NOVARTIS

Clinical Development

SEG101/Crizanlizumab/Adakveo®

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)

Statistical Analysis Plan (SAP)

Author:	Trial Statistician; Lead Statistician
Document type:	SAP Documentation
Document status:	Final Amendment 4
Release date:	20-Feb-2024
Number of pages:	50

Template Version 4.0, Effective from 23-Apr-2021

Parent document: SOP-7012383

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
12-Jul-2019	Prior to DB Lock	Creation of final version	Not applicable - First version	Not applicable
24-Jan-2023	Prior to DB Lock	Creation of amendment 1	Alignment with most recent protocol (protocol v1.0, v2.0 and v3.0) and minor edits (including fixing typos)	All
			Update study design; The total number of subjects eligible for the study updated from 56 to 36 patients; The study design changed from age 16 years to lower the age of inclusion to 12 years old; Updated definition of baseline; Removed the phrase 'Mandatory safety follow-up period'; Information added related to safety follow-up period	Section 1.1 Study design
			Update on primary and secondary endpoints (Replaced "greater than" and "more than" by "at least"); Added the word "or" to align the definition of acute priapic events to that of priapism	Section 1.2 Study objectives and endpoints
			[redacted]	
			Added information on primary estimand(s)	Section 1.2.1 Primary estimand(s)
			Lower quartile (Q1) and upper quartile (Q3) were included in	Section 2 Statistical methods

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			the summary statistics of sub-sections of section 2 statistical methods	
			Updated definition of baseline period and added definition for Baseline (adjusted for 26 weeks); detailed summary measure is percentage change from baseline; Added text for reduction; Updated visit windows	Section 2.1.1 General definitions
			Updated definition of full analysis set (FAS)	Section 2.2 Analysis sets
			Added information on subgroup analyses by age group and other updates	Section 2.2.1 Subgroup of interest
			Added information on duration of exposure will be assessed in weeks rather than days to align with other Novartis SEG101 studies	2.4.1 Study treatment / compliance
			The sentence “The primary time point is week 26” was deleted as it was redundant given the previous sentence.	2.5.1 Primary endpoint(s)
			Text added related to uniformity of occurrence of priapic events, how baseline was adjusted for 26 weeks for analysis purpose; The <7 category was included as a new number of priapic events category in a subgroup analysis of the primary endpoint	2.5.2 Statistical hypothesis, model, and method of analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Added information on estimand framework to handle missing data caused by intercurrent events (Primary estimand)	2.5.3 Handling of intercurrent events
			Information on handling of missing values added	2.5.4 Handling of missing values not related to intercurrent event
			Information on sensitivity analyses added	2.5.5 Sensitivity analyses
			Information updated on secondary endpoints; added definition for end date of annualize rate of priapic events	2.6.2 Statistical hypothesis, model, and method of analysis
			Updated information on AEs; detailed legal requirement of clinicaltrials.gov and EudraCT	2.7.1 Adverse events (AEs)
			Updated information on deaths	2.7.2 Deaths
			The word “albumin” deleted from the laboratory data; other information updated	Section 2.7.3 Laboratory data
			Information updated on other safety data	Section 2.7.4.1 ECG and cardiac imaging data

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	[redacted]
			[redacted]	[redacted]
			Added additional relevant information required for statistical analysis implementation which are not detailed in study protocol	Section 2.13 Interim analysis
			The statistical power of the study changed from 90% to 80% , which reduces the number of evaluable subjects 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; 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	Section 3 Sample size calculation

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			To clarify the change information in this section	Section 4 Change to protocol specified analyses
			A detailed description of the analysis provided	Section 5.4.1 Analysis supporting primary objective(s)
			Added relevant references Barnard and co; Edmond and co, Ratich and co, ICH E9(R1) guideline and A Phase 3 Trial of l-Glutamine in Sickle Cell Disease (Endari™) as well as the SAS/STAT® 14.2 User's Guide were added.	Section 6 Reference
22-Nov-2023	Prior to DB Lock	Creation of amendment 2	Update on visit window; Added text for visit windows, upper limit extension for EoT. Note- Based on medical judgement and data, upper limit of EoT extended upto maximum value day 403.	Section 2.1.1 General definitions
			[redacted]	[redacted]
			To clarify the change information in this section	Section 4 Change to protocol specified analyses
15-Dec-2023	Prior to DB Lock	Creation of amendment 3	Update on visit window, change EoT upper limit from day 403 to day 447.	Section 2.1.1 General definitions

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20-Feb-2024	Prior to DB Lock	Creation of amendment 4	Added note on tipping point analysis will be performed if there are significant number of missing data.	2.5.5 Sensitivity analyses
			Information on “baseline adjusted for 52 weeks for analysis purpose“ included in supportive analysis 2. This decision was made based clinical trial team (CTT) suggestion.	2.5.6 Supportive analyses
			Based on clinical trial team (CTT) suggestion, note added for secondary endpoint analysis 2 “this analysis will only be performed if an adequate number of subjects are present”.	2.6.1 Secondary endpoint(s)
			The word “tricuspid regurgitation jet velocity (TRV)” added for cardiac imaging data.	Section 2.7.4.1 ECG and cardiac imaging data
			[redacted]	[redacted]
			[redacted]	[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	[redacted]
			[redacted]	Section 6 Reference

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List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
[redacted]	[redacted]
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CM	Concomitant Medication
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose Intensity
DRL	Drug Reference List
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EoT	End of Treatment
ER	Emergency Room
FAS	Full Analysis Set
GGT	Gamma-glutamyl Transferase
GPS	Global Programming and Statistical environment
HDL	High-density Lipoproteins
HR	Heart Rate
INR	International Normalized Ratio
IV	Intravenous
LDH	Lactate Dehydrogenase
LDL	Low-density Lipoproteins
LVEF	Left Ventricular Ejection Fraction
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	milligram(s)
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PD	Pharmacodynamic
PDI	Planned Dose Intensity
[redacted]	[redacted]
PK	Pharmacokinetics
PT	Preferred Term
RAP	Reporting and Analysis Process
RBC	Red Blood Cells

RDI	Relative Dose Intensity
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCD	Sickle Cell Disease
SD	Standard Deviation
SEG101	Novartis humanized anti-P-selectin monoclonal antibody variant
SOC	System Organ Class
TBIL	Total Bilirubin
TFLs	Tables, Figures, Listings
VOC	Vaso-occlusive Crisis
WHO	World Health Organization

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses, which will be used in the phase II clinical trial SEG101AUS05.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

Data will be analyzed by Novartis using statistical software SAS version 9.4 according to the data analysis section 12 of the study protocol, which is available in Appendix 16.1.1 of the CSR. The statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section 16.1.9 of CSR.

The content of this SAP is based on protocol CSEG101AUS05 Amendment (version 3.0, release date 16-Dec-2022). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in Tables, Figures, and Listings, (TFL) shells and Programming Datasets Specifications (PDS) documents, respectively.

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the CSR after the analysis has taken place.

1.1 Study design

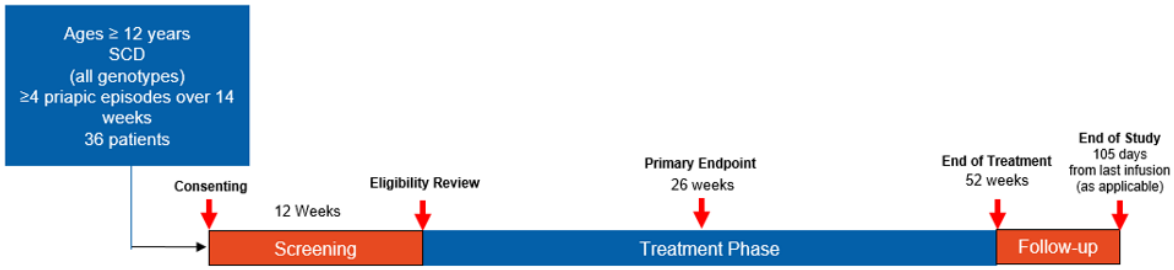
This is a multicenter, prospective, phase II, single-arm, open-label study to assess the efficacy and safety of crizanlizumab in SCD (Sickle Cell Disease) subjects with priapism.

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 79-weeks (including 12 weeks of screening, 52 weeks of treatment and 15 weeks of follow-up period). The primary analysis of the study will be conducted by 26 weeks to assess efficacy of crizanlizumab in those subject 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 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.

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimands

Table 1-1 Study Objectives and 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]

1.2.1 Primary estimand(s)

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

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 2.5.3

1.2.2 Secondary estimand(s)

Not applicable

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or a designated contract research organization (CRO) (if applicable). It is planned that the data from all centers that participate in this protocol will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

General analysis conventions

Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation (SD), minimum, lower quartile (Q1), median, upper quartile (Q3), maximum. Summary statistics for discrete variables will be presented in the number and percent of subjects in each category. Summary statistics will also be presented graphically wherever applicable.

If not otherwise specified, p-values and confidence interval (CI) will be presented as two-sided. Unless otherwise stated, the default level of significance will be set to 5%.

For categorical data, percentages will be rounded up to one decimal place. For continuous data, mean, and median will be rounded up to one additional decimal place compared to the original data. Standard deviation will be rounded up to two additional decimal places. Minimum and maximum will be displayed with the same accuracy as in the original data. Wherever changes from baseline will be used, change will be calculated as “post-baseline value – baseline value”. The number of decimal places for the “change from baseline” variables will be the same as for the original measurement.

The analysis will be conducted on all subjects' data at Week 26 and at the time, the trial ends (Week 52).

Unscheduled assessments

The following points summarize the rules for unscheduled assessments:

- All unscheduled assessments at the baseline before the first dose should be included for consideration when calculating the baseline value.
- In summary tables by visit, unscheduled assessments should not be included unless they qualify as baseline.

- In shift and abnormality tables, all unscheduled assessments are included.

Unscheduled assessments will be reported along with the scheduled assessments in the listings.

Data included in analysis

All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g., vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations at the time of the primary analysis.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cutoff date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

For the final analysis, all data collected will be used, without notion of cut-off date.

2.1.1 General definitions

Study treatment: Study treatment refers to Crizanlizumab (SEG101) 5.0 mg/kg provided by IV infusion.

Study treatment start and end date: Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the core study.

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

- For the analysis purpose, in the tables and figures, baseline is considered from Day -91 to one day prior to dosing. Similarly, for "by week 26 analysis" from the first dose date to one day prior to Week 27 Day 1 visit date and for "by week 52 analysis" from the first dose date to one day prior to Week 53 Day 1 visit date will be considered.
- For subjects missing "Week 27 Day 1" visit or "Week 53 Day 1" visit, the scheduled visit day will be considered for cut-off.
- For listings, all available data will be considered.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as ''baseline" assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g. ECGs), where study requires multiple replicates per time point, the average of these measurements will be calculated for baseline (if not already available in the database).

In cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last entry should be considered as baseline.

If subjects have no value as defined above, the baseline result will be missing.

Post baseline: Any measurements taken after baseline will be considered as post-baseline measurements.

Change from baseline: Post baseline value – baseline value

Percent change from baseline: (Post baseline value – baseline value) *100/ Baseline value;

(relative change from baseline).

Reduction: The negative change from baseline.

Study day: The study day, describes the day of the event or assessment date, relative to the start of study treatment. Study Day 1 for all assessments is taken to be the start of study treatment.
The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) - Start of study treatment + 1, if event is on or after the start of study treatment;
- The date of the event (visit date, onset date of an event, assessment date etc.) - Start of study treatment, if event precedes the start of study treatment.

The study day will be displayed in the data listings. If an event starts before start of study treatment, the study day displayed in the listing will be negative.

On-treatment assessment/event:
For AE reporting the overall observation period will be divided into three 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)

Note: If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.
Safety summaries (tables, figures) include only data from the on-treatment period, unless specified otherwise, with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries).

Time unit: A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Visit windows

Visit-windows will be applied for vital signs, laboratory and PRO assessments.

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-1. These apply to measurements taken at every visit.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows (e.g., if the Week 4 visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window Week 8). In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Table 2-1 Assessment windows for scheduled visits

Analysis Visit	Week (k)	Scheduled Day/ Target day [d=(k-1)*7+1]	Visit Window (in study days)
Baseline	BSL		-91 days to Day -1*
Week 1 Day1	1	1	Day 1-7
Week 3 Day 1	3	15	Day 8-29
Week 7 Day1	7	43	Day 30-57
Week 11 Day 1	11	71	Day 58-85
Week 15 Day 1	15	99	Day 86-113
Week 19 Day 1	19	127	Day 114-141
Week 23 Day 1	23	155	Day 142-169
Week 27 Day 1	27	183	Day 170-197
Week 31 Day 1	31	211	Day 198-225
Week 35 Day 1	35	239	Day 226-253
Week 39 Day 1	39	267	Day 254-281
Week 43 Day 1	43	295	Day 282-309
Week 47 Day 1	47	323	Day 310-337
Week 51 Day 1	51	351	Day 338-358
EoT	53	365	Day 359-371**

*Baseline measurement prior to first infusion of study drug.

**Based on medical judgement and data, upper limit of EoT will be extended upto maximum value day 447.

Laboratory assessments will be taken from Screening Visit 3 as per the protocol and the window does not include pre-screening period. Thus, window for laboratory assessments will be Day -28 to Day -1.

Multiple assessments within visit windows

In order to summarize laboratory assessments over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied:

- If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used.
- If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used.
- If multiple assessments are on the same date then the worst case will be used (minimum or maximum depending of the parameter direction).

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

2.2 Analysis sets

The analysis sets to be used are defined as below.

All efficacy analyses will be performed on subjects in FAS who have completed treatment. The Safety Set will be used for all the safety analysis.

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 Set (SAF)

The SAF will consist of all subjects who received at least 1 dose of study treatment.

2.2.1 Subgroup of interest

- The primary analysis will be conducted on a subgroup of subjects with stuttering (duration of priapic events from 1 to <=4 hours) and acute priapism. Acute priapic events are defined as an unwanted, painful erection that lasts more than 4 hours and need a visit to emergency room.

- Additional subgroup analysis will be performed based on duration of priapic events (i.e., <1, 1 to ≤4, >4 to ≤6, >6 to ≤12, >12 hours).
- 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 (12 weeks) and baseline (adjusted for 26 weeks). The priapic events categories may be re-grouped to ensure that there is adequate number of subjects in each category for analysis.
- Note that, subgroup analyses of the primary endpoint by age group will only be performed if an adequate number of subjects are present in each subgroup class.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The following summaries will be provided for subject disposition in different study phases:

- Number (%) of subjects who were screened, screen failures, reasons of discontinuation from screening phase (based Screening phase disposition page), with % based on all subjects in Screening phase).
- Number (%) of subjects who completed study treatment phase, discontinued study treatment, primary reason for study treatment phase discontinuation (based on the 'Treatment disposition' page), with % based on FAS subjects.
- Number (%) of subjects who have entered post-treatment follow up phase, completed the follow up phase, discontinued from follow up phase and reasons for discontinuation (based on Follow-up disposition page), with % based on FAS subjects.

Subject disposition data will be listed.

Screened subjects not treated will be listed.

Protocol Deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit checks specifications). All protocol deviations will be listed.

In addition, pandemic related protocol deviations will be summarized by category and relationship. All COVID-19 related protocol deviations will also be listed.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline characteristics will be listed and summarizes descriptively for all subjects in the FAS.

Continuous variables will be summarized using n, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

Following demographic variables will be summarized:

- Age (years)
- Ethnicity
- Race

Following baseline characteristic variables will be summarized:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- VOC events

Medical History

Any condition recorded on the Medical History CRF will be coded using the MedDRA dictionary. These will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

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, $HbS\beta^0$, HbSC, $HbS\beta^+$, 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.

All above baseline characteristics will be summarized and listed.

Analyses will be based on FAS subjects.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

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 descriptively.

The number (%) of subjects with dose interruption or permanent discontinuation and the reasons will be summarized.

All dosing data will be listed.

Duration of exposure to study treatment

Duration of exposure to study treatment (week) = ((last date of exposure to study treatment) – (date of first administration of study treatment) + 1)/7.

The last date of exposure to study treatment the earliest of the last date of treatment + 27 days, the date of death (if the subject died), and the date of data cutoff.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (less than 1 weeks, at least 4 weeks, at least 14 weeks, at least 26 weeks, at least 52 weeks) and continuous summaries (i.e. mean, standard deviation (SD) etc.).

Cumulative dose

Cumulative dose of the study treatment is defined as the total dose given during the study treatment exposure and will be summarized.

The planned cumulative dose refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

The actual cumulative dose refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the Dose Administration CRF.

Dose intensity and relative dose intensity

Dose Intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

DI (mg/kg/28 days) = Actual Cumulative dose (mg/kg) / Duration of exposure to study treatment (week) $\times$ 4.

Planned dose intensity (PDI) is defined as follows:

PDI (mg/kg/28 days) = Planned Cumulative dose (mg/kg) / Duration of exposure (week) $\times$ 4.

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/kg/28 days) / PDI (mg/kg/28 days).

DI and RDI will be summarized.

2.4.2 Prior, concomitant and post therapies

Prior and Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system using the latest version available prior to clinical database lock and summarized by lowest ATC class and preferred term.

The ATC class will be presented in alphabetical order. Preferred terms will be sorted by decreasing proportion and alphabetical order.

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment.

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a subject coinciding with the study treatment period. Concomitant therapy includes medications (other than study treatments) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Summaries for concomitant medications will include:

1. Medications starting on or after the start of study treatment but no later than 105 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Prior and concomitant medications for analgesics and hydroxyurea will be summarized separately.

Prior and concomitant non-drug therapies/procedures will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all subjects.

All prior and concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 105 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

Rescue medications

Rescue medication is defined as medication used to control symptoms that are not adequately controlled on study treatment.

As per protocol, any standard medications that are used for management of VOC [redacted] should follow the recommendation from Dr Minniti publication (Minniti et al 2010). Thus, these medications will be identified by the medical team and provided for analysis.

Rescue medication will be summarized similarly to concomitant medication.

2.5 Analysis supporting primary objective(s)

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.

2.5.1 Primary endpoint(s)

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.

Percentage change from baseline = (Post baseline value –Baseline value) * 100 / Baseline value; (relative change from baseline).

Percentage reduction from baseline is the negative percentage change from baseline.

2.5.2 Statistical hypothesis, model, 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 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.

Baseline (adjusted for 26 weeks): Number of priapic events in 12 weeks screening period * (26/12) and percentage change from baseline = (Post baseline value –Baseline (adjusted to 26 weeks) value) * 100 / Baseline (adjusted to 26 weeks) value.

Percentage reduction from baseline is the negative percentage change from baseline.

Percent reduction from baseline in priapic events will be tested using a non-parametric test (i.e., Wilcoxon's Sign Rank test) and p-value will be reported. The study would be declared a success, if percentage reduction in events is ≥ 25 % and $p<0.05$ is obtained from 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.

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 n, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum and maximum.

Graphical representation of percentage reduction, through box plot or bar graph or waterfall plot, will be performed as appropriate by 26 weeks.

In addition, subgroup analysis of the primary endpoint will be performed based on the number of priapic events categories (i.e. <7, 7 - 13, 14 - 21, ≥ 22) at baseline (12 weeks) and baseline (adjusted for 26 weeks). Additional analyses of the primary endpoint will also be performed for the subgroups of subjects with stuttering and acute priapism. Summary statistics for percentage reduction by 26 weeks will be presented for each subgroup.

The priapic events categories may be re-grouped to ensure that there is adequate number of subjects in each 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.

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

2.5.3 Handling of intercurrent events

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.
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 as described in Section 2.5.4).
- **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 as described in Section 2.5.4).
- **For the intercurrent events 4c:** Data after intake of analgesic (including opioids) or ad hoc transfusions administered temporarily will be included (treatment policy strategy).

2.5.4 Handling of missing values not related to intercurrent event

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 (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 are mentioned in the Section 5.4.1.

2.5.5 Sensitivity analyses

Sensitivity analysis 1: Tipping point analysis

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. Note that, tipping point analysis will be performed if there are significant number of missing data.

Further details are provided in Section 5.4.1.

Sensitivity analysis 2

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 2.5.3.

Note: Handling of intercurrent event 4c and missing data not related to intercurrent event will be same as described for the primary analysis.

Sensitivity analysis 3: Observed case analysis

As part of the sensitivity analysis, the primary analysis will be analyzed on all subjects in FAS without missing data.

Sensitivity analysis 4: For COVID 19 impact

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.

2.5.6 Supportive analyses

The supportive analyses described below will be performed on all FAS patients who have completed 26 weeks on treatment. Missing values will be imputed as stated in Section 2.5.4

Supportive analysis 1:

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.

Supportive analysis 2:

Percent reduction from baseline in priapic events will also be assessed by Week 52. Assuming uniformity in the occurrence of priapic events before exposure to crizanlizumab treatment, baseline will be adjusted for 52 weeks for analysis purpose.

Baseline (adjusted for 52 weeks): Number of priapic events in 12 weeks screening period * (52/12) and percentage change from baseline = (Post baseline value –Baseline (adjusted to 52 weeks) value) * 100 / Baseline (adjusted to 52 weeks) value.

Percentage reduction from baseline is the negative percentage change from baseline.

Supportive analysis 3:

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). For the analysis purpose, for 0-12 weeks: Day 1 to Day 84 and for 15-26 weeks: Day 105 to Day 182 will be used.

Supportive analysis 4:

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. For the analysis purpose, for 0-12 weeks: Day 1 to Day 84 and for 15-26 weeks: Day 105 to Day 182 will be used.

2.6 Analysis supporting secondary objectives

Not applicable

2.6.1 Secondary endpoint(s)

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

The following secondary efficacy endpoints will be analyzed on all FAS subjects who have completed 26 and 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 (defined as an unwanted, painful erection that lasts more than 4 hours and need a visit to emergency room) by 26 and 52 weeks of treatment. Note that, this analysis will only be performed if an adequate number of subjects are present.

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 and summarized by 26 weeks and by 52 weeks .

2.6.2 Statistical hypothesis, model, and method of analysis

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

Annualized rates will be calculated for the secondary endpoints.

The annualized rate of events is defined as the total number of events for a subject occurring from the date of initial infusion to the last contact date of the Treatment Phase of the study x 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.

Annualized events rate = Total number of events x 365.25 / (end date – treatment start date +1), where end date is defined as the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine - or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin, cut-off date).

Descriptive summary statistics including n, mean, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), minimum, and maximum will be presented for the annualized 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, median, standard deviation (SD), lower quartile (Q1), median, upper quartile (Q3), and minimum and maximum.

Graphical representation of annualized rates, through box plots or bar graphs or swimmer plot, as appropriate, will also be performed.

The Annualized 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), standard deviation and minimum and maximum.

Additionally, cumulative number of acute priapic events, uncomplicated and complicated VOC events will also be summarized over time (like 0-12 weeks, 0-26 weeks, 0-40 weeks and 0-52 weeks).

Subgroup analyses displaying annualized rate, for complicated and uncomplicated VOC events will be performed based on use of hydroxyurea versus no use of hydroxyurea by 26 weeks and 52 weeks.

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 acute priapic events with associated 95% CI using a Hodges-Lehmann estimate will be reported. The median percent reduction will also be presented by Week 26 and Week 52.

2.6.3 Handling of intercurrent events

Not applicable

2.6.4 Handling of missing values not related to intercurrent event

Not applicable

2.6.5 Sensitivity analyses

Not applicable

2.6.6 Supplementary analyses

Not applicable

2.7 Safety analyses

All safety analyses will be based on the Safety Set unless otherwise specified. Safety summaries include only on-treatment assessments. Safety listings include all assessments with those more than 105 days after last study treatment, flagged.

2.7.1 Adverse events (AEs)

For reporting of AEs, the overall observation period will be divided into three 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)

Reporting of AEs will be based on MedDRA version 25.0 or higher and the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher.

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs outside of on-treatment period will be flagged in the listings.

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.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in all subjects.

Serious adverse events will be tabulated. All deaths (on-treatment death and post-treatment death) will be summarized.

All AEs 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. SAEs will be summarized and listed.

Separate summaries for AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption, requiring additional therapy and leading to fatal outcome.

In addition, for the legal requirements of clinicaltrials.gov and EudraCT, two required tables (plus standard safety XML files) on on-treatment adverse events which are not SAEs with an incidence greater than 5% and on on-treatment serious adverse events and SAEs suspected to be related to crizanlizumab will be provided by SOC and PT.

If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE/SAE suspected to be related to crizanlizumab /non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.7.1.1 Adverse events of special interest / grouping of AEs

Not applicable

2.7.2 Deaths

All deaths (on-treatment death and post-treatment death) will be summarized. Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced system organ class and preferred term.

All deaths will be listed using Safety set. All deaths those collected during the pre-treatment and post treatment period will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.7.3 Laboratory data

On analyzing laboratory values, data from all sources (central and local laboratories) will be combined as per Section 8.3.2 of the protocol. The summaries will include all assessments available for the lab parameter collected no later than 105 days after the last study treatment administration date. Following lab parameters will be analyzed :

Table 2-1

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
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), done locally: Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen **Microscopic Panel** (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
Additional tests	HIV Ab

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.

The following summaries will be produced for laboratory data by laboratory parameters:

Separate summaries of change from baseline for each lab test category.

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.

- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value; for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTCAE grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTCAE grade 2, 3, or 4 laboratory toxicities.

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

Hepatitis markers and additional tests only performed at screening will be summarized and listed.

Urine creatinine/protein ratio will be summarized descriptively at screening visit 3 and EoT visit, and summary of change will be presented.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

When ECG triplicates are collected at any assessment, the average of the ECG parameters at that assessment will be used in the analyses.

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

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

- QT, QTcF
    - New value of > 450 and ≤ 480 ms
    - New value of > 480 and ≤ 500 ms

- New value of > 500 ms
- Increase from baseline of > 30 ms to ≤ 60 ms
- Increase from baseline of > 60 ms

- HR
  - Increase from baseline >25% and to a value >100 bpm
  - Decrease from baseline >25% and to a value <50 bpm
- PR
  - Increase from baseline >25% and to a value >200 ms
  - New value of >200 ms
- QRS
  - Increase from baseline >25% and to a value >120 ms
  - New values of QRS >120 ms

For cardiac imaging data, left ventricular ejection fraction (LVEF), mean pulmonary arterial pressure (mPAP), and tricuspid regurgitation jet velocity (TRV) will be summarized at screening and end of treatment visit. In addition, all data will be listed.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: weight (kg), body temperature (^{o}C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg), respiratory rate and oxygen saturation.

Vital signs collected on-treatment will be summarized descriptively. Values measured during pre- and post- treatment period will be flagged in listings.

The number and percentage of subjects with notable vital sign values will be presented over time. Notable values will be flagged in the listings. For analysis, clinically notable vital sign criteria are provided in Table 2-2 below:

Table 2-2 Clinically notable changes in vital signs

Vital sign (unit)	Criteria	< 18 years at baseline and < 18 years at time of assessment	< 18 years at baseline and ≥ 18 years at time of assessment	≥ 18 years at baseline
Systolic blood pressure (mmHg)	High	≥ 95th percentile of the age and height group[1]	≥ 180 with increase from updated baseline[5] of ≥20	≥180 with increase from baseline of ≥20
	Low	≤ 5th percentile of the age and height group[1]	≤ 90 with decrease from updated baseline[5] of ≥20	≤90 with decrease from baseline of ≥20

Vital sign (unit)	Criteria	< 18 years at baseline and < 18 years at time of assessment	< 18 years at baseline and ≥ 18 years at time of assessment	≥ 18 years at baseline
Diastolic blood pressure (mmHg)	High	≥ 95th percentile of the age and height group[1]	≥ 105 with increase from updated baseline[5] of ≥15	≥105 with increase from baseline of ≥15
	Low	≤ 5th percentile of the age and height group[1]	≤ 50 with decrease from updated baseline[5] of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	High	12-15 years: >96 ≥15 years: >92	≥120 with increase from updated baseline[5] of ≥15	≥100 with increase from baseline of >25%
	Low	12-15 years: <62 ≥15 years: <58	≤50 with decrease from updated baseline[5] of ≥15	≤50 with decrease from baseline of >25%
Weight (kg)	High	increase from baseline[3] of ≥2 BMI-for-age percentile categories[4]	increase from updated baseline[5] of ≥10%	increase >10% from baseline
	Low	decrease from baseline[3] of ≥2 BMI-for-age percentile categories[4]	decrease from updated baseline[5] of ≥10%	decrease >10% from baseline
Respiratory rate (breath per minute)[2,6,7]	High	12-15 years: >21 ≥15 years: >20	≥30	≥30
	Low	12-15 years: < 15 ≥15 years: <13	≤10	≤10
Oral body temperature (°C)	High	≥38.4	≥39.1	≥39.1
	Low	≤35.0	≤35.0	≤35.0

bpm=beats per minute; NHLBI= National Heart, Lung, and Blood Institute;

[1] Blood pressure percentiles are calculated for each blood pressure record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555.

[2] Fleming S, 2011

[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile);

[4] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts;

[5] Updated baseline is the last value collected before the 18th birthday.

[6] Eldridge L, 2014;

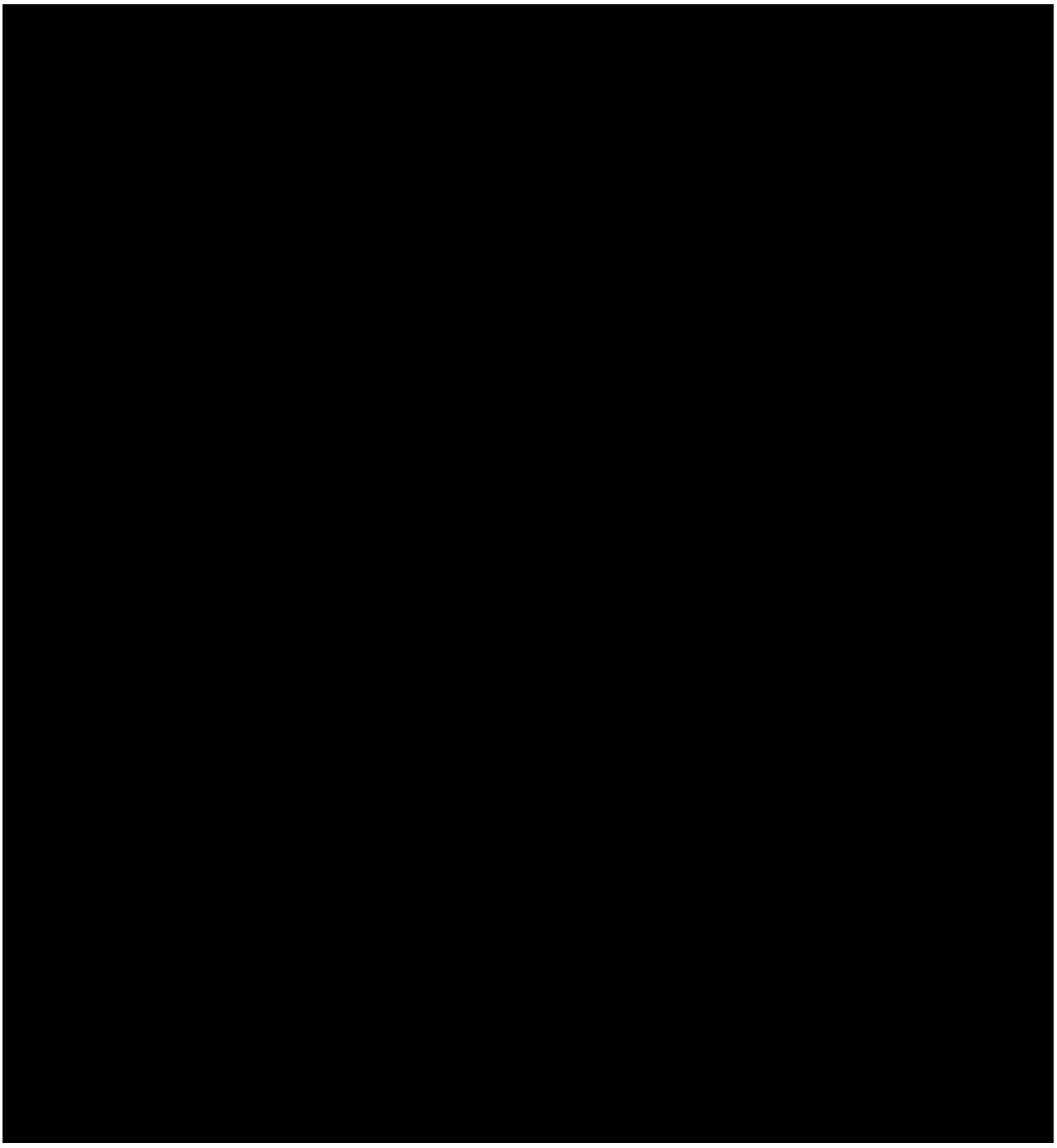
[7] Kou .R, 2009.

2.8 Pharmacokinetic endpoints

Not applicable

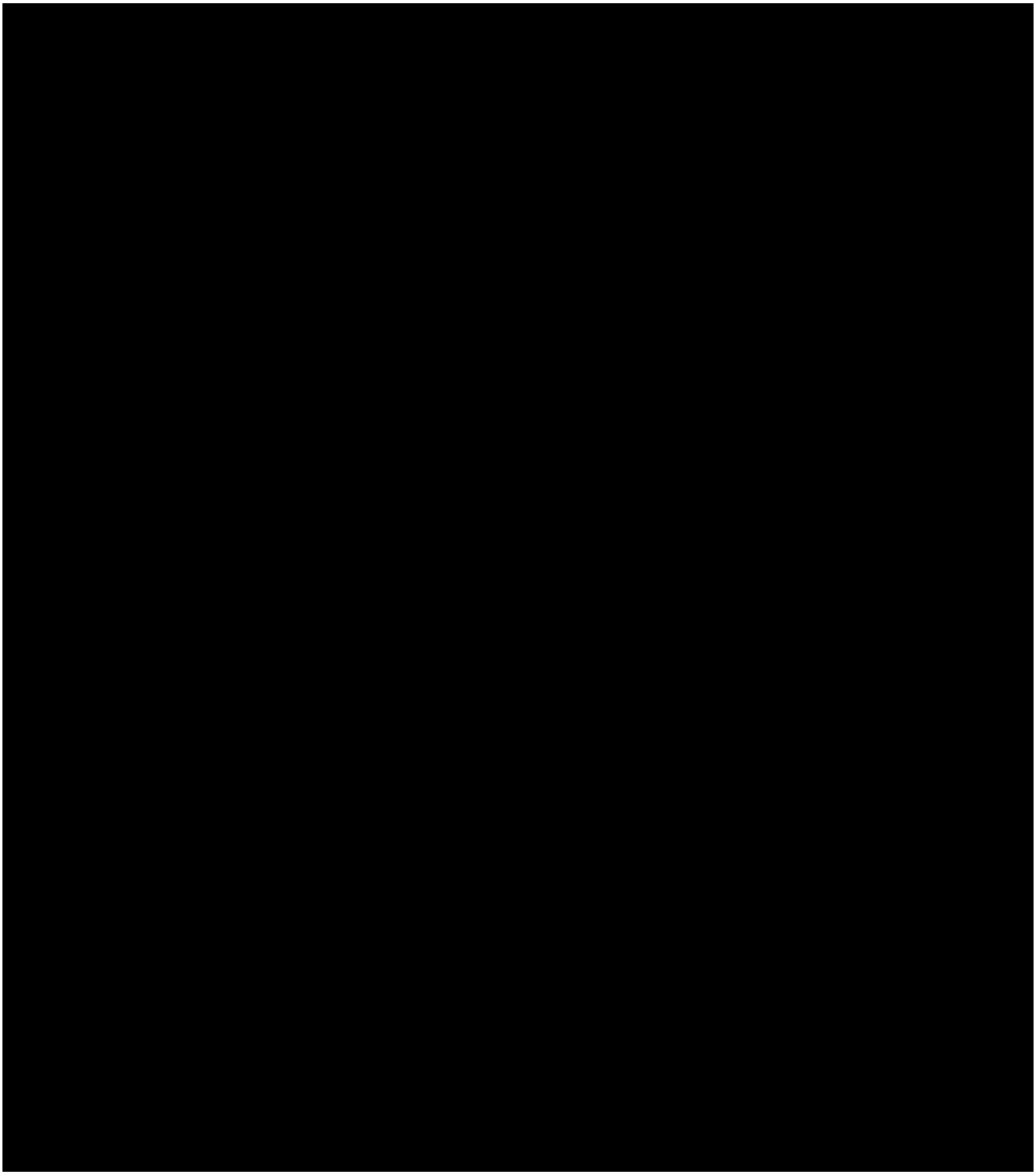
2.9 PD and PK/PD analyses

Not applicable



2.11 Biomarkers

No biomarker analyses will be included in the CSR. Separate reports will be generated if applicable.



2.13 Interim analysis

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.

The primary analysis of the study will be performed after the last subject has completed Week 26 visit or discontinued earlier. For this analysis, all subjects will have completed the assessments related to the primary, secondary [redacted] objectives including all variables outlined up to Week 26 and all available visit-based safety assessments. Separate SAP documentation will be prepared for this primary analysis if applicable.

3 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.

4 Change to protocol specified analyses

After finalization of the protocol amendment, CSEG101AUS05 Protocol Version 03, the study team noted that a few sentences which were intended to be deleted were still in the document. The changed information will be incorporated into the next version of the protocol, if amended. Team has incorporated those changes in this SAP amendment 1. These changes do not alter the purpose or intent of the amendment. The aim of this memorandum is to clarify these sentences.

Protocol amendment version 03:

- Protocol summary: Finally an analysis using a mixed effects regression model will be performed using median event counts within pre-specified time windows.
    - *The above line is proposed to be removed, as this was added in error in only this part of the protocol.*
- Section 2.6.1: Secondary efficacy endpoints will be analyzed on all FAS subjects who have completed 52 weeks on treatment to evaluate clinical efficacy of crizanlizumab 5 mg/kg.

- *Secondary efficacy endpoints will be analyzed on all FAS subjects who have completed 26 and 52 weeks on treatment to evaluate clinical efficacy of crizanlizumab 5 mg/kg.*

- Section 12.4.2: 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.
  - *Percent reduction from baseline in priapic events will be tested using a nonparametric test (i.e. Wilcoxon's Sign Rank test) with $\alpha = 0.05$.*

    Hodges-Lehmann estimate of median percent reduction in priapic events will also be reported, along with corresponding 95% confidence intervals.
- Section 12.4.4: 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.

- *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.*
  - *Percent reduction from baseline in priapic events will be tested using a nonparametric test (i.e. Wilcoxon's Sign Rank test) with $\alpha = 0.05$.*

    Hodges-Lehmann estimate of median percent reduction in priapic events will also be reported, along with corresponding 95% confidence intervals.

The below change is incorporated into SAP amendment 2 as per clinical trial team (CTT)suggestion. This change do not alter the purpose or intent of the amendment. The aim of this memorandum is to clarify this sentence.

Protocol amendment version 03:

- Section 12.2: 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.
    - *Demographic and other baseline disease characteristics will be listed and summarized descriptively for all subjects in the FAS.*

The below changes are incorporated into SAP amendment 4 as per clinical trial team (CTT) suggestion. These changes do not alter the purpose or intent of the amendment. The aim of this memorandum is to clarify these sentences.

Protocol amendment version 03:

[redacted]

- Section 12.4.4 (Supportive analyses): Percent reduction from baseline in priapic events will also be assessed by Week 52.
    - *Percent reduction from baseline in priapic events will also be assessed by Week 52. Assuming uniformity in the occurrence of priapic events before exposure to crizanlizumab treatment, baseline will be adjusted for 52 weeks for analysis purpose.*
- Section 12.5.1: The percent reduction from baseline in acute priapic events by 26 and 52 weeks of treatment.
    - *The percent reduction from baseline in acute priapic events (defined as an unwanted, painful erection that lasts more than 4 hours and need a visit to emergency room) by 26 and 52 weeks of treatment. Note that, this analysis will only be performed if an adequate number of subjects are present.*

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule will be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no end of treatment (EOT) page and no death date, the subject is considered as on-going:

The subject should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Subjects with missing start dates will be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date will not be imputed.

5.1.2 AE date imputation

Table 5-1 Imputation of start date

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end date

Missing Element	Rule (*=last treatment date plus 105 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period

Any AEs with partial/missing dates will be displayed as such in the data listings.

Any AEs which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

For AEs with start date before or on the cut-off date and end date after the cut-off date, the outcome will be reported as unknown.

5.1.3 Concomitant medication date imputation

Table 5-3 Imputation of start dates

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY o Else set start date = study treatment start date. • If available year > year of study treatment start date then 01JanYYYY

Missing Element	Rule
	• If available year < year of study treatment start date then 01JulYYYY
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-4 Imputation of end dates

Missing Element	Rule (*=last treatment date plus 105 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period

Any concomitant medications with partial/missing dates will be displayed as such in the data listings.

Any concomitant medications which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.3.1 Prior therapies date imputation

Refer Section 5.1.3

5.1.3.2 Post therapies date imputation

Refer Section 5.1.3

5.1.3.3 Other imputations

Table 5-5 Imputation of start dates assessments (laboratory, ECG, vital signs)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  ○ Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in the Novartis internal

criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTCAE grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of white blood cells (WBC).

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTCAE grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTCAE grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Primary analysis

Wilcoxon signed rank test

The SAS procedure PROC UNIVARIATE will be used to perform Wilcoxon signed-rank test.

Hodges-Lehmann Estimation

The SAS procedure PROC NPAR1WAY will be used to compute the Hodges-Lehmann estimate.

Handling of missing data

Generating the multiple imputation

The missing values will be imputed for the primary analysis.

- To filled in the missing values (i.e. number of priapic events by 26 weeks), generate Poisson distributed random variables with a rate parameter based on the same effect as observed data. Compute 1000 such complete datasets. Use seed 10105.
- Each datasets will be analyzed using the same method as described in primary analysis.

Analyzing the imputated data

- The resulting estimates and standard errors will be combined using Rubin's rule (Barnard J and Rubin DB 1999), by the SAS procedure MIANALYZE.

Tipping point analysis for priapic events by 26 weeks

As a sensitivity analysis to evaluate the impact of missing data, a tipping point analysis will be performed for the primary endpoint.

The primary endpoint will be re-analyzed on the delta-adjusted datasets to see if the conclusions change. If not, a larger delta is chosen and the process will be repeated until the conclusion is overturned. The tipping point is the delta value which will cause the primary endpoint to be no longer statistically significant. A series of analyses on a range of delta values (i.e.,1,2,3,.....) will be performed to find the tipping point.

For each delta value, the following steps will be performed.

1. Impute the missing values (i.e. number of priapic events by 26 weeks) by generating Poisson distributed random variables with a rate parameter based on the same effect as observed data. Use seed 10105.
2. After the imputation obtained in above step, make the imputed value worse by a value of delta (i.e., add delta to the imputed value). Note: delta = 0 represents the standard missing at random (MAR).
3. The final imputed delta-adjusted dataset where all missing values are filled, will be analyzed using method as described in the primary analysis.
4. The results from the 1000 delta-adjusted datasets will then be combined using Rubin's rule. If the combined results does not change the conclusion (i.e., if percentage reduction in events is $\geq$ 25 % statistically significant), a larger delta will be chosen and Steps 1-4 will be repeated using the datasets from Step 1 until the tipping point is found (when $p > 0.05$).

5.4.2 Analysis supporting secondary objective(s)

Not applicable

5.5 Rule of exclusion criteria of analysis sets

Not applicable

6 Reference

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