NOVARTIS

Clinical Development

SEG101

CSEG101A2301 / NCT03814746

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

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Final – amendment 4
Release date:	13-Sep-2021
Number of pages:	57

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
21-Jun-2019	Prior to DB lock	Creation of final version	N/A - First version	NA
24-Jan-2020 Amendment 1	Prior to DMC1 snapshot	Clarify endpoint number of days with VOC is in fact assessed using duration of VOC as per analysis planned in section 2.7.2	Naming "Duration of VOC" added to "Number of days with VOC"	Section 1.2 study objectives and endpoints, Section 2.7 Analysis of secondary efficacy objectives
		Correct typo in definition of PAS1	"Primary" term removed for PK parameter as no primary PK parameter defined	Section 2.2 Analysis sets, Section 2.9 Pharmacokinetic endpoints
		Correct that weight and height at screening will be used for demographic analysis as per TFLs shells	Weight and height at screening instead of baseline	Section 2.3 Subject disposition, demographics and other baseline characteristics
		Adapt data to be presented as per data collected in CRF	Remove permanent discontinuation from study treatment section and add dose change	Section 2.4.1 Study treatment / compliance
		Update analysis planned for DMC	Surgical and medical procedures added	Section 2.5.2 Statistical hypothesis, model, and method of analysis
		Clarify closure principle in the testing strategy	Added that hypothesis will be rejected if all corresponding intersections are rejected	Section 2.6.2 Statistical hypothesis, model, and method of analysis

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Specify analysis planned for VOC free	Logistic regression model added for the number of subjects free from VOC endpoint	Section 2.7. Statistical hypothesis, model, and method of analysis 2
		Specify secondary efficacy endpoints	List of secondary efficacy endpoints added	Section 2.7.1 Secondary endpoints
		Update endpoint terminology consistently within the document	Clinic added to hospitalization and ER visits related endpoints	Section 2.7.2 Statistical hypothesis, model, and method of analysis
		Remove duplicate analyses already planned as part of the lab CTC shift tables	Shift table for leukocytes, neutropenia and thrombocytopenia removed	Section 2.8.3 Laboratory data
		Growth and sexual maturation will only be listed considering limited subjects expected to be enrolled for those analyses	Remove table for growth and sexual maturation	Section 2.8.5.3 Growth and sexual maturation
		Based on distribution of the PD observations	Geometric mean replaced by median and figure of pre dose inhibition removed	Section 2.10 PK and PK/PD analyses
		[redacted]		
		Add derivation of age at a given	Section added	Section 5.1.3

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		assessment to cover situation when only the year of birth is known		
20-Aug-2020 Amendment 2	Prior to DB lock	Alignment with protocol version 03	Updated reference to protocol version	Section 1 Introduction
			Updated study design figure consistent with minor corrections made in protocol	Section 1.1 Study design
			Updated objectives table to align with protocol v03	Section 1.1 Study design
			Added summary of reasons for not receiving HU/HC	Section 2.4.2 Prior, concomitant and post therapies
			Updates to specify that VOCs after initiation or discontinuation of other therapies (beyond HU/HC or L-Glutamine) used to treat SCD and/or prevent/reduce VOCs will also not be included for the primary analysis, and also added these other therapies to the analysis of time to initiation or discontinuation of HU/HC or L-Glutamine	Section 2.5 Analysis of the primary objective
			[redacted]	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			[redacted]	
			Added summary of COVID-19 Ab test results	Section 2.8.3 Laboratory data
			Deleted the existing list of changes compared to protocol specified analysis since the amended protocol is aligned with the changes initially made in the SAP	Section 4 Changes to protocol specified analyses
			Updated subject to participant throughout the document	All sections
		Clarify time window for 105d follow-up assessment	Added target day of assessment and clarified time interval	Table 2-1
		Address the case of a mis-randomized participant being discontinued and re-randomized	Updated definition of FAS to account for this scenario	Section 2.2 Analysis sets
		Clarify efficacy analyses for participants who were randomized but not treated	Specified for each analysis	Section 2.5 to 2.7
		Clarification of supportive analyses	Clarified the imputation rules specifically for each arm for supportive analysis 2.	Section 2.5.4 Supportive analyses
			Clarified the analyses of time to treatment discontinuation and time to change in background SCD therapy, and added	

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			an analysis for the time to the first of these.	
		Clarify/update analyses of SCD-related renal damage	Clarified observation period for shift table and specified change from baseline summaries every 6 months	Section 2.7.2
		Updates to consider COVID-19 pandemic situation	Text added specifying summary of protocol deviations and other issues related to COVID-19	Section 2.3.1 Disposition
			Added text describing analysis of COVID-19 related AEs	Section 2.8.1 Adverse events
		Updates for consistency with data collection	Updated list of AE summaries to accommodate AEs leading to dose reduction	Section 2.8.1 Adverse events
		Updates for consistency with latest Novartis standards for reporting of hepatic lab values	Updated section defining notable hepatic values	Section 2.8.3 Laboratory data
		Clarification of notable vital signs criteria	Footnote clarifications for baseline and post-baseline notable weight change criteria	Section 2.8.5 Other safety data
		[redacted]		
01-Jul-2021 Amendment 3	Prior to DB lock and DMC3 snapshot	Alignment with protocol version 04	Updated study design description consistent with minor corrections made in protocol. Addition of capping in one of the strata.	Section 1.1 Study design

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Alignment with protocol version 05	Clarified post-treatment follow-up for participants continuing crizanlizumab outside of the study	Section 1.1 Study design
			Updates consistent with minor corrections made in protocol	Section 1.2 Study objectives and endpoints
			Updated on-treatment and post-treatment periods to account for participants who will continue crizanlizumab outside of the study	Section 2.1.1 General definitions
			Added summary for participants who will continue crizanlizumab outside of the study	Section 2.3.1 Participant disposition
		Clarification on windows for multiple assessments	Clarified that rules for creating the assessment windows is not applicable to baseline	Section 2.1.1 General definitions
		Alignment with protocol amendment 1	Updated definition of the Pharmacokinetic Analysis Sets to account for steady state	Section 2.2 Analysis sets
		APC history added in the eCRF	Added APC as part of the baseline characteristics	Section 2.3 Participant disposition, demographics and other baseline characteristics
		Updates for consistency with SEG101 studies	Updated unit of duration of exposure from months to weeks	Section 2.4.1 Study treatment / compliance
		Clarification on definition of observation period	Clarified last dose date will be used	Section 2.5 Analysis of the primary objective

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Updates to consider COVID-19 pandemic situation	Added supportive analysis of the number of VOCs managed at home	Section 2.6.4 Supportive analyses
			[redacted]	
		Clarifies use of definition of time windows	Added reference to the time windows definition to SCD-related renal damage	Section 2.7.2 Statistical hypothesis, model, and method of analysis
		Updates in analysis to account for absence of normal ranges in some laboratory parameters	Replaced shift table based on normal ranges by shift table using pre-specified thresholds	Section 2.7.2 Statistical hypothesis, model, and method of analysis
		Correct name of lab parameters per protocol	Replaced reticulocyte count by reticulocyte	Section 2.8.3 Laboratory data
		Updates to consider platelets clumping that occurred with citrate tube	Added analyses of clumping in platelets	Section 2.8.3 Laboratory data
		Correct typo	Corrected reference to footnote in the table of clinically notable changes in vital signs	Section 2.8.5 Other safety data
		[redacted]		
		Addition of time information for infusion related reaction in the eCRF	Updates to the imputation rules of AE start time	Section 5.1.2 AE, concomitant medications and safety assessment date imputation
		Change in the version of the Novartis guideline for	Reference to version number removed	Section 5.3 Laboratory parameters derivations

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		implementation of CTCAE		Section 6 Reference
13-Sep-2021 Amendment 4	Prior to DB lock and after DMC3 snapshot	Change in the definition of date of first administration and date of last administration	Removed condition of non-zero dose and added condition of records not flagged as dose interruption	Section 2.1.1 General definitions

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List of abbreviations

AC	Adjudication committee
ACR	Albumin creatinine ratio
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
[redacted]	[redacted]
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
Cmax	Maximum concentration
CRF	Case report/record form (paper or electronic)
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DBILI	Direct bilirubin
DI	Dose intensity
DMC	Data monitoring committee
[redacted]	[redacted]
DRL	Drug reference listing
ECG	Electrocardiogram
eCRF	Electronic case report form
eCRS	Electronic case retrieval sheet
eDISH	Evaluation of drug-induced serious hepatotoxicity
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ER	Emergency room
[redacted]	[redacted]
e.g.	For example
FAS	Full analysis set
FPFV	First patient first visit
FWER	Family-wise type I error rate
HGLTs	High level group terms
HIV	Human immunodeficiency virus
HLT	High level terms
HR	Hazard ratio
HU/HC	Hydroxyurea/hydroxycarbamide

[redacted]	[redacted]
IL-1b	Interleukin 1b
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-10	Interleukin 10
IRT	Interactive response technology
IV	Intravenous
LVEF	Left ventricular ejection fraction
MedDRA	Medical dictionary for drug regulatory activities
mg	Milligram(s)
[redacted]	[redacted]
NCA	Non-compartmental analysis
NMQ	Novartis MedDRA queries
PAP	Pulmonary arterial pressure
PAS1	pharmacokinetic analysis set 1
PAS2	pharmacokinetic analysis set 2
PD	Pharmacodynamic
PDI	Planned dose intensity
PDS1	Pharmacodynamics analysis set 1
PDS2	Pharmacodynamics analysis set 2
PGI-C	Patient global impression of change
PGI-S	Patient global impression of severity
PK	Pharmacokinetics
PRO	Patient-reported outcomes
PT	Preferred term
PT-INR	Prothrombin time / international normalized ratio
RDI	Relative dose intensity
SAP	Statistical analysis plan
SCD	Sickle cell disease
[redacted]	[redacted]
SD	Standard deviation
SEG101	Novartis humanized anti-P-selectin monoclonal antibody variant
SMQs	Standardized MedDRA queries
SOC	System organ class
[redacted]	[redacted]
TBL	Total bilirubin
TFLs	Tables, figures, listings
Tmax	Time to reach maximum concentration
TNF-a	Tumor necrosis factor alpha
TRV	Tricuspid regurgitant jet velocity
ULN	Upper limit of normal
[redacted]	[redacted]
VOC	Vaso-occlusive crisis

vWF	Von willebrand factor antigen
WBC	White blood cells
WHO	World health organization

1 Introduction

This statistical analysis plan (SAP) describes the primary analyses of the study CSEG101A2301, a Phase 3, multicenter, randomized, double-blind study to assess efficacy and safety of two doses of crizanlizumab versus placebo, with or without hydroxyurea/hydroxycarbamide (HU/HC) therapy, in adolescent and adult sickle cell disease (SCD) subjects with vaso-occlusive crises (VOC).

This SAP describes the primary analysis for which a clinical study report (CSR) is planned to be written, i.e. at the time of the primary cut-off once all randomized participants have reached one-year of treatment or discontinued within year 1. Unless the study is stopped at an earlier point in time, one CSR update is also planned to be written at the end of the study and the corresponding analyses for this study completion CSR will be described in a separate SAP. In addition, a Data Monitoring Committee (DMC) will review safety data at regular intervals. The specifications (definitions, rules) for the DMC analysis are covered by this SAP; however, corresponding deliverables, i.e. subset of tables figures listings (TFLs) which will be re-run for the DMC, will be documented in the TFL shells document.

The content of this SAP is based on protocol CSEG101A2301 version 05. All decisions regarding primary analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data.

1.1 Study design

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

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

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

Following randomization, participants will receive their first dose of investigational treatment (crizanlizumab or placebo) via intravenous (IV) administration on

Week 1 Day 1, followed by a second dose 14 days later

(Week 3 Day 1), and then investigational treatment administration will take place every

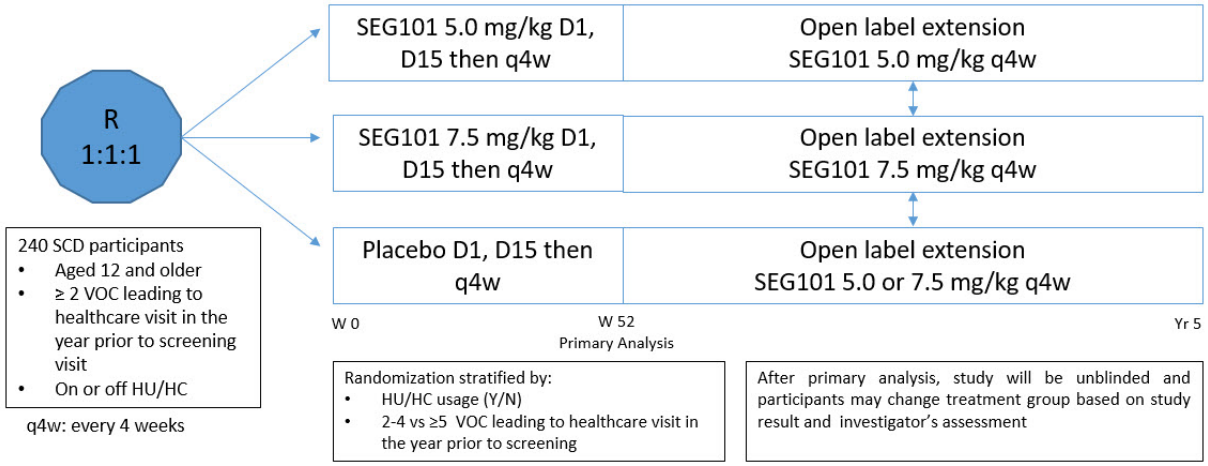
4 weeks for a total on-study treatment period of up to 5 years. Following conduct of the primary analysis, once all randomized participants have reached one year of investigational treatment or discontinued within year one, unblinding and change from placebo to crizanlizumab or to an

alternative dose of crizanlizumab will be permitted for each individual participant. It is planned to observe participants for 5 years on investigational treatment, however early termination of the study could be considered.

Participants will continue on study until 105 days after discontinuing drug or until receiving crizanlizumab commercially or through a different study or drug access program (after a year of follow-up, that is, at switching?). The participants continuing crizanlizumab upon completion of their EOT visit via commercial supply or post-trial access (e.g. enrollment in a Novartis post-trial access program to provide continued study treatment), do not have to complete the post-treatment follow-up.

No formal interim efficacy analysis is planned in this study. A DMC will monitor unblinded safety. The first DMC meeting will occur approximately 6 months after the first patient first visit (FPFV) and then meetings will occur approximately every 9 months during the conduct of the trial and until the primary analysis.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

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

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

Objective(s)	Endpoint(s)
	• Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab

2 Statistical methods

2.1 Data analysis general information

All analyses will be performed by Novartis and/or a designated contract research organization (CRO). SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

The cut-off date for primary efficacy analysis is defined as the date where all randomized participants have reached one-year of treatment or discontinued within year 1.

Data included in the analyses

All data collected in the database will be used for the statistical analysis. For the primary and each DMC analyses, a new ***cut-off date*** will be determined. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an AE) 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 or DMC analyses.

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 cut-off date and not having documented end date. This approach applies, in particular, to AE, VOC and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small size of enrollment at individual centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment group; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by treatment group. For selected parameters, 25th and 75th percentiles will also be presented.

For PK concentration and PK parameters, coefficient of variation (CV) (%), geometric mean, and geometric CV% will be presented in addition to the previously mentioned summary statistics.

CV (%) is calculated as follows:

100*(Standard deviation (SD)/arithmetic mean).

Geometric CV (%) is calculated as follows:

sqrt (exp (variance for log transformed data)-1)*100.

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug refers to SEG101 only. Whereas, study treatment refers to crizanlizumab and placebo. The term investigational treatment may also be referred to as study treatment which is used throughout this document.

Treatment and group

For presentation in the outputs, **treatment** refers to crizanlizumab 5.0 mg/kg, crizanlizumab 7.5 mg/kg and placebo.

Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when investigational drug is administered and recorded on the Study Treatment – Infusion case report

form (CRF) and not flagged as a dose interruption. The date of first administration of investigational drug will also be referred as start of investigational drug.

Note: as the Study Treatment – Infusion CRF is blinded, the process to scramble these data will be described in the blinding document.

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when investigational drug is administered and recorded on Study Treatment CRF and not flagged as a dose interruption. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of first administration of study treatment

The date of first administration of study treatment is the same as the date of first administration of investigational drug or placebo.

Date of last administration of study treatment

The date of last administration of study treatment is the same as the date of last administration of investigational drug or placebo.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is calculated as:

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

The reference start date for safety assessments (e.g. AE onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK, electrocardiogram (ECG), etc.) is the start of study treatment.

The reference start date for all other, non-safety assessments (i.e., VOC, healthcare resource utilization, [redacted] is the date of randomization.

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

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.

Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, [redacted] other acute pain crisis.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken or ''baseline" assessment.

In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), 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 would 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, furthers details to cover case by case situation may be described in the programming data specifications.

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

For safety parameters other than ECG, scheduled pre-dose collections as well as unscheduled collections on Day 1 for which no time is available will be considered as pre-dose.

For ECG, study Day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to start of study treatment if dosing time or ECG time is missing and used in the calculation of the baseline value. If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from

baseline summaries). In addition, **a separate summary for death including on treatment and post treatment deaths will be provided**. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (**treatment-emergent** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize laboratory assessments [redacted] over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows (for baseline refers to definition above): 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 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.

Table 2-1 Time windows for laboratory assessments

Assessment	Target day of assessment	Time interval
Baseline	1	≤ Study Day 1
Week 3 Day 1	15	Study Day 2 to Study Day 29
Week k Day 1	d=(k-1)*7+1	Study Day d-13 to Study Day d+14 Note: Data from End of Treatment visit will be included if obtained within 28 days from last infusion
End of Treatment		Assessment taken at the end of treatment visit
105-day follow-up	105 days after last infusion	Any time after last infusion + 28 days

[redacted]

2.2 Analysis sets

Full Analysis Set

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be

analyzed according to the treatment and strata, they have been assigned to during the randomization procedure.

If a participant is mis-randomized (randomized despite not meeting all eligibility criteria), discontinues without receiving study treatment, and is subsequently re-screened and re-randomized, only the second randomization will be included in the FAS.

Safety Set

The safety set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where

treatment received is defined as the randomized treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

Pharmacokinetic Analysis Sets

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

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

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

Pharmacodynamics Analysis Sets

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

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

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

Participant classification

Participants may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific classification rules defined in Table 2-3.

Table 2-3 Participant classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non-protocol deviation leading to exclusion
FAS	No written inform consent	Not randomized (see also definition of FAS for further detail)
Safety set	No written inform consent	No dose of study treatment
PAS1	No written inform consent	Not meeting the definition for inclusion in the PAS1
PAS2	No written inform consent	Not meeting the definition for inclusion in the PAS2
PDS1	No written inform consent	Not meeting the definition for inclusion in the PDS1
PDS2	No written inform consent	Not meeting the definition for inclusion in the PDS2

Withdrawal of Informed Consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the trial will not be included in the analysis. The date on which a participant withdraws full consent is recorded in the CRF.

Additional data for which there is a separate informed consent, (e.g. pharmacogenetic), collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

Efficacy

The primary efficacy endpoint will be summarized by the following subgroups to examine the homogeneity of treatment effect provided that there is at least 15 participants in each category allowing such analysis:

- Stratification factors (based on randomization data from interactive response technology (IRT)):
  - Categorized Crisis (VOC) History: 2-4 and ≥ 5
  - HU/HC usage: YES and NO
- Genotype: HbSS and HbSβ^+ /HbSC/HbSβ^0 /Other
- Gender: Male and Female
- Ethnicity: Hispanic/Latino and Other
- Age group: 12-<18, ≥18 years
- Race: Black or African American, White and Other. Note that ‘multiple race’ will go to ‘other’

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95%-confidence intervals (CI) will be provided (see Section 2.5.4 for further analysis details). The objective of the efficacy subgroup analysis is to demonstrate homogeneity of treatment effect in the above subgroups.

Safety

Safety subgroup analyses will use the same method as for the analysis in the overall analysis set. The following key safety analyses:

- Overview of AEs and deaths
- AEs by system organ class (SOC) and preferred term (PT)
- Worst post-baseline for laboratory parameters

will be repeated on safety set in the following subgroups:

- Age group: 12-<18, ≥18 years
- Gender: Male and Female
- Race: Black or African American, White and Other
- Ethnicity: Hispanic/Latino and Other
- HU/HC usage (yes | no) (as per CRF)

The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of participants, or safety issues that are more commonly observed in a subgroup of participants.

Summary tables will only be performed if at least 10 participants are present in each subgroup.

Other analysis sets

The subgroup of age ("12-<18" and "18 years and above") will be considered for the pharmacokinetic and pharmacodymamic analyses.

2.3 Participant disposition, demographics and other baseline characteristics

The FAS will be used for all baseline and demographic summaries and listings unless specified otherwise. Summaries will be reported by treatment group and for all participants and listings will be reported by treatment group to assess baseline comparability. No inferential statistics will be provided.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by treatment group. Categorical data (e.g. age, gender, race, ethnicity, performance status) will be summarized by frequency counts and percentages; the number and percentage of participants with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index (BMI)) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum). For selected parameters, 25th and 75th percentiles will also be

presented. BMI (kg/m2) will be calculated as weight[kg] / (height[m]^2) using weight and height at screening.

Baseline stratification factors

The number (%) of participants in each stratum (HU/HC usage: yes, no and baseline rate of VOCs leading to healthcare visit in 12 months prior to screening visit: 2-4, ≥ 5 VOCs) based on data obtained from the IRT system will be summarized overall and by treatment group for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on electronic case report form (eCRF) will be cross-tabulated and listed.

Sickle cell, VOC and APC history

Summary statistics will be tabulated for sickle cell, VOC and APC history. This analysis will include the following: genotype, baseline rate of VOCs leading to healthcare visit in 12 months prior to screening visit as per CRF, baseline rate of APC leading to healthcare visit in 12 months prior to screening visit as per CRF.

Medical history

Medical history and ongoing conditions entered on eCRF will be summarized and listed by treatment group. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary SOC, PT and treatment group. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

All demographic data and other baseline characteristics (e.g., medical history, VOC history including genotype and HU/HC usage, alcohol history, smoking history, hepatitis and human immunodeficiency virus (HIV) screen, drug screen and pregnancy test etc.) will be listed.

2.3.1 Participant disposition

Enrollment by country and center will be summarized for all screened participants and also by treatment group using the FAS. The number (%) of randomized participants included in the FAS will be presented overall and by treatment group. The number (%) of screened and not-randomized participants and the reasons for screening failure will also be displayed. The number (%) of participants in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment group.

The following summaries will be provided (with % based on the total number of FAS participants):

- Number (%) of participants who were randomized (based on data from IRT system)
- Number (%) of participants who were randomized but not treated (based on ‘Study Treatment - Infusion’ eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on ‘disposition’ eCRF page)

- Number (%) of participants who were treated (based on 'Study Treatment - Infusion' eCRF pages with non-zero dose administered)
- Number (%) of participants who are still on-treatment (based on the 'disposition' page not completed);
- Number (%) of participants who discontinued the study treatment phase (based on the 'disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'disposition' page)
- Number (%) of participants who have planned to continue crizanlizumab via commercial supply or post-trial access
- Number (%) of participants who have entered the post-treatment follow-up;
- Number (%) of participants who have discontinued from the post-treatment follow-up;
- Reasons for discontinuation from the post-treatment follow-up;

Protocol deviations

The number (%) of participants in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study edit checks specifications) overall and by treatment group for the FAS.

In addition, COVID-19 related protocol deviations and issues with potential impact on quality will be summarized.

All protocol deviations and COVID-19 related issues with potential impact on quality will be listed.

Analysis sets

The number (%) of participants in each analysis set (defined in Section 2.3) will be summarized by treatment group and stratum. Participants included in each analysis set will be listed.

DMC

For the DMC, corresponding summaries and listings will be provided for:

- Basic demographic and background data
- Sickle cell and VOC history
- Relevant medical histories and current medical conditions
- Participant disposition
- Protocol deviations
- Analysis sets

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

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment group. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of participants in each interval. The number (%) of participants who have dose interruptions, and the reasons, will be summarized by treatment group.

Participant level listings of all doses administered on treatment along with dose adjustments (interruption or dose change) and the reasons will be produced.

The safety set will be used for all summaries and listings of study treatment. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug:

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

The last date of exposure to study treatment is the earliest date between:

- last date of treatment + 27 days
- date of death (if the participant died)
- date of data cut-off.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (less than 26 weeks, at least 26 weeks, at least 54 weeks months, at least 106 weeks, at least 158 weeks, at least 210 weeks) and continuous summaries (i.e. mean, SD etc.).

Cumulative dose

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

The **planned cumulative dose** for a study treatment component 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 participant is on the study treatment as documented in the Study Treatment – Infusion eCRF. In order to determine the actual cumulative dose, the dose administered as reported in the eCRF in mg will be divided by the last weight of a given participant at time of the dosing.

Dose intensity and relative dose intensity

DI for participants with non-zero duration of exposure is defined as follows:

DI (mg/kg/28days) = (Actual cumulative dose (mg/kg) / Duration of exposure to study treatment (weeks)) x 4.

Planned dose intensity (PDI) is defined as follows:

PDI (mg/kg/28days) = (Planned cumulative dose (mg/kg) / Duration of exposure (weeks)) x 4.

RDI is defined as follows:

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

DI and RDI will be summarized by treatment group.

Dose reductions, interruptions

The number of participants who have dose reductions or dose interruptions, and the reasons, will be summarized separately by treatment group.

A dose change is either 'partial dose administered' or 'dosing error' where actual dose administered is different from the prescribed dose.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered is lower than the calculated dose amount based on the prescribed dose. Therefore, any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, and number of reductions will be derived programmatically based on the change and the direction of the change.

Interruptions are considered as infusion completely skipped or delayed.

Interruption: A dose cannot be administered within 7 days of the scheduled day of infusion as per protocol. If a dose was temporarily stopped during infusion, it should not be considered as a dose interruption. Duration of a dose interruption is calculated as the time between the scheduled date of infusion and the actual date of infusion after the interruption.

'Dose change' and 'Dose interrupted' fields from the Study Treatment - Infusion CRF pages will be used to determine the dose reductions and the dose interruptions.

The corresponding field 'Reason for dose change/dose interrupted' will be used to summarize the reasons.

2.4.2 Prior, concomitant and post therapies

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a participant coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) 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.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and PT using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT. These summaries 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.

All concomitant therapies will be listed. Separate listings will be provided for HU/HC, L-Glutamine, Analgesics, and Anticoagulants. 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 the concomitant medication tables and listings. Non-drug therapies and medical procedures will be coded using MedDRA and summarized by SOC and PT.

HU/HC and L-Glutamine

The number and percentage of participants who were treated with HU/HC or L-Glutamine or HU/HC in combination of L-Glutamine (as recorded in the "Sickle Cell – VOC History" eCRF page) prior to study start and the number of participants who started or stopped these medications during the on-treatment period (as recorded on the corresponding Prior and Concomitant Medication Hydroxyurea and L-Glutamine eCRF pages) will be summarized by treatment group using FAS.

HU/HC or L-Glutamine starting on or after the start date of study treatment will be listed using FAS.

The number and percentage of participants who were receiving HU/HC at study entry will be summarized. For participants not receiving HU/HC at study entry, the reason for prior discontinuation of HU/HC (or reason for never having received HU/HC, as applicable) will also be summarized.

Analgesics

Separate summaries will be provided to present the number and percentage of participants who received analgesics (as entered on "Prior and Concomitant Medications Analgesics" eCRF page) on or after the start of study treatment but no later than 105 days after start of last dose of study treatment.

Transfusions

The proportion of participants who received transfusion and the number of transfusions during the on-treatment period will be summarized descriptively. All transfusion will be listed.

DMC

For the DMC, corresponding summaries and listings will be provided for:

- Duration of exposure to study treatment
- Dose interruptions and dose changes
- Concomitant medications by ATC class and PT
- Surgical and medical procedures by SOC and PT
- Number of participants treated with HU/HC or L-Glutamine
- Concomitant medications with Analgesics by ATC class and PT
- Number of participants who received transfusions

2.5 Analysis of the primary objective

The primary objective is to compare the efficacy of 7.5 mg/kg and 5.0 mg/kg of crizanlizumab respectively versus placebo (in addition to standard of care) for preventing VOCs leading to healthcare visits over the first year post randomization in SCD participants 12 years and older at the time of study entry.

2.5.1 Primary endpoint

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

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

The primary efficacy endpoint, annualized rate of VOC leading to healthcare visit, will be analyzed based on the data from the FAS according to the treatment group and the stratification factors participants were randomized to. In line with the treatment effect of interest, the primary observation period will include only data before study treatment discontinuation and before initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin); while data after intake of analgesic (including opioids) or ad hoc transfusions administered temporarily until one year post randomization, will be included. Since the treatment effect of interest is on treatment, participants who were randomized but not treated will be excluded from this analysis.

The primary observation period will be defined as the time from the date of the randomization to the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation

or discontinuation of HU/HC or L-Glutamine/other SCD therapies, date of randomization + 365 days).

More details are provided in the estimand charter.

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

To control the overall family-wise type I error rate (FWER) an appropriate multiplicity adjustment procedure using a closed testing strategy will be applied to the analyses of the primary and key secondary endpoints for the 2 doses comparisons to placebo. This strategy to preserve the overall FWER at $\alpha = 5\%$ (two-sided) is described in Section 2.6.1.

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

The primary statistical null hypotheses are:

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

These hypotheses will be tested using the Wald test statistic within generalized linear model assuming a negative binomial distribution and will compare 7.5 mg/kg and 5.0 mg/kg crizanlizumab versus placebo at the appropriate α-level adjusted considering multiple testing (as described in Section 2.6.1).

The annualized rate of VOC leading to healthcare visit will be summarized by treatment group.

2.5.3 Handling of missing values/censoring/discontinuations

By using as primary endpoint the annualized rate of VOCs leading to healthcare visit, the intrinsic assumption is that the frequency of VOCs before treatment discontinuation would have been observed also for the entire first year of treatment. Supportive analyses are exploring different assumptions to handle missing data (Section 2.5.4).

2.5.4 Supportive analyses

Supportive analysis 1

For the supportive analysis 1, the treatment effect regardless of treatment discontinuation, initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) during year 1 is of interest. Consequently, all VOC leading to healthcare visit collected over one year post randomization will be included in the analyses (including VOC leading to healthcare visit after treatment

discontinuation and VOC leading to healthcare visit after initiation or discontinuation of HU/HC, L-Glutamine or other SCD therapies).

The observation period of this supportive analysis 1 will be defined as the time from the date of the randomization to the minimum of (end of study date, date of randomization + 365 days). Since for this analysis the treatment effect of interest is regardless of study treatment, all randomized participants will be included, regardless whether treated or not.

Supportive analysis 2

For the supportive analysis 2, different imputation methods will be used for different reasons for treatment discontinuation and other events mentioned above.

VOC leading to healthcare visit over one year post randomization will be included but the VOC after treatment discontinuation and after initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) will be excluded and considered as missing data. VOC after treatment discontinuation and VOC after initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) will be imputed using a reference-based approach considering a mixture of missing at random and jump to reference approach as proposed by (Keene et al 2014) depending of the events and reasons. A Bayesian log-linear negative binomial model with non-informative prior to the data will be fitted. This model will include stratification factors as covariates and the logarithm of observation period as offset. Missing data on VOC leading to healthcare visit will be imputed by drawing independent samples from the posterior for the parameters of this model in the conditional distribution of the missing data given the observed data.

Imputation will be done considering to the following cases:

- In the crizanlizumab treatment arms:
  - Missing data after treatment discontinuation due to “AE”, “death”, or “unsatisfactory therapeutic effect”, or after initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) will be imputed assuming rate of VOC leading to healthcare visit in the placebo arm (jump to reference)
  - Missing data after treatment discontinuation due to “lost to follow-up”, “physician decision”, “subject/guardian decision” or “other” will be imputed assuming rate of VOC leading to healthcare visit in the same arm before discontinuation (missing at random)
- Missing data after treatment discontinuation in placebo participants will be imputed assuming event rate in the placebo arm before discontinuation (missing at random)

One thousand imputations will be performed and each dataset will be analyzed using negative binomial regression model concomitant HU/HC usage at randomization and number of VOC leading to healthcare visit in the prior 12 months as covariates and the natural logarithm of the observation period as an offset variable. The results will be combined on the log-scale using Rubin’s rule (Barnard and Rubin 1999).

Since for this analysis the treatment effect of interest is the treatment effect had participants not discontinued study treatment, participants who were randomized but not treated will be excluded. The observation period of this supportive analysis will be defined as the time from the date of the randomization to the date of randomization + 365 days.

Supportive analysis 3

For the supportive analysis 3, all the VOCs leading to healthcare visits collected until the primary analysis cut-off and before treatment discontinuation and initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as Voxelotor and erythropoietin) will be included.

The observation period of this supportive analysis will be defined as the time from the date of the randomization to 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), primary analysis cut-off). Since for this supportive analysis, as for the primary analysis, the treatment effect of interest is on treatment, participants who were randomized but not treated will be excluded.

Corresponding summaries will be provided overall and per year.

Details of these supportive analyses are provided in the estimand charter.

The same analyses as for the primary analysis will be repeated for the 3 supportive analyses described above.

Other supportive analyses

The time to treatment discontinuation, the time to 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), and the time to the earliest of the aforementioned events, will be summarized by treatment using Kaplan-Meier methods. Median time, 25th and 75th percentiles along with 95% confidence interval will be summarized. Participants who were randomized but not treated will be excluded from these analyses. For all three analyses, the observation period for supportive analysis 3 will be used. In the absence of an event (as defined below) during this observation period, participants will be censored at the end date of this period.

- The time to treatment discontinuation will be defined as the time from the date of randomization to the date of last dose date until treatment discontinuation + 27 days.
- The time to initiation or discontinuation of HU/HC or L-Glutamine (or other therapies to treat SCD and/or to prevent/reduce VOCs such as Voxelotor and erythropoietin) will be defined as the time from the date of randomization to the minimum of (start date of HU/HC or L-Glutamine [or other SCD therapy] starting on or after the date of randomization, end date of HU/HC or L-Glutamine [or other SCD therapy] starting prior to the date of randomization).
- The time to treatment discontinuation or initiation/discontinuation of HU/HC, L-Glutamine or other SCD therapy will be defined as the time from the date of randomization to the date of the earliest occurrence among the events defined above.

The number of VOCs leading to healthcare visit that have been adjudicated will be summarized by treatment group in order to assess the concordance between assessments from the investigator and from the AC. The primary observation period will be used for this summary; therefore, participants who were randomized but not treated will be excluded from the analysis.

Subgroup analyses of the primary endpoint, i.e. annualized rate of VOC leading to healthcare visit, will be performed on the FAS with the same statistical model used for the point estimate in the full population. Analyses will be performed for each subgroup as listed in Section 2.2.1, one by one, i.e. fitting a model using only participants available in the subgroup of consideration. Summary tables and forest plots will present the estimates of the rates with their corresponding 95% CI.

2.6 Analysis of the key secondary objective

The key secondary objective is to assess the annualized rate of all VOCs (managed at home + leading to healthcare visit) over the first year post randomization.

2.6.1 Key secondary endpoint

The key secondary efficacy endpoint is the annualized rate of all VOCs (managed at home + leading to healthcare visit) over the first year post randomization.

2.6.2 Statistical hypothesis, model, and method of analysis

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

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

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

Table 2-4 Intersection hypotheses and local significance levels

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

*adjusted alpha using Dunnett's procedure

2.6.3 Handling of /discontinuations

By using as key secondary endpoint the annualized rate of all VOCs, the intrinsic assumption is that the frequency of VOCs before treatment discontinuation would have been observed also for the entire first year of treatment.

2.6.4 Supportive analyses

The number of VOCs managed at home and whether the specific COVID-19 pandemic situation led those VOCs to be managed at home rather than by a healthcare visit will be described by treatment group.

2.7 Analysis of secondary efficacy objective(s)

Other secondary objectives over the first year post randomization include rate of participants free from VOC leading to healthcare visit, time for first and second VOC leading to healthcare visit, number of days with VOC (=duration of VOC) leading to healthcare visit, healthcare resource utilization (visits to clinic, ER, hospitalizations), SCD-related renal damage and PK and PD (P-selectin inhibition). Another set of secondary objectives which will not be covered by this SAP for the primary analysis will evaluate the long-term efficacy, safety and immunogenicity of crizanlizumab not only over the first year post randomization but over the entire study period.

2.7.1 Secondary endpoints

The secondary efficacy endpoints include the following.

- Number of days with VOC (=duration of VOC) leading to healthcare visit over the first year post randomization
- Number and percentage of participants free from VOCs leading to healthcare visit in each group over the first year post randomization
- The time to first and second VOC calculated respectively as the time from date of randomization until the first and the second VOC leading to healthcare visit over the first year post randomization
- Annualized rate of visits to clinic, ER and hospitalizations, both overall and VOC-related over the first year post randomization
- Evolution of albuminuria and albumin creatinine ratio (ACR) over the first year post randomization
- PK parameters after the first and fifth dose (e.g., area under the curve (AUC), Cmax, Tmax, half-life)
- PD parameter (P-selectin inhibition) after the first and fifth dose

Secondary efficacy endpoints will be analyzed using the FAS.

2.7.2 Statistical hypothesis, model, and method of analysis

For all other secondary endpoints described below, estimates and confidence intervals will be presented, but no formal statistical testing will be conducted. Participants who were randomized but not treated will be excluded from the below analyses.

The same analyses as for the primary endpoint will be repeated for each subtype of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration and priapism) leading to healthcare visit.

The number of participants free from VOC leading to healthcare visit will be presented, odds ratio along with 95% CI will be provided using a logistic regression model including stratification variables.

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

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

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

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

VOCs endpoints and clinic, hospitalizations and ER visits endpoints will be listed.

SCD-related renal damage

The renal function parameters include microalbumin, ACR, estimated glomerular filtration rate (eGFR) and creatinine. Shift tables using common terminology criteria for adverse events (CTCAE) grades, or using pre-specified thresholds mentioned in TFL shells documentif CTCAE grades are not defined, to compare baseline to the worst value during the observation period used for supportive analysis 3 (as defined in Section 2.5.4), will be provided for the renal function parameters. In addition, change from baseline every six months will be presented on the FAS as per time windows definition in Table 2-1.

2.7.3 Handling of missing values/censoring/discontinuations

Missing values or data will not be imputed and will be treated as missing, except that when computing annualized rates of events, the assumption is done that the frequency of events before treatment discontinuation would have been observed also for the entire first year of treatment.

2.8 Safety analyses

For all safety analyses, the safety set will be used. Safety summaries include only on-treatment assessments; safety listings include all assessments with those more than 105 days after last study treatment flagged. All listings and tables will be presented by treatment group.

2.8.1 Adverse events (AEs)

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

AEs will be summarized by number and percentage of participants having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT 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 SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in the crizanlizumab 7.5 mg/kg group.

The following AE summaries will be produced by treatment group; overview of AEs and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment

discontinuation, leading to dose interruption or dose reduction, requiring additional therapy and leading to fatal outcome. In addition, for EudraCT requirements a summary of (1) Serious AEs and deaths, with number of occurrences and (2) Non-serious AEs, with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same PT).

All AEs and serious AEs (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.

Adverse events identified in the Novartis MedDRA Query (NMQ) topic of "COVID-19 diagnosis, manifestations, risks and complications including death" will be summarized and listed. Summaries will be provided overall for this COVID-19 topic and by different classification levels defined within the topic.

2.8.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of AEs that are of scientific and medical concern specific to compound crizanlizumab. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs. Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on treatment period will be summarized. The list of AESI to be taken into account for crizanlizumab trials is documented in electronic case retrieval sheet (eCRS) for the project. The most up to date version of the eCRS available at the time of a database lock for an analysis will be used to define on which AESIs the analysis will be conducted.

Summaries of these AESIs will be provided by treatment group, (specifying grade, serious AE, relationship, leading to treatment discontinuation, leading to dose interruption).

A listing of all grouping levels down to the MedDRA PTs used to define each AESI will be generated.

DMC

For the DMC, the sort order for the PT will be based on their frequency in the total column. The following summaries will be provided:

- Overview of AEs and deaths
- AEs by SOC and PT
- AEs suspected to be related to study treatment by SOC and PT
- Serious AEs by SOC and PT
- AEs leading to treatment discontinuation
- AESI
- COVID-19 NMQ AEs

In addition, all AEs and serious AEs will be listed.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by treatment group, SOC and PT.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

DMC

For the DMC, summaries of on-treatment and all deaths will be produced. In addition, all deaths will be listed.

The time to on-treatment deaths will be presented using Kaplan-Meier plots, if at least 20 deaths are observed during the on-treatment period across treatment arms. The time to on-treatment deaths will be defined as the time from the first administration of study treatment to the date of death. In the absence of on-treatment death, participants will be censored at time of the minimum of (last dose + 105 days, follow-up visit, cut-off date).

2.8.3 Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 105 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology (including coagulation), biochemistry and urinalysis (macroscopic only) laboratory data (by laboratory parameter and treatment group):

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only 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 values flagged to show the corresponding CTCAE v5.0 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 3 or 4 laboratory toxicities
- Microscopic urinalyses tests will be provided in listings only.

For hemoglobin and leukocytes parameters, summary and box plot of the absolute change from baseline over time based on time windows will be provided.
In addition, the analysis of clumping in platelets will be performed as follows:

- Summary table by time windows of the number (and %) of participants and samples with missing platelet values due to clumping and due to other reason, based on central lab
- Summary table by time windows of the number (and %) of participants and samples with missing platelet values due to clumping and due to other reason, based on local lab
- Boxplot figures on platelet change from baseline by time windows:
  - A figure only based on evaluable platelet counts collected at scheduled visits from central laboratory
  - A figure where the missing central platelet counts will be replaced by local values available at the same assessment date.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), direct bilirubin (DBILI), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP). The number (%) of participants with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized in addition to the baseline values.

Shift tables using ALT, AST and TBL will be generated, respectively. Evaluation of drug-induced serious hepatotoxicity (eDISH) plot will be produced and a similar plot of DBILI vs. ALT will also be generated. Individual participant plots will be produced for participants with potential severe drug induced liver injury (as defined below). Individual participant reticulocyte plot, and a plot of prothrombin time / international normalized ratio (PT-INR) and albumin over time will also be produced for the same participants. A corresponding listing of participants with potential severe drug induced liver injury will be generated.

The following summaries will be produced based on peak post-baseline values for each parameter (i.e. not necessarily concurrent assessments for combinations of parameters):

- ALT or AST > 3xULN (upper limit of normal)
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- DBILI > 2xULN
- DBILI > 3xULN
- For participants with AST and ALT ≤ ULN at baseline:
  - Elevated ALT or AST (*) & TBL > 2xULN
  - Elevated ALT or AST (*) & TBL > 2xULN & ALP < 2xULN (potential Hy's law)
  - Elevated ALT or AST (*) & TBL > 2xULN & ALP ≥ 2xULN

  - Elevated ALT (*) & DBILI >2xULN & ALP <2xULN (potential severe drug induced liver injury)
- For participants with AST or ALT > ULN at baseline:
  - Elevated ALT or AST (*) & TBL(>2x Bsl and 2x ULN)
  - Elevated ALT or AST (*) & TBL(>2x Bsl and 2x ULN) & ALP ≥2x ULN
  - Elevated ALT or AST (*) & TBL(>2x Bsl and 2x ULN) & ALP <2x ULN (potential Hy's law)
  - Elevated ALT (*) & DBILI (>2x Bsl and 2x ULN) & ALP <2x ULN (potential severe drug induced liver injury)

* Elevated ALT or AST defined as: >3x ULN if ≤ ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

Other Laboratory parameters

Hepatitis markers and additional tests only performed at screening will only be listed. COVID-19 antibody test results will be listed and % positivity will be presented by treatment arm and time point, separately for participants who entered the study before vs after the protocol amendment 3.

DMC

For the DMC, the following summaries will be produced:

- Shift tables to compare baseline to the worst on-treatment value
- The number (and %) of participants with worst post-baseline value for the liver function parameters
- TBL vs ALT/AST and DBILI vs ALT plots
- Individual participant plots for participants with potential severe drug induced liver injury
- Individual participant reticulocyte plot for participants with potential severe drug induced liver injury
- Plot PT-INR and albumin over time for participants with potential severe drug induced liver injury

In addition, the following listings will be provided:

- all CTCAE grade 3 or 4 laboratory toxicities
- Listing of participants with potential severe drug induced liver injury
- Listings of all laboratory data

2.8.4 Immunogenicity

The number of ADA positive participants by treatment group will be summarized and listed. The table will show the total number of participants in the treatment group, number and

percentage of total ADA positive participants (positive at baseline and/or post-baseline), and number and percentage of ADA positive participants post baseline by treatment group.

2.8.5 Other safety data

2.8.5.1 ECG

Data handling

For ECG replicates, the average of the ECG parameters at that assessment will be used in the analyses.

Data analysis

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

The number and percentage of participants with notable ECG values will be presented by treatment group.

- 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 ≤ 60ms
  - 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

A listing of all ECG assessments will be produced by treatment group and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

DMC

For the DMC the notable ECG values will be summarized and listed.

2.8.5.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable criteria are provided in Table 2-5 below.

Table 2-5 Clinically notable changes in vital signs

Vital sign (unit)	Criteria	< 18 years at screening and < 18 years at time of assessment	< 18 years at screening and ≥ 18 years at time of assessment	≥ 18 years at screening
Systolic blood pressure (mmHg)	High	≥ 95th percentile of the age and height group[1]	≥ 180 with increase from updated baseline[4] 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[4] of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	High	≥ 95th percentile of the age and height group[1]	≥ 105 with increase from updated baseline[4] 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[4] 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[4] of ≥15	≥100 with increase from baseline of >25%
	Low	12-15 years: <62 ≥15 years: <58	≤50 with decrease from updated baseline[4] of ≥15	≤50 with decrease from baseline of >25%
Weight (kg)	High	increase from baseline of ≥2 BMI-for-age percentile categories[3]	increase from updated baseline[4] of ≥10%	increase >10% from baseline
	Low	decrease from baseline of ≥2 BMI-for-age percentile categories[3]	decrease from updated baseline[4] of ≥10%	decrease >10% from baseline
Respiratory rate (breath per minute)[2,5,6]	High	12-15 years: >21 ≥15 years: >20	≥30	≥30

Vital sign (unit)	Criteria	< 18 years at screening and < 18 years at time of assessment	< 18 years at screening and ≥ 18 years at time of assessment	≥ 18 years at screening
	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] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts;

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

[5] Eldridge L, 2014;

[6] Kou .R, 2009.

The number and percentage of participants with notable vital sign values (high/low) will be presented by treatment group.

A listing of all vital sign assessments will be produced by treatment group and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

DMC

For the DMC, the notable vital signs values will be summarized and listed.

2.8.5.3 Growth and sexual maturation

Data on growth and sexual maturation (Tanner stage) will be listed for adolescents by gender, visit and treatment group.

2.9 Pharmacokinetic endpoints

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

The inter-participant variations and CV% will be presented for the PK parameters. The point estimate and the corresponding two-sided 90% CI for the mean of the log-transformed PK parameters after single dose and multiple doses will be derived respectively in each treatment group. The point estimate and CI will be anti-log transformed to obtain the point estimate and the 90% CI for the geometric mean on the original scale.

The descriptive statistics (n, mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters defined in Table 2-6 except Tmax, where only n, median, minimum and maximum will be presented since it is generally evaluated by a nonparametric method. Zero concentrations will not be included in the geometric mean calculation. The descriptive statistics will also be presented by the dose and age groups (adolescents and adults).

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

Table 2-6 Non-compartmental pharmacokinetic parameters

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

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

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

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

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

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

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

2.10 PD and PK/PD analyses

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

The descriptive statistics will also be presented by the dose and age groups (adolescents and adults).

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

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

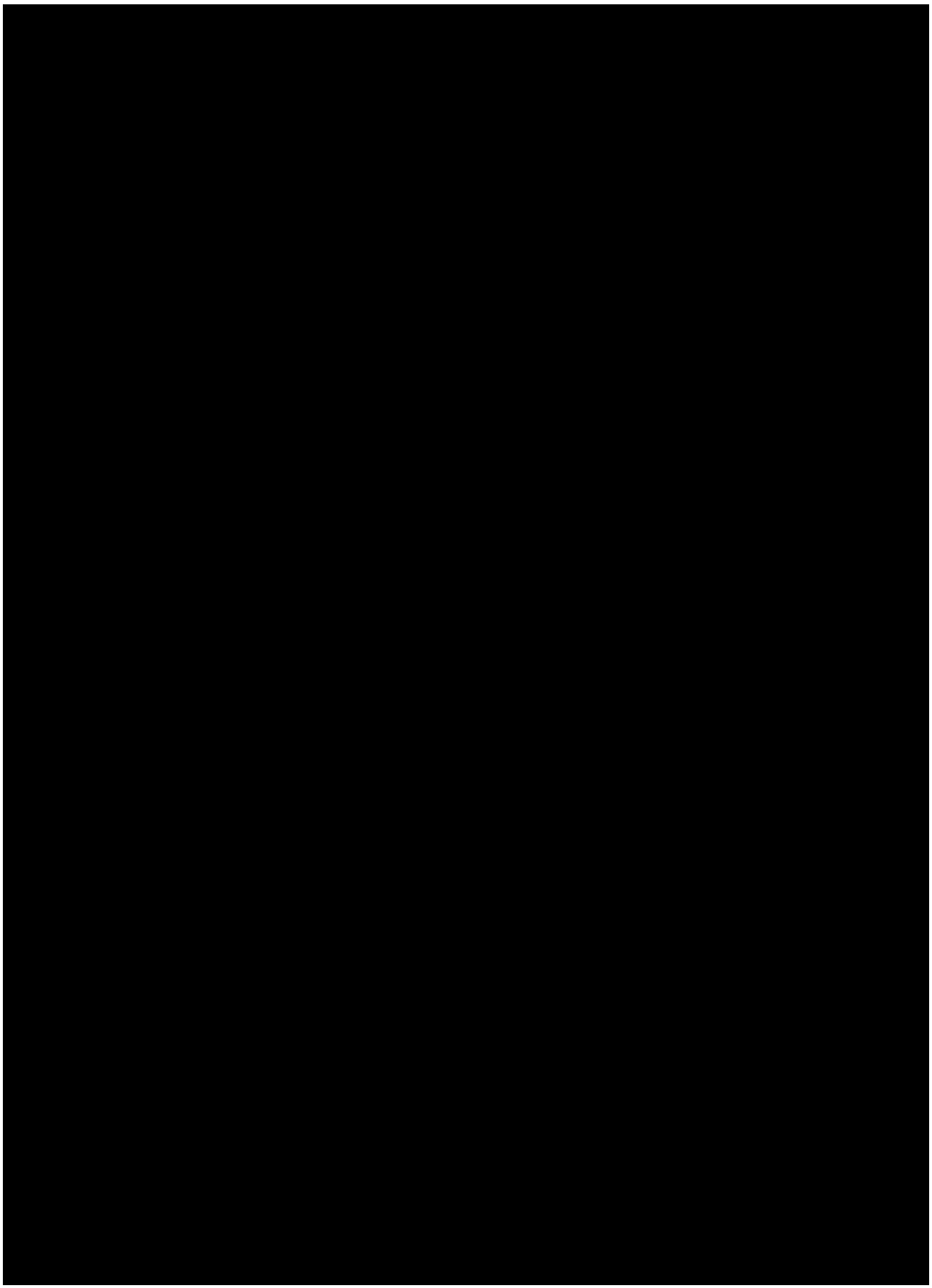
In addition, the mean (+/- SD) and median PD-time profiles over time will be displayed graphically on the linear and semi-log view.

All individual PD parameters and PD data will be listed.

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

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

[redacted]



3 Sample size calculation

3.1.1 Primary endpoint

The sample size calculation is based on the primary variable annualized rate of VOCs leading to healthcare visit over the first year post randomization. The hypotheses to be tested and details of the testing strategy are described in Section 2.5.2 and Section 2.6.2.

Based on available data from CSEG101A2201 study, the mean VOC rate was 3.74 in placebo group and the ratio of VOC rate between 5.0 mg/kg and placebo was 0.65 (both estimates from a negative binomial regression with treatment, HU/HC use, and VOC rate in 12 months prior to screening (2-4 vs ≥ 5-10 VOC) as covariates).

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

power calculation based on normal approximation and Dunnett's adjustment and software SAS (9.4).

3.1.2 Secondary endpoints

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

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

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

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

4 Change to protocol specified analyses

Table 4-1 Changes to protocol specified analysis or descriptions and rationale

Protocol section	Protocol description	Change	Rationale
Not applicable			

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 participant is considered as on-going:

The participant 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 EOT completion date 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 dosing 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

Participants 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, concomitant medications and safety assessment date imputation

Table 5-1 Imputation of start dates/times (AE, concomitant medications)

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 • 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
time (for AE only)	• If AE available day, month and year = day, month and year of study treatment start date then o If AE stop date/time contains a full date/time (time, day, month and year) and AE stop date/time is earlier than study treatment start date/time then set start date/time = DDMONYYYY:00:01. o If Infusion related reaction = "Yes" and "when did the Infusion related reaction start" = "During the infusion" then set start date/time = study treatment start date/time o If Infusion related reaction = "Yes" and "when did the Infusion related reaction start" = "Within 24 hours after the infusion" then set start date/time = study treatment infusion end date/time +01 min of that day of AE o Else set start time = study treatment start time • Otherwise if day, month and year < day, month and year of study treatment start date or if day, month and year > day, month and year of study treatment start date do not impute the AE start time and leave it blank

Table 5-2 Imputation of end dates (AE, concomitant medications)

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

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

5.1.3 Age at time of assessment

In order to calculate the age at time of a given assessment, the following rules will be applied:

Scenario 1: If the age at screening visit in months is known, the age at visit x will be calculated based on an estimated date of birth:

Considering, screening visit date on ddmmmyyyy,

estimated day of birth = dd, with dd the day of the screening visit

estimated month and year of birth = screening visit date – age in months

For example, if a participant is 15 years + 4 months (total of 184 months) at screening visit on 15Jun2020, then estimated date of birth is 15Feb2005.

Scenario 2: If the age at screening visit in years only is known, the age at visit x will be calculated based on an estimated date of birth:

Considering, screening visit date on ddmmmyyyy,

estimated day of birth = dd, with dd the day of the screening visit

estimated month of birth = mmm, with mmm the month of the screening visit

estimated year of birth = screening visit year – age in years

For example, if a participant is 15 years at screening visit on 15Jun2020, then estimated date of birth is 15Jun2005.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology.

AEs will be assessed according to the 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 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 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 v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) 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

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.

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).

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 Primary analysis

Negative binomial model

The SAS procedure GENMOD will be used with the following code:

```
proc genmod data=....;
  class trt stratum1 stratum2;
  model aval = trt stratum1 stratum2/
                 dist=nb link=log offset=lobs;
  lsmeans trt / cl diff exp;
run;
```

where aval = number of VOC leading to healthcare visit in the observation period
trt = planned treatment

stratum1 = concomitant HU/HC usage (yes/no)

stratum2 = baseline rate of VOCs leading to healthcare visit in 12 months prior to screening visit (2-4 vs ≥ 5 VOCs)

lobs = log (observation period in years)

The estimates of annualized VOC rates between treatment groups and their 95% confidence intervals will be provided. The p-value will be provided by Wald test statistics.

5.4.2 Secondary analysis

Analyses for time to first occurrence of VOC leading to healthcare visit are described in section 2.7.2.

Kaplan-Meier estimates

To analyze time to event variables (e.g. time for first occurrence of VOC leading to healthcare) an estimate of the survival function will be constructed using ***Kaplan-Meier (product-limit) method*** as implemented in PROC LIFETEST with METHOD=KM option.

Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures.

Median survival will be obtained by treatment group along with 2-sided 95% CIs calculated from PROC LIFETEST output using the method of (Brookmeyer & Crowley, 1982).

Kaplan-Meier estimates with 2-sided 95% CIs at specific timepoints will be summarized by treatment group. The CIs will be constructed using Greenwood's formula (Collett, 1994, p.23) for the standard error of the Kaplan-Meier estimate.

The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The CONFTYPE option specifies the transformation applied to the survival function to obtain the point-wise confidence intervals and the confidence intervals for the quartiles of the survival times. The LOGLOG keyword specifies the complementary log-log transformation (Collett, 1994; Lachin, 2000) g(x)=log(-log(x)) which ensures that the point-wise confidence intervals are always within interval [0,1].

The Kaplan-Meier graphs will be constructed using SAS software.

Hazard ratio estimates

Hazard ratio as a treatment effect measure will be derived from the ***Cox proportional hazards model*** using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

The ***stratified unadjusted Cox model*** will be used (where the baseline hazard function is allowed to vary across strata), i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variables.

```
PROC PHREG data=dataset;
      MODEL survtime*censor(1)=trt / TIES=EXACT;
      STRATA stratum1 .. <stratum k>;
RUN;
/* survtime represents variable containing event/censor times;
   censor represents censoring variable (1=censored, 0=event);
   trt represents treatment group variable;
   stratum1 to stratumk represent stratification variables */
```

Hazard ratio with two-sided 95% confidence interval will be based on ***Wald test***.

6 Reference

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