NOVARTIS

Clinical Development

SEG101/Crizanlizumab

CSEG101B2201 / NCT03474965

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

# Statistical Analysis Plan (SAP)

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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) |
|---|---|---|---|---|
| 24-August-2018 | Prior to FPFV | CSR_1_Primary: Creation of final version | N/A - First version | NA |
| 21-January-2019 | Prior to first analysis | CSR_1_Primary: Amendment 1 Added section on DMC | V2.0 | NA |
| 29 – July 2019 | Prior to the first single dose analysis | CSR_1_Primary: Amendment 2 | Updated planned dose window for PAS1 | Section 2.2 |
| | | | The disposition summaries for all screened patients will not be provided. All protocol deviations are already analyzed and displayed by types in one analysis, there is thus no need to redo a dedicated table for major protocol deviations leading to exclusion from analysis sets | Section 2.3 |
| | | | Added the definition for dose interruption | Section 2.4.1 |
| | | | Deleted the text relating to urinalysis listing, boxplot for hemoglobin parameter, neutropenia and thrombocytopenia summaries in line with project standards for safety assessment and to avoid overlap with other analyses | Section 2.8.3 |
| | | | Analyses about liver have been updated to take into account project standards related to known liver function specificities in SCD patients | Section 2.8.3 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Deleted the repetition in the text of QTcF categories provided earlier in the same section | Section 2.8.4.1 |
| | | | Analysis of protein/creatinine ratio is added in line with project standard safety analyses | Section 2.13.2 |
| | | | Updated CTCAE version to 5.0 | Throughout |
| | | | Addressed typographical and editorial errors | Throughout |
| 17 – August 2020 | Prior to Group 1 primary analysis DBL | CSR_1_Primary: Amendment 3 | Updated reference to protocol version. | Section 1 |
| | | | Implement updates from protocol v03, mainly:<br>• Update and clarify the criteria and process for dose confirmation in Part A of each group. | Section 1.1 |
| | | | • Clarify that at the time of primary analysis for each group, it will be possible to also conduct an analysis of data from other groups, if needed to support regulatory filings or potential Health Authority requests. | Section 2.1 |
| | | | Implement updates from protocol v02 which remain valid in protocol v03, mainly:<br>• [redacted] | Sections 1.2, 2.2, 2.5.1<br>Section 1.2 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | • Change the wording "number of" to "annualized rate of" in all the secondary objectives to assess the long-term efficacy [redacted] | Sections 1.2 and 2.13.1<br>Sections 2.5.2 and 2.10 |
| | | | • Clarify the PK PD analyses | |
| | | | Clarify baseline definition for ECG, aligned with other SEG101 studies | Section 2.1.1 |
| | | | Remove time window definition for vital sign and ECG summaries by time point as no such summaries are required in planned analyses. Clarify time window for laboratory data summary, aligned with A2301 study. | Section 2.1.1 |
| | | | Correct that weight and height at screening will be used for demographic analysis, as per TFL shell. Remove listings of drug screen, smoking and alcohol history as collection of these data was removed since protocol v02. | Section 2.3 |
| | | | Add analyses (on protocol deviations and other issues, AEs) to assess COVID-19 impact during the study. | Sections 2.3.1 and 2.8.1<br>Section 2.4.1 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Clarify the analysis of dose interruptions/reductions. Update data to be presented as per data collected in CRF. | Section 2.4.2 |
| | | | Clarify the start date of concomitant medication to be included in summaries, aligned with other SEG101 studies. Mention and detail separate listings will be provided for HU/HC, L-Glutamine and Analgesics. | Section 2.7.2 |
| | | | As per protocol v02-03, the analysis of annual rate of VOC will exclude data post initiation/discontinuation of HU/HC or L-glutamine. A sensitivity analysis will evaluate results with inclusion of those data. The end date for the VOC analyses is defined accordingly. Add clarifications for efficacy analysis as needed. Add subgroup analyses for main efficacy end-points as required for SCE. | Section 2.8.1 |
| | | | Update list of AE summaries to accommodate AEs leading to dose reduction, for consistency with data collection. | Section 2.8.3 |
| | | | Specify that summary over time for change from baseline of hemoglobin parameter will be performed. Update criteria to be used in reviewing and presenting hepatic lab values, following Novartis Hepatotoxicity Guideline 2019 and standard output updates. | |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Remove shift table for leukocytosis by ≤ 100,000 mm3 vs > 100,000 mm3, considering the overlap with the shift table by CTC grade for this parameter. | Section 2.8.4.2 |
| | | | Update vital signs section to add head circumference in the list of vital sign data collected. Add the notable criteria for participants 6-12 months and clarify footnote for baseline/post-baseline notable weight change in Table 2.2. | Section 2.13.2<br>Section 2.12 |
| | | | [redacted] | [redacted] |
| | | | Add derivation of age at a given assessment as it is relevant in a study including adolescents. | Throughout |
| | | | Address typographical and editorial errors. Updates as per SAP template/ LEAN SAP principle. Update “subject” or “patient” to “participant” to align with protocol template. Add clarifications when needed. | |
| 21 May 2021 | Prior to Group 2 multiple dose analysis DBL | CSR_2_Primary: Updates applicable starting from Group 2 multiple dose analysis, | Implement updates from protocol v04, mainly:<br>• Update definition of the on-treatment and post-treatment periods, as patients continuing | Section 2.1.1 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | unless otherwise specified. | crizanlizumab via commercial supply or post-trial access will not need to be followed after their EOT.<br>Update disposition summary accordingly.<br>• Clarify definition of End date for observation period in efficacy analyses. | Section 2.3.1<br>Sections 2.7.1 and 2.13.2 |
| | | | Update imputation rule of AE start date, once the AE CRF will be updated to collect precise information on timing of infusion related reactions (*not applicable yet to Group 2 multiple dose analysis).* | Section 5.1.2 |
| | | | Clarify that shift tables based on normal ranges are performed only on parameters for which normal ranges are provided by the laboratory. | Section 2.8.3 |
| | | | Replace urine protein creatinine ratio by urine albumin creatinine ratio, as per protocol schedule of assessment. | Section 2.13.2 |
| | | | Address typographical and editorial errors. | Throughout |
| 4 – June 2021 | Prior to Group 2 multiple dose DBL | CSR_2_Primary: Amendment 1 | Clarify the baseline definition rule in time window section. | Section 2.1.1 |
| | | | Remove reference to the version of Novartis guidance for CTCAE v5, i.e. the latest version available at time of the analysis will be used. | Section 5.3 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 24-Nov-2021 | | CSR_2_Primary: Amendment 2 | Update concomitant medication listings: Erythropoietin simulating agent (collected on specific page as per updated CRFs) will be displayed in separate listing (with HU/HC and L-glutamine). | Section 2.4.2 |
| | | | Add summary table of HU/HC treatment status at study entry, and reason for non-administration, as collected on "Sickle Cell – Reasons for Non-Administration of HU/HC" CRF | Section 2.4.2<br>Section 2.7.1 |
| | | | Clarify definition of baseline VOCs leading to healthcare visit. Update definition of baseline hospitalizations/ER visits to align with baseline VOC definition. | Sections 2.8.3, 2.13.2 |
| | | | Replace the parameter name "reticulocyte count" by "reticulocyte" (reported in %). | Throughout |
| | | | Address typographical and editorial errors. | |
| 13-April-2022 | Prior finalization of group 1 primary analysis CSR | Amendment 4 | To clarify that when an AE has a start date before cut-off and an end date post cut-off, the outcome for this AE should be reported as unknown. | Sections 2.1 and 5.1.2 |
| 06-June-2022 | Prior finalization of group 1 analysis CSR | Amendment 3 | Clarify the definition of End date for calculation of the annualized rate of VOC, dactylitis, hospitalizations and transfusions, | Sections 2.7.2 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | Removed eGFR shift table | Section 2.8.3 |
| 15-Oct-2024 | Prior to Final DBL | Final CSR | Elaborate the definition for dose interruption, Specify the analysis for tanner stage, updated Table 5-2 | Sections 2.4.1, 2.8.4.3,5.1.2 |
| | | | Corrections are performed regarding analyses of Group 3 according to the protocol Amendment 6 (14-Mar-2024). | Throughout the document |
| | | | In the vital signs section, the age of patients whose head circumference data were collected was updated according to protocol Amendment 6 (14-Mar-2024) | Section 2.8.4.2 |
| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |
| | | | In sample size calculations, the wording is updated according to the protocol Amendment 6 (14-Mar-2024). | Section 3 |

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## List of abbreviations

| | |
|---|---|
| ADA | Anti-Drug Antibody |
| AE | Adverse event |
| AESI | Adverse events of special interest |
| ALP | Alkaline Phosphatase |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| BLQ | Below the limit of quantitation |
| BMS | Body mass index |
| CD40L | CD40 Ligand |
| CM | Concomitant Medications |
| CRP | C-Reactive Protein |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of variation |
| DI | Dose intensity |
| DAR | Dosage Administration Record |
| DRL | Drug Reference Listing |
| ECG | Electrocardiogram |
| (e)CRF | Electronic Case Report Form |
| EA | Early access |
| ER | Emergency Room |
| ET | Endothelin |
| FAS | Full Analysis Set |
| HU/HC | Hydroxyurea/Hydroxycarbamide |
| HLGT | High level group terms |
| HLT | High level terms |
| ICAM | Intercellular Adhesion Molecule |
| IL | Interleukin |
| i.v. | intravenous(ly) |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MIP-1a | Macrophage Inflammatory Protein 1-alpha |
| NCI | National Cancer Institute |
| NMQ | Novartis MedDRA queries |
| PAI-1 | Plasminogen Activator Inhibitor-1 Antigen |
| PD | Pharmacodynamics |
| PDI | Planned dose intensity |
| PK | Pharmacokinetics |
| PKPDS | Pharmacokinetic-Pharmacodynamics Analysis Set |
| PT | Preferred term |

| | |
|---|---|
| RDI | Relative dose intensity |
| SAE | Serious adverse events |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SMQ | Standardized MedDRA queries |
| SOC | System Organ Class |
| TAT | Thrombin Antithrombin Complexes |
| TBL | Total Bilirubin |
| TNF | Tumor Necrosis Factor Alpha |
| TSP1 | Thrombospondin-1 |
| ULN | Upper Limit Normal |
| VCAM | Vascular Cell Adhesion Molecule |
| VOC | Vaso-Occlusive Crisis |
| vWF | von Willebrand factor antigen |
| WHO | World Health Organization |

# 1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CSEG101B2201, a Phase II, multicenter, open-label study to confirm and to establish appropriate dosing and to evaluate the safety in pediatric participants aged 2 to <18 years receiving crizanlizumab for up to 2 years.

The content of this SAP is based on protocol CSEG101B2201 version 06. All decisions as defined in the present SAP document, are applicable starting from Group 2 multiple dose DMC analysis (post Group 1 primary CSR), unless otherwise specified.

## 1.1 Study design

This is a multicenter, single-arm, open-label study to confirm and to establish appropriate dosing and to collect safety data in pediatric participants aged 2 to <18 years receiving crizanlizumab for up to 2 years.
In Part A of the study across the ages 2 to <18 years, the dose for each group will be first confirmed on the basis of single & multiple dose PK data and key safety data from an initial subgroup of participants. In Part B of Group 1 and Group 2, safety and efficacy data will be collected from additional participants from 6 to <18 years.

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

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

All participants will receive SEG101. The first participants enrolled in Group 1 via trial Part A will receive SEG101 at 5.0 mg/kg intravenous (IV) on Week 1 Day 1, Week 3 Day 1 and then every 4 weeks. Full PK/Pharmacodynamics (PD) sampling will occur following the first dose and at presumed steady state. Those enrolled participants are expected to provide at least 6 evaluable participants for first dose PK evaluation.

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

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

If the evaluated dose is not confirmed, then an appropriate dose adjustment will be defined based on the PopPK model (or equivalent methods), at least an additional 8 participants will be enrolled in Group 1 Part A and the process will be restarted at this newly-defined dose. The previous participants enrolled in Group 1 Part A will then also begin receiving the newly-defined dose at the next scheduled treatment visit and will enter Part B at the time they will start under the new dose.
Once the dose is confirmed on the basis of the single dose PK and key safety data analysis in Group 1 Part A as described above, enrollment in Group 1 part B and Group 2 Part A will be initiated at the confirmed dose. At least 18 additional participants will be enrolled in Group 1 Part B to ensure at least 26 participants in total in that age group are enrolled under the confirmed dose.
Following the dose confirmation, an additional evaluation of PK and PD, together with key safety parameters, will be conducted within the same enrolled Group 1 Part A participants, when multiple dose PK and PD are available. Results of this second evaluation will further ensure the validity of the tested dose or inform if additional modifications are required to the already confirmed dose.

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

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

Participants will receive treatment for up to 2 years or until study treatment is permanently discontinued due to any reason. Participants will remain in the study until completion of the 105 day follow up visit, except the ones continuing crizanlizumab after their EOT visit, via commercial supply or post-trial access (e.g. enrollment in a Novartis roll-over protocol to provide continued drug treatment).

The end of the study will occur when all the participants have either completed or discontinued the study treatment and/or the 105-days follow-up visit.

No formal interim efficacy analysis is planned in this study. A DMC will monitor key safety and PK (and PD, if applicable) data at each dose confirmation during the conduct of the trial. The need for additional DMC consultation or review of data will be assessed on an ongoing basis until final database lock.

## 1.2 Study objectives and end points

| Objective | Endpoint | Analysis |
|---|---|---|
| **Primary** | | |
| To confirm and establish appropriate dosing of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Part A and B) | Participants aged 2 to <18 years (Part A)<br>-PK parameters after the starting dose and at multiple dose<br>-PD Parameter (%P-Selectin inhibition) after starting dose and at multiple dose | Refer to Section 2.5 |
| To evaluate the safety of crizanlizumab in participants aged 2 to <18 years at the time of study entry (Parts A and B) | - Frequency of any adverse events (AE) | Refer to Section 2.8 |
| **Secondary** | | |
| To assess the long-term efficacy of crizanlizumab in participants aged 2 to < 18 year old participants at the time of study entry (Parts A and B) | - Annualized rate of Vaso-Occlusive Crisis (VOC) events leading to healthcare visit in clinic/Emergency Room (ER)/hospital<br>- Annualized rate of VOC events treated at home (based on documentation by health care provider following phone contact with participant)<br>- Annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism)<br>- Annualized rate of hospitalizations and ER visits (both overall and VOC-related)<br>- Annualized rate of days of ER/ hospitalization (both overall and VOC-related)<br>- Annualized rate of dactylitis events | Refer to Section 2.7 |
| To assess other safety measures in participants aged 2 to < 18 years at the time of study entry | - Number, seriousness, severity, and causality assessments of treatment emergent AEs and other safety data as considered appropriate<br>- Absolute change from baseline in hemoglobin<br>- Immunogenicity: measurement of anti-drug antibodies (ADA) to crizanlizumab | Refer to Section 2.8 |

| Objective | Endpoint | Analysis |
|---|---|---|
| | - ECGs at relevant PK time points<br>- Growth and sexual maturation assessments (Tanner stage) | |
| Characterize long-term PK and PD of crizanlizumab in participants aged 2 to <18 years at the time of study entry. | - Trough (pre-dose) concentrations prior to each study drug dose.<br>- % P-Selectin inhibition prior to dosing | Refer to Section 2.10 |

[redacted]

# 2 Statistical methods

## 2.1 Data analysis general information

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

In addition, exploration of early access (EA) PK data may occur for preliminary PK and PD analysis prior to clinical data base lock. PK samples may be batched and shipped for expedited EA PK analysis and data will be uploaded by the bioanalyst via PKLink. For the derivation of PK and PD parameters nominal time instead of actual elapsed time may be used. The analyses will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

### Data included in the analysis

The cut-off for the first dose PK analysis for Part A of each group will occur when at least 6 participants with evaluable PK have been enrolled in Part A and have completed the Week 7 Day 1 visit. This evaluation would be based on PK, dose, demography, other baseline characteristics data and key safety data (mainly AEs). If for a given age group the dose is not confirmed, then another group of participants will be recruited and an additional cut-off will be defined.

The cut-off for the multiple dose analysis for Part A of each group (participants from 24 months of age) will occur when at least 6 participants with evaluable PK and PD have been enrolled in part A and have completed multiple dose PK/PD sampling. This evaluation would be based on PK, PD, dose, demography, other baseline characteristics and key safety data.

The cut-off for the primary analysis for Part A+B of each group will occur after multiple dose analysis and when all the participants enrolled in that group have completed the first 26-weeks of treatment period or discontinued the study treatment in that group. The intent is to be able to evaluate data for participants from each group separately without having to wait for completion of subsequent groups. However, should the cut-off dates for groups 1 and 2 be close to each other, the primary analyses time points will be grouped together. At the time of the primary analysis for Parts A+B of group 1 and 2, available data from the other groups up to the cut-off date may be included in the reporting if needed to support regulatory filings or potential Health Authority requests. For all analyses, demographics and other baseline characteristics, safety, efficacy and pharmacokinetics, pharmacodynamic data will be reported. [redacted]

All statistical analyses will be performed using all data collected in the database up to the data cutoff date. 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.

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 and concomitant medication (CM) reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

The additional data for any participants continuing to receive study treatment, as allowed by the protocol, will be further summarized in a final study report once all participants from all groups included in the trial (aged 2 to <18 years), have completed or early discontinued from the study.

## General analysis conventions

**Pooling of centers:** Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of participants enrolled at each center, no center effect will be assessed.

**Qualitative data** (e.g., gender, race, etc.) will be summarized by means of contingency tables by age group and by starting dose within each age group as applicable; 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, maximum, 1$^{st}$ quartile and 3$^{rd}$ quartile) by age group and by starting dose within each age group as applicable.

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

Coefficient of variation (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.

## Unscheduled assessments

The following points summarize the rules for unscheduled assessments, unless otherwise specified:

- Baseline: All unscheduled assessments before the first dose should be included for consideration when calculating the baseline value.
- In summary tables by visit, unscheduled assessments should *not* be included unless they qualify as baseline.
- In shift and abnormality tables, all unscheduled assessments are included.

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

### 2.1.1 General definitions

#### Investigational drug and study treatment

Investigational drug will refer to SEG101. The term investigational treatment may also be referred to as study treatment which is used throughout this document.

#### Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a nonzero dose of investigational drug is administered and recorded on the Study Treatment – Infusion (e)CRF. The date of first administration of investigational drug will also be referred as start of investigational drug.

#### Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug is administered and recorded on the Study Treatment - infusion (e)CRF. 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 derived as the first date when a nonzero dose of study treatment was administered as per the Study treatment- infusion (e)CRF. The date of first administration of study treatment will also be referred as start of study treatment.

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

#### Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment was administered as per the Study Treatment- infusion (e)CRF.

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

#### Study day

Study day 1 for all assessments is taken to be the start of study treatment.

The study day for all assessments will be calculated as follows:

1. If date of assessment occurred on or after the start of study treatment, then
   Study day = Date of assessment - Start of study treatment + 1.
2. If date of assessment occurred before the start of study treatment, then
   Study day = Date of assessment - Start of study treatment.

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

For safety parameters (e.g. Electrocardiogram (ECG)), where the study requires multiple replicates per time point, the average of these measurements would be calculated (if not already available in the database) before determining baseline.

In rare 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), then the last value should be considered as baseline. In case of ECG’s these measurements are the average of triplicates.

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 and observation periods

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

1. ***pre-treatment period***: from day of participant’s informed consent to before date of first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment till:
    - For participants who completed the treatment and entered into the post treatment follow-up consider the end date of on treatment period as 105 days after the date of last administration of study treatment .
    - For participants who continue crizanlizumab after their EOT via commercial supply or post-trial access where SVSPID is marked as “OUTSIDE” in SV domain then consider the end date of on treatment period as DSSTDTC from the DS data set where DSSCAT = “TREATMENT DISPOSITION”.

- For patient who were recruited before protocol amendment v04 where patients could have switched under crizanlizumab after EOT (via commercial supply or post-trial access) but still have completed the FU period, for such cases the end date of on treatment period will be the earliest date the patient has record in CM data with concomitant medication as "Adakveo" after the last administration of the Treatment from the disposition.
- In case of death, data cut-off or withdrawal of consent, the end date of on treatment period will be death date, cut-off date or the withdrawal of consent date respectively.

3. ***post-treatment period***: starting at day 106 after last administration of study treatment, or after EOT date for participants continuing crizanlizumab after their EOT via commercial supply or post-trial access program.

*Note*: If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period 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 over time (including unscheduled visits) by time point, 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.

### Time windows for laboratory assessments

| *Assessment* | *Target day of assessment* | *Time Interval* |
|---|---|---|
| *Baseline* | *1* | *≤ Day 1* |
| *Week 3 Day 1* | *15* | *Day 2 to day 29* |
| *Week 7 Day 1* | *43* | *Day 30 to day 57* |
| *Week11 Day 1* | *71* | *Day 58 to day 85* |
| *Week 15 Day1* | *99* | *Day 86 to day 113* |

| Assessment | Target day of assessment | Time Interval |
|---|---|---|
| *Week 19 Day 1* | *127* | *Day 114 to day 141* |
| *Week 23 Day 1* | *155* | *Day 142 to day 169* |
| *Week 27 Day 1* | *183* | *Day 170 to day 197* |
| *Week 31 Day 1* | *211* | *Day 198 to day 225* |
| *Week 35 Day 1* | *239* | *Day 226 to day 253* |
| *Week 39 Day1* | *267* | *Day 254 to day 281* |
| *Week 43 Day 1* | *295* | *Day 282 to day 309* |
| *Week 47 Day 1* | *323* | *Day 310 to day 337* |
| *Week 51 Day 1* | *351* | *Day 338 to day 365* |
| *Week 55 Day 1* | *379* | *Day 366 to day 393* |
| *Week 59 Day 1* | *407* | *Day 394 to day 421* |
| *Week 63 Day 1* | *435* | *Day 422 to day 449* |
| *Week 67 Day1* | *463* | *Day 450 to day 477* |
| *Week 71 Day 1* | *491* | *Day 478 to day 505* |
| *Week 75 Day 1* | *519* | *Day 506 to day 533* |
| *Week 79 Day 1* | *547* | *Day 534 to day 561* |
| *Week 83 Day 1* | *575* | *Day 562 to day 589* |
| *Week 87 Day 1* | *603* | *Day 590 to day 617* |
| *Week 91 Day 1* | *631* | *Day 618 to day 645* |
| *Week 95 Day1* | *659* | *Day 646 to day 673* |
| *Week 99 Day 1* | *687* | *Day 674 to day 701* |
| *Week 103 Day 1* | *715* | *Day 702 to day 729*<br>*Note: Data from End of Treatment visit will be included in the time window for the Week X Day 1 visit of the last infusion, if obtained within 28 days from last infusion* |
| *End of treatment* | | *Assessment taken at the end of treatment visit* |
| *105 days post treatment* | *105 days after last infusion* | *Any time after last infusion date + 27 days* |

## 2.2 Analysis sets

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

- Group 1: 12 years to <18 years, 5 mg/kg
- Group 2: 6 years to <12 years, 5 mg/kg
- Group 2: 6 years to <12 years, 8.5 mg/kg

- Group 3: 2 to <6 years, 8.5 mg/kg.

### Full analysis set

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

### Safety set

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

### Pharmacokinetic analysis set

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

- Participant receives the planned treatment of 5.0 mg/kg or other tested dose before single dose PK profile, or before multiple dose PK profile (ie. at least 3 full consecutive doses administered following the loading dose at Week 3 Day 1)
- Participant provides at least one primary PK parameter
- Participant does not have any transfusion of blood product in the last 4 weeks before the first PK sample of the full PK profile, or during the full PK profile.

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

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

A participant is considered to receive the planned treatment if the actual dose received divided by the last weight measured before the dose is within a ±x% window of the planned dose (e.g. x = 5 for participants 40 kg and above, x = 10 for participants 6 kg to below 40 kg, as per current Pharmacy Manual).

### Other analysis sets

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

- Participant receives the planned treatment of 5.0 mg/kg or tested dose before single dose PD profile, or before multiple dose PD profile (ie. at least 3 full consecutive doses administrated following the loading dose at Week 3 Day 1)
- Participant provides at least one PD-AUC (single dose or multiple dose) parameter
- Participant does not have any transfusion of blood product in the last 4 weeks before the first PD sample of the full PD profile, or during the full PD profile

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

The pharmacodynamics analysis set 2 (PDS2) includes all participants of Part A and B who receive at least one dose of crizanlizumab and provide at least one corresponding evaluable PD assessment. A P-selectin % inhibition value is considered evaluable if not flagged by the pharmacokineticist.

The pharmacokinetic-pharmacodynamics analysis set (PKPDS) includes all participants of Part A and B included in the Safety set who have at least one measured pre-dose concentration and one matching P-selectin % inhibition value.

### Details on pharmacokinetic analysis

If a profile is not evaluable per PAS1 or PAS2 definition, all scheduled concentrations for that profile as well as corresponding parameters will be flagged for exclusion from summaries and figures. Additionally, if Rsq_adj < 0.75 or AUC%Extrap > 20%, then Lambda_z, T1/2, AUCinf, Vz/F (VZ), CL/F (CL) will be flagged for exclusion from summaries and figures.

Only PK parameters and concentrations which are not flagged for exclusion programmatically or by the pharmacokineticist (e.g. due to CMs, high concentration despite dose modification, etc.) will be used for figures and summaries. All values will be listed with excluded values flagged in the listings.

### 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 participant classification rules defined in Table 2-1.

**Table 2-1 Participant classification based on protocol deviations and non-PD criteria**

| Analysis set | Protocol deviations leading to exclusion | Non protocol deviation leading to exclusion |
|---|---|---|
| FAS | No written informed consent | No dose of study treatment |
| Safety set | No written informed consent | No dose of study treatment |
| PAS1 | No written informed consent | No dose of study treatment<br>No evaluable PK profile |
| PAS2 | No written informed consent | No dose of study treatment<br>No evaluable PK concentration |
| PDS1 | No written informed consent | No dose of study treatment<br>No evaluable PD profile |
| PDS2 | No written informed consent | No dose of study treatment<br>No evaluable PD assessment |
| PKPDS | No written informed consent | No dose of study treatment<br>No pre-dose concentration<br>No p-selectin inhibition data |

### 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. PK, [redacted] etc.), 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

Wherever applicable, subgroup analyses of the main efficacy and/or safety analyses will be performed by:

- Age (Group 1 age 12 to <18 years; Group 2 age 6 to <12 years; Group 3 aged 2 to <6 years),
- HU/HC use at time of study entry
- Categories of number of VOC leading to healthcare visit at baseline (< 5 vs ≥ 5) or categories of number of dactylitis at baseline (0 vs ≥1). Depending on the distribution of the events (VOC's and dactylitis), alternate categories can be suggested.
- Gender
- Race (black vs non black)

Details of which analyses will be performed on which subgroup are provided in the dedicated sections.

## 2.3 Participant disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries and listings will be reported by age group and dose 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 age group and dose. Categorical data (e.g. gender, race, ethnicity, genotype, HU/HC use at baseline, VOC history, dactylitis history, Lansky 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, Karnofsky Performance Status) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum, maximum, 1st quartile and 3rd quartile). Body mass index (BMI) (kg/m2) will be calculated as (weight[kg] / (height[m])$^2$) using weight at screening.

### Medical history

Medical history and ongoing conditions entered on (e) CRF will be summarized and listed by age group and dose. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and age 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, vaso-occlusive crisis history including genotype and HU/HC use, and pregnancy test etc.) will be listed.

### 2.3.1 Participant disposition

The number (%) of treated participants included in the FAS will be presented overall,by age group and dose. 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 age group and dose.

The following summaries will be provided (with % based on the total number of FAS participants (overall or within the age group and dose described as applicable)):

- Number (%) of participants who are still on-treatment (based on 'Treatment Disposition' page not completed)
- Number (%) of participants who discontinued the study treatment phase (based on 'Treatment Disposition' page completed);
- Primary reason for study treatment phase discontinuation (based on the 'Treatment Disposition' page)
- Number (%) of participants who have continued crizanlizumab via commercial supply or post-trial access
- Number (%) of participants who have entered the post-treatment follow-up (based on the 'Participant status follow up' page);
- Number (%) of participants who have discontinued from the post-treatment follow-up (based on the 'Study Disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'Study Disposition' page);

Participant disposition data will be listed.

Screened participants not treated will be listed.

### 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 specification) overall and by age group and dosefor 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 will be listed.

### Analysis sets

The number (%) of participants in each analysis set (defined in Section 2.2) will be summarized for the FAS by age group and dose. Participants included in each analysis set will be listed.

## 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 age group and dose. 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 age group and dose.

Participant level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

#### 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 of the last date of treatment + 27 days, the date of death (if the participant died), and the date of data cutoff.

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (less than 6 weeks, at least 6 weeks, at least 26 weeks, at least 54 weeks, at least 106 weeks) and continuous summaries (i.e. mean, standard deviation 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 age group and dose.

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

The actual cumulative dose refers to the total actual dose administered, over the duration for which the participant is on the study treatment as documented in the Study Treatment – Infusion eCRF.

#### Dose intensity and relative dose intensity

**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.

**Relative dose intensity** (RDI) is defined as follows:

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

DI and RDI will be summarized.

### Dose reductions or interruptions

The number of participants who have dose reductions or interruptions, and the reasons for it, will be summarized separately by age group and dose, and all dosing data will be listed.

Following rules will be used to derive dose reductions and interruptions in exposure analysis.

**Reduction:** determined from dose change records where actual non-zero dose administered is different from the protocol intended dose.

Dose reduction is a dose change where the actual dose administered is lower than the calculated dose amount based on the protocol intended dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the Study Treatment – Infusion CRF, and number of reductions will be derived programmatically based on the change and the direction of the change.

**Interruption**: a dose cannot be administered within 7 days of the scheduled day of infusion and flagged as "dose interrupted" in the CRF. Interruptions are considered as infusion completely skipped or delayed. If a dose was temporarily stopped/paused during infusion and re-started to complete the infusion, it should not be considered as a dose interruption.

Duration of a dose interruption is calculated as follows whichever is earlier:

- the time between the scheduled date of infusion and the actual date of infusion after the interruption or
- the time between the scheduled date of infusion and the treatment discontinuation after the interruption or
- the time between the scheduled date of infusion and the data cut-off after the interruption

In case of subsequent continuous interruptions of more than 1 infusion, if the reason for interruption is different for each interruption, all the reasons will be reported though it will be counted as one single 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 include medications (other than study drug) 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.

CMs 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 preferred term using frequency counts and percentages. 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, Erythropoietin simulating agent and Analgesics. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 105 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings. Non-drug therapies, surgical and medical procedures will be coded using MedDRA and summarized by SOC and PT.

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.

## 2.5 Analysis of the primary objective

### 2.5.1 Primary endpoint

#### Part A:

The primary variables of Part A (participants from 24 months of age) are the PK and PD parameters after single dose and after multiple doses.

#### Primary PK/PD Parameters

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

The remaining PK parameters will be analyzed as secondary variables.

#### Primary PD Parameters

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

#### Parts A + B:

The primary safety endpoint for Part A + B of all age groups is the frequency of participants with any AEs during the on-treatment period.

### 2.5.2 Statistical hypothesis, model, and method of analysis

**Primary PK/PD analysis:**

Part A (participants from 24 months of age):

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

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

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

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

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

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

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

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

**Primary safety analysis**

**Part A+B (all age groups):** Number and percentage of participants with any AEs will be provided by age group, and by starting dose within each age group as applicable. Safety analysis set will be used for this purpose.

### 2.5.3 Handling missing values/censoring/discontinuations

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

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

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

### 2.5.4 Supportive analyses

#### Part A:

Not applicable

#### Parts A + B:

Not applicable.

## 2.6 Analysis of the key secondary objective

There is no key secondary objective.

## 2.7 Analysis of secondary efficacy objective(s)

### 2.7.1 Secondary endpoints

The secondary efficacy endpoints include the following.

- Annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital
- Annualized rate of VOC events treated at home (based on documentation by health care provider following phone contact with participant)
- Annualized rate of each subcategory of VOC event (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, priapism)
- Annualized rate of hospitalizations and ER visits (both total and VOC-related)
- Annualized days of ER/hospitalization (both total and VOC-related)
- Annualized rate of dactylitis events

### 2.7.2 Statistical hypothesis, model, and method of analysis

All analyses will be based on all FAS participants, unless otherwise specified. The summary and spaghetti plot of annualized rates per year mentioned below for an age group and dose will be performed when all participants of that group have completed or discontinued from the study.

#### VOC

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

The absolute and relative change from baseline of the annualized rate of VOC leading to healthcare visit in clinic/ER/hospital will be provided overall and per year and corresponding spaghetti plot will be presented. The baseline annualized rate of VOC will be defined as the

number of VOCs leading to healthcare visit in clinic/ER/hospital occurring within 12 months prior to screening until first dose, reported in the baseline VOC eCRF.

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

where End date is defined as the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine, or other therapies to treat SCD and/or to prevent/reduce VOCs such as voxelotor and erythropoietin, cut-off date).

Despite all attempt to ensure complete follow-up for all participants, some participants may not be followed for VOC for the whole planned study duration. The annualized rate of VOC calculation will account for early discontinuation by extrapolating the VOC rate of every participant to one year. All VOC occurring until the End date will be taken into account in the summaries. If a participant initiates or discontinues HU/HC or L-glutamine (or other therapies to treat SCD and/or to prevent/reduce VOCs such as voxelotor and erythropoietin) during the study, VOC occurring after the initiation/discontinuation of such therapy will not be taken into account in the analyses. A sensitivity analysis will be performed, including the crises post initiation/discontinuation of HU/HC or L-glutamine (or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin) in the numerator and the corresponding duration of extra follow-up in the denominator, ie. with End date defined as the minimum of (last dose date until treatment discontinuation + 27 days, cut-off date).

Subgroup analyses of annual rate and the change from baseline in annual rate of VOC will be performed by HU/HC use at time of study entry, number of VOC leading to healthcare visit at baseline, gender and race.

The summary statistics on annualized rate along with change from baseline in annualized rate of VOC events leading to healthcare visit in clinic/ER/hospital will be performed for each subcategory of VOC events (uncomplicated pain crisis, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism). These analyses will be performed on the subset of FAS participants having at least one qualified VOC for the considered subcategory, either at baseline or on treatment.

The summary statistics on annualized rate of events will also be performed on:

- VOCs treated at home (based on documentation by health care provider following phone contact with participant), based on the subset of FAS participants having at least one home VOC.
- VOCs leading to healthcare visit and treated at home combined, based on all FAS participants.
- VOCs treated at home, as well as VOCs leading to healthcare visit and treated at home combined, for each subcategory of VOC event: uncomplicated pain crisis, and priapism; on the subset of FAS participants having at least one qualified VOC for the considered subcategory.

Time to first occurrence of VOC leading to healthcare visit will be summarized by age group and dose using Kaplan-Meier methods. Median time, $25^{th}$ and $75^{th}$ percentiles will be summarized and Kaplan-Meier plots will be generated. The time to first occurrence of VOC leading to healthcare visit will be defined as the time from the date of the first dose of study

treatment to the date of the first occurrence of the VOC. In the absence of a VOC, participants will be censored at the time of their respective end date of VOC observation period: defined above as the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine, or other therapies to treat SCD and/or to prevent/reduce VOCs such as voxelotor and erythropoietin, cut-off date). Subgroup analyses of time to first occurrence of VOC will be performed by HU/HC use at time of study entry, number of VOC leading to healthcare visit at baseline, gender and race.

### Dactylitis

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

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

where End date = End date is defined as the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine, or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin, cut-off date).

Subgroup analyses of the annual rate and change from baseline in annual rate of dactylitis will be performed by HU/HC use at time of study entry and number of dactylitis at baseline.

Listing of all dactylitis events experienced by all participants during the study will be provided by age group and dose.

### Hospitalization

The number of hospitalizations and ER visits (both overall and VOC-related) will be summarized descriptively by age group and dose in the FAS. Summaries will be provided for the corresponding annualized rate of hospitalizations and ER visits overall and per year, defined in the same way as the annualized rate of VOC. The absolute and relative change from baseline of the annualized rate will be provided and corresponding spaghetti plot will be presented. The baseline rate of hospitalizations and ER visits are defined based on the number of these events occurring within 12 months prior to screening (reported on Baseline Hospitalization eCRF), and during screening until first dose (reported on Healthcare Resource Utilization - Hospitalization eCRF).

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

where End date is defined as the minimum of (last dose date until treatment discontinuation + 27 days, date of initiation or discontinuation of HU/HC or L-glutamine, or other therapies to treat SCD and or to prevent/reduce VOCs such as voxelotor and erythropoietin, cut-off date).

Subgroup analyses of the annual rate and change from baseline in annual rate will be performed by HU/HC use at time of study entry and number of hospitalizations at baseline, gender and race.

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

#### Chest x-ray

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

### 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 observed over the period of follow up can be extrapolated to a year, even in participants who may have less than a year of follow up.

## 2.8 Safety analyses

All safety analyses will be based on the Safety set unless otherwise specified. Safety summaries include only on-treatment assessments; safety listings include all assessments with those more than 105 days after last study treatment flagged. All safety analyses described below will be performed by age group and by starting dose within each age group if applicable.

### 2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE (e)CRF 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 Common Terminology Criteria for Adverse Events (CTCAE) grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary 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 all participants.

The following AE summaries will be produced by age group and dose; overview of AEs and deaths, AEs by SOC and PT, summarized by relationship, seriousness, leading to treatment discontinuation, leading to dose interruption/reduction 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, number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

Adverse events identified in the Novartis MedDRA Query (NMQ) topic of "COVID-19 Diagnosis including positive, suspected and negative" will be summarized and listed. Summaries for these AEs will be provided by age group and dose and by different classification levels defined within this topic COVID-19 topic, as well as by PT within each level.

#### 2.8.1.1 Adverse events of special interest (AESI)

**Data analysis of AESIs**

An 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 (preferred terms). 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 SEG101 trials is documented in the eCRS for the project. The most up to date version of the eCRS available at the time of a DB 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 age group and dose, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose interruption, hospitalization, death etc.). If sufficient number of events occurred, analysis of time to first occurrence will be applied.

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

### 2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by age group and dose, SOC and PT.

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

The death summaries cover participants from the Safety Set.

### 2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) 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.

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

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.

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

- 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 and normal ranges are provided, 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 corresponding CTC grades relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

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

### Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), 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. A similar plot of direct bilirubin (DBILI) vs. ALT will also be generated. Individual participant plots will be produced for participants with potential severe drug induced liver injury (DILI) as defined below. Individual participant reticulocyte plots, and a plot of PT-INR and albumin over time will also be produced for the same participants. A corresponding listing of participants with potential severe DILI will be generated.

The following summaries will be produced based on peak post-baseline values for each parameter during on-treatment period (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 DILI)

For participants with AST or ALT > ULN at baseline (Bsl):

- Elevated ALT or AST (*) & TBL (> 2xBsl and 2xULN)
- Elevated ALT or AST (*) & TBL (> 2xBsl and 2xULN) & ALP < 2xULN (potential Hy's law)
- Elevated ALT or AST (*) & TBL (> 2xBsl and 2xULN) & ALP ≥ 2xULN
- Elevated ALT (*) & DBILI (> 2x Bsl and 2xULN) & ALP < 2xULN (potential severe DILI)

(*) Elevated ALT or AST is defined as: >3xULN if ≤ ULN at baseline, or (> 3xBsl or 8xULN) if > ULN at baseline.

#### Other Laboratory parameters

Renal disorders will be evaluated using serum creatinine shift table.

Hematuria (defined as urinalysis RBC of 6-8/HPF or more), glycosuria (defined as urine glucose of 1+ or more), and proteinuria (defined as urine protein of 1+ or more) will be evaluated using frequency table by time (baseline vs. post-baseline).

### 2.8.4 Other safety data

#### 2.8.4.1 ECG and cardiac imaging data

#### Data handling

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

#### Data analysis

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

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

- QT, QTcF, or QTcB
  - 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
- RR
  - Increase from baseline >25% and to a value > 1200 ms
  - Decrease from baseline >25% and to a value < 600 ms

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

For cardiac imaging data, LVEF shift table based on CTC grade will be presented by age group and dose. In addition, all data will be listed.

### 2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), head circumference (cm, for participants aged 2 years to 2.5 years old at time of study entry, until the participants turns 3 years old), 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 during the post-treatment period will be flagged in the listings.

#### Data analysis

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

**Table 2-2 Clinically notable changes in vital signs**

| Vital sign | | Participant age at visit | | |
|---|---|---|---|---|
| | | **< 18 years** | | **≥ 18 years** |
| Systolic blood pressure [mmHg] | High | ≥ 95th percentile of the age and height group[1] | | ≥ 180 with increase from updated baseline[4] of ≥20 mmHg |
| | Low | ≤ 5th percentile of the age and height group[1] | | ≤ 90 with decrease from updated baseline[4] of ≥20 mmHg |
| Diastolic blood pressure [mmHg] | High | ≥ 95th percentile of the age and height group[1] | | ≥ 105 with increase from updated baseline[4] of ≥15 mmHg |
| | Low | ≤ 5th percentile of the age and height group[1] | | ≤ 50 with decrease from updated baseline[4] of ≥15 mmHg |
| Oral body temperature [°C] | High | ≥ 38.4°C | | ≥ 39.1°C |
| | Low | ≤ 35.0°C | | ≤ 35.0°C |
| Pulse rate [bpm] [2] | High | 6-12 months | >150 | ≥120 with increase from updated baseline[4] of ≥15 bpm |
| | | 12-18 months | > 140 | |
| | | 18-24 months | > 135 | |
| | | 2-3 years | > 128 | |
| | | 3-4 years | > 123 | |
| | | 4-6 years | > 117 | |
| | | 6-8 years | > 111 | |
| | | 8-12 years | > 103 | |
| | | 12-15 years | > 96 | |
| | | ≥ 15 years | > 92 | |
| | Low | 6-12 months | <110 | ≤50 with decrease from updated baseline[4] of ≥15 bpm |
| | | 12-18 months | < 103 | |
| | | 18-24 months | < 98 | |
| | | 2-3 years | < 92 | |
| | | 3-4 years | < 86 | |
| | | 4-6 years | < 81 | |
| | | 6-8 years | < 74 | |
| | | 8-12 years | < 67 | |
| | | 12-15 years | < 62 | |
| | | ≥ 15 years | < 58 | |

| Vital sign | | Participant age at visit | | |
|---|---|---|---|---|
| | | **< 18 years** | | **≥ 18 years** |
| Weight | High | increase from baseline of ≥ 2 BMI-for-age percentile categories[3] | | Weight increase from updated baseline[4] of ≥ 10% |
| | Low | decrease from baseline of ≥ 2 BMI-for-age percentile categories[3] | | Weight decrease from updated baseline[4] of ≥ 10% |
| Respiratory rate [breath per minute][2,5,6] | High | 6-12 months | > 50 | ≥30bpm |
| | | 12-18 months | > 46 | |
| | | 18-24 months | > 40 | |
| | | 2-3 years | > 34 | |
| | | 3-4 years | > 29 | |
| | | 4-6 years | > 27 | |
| | | 6-8 years | > 24 | |
| | | 8-12 years | > 22 | |
| | | 12-15 years | > 21 | |
| | | ≥ 15 years | > 20 | |
| | Low | 6-12 months | <30 | ≤ 10bpm |
| | | 12-18 months | < 28 | |
| | | 18-24 months | < 25 | |
| | | 2-3 years | < 22 | |
| | | 3-4 years | < 21 | |
| | | 4-6 years | < 20 | |
| | | 6-8 years | < 18 | |
| | | 8-12 years | < 16 | |
| | | 12-15 years | < 15 | |
| | | 15-18 years | < 13 | |

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, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.

[3] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/);

Note: For participants less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length;

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

[5] Eldridge L. What is a Normal Respiratory Rate?, Updated May 16, 2014;

[6] Kou .R., Shuei L., Bradypnea, Department of Physiology, School of Medicine, National Yang-Ming University, Taipei, Taiwan, http://rd.springer.com/referenceworkentry/10.1007%2F978-3-540-29676-8_246

The number and percentage of participants with notable vital sign values (high/low) will be presented by age group and dose. A listing of all vital sign assessments will be produced by age group and dose, and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

#### 2.8.4.3 Growth and sexual maturation

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

Age at menarche will be summarized by age group and dose using Kaplan-Meier methods for female participants with Tanner Stage <=4 at baseline. Median time, 25$^{th}$ and 75$^{th}$ percentiles will be summarized. The time to menarche will be defined as the completed number of years from the date of birth to the date menarche attained. In the absence of menarche occurrence, patients will be censored at the date of latest assessment.

#### 2.8.4.4 Immunogenicity

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

## 2.9 Pharmacokinetic endpoints

Refer to Section 2.5

## 2.10 PD and PK/PD analyses

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for all PK parameters defined in Table 2-3 except Tmax. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter, where only n, median, minimum and maximum will be presented. Zero concentrations will not be included in the geometric mean calculation. Summary statistics will be provided by weight-adjusted dose and by age group for the PAS1 and/or PAS2.

PK concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings.

The PK parameters are derived based on the non-compartmental methods using Phoenix WinNonlin® software version with the most recent version available at the time of analysis. Refer to the Novartis Pharmacokinetic/Pharmacodynamic Analysis Manual (2015).

**Table 2-3 Noncompartmental pharmacokinetic and pharmacodynamic parameters**

| | |
|---|---|
| AUCd15 | The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1) following the first dose |
| AUCtau | The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1) |
| PD-AUCd15 | The AUC of %inhibition from time zero to the last measurable inhibition sampling time (tlast) following the first dose |

| | |
|---|---|
| PD-AUCtau | The AUC of %inhibition calculated to the end of a dosing interval (tau) after multiple dose |
| Cmax | The maximum (peak) observed, serum, drug concentration after single or multiple dose administration (mass x volume-1) |
| Tmax | The time to reach maximum (peak), serum, drug concentration after single or multiple dose administration (time) |
| Lambda_z | Smallest (slowest) disposition (hybrid) rate constant (time-1) may also be used for terminal elimination rate constant (time-1) |
| T1/2 | The half-life during a dosing interval λ (time) |

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

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

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

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

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

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

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

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

All individual PD parameters and PD data will be listed.

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

## 2.11 Participant-reported outcomes

Not applicable.

[redacted]

[redacted]

## 2.14 Interim analysis

No interim analysis will be conducted for this trial.

# 3 Sample size calculation

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

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

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

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

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

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

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

assessment of the primary safety analysis for Part A + B of groups 1 and 2 based on the Rule of Three. For the primary safety analysis of group 3, no statistical computation was performed to assess the sample size. Based on the objective of the Part A and feasibility of enrollment in this younger age group, at least 8 participants will be enrolled..

**Table 3-1 Probability to observe at least one AE for different incidence rates**

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

# 4 Change to protocol specified analyses

No change from protocol specified analyses was made.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Missing dates for study drug administration should be queried and 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<br>  o If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY<br>  o Else set start date = study treatment start date.<br>• If available year > year of study treatment start date then 01JanYYYY<br>• 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<br>o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.<br>o Else set start date = study treatment start date.<br>• If available month and year > month and year of study treatment start date then 01MONYYYY<br>• If available month and year < month year of study treatment start date then 15MONYYYY |
| time (for AE only) | Applicable following AE CRF update to include precise information on timing of infusion related reactions:<br>• If available day, month and year = day, month and year of study treatment start date then<br>o If stop date/time contains a full date/time (time, day, month and year) and stop date/time is earlier than study treatment start date/time then set start date/time = DDMONYYYY-00:01.<br>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<br>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<br>o Else set start time = study treatment start time<br>• 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 will be imputed by the end date of the on-treatment period only if start date ≤ 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.<br>If start date > end date of the on-treatment period, set end date = 31DecYYYY |
| 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.<br>If start date > end date of the on-treatment period, set end date = last day of the month |

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

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

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

### 5.1.3 Age at time of assessment

In order to calculate the age at time of a given assessment (for assigning notable vital signs criteria and laboratory normal ranges or CTC grading), the following rules will be applied:

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.

## 5.2 AEs coding/grading

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

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

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

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

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

### Imputation Rules

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.

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of 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 CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

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

# 6 Reference

Oncology Guideline for Safety Analyses, *Novartis*, 9 June 2016.

Pharmacokinetic / Pharmacodynamic Analysis Manual, *Novartis*, 17 Dec 2015.

Smith B, Vandenhende FR, DeSante KA, Farid NA, Welch PA, Callaghan JT and Forgue ST . Confidence Interval Criteria for Assessment of Dose Proportionality. *Pharmaceutical Research*, 17(10), 1278-83 (2000).