or vaccination failure.

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

Infusion related reactions have been observed with crizanlizumab administration. Prophylactic 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. 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).

Further guideline on management of crizanlizumab infusion related reactions is provided in Table 6-2. If a subject experiences a Grade 3 or 4 infusion related reaction, the study treatment will be discontinued.

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

6.2.2 Prohibited medication

The use of other investigational drugs is prohibited during the study. In addition, the administration of monoclonal antibodies other than the investigational treatment is prohibited, due to the theoretical potential for cross-reactivity and/or overlapping toxicities with other monoclonal antibodies. If investigational agents have been used in the past, they must have been discontinued at least 30 days or 5 half-lives of that agent, (whichever is greater) prior to the screening visit. Patients who have received a monoclonal antibody or immunomodulatory agent within 1 year of screening, or have documented immunogenicity to a prior biologic are not allowed to participate. Patients that have received prior treatment with crizanlizumab are not allowed to enroll in this study. Use of approved crizanlizumab or other selectin targeting agents is prohibited during the entire study duration.

6.2.3 Rescue medication

Any standard medications that are used for management of VOC and acute priapic events are allowed. [redacted]

[redacted]

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

This is a single arm study. Therefore, no randomization will be performed in this study.

6.4 Treatment blinding

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

6.5 Dose modification

If a subject does not tolerate the protocol-specified dosing schedule, dose interruptions are either recommended or mandated in order to allow subjects to continue the study treatment until the next scheduled dose. Dose reductions are not allowed.

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

These dose interruptions are summarized in Table 6-2. Deviations to mandatory dose interruptions are not allowed. Permanent treatment discontinuation is mandatory for specific events indicated as such in Table 6-2.

Dose interruptions must be recorded in the Dosage Administration Record CRF. Every effort should be made to maintain the subject on the protocol-defined dosing schedule. In case of dose delay for any reason, the dose should be given as soon as possible. If that infusion visit occurs within ± 7 days of a protocol-scheduled visit, then the dose and all required assessments will be assigned to the nearest protocol-scheduled visit. However, if that infusion visit does not fall within ± 7 days of a protocol-scheduled visit, the dose and corresponding assessments will be documented as an unscheduled visit. At that point, every effort should be made to bring the subject's infusions back onto the protocol-defined schedule (within the ± 7 day window).. If a subject misses two consecutive doses of crizanlizumab due to ADR (i.e., an AE attributable to study drug), the subject should be discontinued from crizanlizumab. A subject with Grade 3 or 4 IRR will be permanently discontinued from crizanlizumab. A subject with a Grade 4 ADR will be permanently discontinued from the study.

[redacted]

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

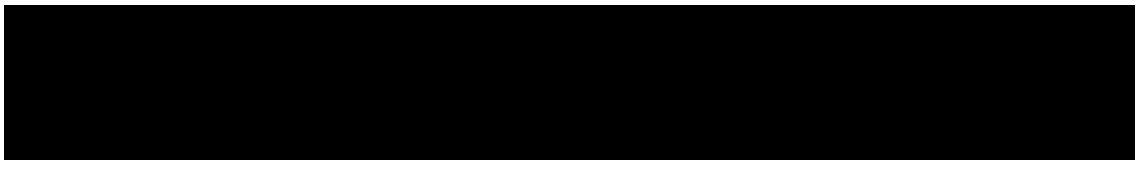


Table 6-2 Criteria for dose interruption and re-initiation of crizanlizumab treatment for adverse drug reactions.

Dose modifications for crizanlizumab	
Worst toxicity CTCAE[a] Grade (CTCAE version 5) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L)	Recommendation: Maintain dose
Grade 2 (ANC < 1.5 x 10^9/L-1.0 x 10^9/L)	Recommendation: Maintain dose
Grade 3 (ANC < 1.5 x 10^9/L-0.5 x 10^9/L)	**Mandatory:** Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue the subject from the study.
Grade 4 (ANC < 0.5 x 10^9/L)	**Mandatory**: Permanently discontinue the subject from the study.
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.3°C)	**Mandatory**: Interrupt dose until resolved or next dose schedule. If abnormality persists, permanently discontinue the subject from the study.
Trombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L)	Recommendation: Maintain dose
Grade 2 (PLT < 75 - 50 x 10^9/L)	Recommendation: Maintain dose
Grade 3 (PLT < 50 - 25 x 10^9/L)	Recommendation: Interrupt dose until resolved to ≤ Grade 2 or next dose scheduled. If abnormality persists, permanently discontinue the subject from the study.
Grade 4 (PLT < 25 x 10^9/L)	**Mandatory**: Permanently discontinue the subject from the study.
Investigations (Hepatic)	
Isolated Direct Bilirubin	
Grade 1 (>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal)	Recommendation: Continue study treatment

[redacted]

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. 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 from study treatment.
Isolated ALT elevation	
Grade 1 (> ULN - 3.0 x ULN)	Recommendation: Maintain dose
Grade 2 (> 3.0 - 5.0 x ULN)	Recommendation: Maintain dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; if abnormal lab values are confirmed upon the repeat test, then monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. If resolved, then continue with next dose scheduled.
Grade 3 (> 5.0 - 20.0 x ULN)	Recommendation: Interrupt dose. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN. If resolved, then continue with next dose scheduled
Grade 4 (> 20.0 x ULN)	**Mandatory:** Permanently discontinue the subject from the study.
Combined [c] elevations of ALT and bilirubin (direct [conjugated])	
For subjects with normal baseline ALT and direct bilirubin value: • ALT > 3.0 x ULN combined with direct bilirubin > 2.0 x ULN without evidence of cholestasis[c] OR For subjects with elevated baseline ALT or direct bilirubin value: • ALT > 2 x baseline AND direct bilirubin > 2.0 x baseline	**Mandatory:** In the absence of cholestasis[c] (ALP < ULN), subject should be immediately discontinued from study treatment. Repeat LFTs[b] as soon as possible, preferably within 48 hours from awareness of the abnormal results, then with weekly monitoring of LFTs[b]), or more frequently if clinically indicated, until ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks. Refer to Section 6.5.1.1 for additional follow-up evaluations as applicable.
Infections	

[redacted]

Grade 1	Recommendation: Maintain dose level
Grade 2	Recommendation: Maintain dose level
Grade 3	**Mandatory**: Interrupt dose until resolved. If resolved, then continue with next dose scheduled.
Grade 4	**Mandatory**: Permanently discontinue the subject from the study.
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 subject 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 subject is deemed medically stable in the opinion of the investigator.
	• Administer appropriate medical therapy (e.g. analgesics such as paracetamol /acetaminophen or NSAIDs and anti-histamines), as per local institutional guidelines and clinical presentation.
	  ○ Steroids should be used with caution unless clinically indicated (e.g. management of hypersensitivity/anaphylaxis).
	• If symptoms resolve, restart infusion per investigator discretion at a slower rate 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 for prophylaxis of infusion related reactions, including subsequent infusions.
	• In case of recurring infusion reactions despite premedication and prolonged infusion, consider discontinuation of study treatment.

[redacted]

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.

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

[a] Common Terminology Criteria for Adverse Events (CTCAE Version 5.0)

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], and alkaline phosphatase

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

6.5.1 Follow-up for toxicities

Subjects whose study drug treatment is interrupted or permanently discontinued due to an AE must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts (e.g. ophthalmologist, endocrinologist, dermatologist, psychiatrists etc.) should be consulted as deemed necessary. All subjects must be followed up for AEs and SAEs for 105 days as applicable following the last dose of study of treatment.

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

Subjects with an elevation of transaminases in combination with an increase of total bilirubin (TBIL) and a normal ALP may be indicative of potential DILI, and should be considered as clinically important events.

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

Subjects meeting any of the following criteria will require further follow-up as outlined below:

- **For subjects with normal ALT and direct bilirubin value at baseline:**
  ALT > 3.0 × ULN combined with direct bilirubin > 2.0 × ULN without evidence of cholestasis
- **For subjects with elevated ALT or direct bilirubin value at baseline:**
  ALT > 2 × baseline AND direct bilirubin > 2 × baseline
- **For subjects with normal ALT at baseline:** ALT > 5.0 × ULN for more than 2 weeks
- **For subjects with elevated ALT at baseline:** ALT > 3.0 × baseline for more than 2 weeks

For these subjects, repeat LFTs as soon as possible, preferably within 48-72 hours. Subjects should be closely monitored and workup for competing etiologies initiated, including hemolysis or cholestasis, defined as ALP elevation > 2.0 × 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).

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

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR, and ALP.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

[redacted]

3. Further central testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Additional central 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 and meets the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus, meet the definition of SAE and should be reported as a SAE using the term "potential drug-induced liver injury". All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

6.6.2 Recommended treatment of adverse events

Treatment for AEs will be determined by the study investigator. Medication used to treat AEs must be recorded on the appropriate CRF Preparation and dispensation.

6.7 Handling of study treatment and additional treatment

6.7.1 Handling of study treatment

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

The pharmacist or delegate will inventory and acknowledge receipt of all shipments of investigational treatment. The pharmacist will also keep accurate records of the quantities of study drug dispensed and used by each subject. Monitoring of drug accountability will be performed by field monitors during onsite or remote monitoring visits, and at the completion of the trial.

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

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

[redacted]

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

6.7.2 Instruction for prescribing and taking study treatment

All the instructions will be provided in the pharmacy manual.

7 Informed consent procedures

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

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

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

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

Information about common side effects already known about the investigational drug can be found in the Investigator’s Brochure. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator’s Brochure 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 subject.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

The study includes an optional biomarker component which requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the investigator presents this option to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional biomarker assessments will in no way affect the subject’s ability to participate in the main research study.

[redacted]

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

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

8 Visit schedule and assessments

Table 8-1 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 subject's source documentation.

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

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

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

Allowed visit windows are specified as follows:

- Screening assessments must occur within 84 days (12 weeks) ± 7 days prior to the enrollment as per Table 8-1.
- For all screening visits a general ± 7 day visit window is allowed
- A ± 7 day visit window is allowed at Week 1 Day 1 (calculated from day of consent)
- A ± 3 day visit window is permitted on assessments at Week 3 Day 1.
- For all other dosing visits a general ± 7 day visit window is permitted on assessments
- A ± 7 day visit window for the end of treatment phase (last infusion + 2 weeks) is allowed.
- A + 7 day visit window for the end of the safety follow-up phase (last infusion + 105 days) is allowed.

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

[redacted]

Table 8-1 Assessment Schedule

	Reference to protocol section	Screening phase			Treatment phase						End of treatment (EOT)	Follow up phase (as applicable)[f]
Visit Number		**1**	**2**	**3**	**101**	**102**	**In every 4th Cycle**	**108**	**In every 4th Cycle**	**114**		
Visit on Day1 of the week (unless otherwise specified)[a]		**Screening (-Day 84 to Day -1)**			**Wk1**	**Wk3**	**Wk7, 11, 4qWk**	**Wk27**	**Wk31, 35, 4qWk**	**Wk 51: last infusion**	**Wk 53**	**Last infusion + 105d**
		Day -84 to Day -57	**Day -56 to Day -29**	**Day-28 to Day -1**								
Screening												
Obtain Study Informed Consent	8.1	X										
Priapism medical history questionnaire	8.1	X										
Obtain optional Informed Consent for future biomarker studies	8.1	X										
Disposition assessment												
End of phase disposition	8			X							X	X
Subject history												
Demography	8.1.3	X										
Inclusion/exclusion criteria	5.1/5.2	X										
Medical History	8.1.3	X										
Sickle Cell – VOC history	8.1	X										
Priapism History[e]	8.1	X										
Alcohol history	8.1	X										

[redacted]

	Reference to protocol section	Screening phase			Treatment phase						End of treatment (EOT)	Follow up phase (as applicable)[f]
Visit Number		**1**	**2**	**3**	**101**	**102**	**In every 4th Cycle**	**108**	**In every 4th Cycle**	**114**		
Visit on Day1 of the week (unless otherwise specified)[a]		**Screening (-Day 84 to Day -1)**			**Wk1**	**Wk3**	**Wk7, 11, 4qWk**	**Wk27**	**Wk31, 35, 4qWk**	**Wk 51: last infusion**	**Wk 53**	**Last infusion + 105d**
		Day -84 to Day -57	**Day -56 to Day -29**	**Day-28 to Day -1**								
Smoking history	8.1	X										
Drug history	8.1.3	X										
Physical rxamination												
Physical examination	8.3.1			X							X	
Abbreviated physical exam	8.3.1				X	X	X	X	X	X		
Vital signs	8.3.1			X	X	X	X	X	X	X	X	
Height	8.3.1			X								
Weight	8.3.1			X	X	X	X	X	X	X		
Laboratory assessments												
Hematology	8.3.2			X	X	X	X	X	X	X	X	X
Platelets (Local)[d]	8.3.2			X	X	X	X	X	X	X	X	X
Chemistry	8.3.2			X	X	X	X	X	X	X	X	X
Coagulation	8.3.4			X	X	X	X	X	X	X	X	X
Urinalysis	8.3.3			X	X	X	X	X	X	X	X	X
Hepatitis testing	8.3.6			X								
HIV test	8.3.8			X								
Optional blood sample for future biomarker	8.5			X							X	
Efficacy assessments												
Priapic Events	8.2.2.1 and 8.2.2.2	X	X	X	Continuous							

[redacted]

	Reference to protocol section	Screening phase			Treatment phase						End of treatment (EOT)	Follow up phase (as applicable)[f]
Visit Number		**1**	**2**	**3**	**101**	**102**	**In every 4th Cycle**	**108**	**In every 4th Cycle**	**114**		
Visit on Day1 of the week (unless otherwise specified)[a]		**Screening (-Day 84 to Day -1)**			**Wk1**	**Wk3**	**Wk7, 11, 4qWk**	**Wk27**	**Wk31, 35, 4qWk**	**Wk 51: last infusion**	**Wk 53**	**Last infusion + 105d**
		Day -84 to Day -57	**Day -56 to Day -29**	**Day-28 to Day -1**								
Sickle Cell – VOC Event	8.2.2	Continuous										
Chest x-ray[b]	8.2.2	X			As clinically indicated							
Hospitalization	8.2.2	X	X	X	Continuous							
Prior/concomitant medications – Analgesic	8.2.2	X	X	X	Continuous							
Prior/concomitant medications - Hydroxyurea	8.2.2	Continuous										
Transfusion	8.2.2	Continuous										
Employment status and sick time	8.2.2	X	X	X							X	
[redacted]												
Safety assessments												
ECG	8.3.5.1	-		X							X	
Cardiac imaging	8.3.5.2	X									X	
Urine protein/creatinine ratio	8.3.7	-		X							X	

[redacted]

	Reference to protocol section	Screening phase			Treatment phase						End of treatment (EOT)	Follow up phase (as applicable)[f]
Visit Number		**1**	**2**	**3**	**101**	**102**	**In every 4th Cycle**	**108**	**In every 4th Cycle**	**114**		
Visit on Day1 of the week (unless otherwise specified)[a]		**Screening (-Day 84 to Day -1)**			**Wk1**	**Wk3**	**Wk7, 11, 4qWk**	**Wk27**	**Wk31, 35, 4qWk**	**Wk 51: last infusion**	**Wk 53**	**Last infusion + 105d**
		Day -84 to Day -57	**Day -56 to Day -29**	**Day-28 to Day -1**								
Adverse Event/ Serious Adverse Event	10	Continuous										
IRR[c]	4.5	Continuous										
Prior/concomitant medications	6.2.1	Continuous										
Study Drug administration												
Crizanlizumab IV	6.1.1				X	X	X	X	X	X		

[a] In case the study drug is interrupted, the dose should be resumed as soon as possible. If the dose is delayed for more than 7 days, every effort should be made to bring the subject's infusions back onto the protocol-defined schedule (Section 6.5).
[b] Chest X-ray must be conducted during the screening period and must be repeated in case of suspected acute chest syndrome, during the during the treatment or follow-up.
[c] Certain adverse events reported in the AE/SAE eCRF as Infusion Related Reactions will require the IRR eCRF to be completed.
[d] Local sampling for platelet assessment will be performed throughout the trial for all subjects.
[e] The date, number, and duration of the priapic events in the 14-week period prior to consenting will be captured in a separate CRF.
[f] Subjects who will receive commercially approved crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up.

[redacted]

8.1 Screening

After signing the study informed consent form (ICF), the screening assessments will be done within the screening window prior to Week 1 Day 1 (see Table 8-1 for list of assessments to be performed). During this screening period, the prospective subjects will need to come to clinic for 3 visits: at Day -84, at Day -56, and at Day-28. At the first screening visit after signing the ICF (at Day -84), subjects will be briefed about the study requirements, including the instruction on how to record the priapic event(s) information as described in Section 8.2.4. At the first screening visit, the prospective subjects will also be asked about their prior medical history related to priapism. This information will be collected via a priapism medical history questionnaire. The investigator will obtain consent/assent of subjects and/or parents according to local procedures. The additional details of the procedure of informed consent has been provided in Section 7.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the subject. If the results from the central laboratory are partial or unavailable before the first infusion, local sampling is allowed. In addition, local re-sampling for platelet count test is allowed at any time in case of clumping or other issues reported from the central laboratory. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the subject will be considered a screening failure. For details of assessments, see Table 8-1. Assessments of subject reported outcomes should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

Re-screening of subjects is allowed if the subject has not been treated and was screened failed. In case of re-screening, site should enter this patient as a new subject with a new ID. A new informed consent form must also be signed. AEs and medical history will be assessed relative to the new informed consent date.

The study includes an optional biomarker component which requires a separate signature if the subject agrees to participate. For details, see Section 7.

8.1.1 Eligibility screening

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

Subject eligibility will be checked by the sponsor once all screening procedures are completed. The eligibility check form will be sent from the site to the sponsor via email for evaluation. Upon confirmation of eligibility, the sponsor will return the signed eligibility check form via email to the site. The investigator site will then be allowed to start treatment to the subject. Please refer and comply with detailed guidelines in the eligibility check user guidelines for the manual process.

8.1.2 Information to be collected on screening failures

Subjects who sign an informed consent but fail to be enrolled (subject who does not enter in the treatment phase) for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic

[redacted]

information, informed consent, Inclusion/Exclusion pages and, if applicable, withdrawal of informed consent must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced an SAE during the screening Phase (see Section 10 for SAE reporting details).

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

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

8.1.3 Subject demographics/other baseline characteristics

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

Following are the examples of the procedures that will be performed at the baseline:

- Background medical information including sickle cell and VOC history, priapism history, blood transfusion history, leg ulcer, ECG, cardiac imaging and urine protein/creatinine ratio.
- Relevant and current medical history; SCD genotypes (HbSS, HbSβ^0, HbSC, HbSβ^+, and others).
- Concomitant medication use; history of analgesic and hydroxyurea use.
- Complete physical examination.
- Vital signs (blood pressure pulse measurement, respiratory rate, oxygen saturation, and body temperature), weight and height.
- Clinical laboratory evaluations
- Chest X-ray, if none has been performed within 3 months of Day 1

Drug, alcohol and smoking history will also be collected. The details of other baseline characteristics and assessments that will be performed at the screening for eligibility are detailed in Table 8-1.

8.2 Efficacy

8.2.1 Primary efficacy endpoint

Priapism is defined as an unwanted or painful penile erection lasting at least 60 minutes. The end of the priapic event will be the duration when the unwanted erection has resolved. This event will be self-reported, and this data should be collected throughout the study period. In order to be treated as independent priapic events, two events will have to be separated by at least 2 hours, and the event would have to return to baseline during those 2 hours. Primary efficacy endpoint will be assessed by evaluating the percent reduction in priapic events by 26 weeks.

[redacted]

8.2.2 Secondary efficacy endpoints

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

8.2.2.1 Priapic events

Priapism, as defined in the primary efficacy endpoint (Section 8.2.1), will also be assessed by evaluating the rate of priapic events by weeks 26 and 52.

8.2.2.2 Acute priapic events

Acute priapic events are defined as unwanted or painful erections that last at least 4 hours and need a visit to the emergency room. Management of ischemic priapism requires aggressive and stepwise procedures to achieve prompt resolution. Aspiration/irrigation, in combination with intracavernous injections of α-agonist is usually the first-line therapy. Penile blood aspiration involves using a transglanular intracorporal angiocatheter insertion or a proximal penile shaft needle access. The percent reduction in acute priapic events from baseline by 26 and 52 weeks of treatment will be assessed.

8.2.2.3 Uncomplicated VOC

An uncomplicated pain crisis is defined as an acute event of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; 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.

8.2.2.4 Complicated VOC

8.2.2.4.1 Acute Chest Syndrome

Acute Chest Syndrome is defined on the basis of the finding of a new pulmonary infiltrate involving at least 1 complete lung segment that was consistent with alveolar consolidation, but excluding atelectasis (as indicated by chest X-ray). At least 1 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. Acute chest syndrome will be considered resolved when the subject is no longer hospitalized (unless for reason other than the acute chest syndrome event) and none of the additional signs or symptoms above are present.

8.2.2.4.2 Hepatic sequestration

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.

[redacted]

8.2.2.4.3 Splenic sequestration

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.

General considerations for VOC assessments

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 themselves to be considered. If such events precipitates VOC, the VOC event will be documented separately.

For each visit to a medical facility for a pain event thought to be a VOC, the following information must be documented in the eCRF; diagnostic evaluation for the event, subject treatment and management, course, duration of the crisis, and outcome. For subjects 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.

Subjects should be encouraged to contact the investigator (or surrogate from the site) when they believe they are experiencing a VOC, which they believe they can manage at home, both for treatment guidance and for accurate information which may be obtained for the VOC eCRF page. VOCs and other acute pain crisis managed at home will be reconciled at regular study visits and captured in the corresponding VOC eCRF.

If a subject experiences a VOC surrounding a protocol-scheduled visit day, and the subject presents for this visit, it will be counted as a VOC that led to a healthcare visit (provided the event meets the criteria for VOC discussed above). VOC is not a known contra-indication, but dosing during a crisis should be at investigator's discretion.

General considerations for Chest X-Rays and transfusions

Chest X-Ray must be conducted during the screening period. Chest X-Ray must be repeated in case of suspected acute chest syndrome.

Transfusion data should be collected during the screening period until the subject end of treatment (EOT). Episodic transfusion in response to worsened anemia or VOC is permitted.

[redacted]

Table 8-2 Vaso-Occlusive Crisis Assessment Collection Plan

Procedure / Assessment collection plan	Screening/Baseline	During Treatment/Follow-up
Chest X-Ray	Mandated	If clinically indicated
Vaso-Occlusive Crisis information	Mandated	Mandated, when VOC crisis occurs
Concomitant medication - Analgesic	If clinically indicated	Mandated, when VOC crisis occurs
Hospitalization details	If clinically indicated	Mandated, when VOC crisis occurs and hospitalization is done
Transfusion	If clinically indicated	If clinically indicated
Employment status and sick time	If clinically indicated	If clinically indicated

[redacted]

8.2.4 Collection of priapic event information

Electronic reporting tools have been shown in adolescents to have additional advantages over the paper format for accuracy as well as compliance in recording PROs (McGrath et al 2008). In SCA subjects, daily reporting tool have been shown a more sensitive means of capturing reported pain frequency than through retrospective interviews (Porter et al 1998).

[redacted]

In this study, an electronic event reporting system, paper system or a call center will be used to collect information on the event by answering a few simple questions. The questionnaire will include information on what triggered the event, the event duration, and how the event was managed.. Subjects will receive daily reminders to record whether or not they have experienced a priapic event. Reconciliation of the events will be conducted by the site personnel at each scheduled study visit.

8.2.5 Appropriateness of efficacy assessments

The primary objective of this study is to evaluate the clinical efficacy of crizanlizumab in SCD-related priapism. A very significant proportion of male patients, ranging from 35% to 89%, with SCD have a history of priapism (Howard and Telfer 2015). Scientific evidences suggested a role of P-selectin for the priapic events. In this study, the hypothesis is that crizanlizumab treatment will reduce priapic events by at least 25% in SCD patients with priapism. Therefore, the current efficacy assessment plan of quantifying the reduction in priapic event is considered appropriate.

Sickle cell–related pain crises were defined as acute events of pain, with no medically determined cause other than a vaso-occlusive event that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drugs. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events. Therefore, the planned assessment could be considered appropriate for this indication.

8.3 Safety assessments

Safety will be monitored by assessing physical examinations, vital signs, ECG, laboratory assessments including hematology, chemistry, coagulation, urinalysis and as well as collecting of the AEs at every visit. For details on AE collection and reporting, refer to Section 10.

8.3.1 Physical assessments

The physical assessments must be performed by the investigator as scheduled in Table 8-3.

[redacted]

Table 8-3 Physical assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination will be performed at screening and within 7 days following last infusion. An abbreviated (short) physical exam will include the examination of general appearance and vital signs (blood pressure [BP] and pulse), as well as additional components of the physical exam, as needed based on observed signs or reported symptoms. A short physical exam will be performed at all visits for which there is a scheduled study drug infusion. Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the subject's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the subject's CRF.
Vital sign	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate, oxygen saturation, and body temperature will be measured as specified in Table 8-1.
Height and weight	Height in centimeters (cm) will be measured at screening. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at screening and all visits for which there is a scheduled study drug infusion (for dosing), as specified in Table 8-1.

8.3.2 Laboratory evaluations

Clinical laboratory analyses (hematology, chemistry, urinalysis, coagulation, hepatitis and HIV markers) are to be performed centrally according to the schedule of assessments and collection plan outlined in Table 8-1. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/. Visit windows are allowed for all visits (see Section 8).

Novartis must be provided with a copy of the central laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a subject 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 subjects in the study and evaluating any abnormalities for clinical significance.

For assessment of subjects' eligibility to the study, only laboratory results from the central laboratory will be used (except in the event that the results from the central laboratory are not available at time of the first infusion, then eligibility may be based on the results from the local laboratory. In such a case, the results of the local laboratory will need to be recorded in the eCRF unscheduled pages and copy of the local lab normal ranges must be provided).

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE if central laboratory results are unevaluable or inconclusive, or when the treating physician cannot wait for central laboratory results for decision making. In this

[redacted]

particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

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

Laboratory assessments can be repeated during the screening period as deemed appropriate by the investigator.

At any time during the study up to safety follow-up, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g. require dose interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. The severity of laboratory data will be graded using the Common Terminology Criteria for Adverse events (CTCAE) version 5.0 or later. Additional analyses are left to the discretion of the investigator.

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

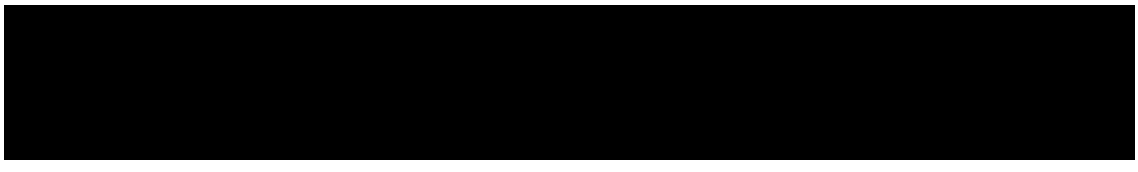


Table 8-4 Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, reticulocytes (%), Platelets*, Red blood cells, White blood cells, RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable)
Chemistry	, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting), estimated glomerular filtration rate (eGFR).
Urinalysis	**Macroscopic Panel** (Dipstick) will be done locally: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, , Specific Gravity, Urobilinogen **Microscopic Panel** will be performed if dipstick is positive: Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells Urine creatinine/protein ratio, Microalbumin
Coagulation	Prothrombin time (PT) , International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR, HCV Ab (at screening only)
Additional tests	HIV Ab (at screening only)

Glomerular filtration rate (using CKD-EPI formula):

Glomerular filtration rate = $141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.159$ [if black]

$\kappa = 0.9$ if male.

$\alpha = -0.411$ if male

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

Scr: Serum creatinine (mg/dL)

8.3.3 Urinalysis

Macroscopic urinalysis dipstick analysis (blood, protein and glucose) will be performed locally according to the schedule of assessments and collection plan outlined in Table 8-1. Detailed urinalysis panel is described on Table 8-4. Microscopic panel will be performed centrally if dipstick is positive.

[redacted]

8.3.4 Coagulation

Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT) will be assessed centrally according to the schedule of assessments and collection plan outlined in Table 8-1.

8.3.5 Cardiac assessments

8.3.5.1 Electrocardiogram (ECG)

Standard 12-lead ECG will be performed (in the supine position) after the subject has been resting for 5-10 min prior to ECG assessments.

A standard 12 lead ECG will be performed

- at screening
- at the end of treatment

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.

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, subject initials (where regulations permit), subject number, date, and kept in the source documents at the study site.

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

8.3.5.2 Cardiac imaging

Cardiac imaging will be performed by Echocardiogram (ECHO) in order to assess the left ventricular ejection fraction (LVEF) and mean pulmonary arterial pressure (mPAP), as estimated from the tricuspid regurgitation jet velocity (TRV) if assessable, or otherwise by other formula (per institutional preference). This assessment will be performed locally, interpreted by site personnel as per Table 8-1, and documented on the CRF page. Each echocardiography must be kept in the source documents at the study site. Clinically significant echocardiography abnormalities present at screening when the subject signed informed consent should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the subject.

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

8.3.6 Hepatitis markers

Hepatitis testing will be performed centrally as per Table 8-1.

[redacted]

8.3.7 Urine protein/creatinine ratio

At screening a urine sample (at least 15 ml) will be collected and sent to the central laboratory for urinary protein/creatinine ratio to assess the eligibility of the subject. The assessment will be repeated at the EOT. First morning void samples must not be used for this analysis.

8.3.8 Additional test

HIV screening will be performed centrally as per Table 8-1.

8.3.9 Appropriateness of safety measurements

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

8.4 Additional assessments

[redacted]

[redacted]

[redacted]

8.4.2 [redacted]

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

[redacted]

[redacted]

8.5 Optional use of biological samples

If the subject agrees, additional blood sample will be collected at screening visit and EOT for future biomarker analysis outside of this study. The sample may be stored up to 15 years for future biomarker analysis and additional studies related to crizanlizumab or SCD. This may include research to help develop ways to detect, monitor or treat SCD. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability. The biological sample collection is optional and necessitates the consenting of the subject as described in Section 7.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Death
- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the subject
- Discontinuation to study treatment due to toxicity that result in treatment discontinuation (see Section 6.5)
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study

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

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

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

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

- new/concomitant treatments
- AE/SAE

Subjects who discontinue study treatment should undergo an EOT visit within 14 days of the last dose of the discontinued study treatment, followed by a 105 day safety follow-up as applicable. At EOT visit, all the assessments as listed in Table 8-1 will be performed. If the

[redacted]

decision to discontinue the subject occurs at a regularly scheduled visit, that visit may serve as the EOT visit rather than having the subject return for an additional visit.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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

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

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

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

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

All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed. Subjects lost to follow up should be recorded as such on the appropriate CRF.

9.1.4 Early study termination by the sponsor

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

[redacted]

visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit (defined as last patient last visit), and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision. Subjects who will receive commercially approved crizanlizumab approximately 4 weeks after their last dose of study treatment, do not need to complete the 105-day follow-up. All other subjects are required to complete the 105-day follow-up.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

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

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.3):

1. The Common Terminology Criteria (CTC) AE grade (version 5.0 or higher*)*. If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an AE or not) will also be collected though a Death form.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a

[redacted]

lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.3 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

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

- Dose not changed
- Drug interrupted/withdrawn
- Its outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown).

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

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

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

Adverse event monitoring should be continued for at least 105 days following the last dose of study treatment as applicable

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

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

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

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

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

[redacted]

10.1.2 Protocol exempt AEs & SAEs

Protocol Exempt AEs & SAEs are implemented in the crizanlizumab program. VOCs must be reported on the VOC page in the eCRF. As VOCs are considered secondary endpoints for the purpose of evaluation of efficacy, AEs and SAEs involving VOCs SHOULD NOT be reported as AEs or SAEs for the purpose of this study. These events will not be considered as SAEs in regard to reporting requirements. Procedures which are directly related to the VOC, e.g. ventilation of a patient with acute chest syndrome are considered part of the VOC and will not be reported as AE/SAEs but entered in the CRF-page "concomitant non-drug therapies/procedures". Additional events or complications which are not VOCs itself will be reported as AE/SAEs. Details will be given in the CRF-completion guidance. In case that new information arises which changes the diagnosis of a VOC, i.e. gives another medically determined explanation than vaso-occlusion in the opinion of the investigator, the event has to be reported according to the rules of Section 10.1 and must be reported to Novartis within 24 hours of learning of the new information.

The events in Table 10-1 will not be reported as AEs/SAEs.

Table 10-1 List of Events Not Requiring AE/SAE Reporting

VOC Events

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

[redacted]

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

10.1.3 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

[redacted]

- 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 subject's general condition
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject 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.

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

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

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

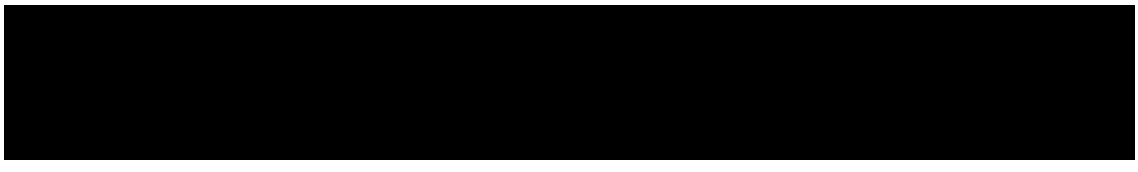
10.1.4 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until up to105 days after the subject has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent events must be reported as follow-up to the original event within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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



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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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 study treatment that this SAE has been reported.

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

10.1.5 Pregnancy reporting

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the 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.

10.1.6 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, subject or consumer (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

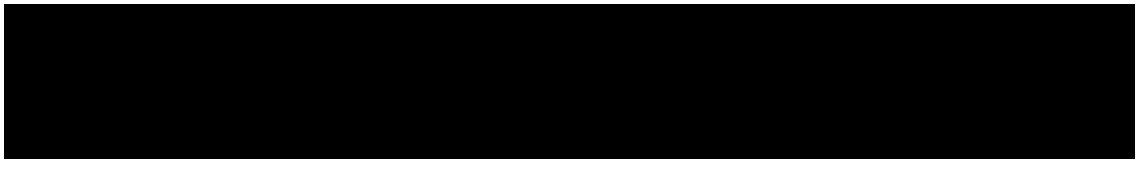


Table 10-2 Guidance for capturing the study treatment errors including misuse/abuse

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

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

10.2 Additional safety monitoring

10.2.1 Steering committee

The steering committee will be established and comprised of SCD and priapism medical experts as well as Novartis representatives from the Clinical Trial Team.

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

11 Data Collection and Database Management

11.1 Data collection

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

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

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

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

[redacted]

11.2 Database management and quality control

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

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

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

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

11.3 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the

[redacted]

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Summary statistics for continuous variables will generally include the number of subjects, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum, and maximum. For categorical or binary variables, the number and percent of subjects in each category will be presented.

The primary analysis of study data for the primary clinical study report (CSR) will be based on all subject data up to the Week 26 (up to assessments taken on Week 27 Day 1 before infusion). The additional data for any subjects continuing to receive study drug after this time, as allowed by the protocol, will be further summarized in a final study report once these subjects have completed or discontinued the study.

Baseline period is defined as the 12 weeks screening period prior to the first infusion of crizanlizumab 5 mg/kg at Week 1 Day 1.

12.1 Analysis sets

Full Analysis Set (FAS): The FAS include all enrolled subjects to whom the study treatment has been assigned regardless of whether or not they have received at least 1 dose of study treatment or have at least 1 post-baseline assessment.

Safety Analysis Set (SAF): The SAF will consist of all subjects who received at least 1 dose of study treatment.

All efficacy analyses will be performed on subjects in FAS who have completed treatment.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline disease characteristics will be listed and summarized descriptively for all subjects in the FAS as well as for those subjects in FAS who have completed the treatment.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum and maximum will be presented.

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

Prior disease information will also be summarized.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum and maximum will be presented.

[redacted]

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

The number of subjects with dose interruption or permanent discontinuation and the reasons will be summarized for all subjects 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 for all subjects.

12.4 Analysis of the primary endpoint

The primary objective of this study is to evaluate clinical efficacy of crizanlizumab 5 mg/kg, over 26 weeks compared to baseline in sickle cell subjects with a history of priapism.

12.4.1 Definition of primary endpoint

The primary endpoint of the study is percent reduction from baseline in priapism events by 26 weeks (i.e. up to pre-infusion Week 27, Day 1). Priapism event is defined as unwanted, or painful erection lasting at least 60 minutes, self-reported.

12.4.2 Statistical model, hypothesis, and method of analysis

It is expected that crizanlizumab treatment reduces priapic events by at least 25% in SCD subjects with priapism. Demonstration of significant percent reduction from baseline in priapic events will be evaluated using the following hypothesis:

H_0: $p < 0.25$, where p is the percent reduction in priapic events by 26 weeks.

H_1: $p \geq 0.25$, where p is the percent reduction in priapic events by 26 weeks.

If the above null hypothesis is rejected, significant reduction in priapic events will be demonstrated statistically.

Assuming uniformity in the occurrence of priapic events before exposure to crizanlizumab treatment, baseline will be adjusted for 26 weeks for analysis purpose.

Percent reduction from baseline in priapic events will be tested using a nonparametric test (i.e. Wilcoxon's Sign Rank test). Hodges-Lehmann estimate of median percent reduction in priapic events will also be reported, along with corresponding 95% confidence intervals. The significance of the efficacy endpoints will be assessed at $\alpha = 0.05$ level.

The primary analysis will be performed on all FAS subjects who have completed 26 weeks on treatment.

Number of priapic events will be summarized at baseline (adjusted for 26 weeks) and by Week 26, and percent reduction from adjusted baseline by Week 26 will be summarized by mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum and maximum. In addition, subgroup analysis of the primary endpoint will also be performed based on the number of priapic events categories (i.e. <7, 7 – 13, 14 – 21, ≥ 22) at baseline. The priapic events categories may be re-grouped to ensure that there is adequate number of subjects in each

[redacted]

category for analysis. Additional analyses will also be performed for the subgroups of subjects with acute priapism and subjects who have experienced priapic episodes lasting less than one hour.

Further details will be provided in the SAP.

The imputation of missing data caused by intercurrent events will be handled by defining the estimand framework. The primary estimand is described by the following four attributes:

1. The target population comprises Sickle Cell Disease Patients with Priapism
2. The primary variable is percent reduction from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks.
3. Treatment of interest: investigational drug will be a crizanlizumab solution provided every 4 weeks with an additional loading dose 2 weeks after the first dosing. Further details about the investigational treatment are provided in Section 6.
4. The intercurrent events are the events occurring after enrollment that may impact the treatment effect. The intercurrent events of interest are listed below:
    a. Treatment discontinuation
    b. 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) or of prophylactic treatment for priapism
    c. Intake of analgesic (including opioids) or ad hoc transfusions administered temporarily
5. The summary measure is the median percentage change from baseline period in priapic events (priapism defined as unwanted, or painful erection lasting at least 60 min self-reported) by 26 weeks.

Handling of the intercurrent events:

The approach of accounting for intercurrent events is as follows:

- **For the intercurrent events 4a:** Only data before study treatment discontinuation will be included. The data between treatment discontinuation and week 26 will be imputed using Poisson distribution (primary method to handle missing data).
- **For the intercurrent events 4b:** Only data before initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) or of prophylactic treatment for priapism will be included. The data between initiation or discontinuation of therapies to treat SCD or of prophylactic treatment for priapism and week 26 will be imputed using Poisson distribution (primary method to handle missing data).
- **For the intercurrent events 4c:** Data after intake of analgesic (including opioids) or ad hoc transfusions administered temporarily will be included (treatment policy strategy).

12.4.3 Handling of missing values/censoring/discontinuations

The missing values will be imputed for the primary analysis. Missing values will be imputed using Poisson distribution, assuming the same effect as observed data. Imputed datasets

[redacted]

(approximately 1,000) will be created, and each dataset will be analyzed using the method described for primary endpoint. The results will be combined using Rubin's rule (Barnard J and Rubin DB 1999) Further details will be outlined in the SAP.

As stated in Section 12.4.4 , the volume of missing data generated due to COVID-19 crisis will also be assessed and sensitivity analyses will be performed.

12.4.4 Sensitivity and supportive analyses

Sensitivity analyses

- To explore the robustness of analysis, sensitivity analysis as a 'tipping point approach will be performed for the primary endpoint to evaluate the impact of a deviation from the MAR assumption. The basic idea is to first impute the missing values using the multiple imputation (MI) method based on the missing at random (MAR) assumption, then adjusted by a delta value. The delta adjusting approach described in Ratitch et al (2013) will be used to find the tipping point, in a spectrum of conservative missing not at random (MNAR) assumptions, at which conclusions change from being favorable to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. A detailed description of the analysis will be provided in SAP.
- As part of the sensitivity analysis, treatment policy strategy (that is, data after the intercurrent events will be included) will also be applied for the intercurrent events 4a and 4b, described in Section 12.4.2.
- As part of the sensitivity analysis, the primary analysis will be analyzed on all subjects in FAS without missing data.
- Additionally, as the study is ongoing during COVID 19 pandemic, the impact of COVID-19 (if any) on the primary endpoint will be assessed in accordance to FDA's guideline entitled "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency". The analysis (as stated below) will be repeated on the FAS excluding the subjects with missing data due to COVID-19.
    - Percent reduction from baseline in priapic events will be tested using a nonparametric test (i.e., Wilcoxon's Sign Rank test). Hodges-Lehmann estimate of median percent reduction in priapic events will also be reported, along with corresponding 95% confidence intervals. The significance of the efficacy endpoints will be assessed at $\alpha = 0.05$ level.

Further details will be provided in the SAP, as needed.

Supportive analyses

- The supportive analyses described below will be performed on all FAS subjects who have completed 26 weeks on treatment. Missing values will be imputed as stated in Section 12.4.3.Annualized priapic Events Rate: The annualized rate of priapic events is defined as the total number of priapic events for a subject occurring from the date of initial infusion to the last contact date of the Treatment Phase of the study × 365.25 divided by the number of days during that same time period. This calculation accounts for early dropouts or lost to follow-up by extrapolating the priapism events rate of every subject to 1 year.

[redacted]

- Percent reduction from baseline in priapic events will also be assessed by Week 52.
- The total number of priapic episodes in the screening period (12 weeks baseline) will be compared to the total number of priapic episodes occurring in the first 12 weeks on treatment (0-12 weeks) using a nonparametric test (i.e. Wilcoxon's Sign Rank test). Additionally, a similar analysis will be performed to compare to the total number of priapic episodes occurring in the last 12 weeks on treatment (15-26 weeks).
- Number of priapic events will be summarized in the screening period (12 weeks baseline), in first 12 weeks on treatment (0-12 weeks), and in the last 12 weeks on treatment (15-26 weeks) and percent reduction from baseline will also be summarized.

12.5 Analysis of secondary endpoints

The secondary objectives in this study are to assess efficacy, safety and tolerability of crizanlizumab 5.0 mg/kg in SCD subjects.

12.5.1 Efficacy endpoints

The following secondary endpoints will be analyzed on all FAS subjects who have completed 52 weeks on treatment to evaluate clinical efficacy of crizanlizumab 5 mg/kg:

a. The rate of priapic events by 26 and 52 weeks of treatment.
b. The percent reduction from baseline in acute priapic events by 26 and 52 weeks of treatment.
c. The rate of uncomplicated VOC events (defined as an acute event of pain with no known cause for pain other than a vaso-occlusive event; and requiring treatment with a parenteral or oral opioids or other parenteral analgesic; but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration or priapism and these events will not be adjudicated) by 26 and 52 weeks of treatment. Events include both healthcare and self-reported events.
d. The rate of complicated VOCs (defined as acute chest syndrome, hepatic sequestration, splenic sequestration, and acute priapism) recorded by healthcare visit, by 26 and 52 weeks of treatment.

The efficacy endpoints will be assessed by 26 weeks and by 52 weeks.

12.5.2 Methods of analyses

Similar analyses on percent reduction in acute priapic events for subjects from full analysis set will be conducted, as done for primary endpoint.

Descriptive summary statistics including n, mean, standard deviation (SD), lower quartile (Q1),, median, upper quartile (Q3), minimum and maximum will be presented for the rate of events and number of priapic events at Baseline, by Week 26 and by Week 52. The change from baseline in Rates of Events at Week 26 (i.e. evaluation at Week 27, Day 1) and Week 52 (i.e. evaluation at Week 53, Day 1) will be summarized by n, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum and maximum.

As appropriate, the estimated median change from Baseline at 26 weeks (i.e. evaluation at Week 27, Day 1) and 52 (i.e. evaluation at Week 53, Day 1) weeks in events or events with

[redacted]

associated 95% CI using a non-parametric approach will be reported. The median percent reduction will also be presented by Week 26 and Week 52.

12.6 Safety endpoints

All the safety analyses will be based on the safety set.

The overall observation period will be divided into 3 mutually exclusive segments:

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

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

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

Serious adverse events will be tabulated.

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

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

Separate summaries will be provided for other significant AEs leading to discontinuation and AEs leading to dose adjustment.

12.6.1 Clinical laboratory evaluations

For results reported by the central laboratory, continuous hematology and chemistry results will be summarized descriptively in SI units at each scheduled time point. Visits summaries will include baseline and post baseline visits, including early termination and Follow-Up. Changes from baseline will also be summarized at each time point.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low or high for each visit value relative to whether the baseline value was normal, low or high. These summaries will be presented by laboratory test.

Coagulation parameters (as described in Section 8.3.4) will be summarized descriptively at each time-point. Changes from baseline will also be summarized.

Urinalysis results will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the

[redacted]

reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

Hepatitis markers and additional tests results will be summarized descriptively at screening only.

12.6.2 Other safety evaluations

Vital signs

Data on vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation, and body temperature) will be tabulated and listed for each visit, notable values will be flagged.

12-Lead ECG

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

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

Notable/abnormal values for safety data will be further specified in the RAP.

Echocardiogram

The assessments for Cardiac Imaging using ECHO will be summarized at screening and end of treatment visit.

Urine protein/creatinine ratio

The assessments for urine protein/creatinine ratio will be summarized descriptively at screening and end of treatment visit.

[redacted]

12.8 Interim analyses

No formal interim analysis will be performed for this study. As required, interim analyses will be performed for publication purposes only. No decision on study continuation will be based on these descriptive reports, and as such, no alpha adjustment will be needed.

12.9 Sample size calculation

A total of 34 evaluable subjects is required for the study to have approximately 80% power to detect at least 25% reduction in rates of priapic events (defined as an unwanted erection lasting at least 60 min reported via daily diary tool) with a mean baseline priapism event rate of 10.0 and standard deviation of the difference of 5.0, by 26 weeks.

The calculations were based on simulation with 5,000 repetitions (from Poisson distribution) using one-sample Wilcoxon's Signed-Rank Test and 2-sided α=0.05.

Retaining the same above assumptions, robustness of the estimated sample size was also validated using a one-sample t test.

Assuming a 5% dropout rate, approximately 36 subjects will be enrolled in the study.

Recruitment of the required number of subjects with priapism will be challenging as the incidence of priapic events are sporadic and varies over time intervals. Also, in the absence of relevant clinical data on priapism, the expected reduction and higher variability in events rates have been conservatively assumed. The above expected 25% reduction in rates of priapic events from baseline is based on medical expert opinion and feedback. L-glutamine (Endari™) was approved by the US FDA in July 2017 for the reduction of vaso-occlusive crises (VOCs), based on a 25% reduction. Since priapism is also considered to be a complicated VOC, the assumption was that the relative risk reduction of 25% (approved for VOC events), would be similar for priapism.

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board (IRB) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

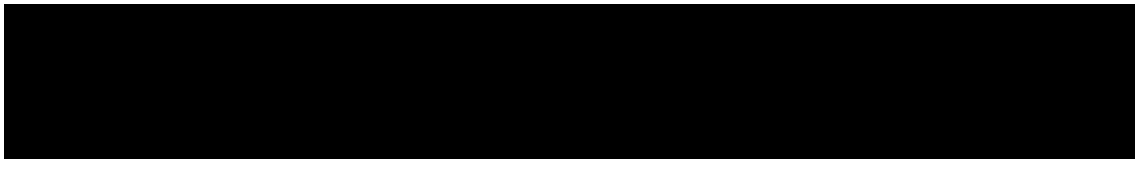
For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

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

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

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



14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject 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 at the study site should be informed according to local regulations.

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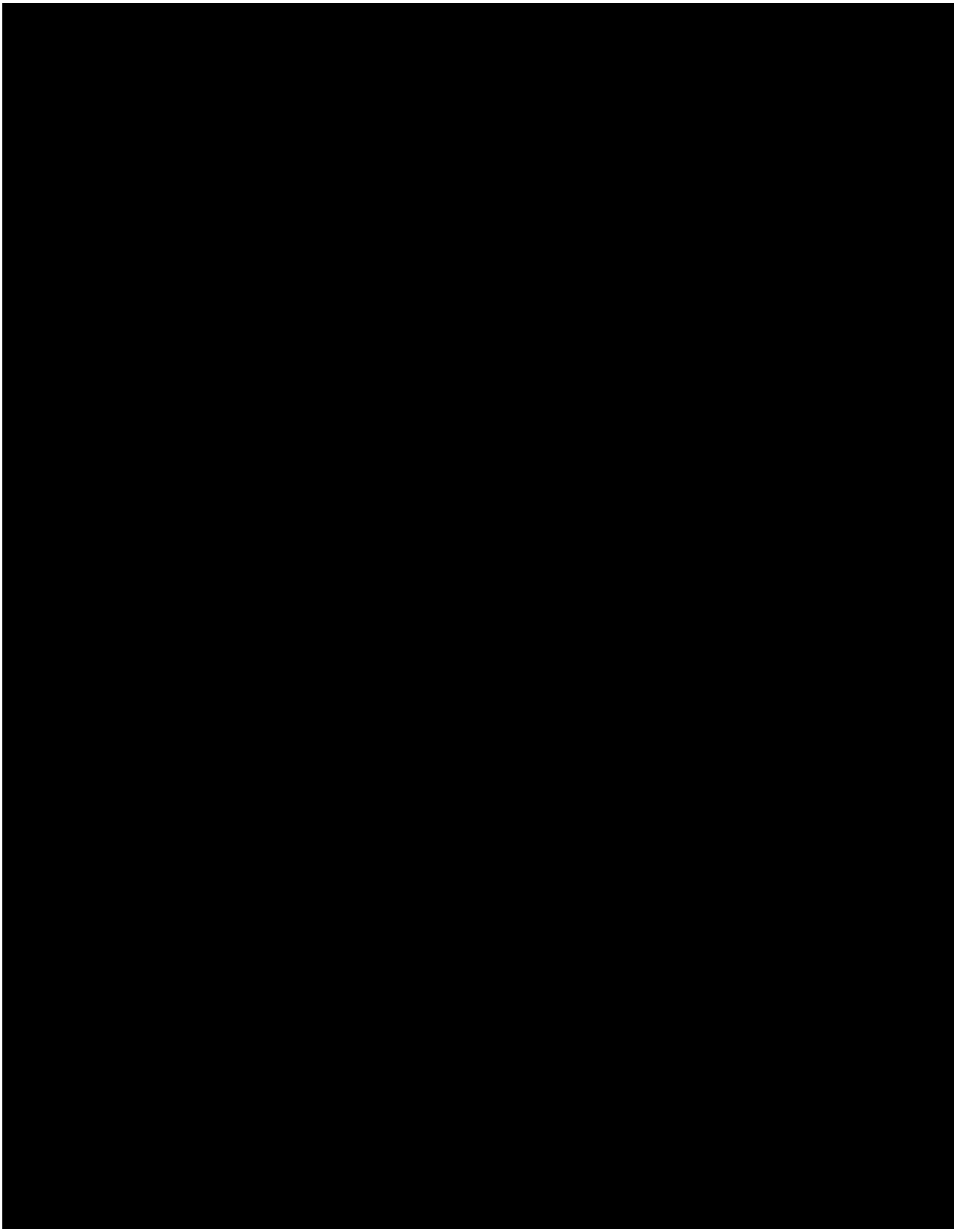
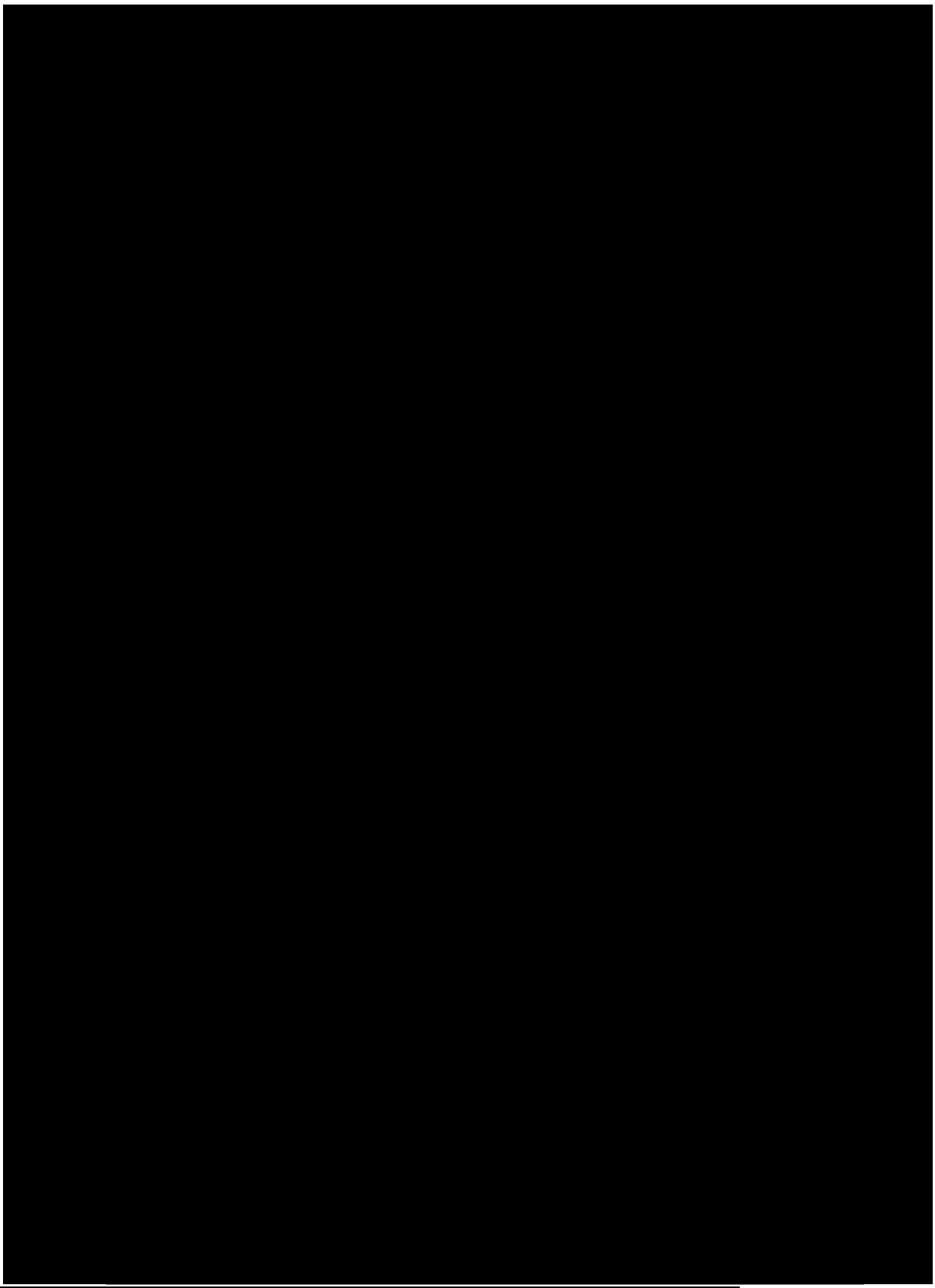
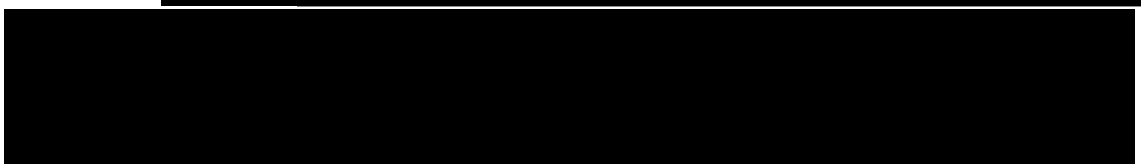
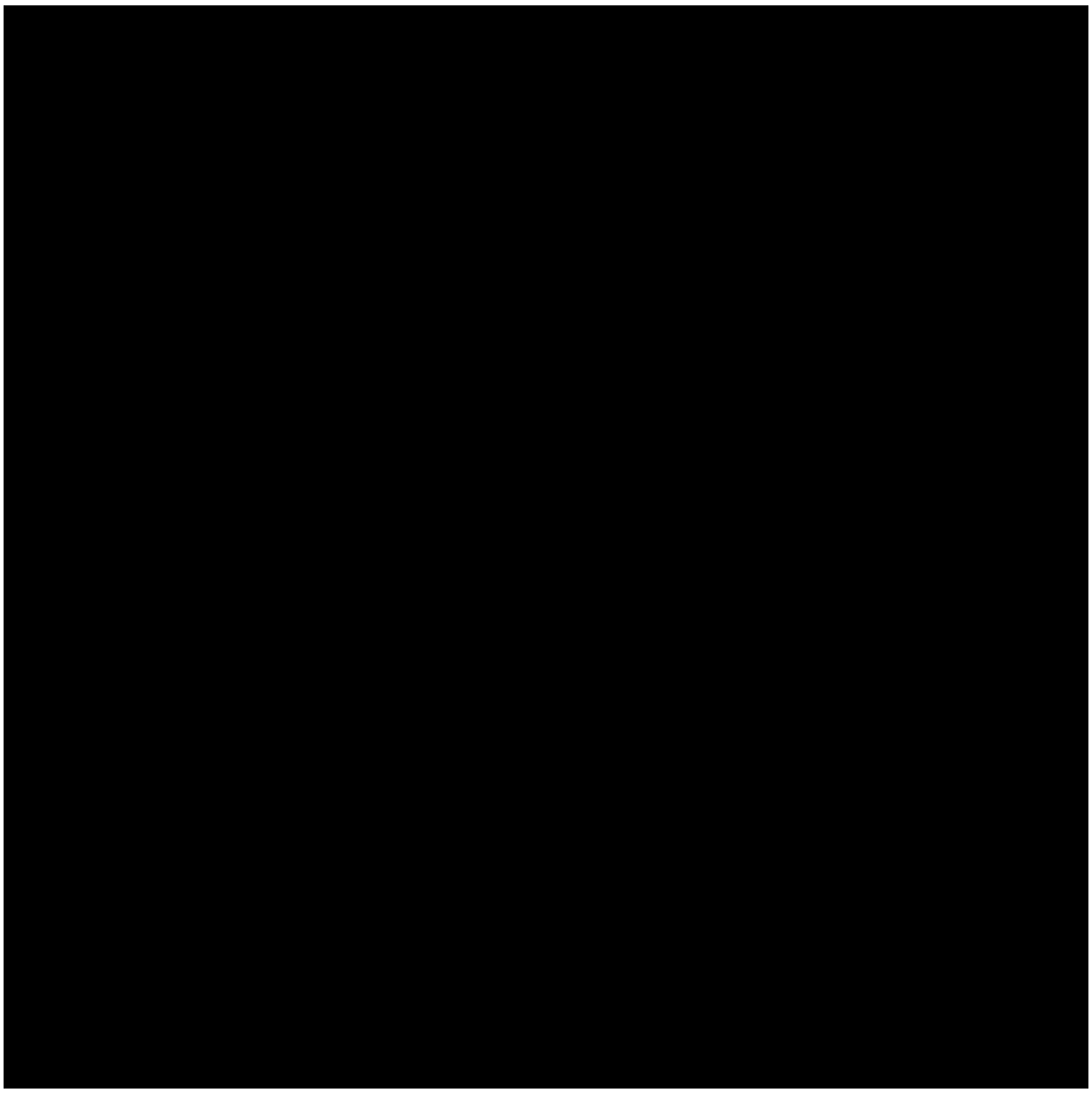
16 Appendices









Appendix 3: Priapism medical history questionnaire

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1. When did you first experience priapism?
   a. Childhood (≤ 12 years old)
   b. Teenager (13-17 years old)
   c. Young adult (18-25 years old)
   d. Adult (> 25 years old)

2. In what situations do you experience priapism? (select all that apply)
   a. Sexual arousal
   b. Sexual intercourse
   c. Sleep
   d. Other: _____

3. How often do you experience priapism?
   a. Daily
   b. Every other day
   c. Once a week
   d. Once a month
   e. Other: _____

4. How long does a typical priapism episode last?
   a. Less than half an hour
   b. 1 hour
   c. 2 hours
   d. 2-5 hours
   e. More than 5 hours

5. Have these priapism episodes caused pain?
   a. Yes
   b. No

6. Have you noticed a deformity or scarring of the penis?
   a. Yes
   b. No

7. What methods, if any, have you used for these priapism episodes? Have they helped? (select all that apply)
   a. Sexual activity ( ) Yes ( ) No
   b. Shower or bath ( ) Yes ( ) No
   c. Cold or hot packs ( ) Yes ( ) No
   d. Exercise ( ) Yes ( ) No
   e. Other: _____ ( ) Yes ( ) No

8. Have you received medical treatment for these priapism episodes? ( ) Yes ( ) No

[redacted]

9. What medical treatments have been given to you, if any? (select all that apply)
   a. Sedation
   b. Pain medication
   c. Anesthesia
   d. Oxygen
   e. Blood transfusions
   f. Hormone shots or pills
   g. Penile injections
   h. Penile surgery
   i. Other: _____

10. Have any of these treatments helped? (Please describe)
    _____

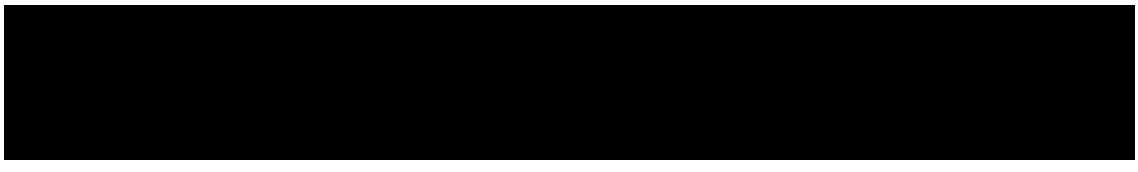
11. Is your priapism condition better or worse since it began?
    a. Better
    b. Worse
    c. About the same

12. Have your erections for "wanted" sexual situations worsened over time? ( ) Yes ( ) No ( ) Not Applicable

13. What treatments, if any, have you used to improve erections for "wanted" sexual situations? (select all that apply)
    a. Herbal supplements
    b. Yohimbine
    c. Viagra or Levitra or Cialis
    d. Penile constrictive ring
    e. Penile injections
    f. Other: _____

14. Has your priapism condition affected your partner relationship? ( ) Yes ( ) No ( ) Not Applicable

15. Has your priapism condition affected your feelings about yourself (self-image)? ( ) Yes ( ) No
    Please mark all that are applicable below:
    a. Exhausted
    b. Confused
    c. Angry
    d. Frustrated
    e. Sad
    f. Embarrassed
    g. Frightened
    h. Depressed
    i. Anxious



1. When did you first experience priapism?
   a. childhood (less than 12 years old)
   b. teenager (13-17 years old)
   c. young adult (18-25 years old)
   d. adult (more than 25 years old)

2. In what situations do you experience priapism?
   a. sexual arousal
   b. sexual intercourse
   c. sleep
   d. other: _____

3. How often do you experience priapism?
   a. daily
   b. every other day
   c. once a week
   d. once a month
   e. other: _____

4. How long does a typical priapism episode last?
   a. less than half an hour
   b. 1 hour
   c. 2 hours
   d. 2-5 hours
   e. more than 5 hours

5. Have these priapism episodes caused pain? ( ) Yes ( ) No

6. Have you noticed a deformity or scarring of the penis? ( ) Yes ( ) No

7. What methods, if any, have you used for these priapism episodes? Have they helped?
   a. sexual activity ( ) Yes ( ) No
   b. shower or bath ( ) Yes ( ) No
   c. cold or hot packs ( ) Yes ( ) No
   d. exercise ( ) Yes ( ) No
   e. other: _____ ( ) Yes ( ) No

8. Have you received medical treatment for these priapism episodes? ( ) Yes ( ) No

9. What medical treatments have been given to you, if any?
   a. sedation
   b. pain medication
   c. anesthesia
   d. oxygen

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e. blood transfusion
f. hormone shots or pills
g. penile injections
h. penile surgery
i. other: _____

10. Have any of these treatments helped? (Please describe)

_____

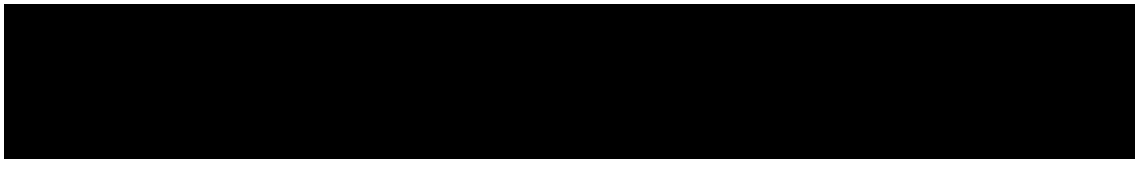
11. Is your priapism condition better or worse since it began?
a. better
b. worse
c. about the same

12. Have your erections for "wanted" sexual situations worsened over time?
( ) Yes ( ) No ( ) Not applicable

13. What treatments, if any, have you used to improve erections for "wanted" sexual situations?
a. herbal supplements
b. yohimbine
c. Viagra or Levitra or Cialis
d. penile constrictive ring
e. penile injections
f. other: _____

14. Has your priapism condition affected your partner relationship?
( ) Yes ( ) No ( ) Not applicable
Please describe: _____

15. Has your priapism condition affected your feelings about yourself (self-image)?
( ) Yes ( ) No
Please mark all that are applicable below:
a. exhausted
b. confused
c. angry
d. frustrated
e. sad
f. embarrassed
g. frightened
h. depressed
i. anxious



Appendix 5: List of drugs that may induce priapism

Table 16-1 List of non-antipsychotic and non-antidepressant drugs that may Induce Priapism

Category	Substances
Medicines associated with increased risk of priapism*	
Vasoactive erectile agents**	alprostadil, papaverine, phentolamine
α-adrenergic receptor antagonists	doxazosin, tamsulosin, terazosin, prazosin
Antihypertensives	hydralazine, propranolol, guanethidine
Anticoagulants	heparin, warfarin
Hormones	testosterone, gonadotropin-releasing hormone
Medicines that have been reported to cause priapism*	
Phosphodiesterase type 5 inhibitors	sildenafil, tadalafil
Anti-anxiety agents (including ADHD drugs)	methylphenidate, atomoxetine, hydroxyzine
Recreational Drug	Cocaine, crack cocaine
Herbal Supplement	Any herbal supplement to treat ED: including (but not limited to) the following products containing Tribulus terrestris, Saw palmetto extract, Panax ginseng, Dehydroepiandrosterone (DHEA), L-arginine, Rhodiola rosea, Yohimbe, Propionyl-L-carnitine, Horny goat weed (epimedium)

* PO drugs unless specified; ** Injectable solutions

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https://www.webmd.com/erectile-dysfunction/features/natural-remedies-for-erectile-dysfunction#1

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Table 16-2 List of Antidepressants and Antipsychotics that may induce priapism

USAN	Trade Names*	Type of Medication	Reference*
Buproprion	Wellbutrin, Zyban	Antidepressant	Am J Psychiatry. 1995;152(5):813
Trazodone	Desyrel	Antidepressant	Prim Care Companion J Clin Psychiatry. 2010; 12(2): PCC.09l00816.
Risperidone	Risperdal	Antipsychotic	Prim Care Companion J Clin Psychiatry. 2009; 11(4): 174–175. J Clin Psychiatry 2010-12(5)-e1–e2
Olanzapine	Zyprexa	Antipsychotic	J Clin Psychopharmacol. 1998 Aug;18(4):351-3; Am J Psychiatry. 2000;157(4):659; J Clin Psychiatry 2010-12(5)-e1–e2
Clozapine	Clozaril	Antipsychotic	Am J Psychiatry. 2000;157(4):659; J Clin Psychiatry 2010-12(5)-e1–e2
Choropromazine	Thorazine and Largactil	Antipsychotic	Int J Clin Pract. 1999 Mar;53(2):152-3.
Quetiapine	Seroquel	Antipsychotic	West J Emerg Med. 2014 Feb; 15(1): 114–116.
Sertraline	Zoloft	Antidepressant	J Am Acad Child Adolesc Psychiatry 46:7-July 2007
Citalopram	Celexa	Antidepressant	Pharmacotherapy 2002;22(4):538–541
Escitalopram	Lexapro	Antidepressant	Fed Pract. 2019 Feb 36(2), 92-96; J Inst Med. 2014;36(1):118–120.
Fluoxetine	Prozac, Sarafem	Antidepressant	J Pak Med Assoc 1996; 46: 45–6
Trifluoperazine	Stelazine	Antipsychotic	
Pericyazine	Neulactil	Antipsychotic	Postgrad Med J. 1974 Aug; 50(586): 523–524.
Paroxetine	Paxil, Seroxat	Antidepressant	Int J Psychiatry Med. 2015;50(3):326-34
Fluvoxamine	Faverin, Luvox	Antidepressant	Same MoA as citalopram, paroxetine and fluoxetine
Aripiprazole	Abilify	Antipsychotic	Ind Psychiatry J. 2016 Jan-Jun; 25(1): 119–121.
Haloperidol	Haldol	Antipsychotic	Encephale. 2014 Dec;40(6):518-21.
Amisulpride	Solian	Antipsychotic	Bulletin of Clinical Psychopharmacology 2016;26(1):85-6
Duloxetine	Cymbalta	Antidepressant	Ment Health Clin [Internet]. 2016;6(4):197-200.
Ziprasidone	Geodon	Antipsychotic	Pharmacotherapy 2002;22(8):1070–1073
Venlafaxine	Effexor	Antidepressant	J Am Acad Child Adolesc Psychiatry. 2000 Jan; 39(1):16-7.
Desvenlafaxine	Pristiq	Antidepressant	Same MoA as duloxetine and venlafaxine
Mirtazapine	Remeron	Antidepressant	Klinik Psikofarmakoloji Bulteni, suppl. S1; Istanbul Vol. 28, (2018): 233-234

*Other tradenames may exist for the same USAN. ** References are quoted as examples only and are non-exhaustive.

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