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An Indian Multi-centric Phase IV study to assess the safety of Crizanlizumab with or without hydroxyurea therapy in sickle cell disease patients with vaso-occlusive crises.

Statistical Analysis Plan (SAP)

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22-Feb-2024	Prior to DBL		Summary table was added to the description of planned analyses	Section 2.8.4.3
			The analyses for PK were added to the section	Section 2.10
			Imputation rules for end dates were updated	Section 5.1.2
			Title of Table 5-1 was updated to reflect the fact that assessment dates for LB, EG, VS should not be imputed	Appendix, Table 5-1
			Imputation logic for time (AE only) was added	
			Details on which laboratory data will be displayed in the outputs were added	Section 2.8.3
			Details on which baseline laboratory data will be displayed in the outputs were added	Section 2.1.1
			The mentioned CTC grading document has been changed to the latest version	Section 5.3
			CTC grading document has been updated to the latest version	Reference
20-May-2024	After DBL		Typo is corrected	Section 2.4.1

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
CSR	Clinical Study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAR	Dose administration record
DBILI	Direct bilirubin
DI	Dose intensity
DILI	Drug induced liver injury
DRL	Drug Reference Listing
EOS	End of study
FAS	Full Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HGLT	High level group terms
HLT	High level terms
HU/HC	Hydroxyurea/Hydroxycarbamide
i.v	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA queries
PK	Pharmacokinetics
PT	Preferred Term
RDI	Relative dose intensity
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle cell disease
SD	Standard deviation
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TBL	Total bilirubin
ULN	Upper limit of normal
VOC	Vaso-occulsive crisis
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CSEG101A2403, a phase IV, open label safety study in sickle cell disease (SCD) subjects with vaso-occulsive crisis (VOC).

The content of this SAP is based on protocol CSEG101A2403 v00. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a Phase IV open label, single-arm, interventional, multicenter study to evaluate safety of crizanlizumab at a dose of 5.0 mg/kg in addition to standard of care in Indian patients with SCD and a history of VOC leading to healthcare visit.

The study will include 140 participants aged 16 years and older with confirmed diagnosis of SCD (all genotypes are eligible) who have had a history of VOC leading to a healthcare visit prior to screening visit. Participants may receive HU/HC, L-glutamine (Endari™) or erythropoietin-stimulating agents as treatment/concomitant medication for SCD before and during the study.

Participants will receive crizanlizumab 5.0 mg/kg via intravenous (i.v.) infusion on Week 1 Day 1, followed by a second dose 14 days later (Week 3 Day 1), and then every 4 weeks. Participants will receive crizanlizumab for approximately 12 months (until week 51) in the trial or until unacceptable toxicity, death, are lost to follow-up or discontinued from crizanlizumab for any other reasons at the discretion of the investigator or the participant.

Following study treatment discontinuation, participants will perform an end of treatment visit. After the end of treatment visit, all participants will be followed up for safety up to 105 days (15 weeks) after the last infusion of investigational study drug.

The end of the study (EOS) will occur when all the patients have either completed or discontinued the study treatment and/or the 105 days follow-up period.

1.2 Study objectives and endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 2.5
To assess the serious adverse events (SAEs) of crizanlizumab in Indian patients with SCD	Frequency, severity and causality of SAEs during the treatment period	
Secondary		
To assess the overall safety and tolerability of crizanlizumab in Indian patients with SCD	Frequency, severity and causality of treatment emergent adverse events (including Adverse Events of Special Interest (AESI)), as well as labs, vital signs, ECGs and immunogenicity	Refer to Section 2.7

2 Statistical methods

2.1 Data analysis general information

All analysis will be performed by Novartis and/or a designated CRO. 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

All statistical analyses will be performed using all data collected in the database. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) 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.

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 patients 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; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

For 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:

- 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

Both investigational drug and study treatment refer to crizanlizumab. 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 non-zero dose of investigational drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study 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 is the last date when a nonzero dose of investigational drug is administered and recorded on DAR eCRF. 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 DAR 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 DAR (e)CRF.

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

Study day

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

The study day is defined as:

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

The reference date for all assessments (safety, PK etc) is the start of study treatment.

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 defined as "baseline" assessment.

In case time of assessment and time of treatment start is captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

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

For those lab parameters collected only in the local laboratories as per protocol, the last available assessment on or before the start date of study treatment from the local laboratories will be considered as baseline in the tables and figures.

For all other lab parameters, the last available assessment on or before the start date of study treatment from the central laboratories will be considered as baseline in the tables and figures.

If patients have no value as defined above, the baseline result will be missing in the tables and figures.

Listings will display all available baseline patient data, regardless if they were collected from local or central laboratories.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day/time before first administration of study treatment
2. ***on-treatment period***: from date/time of first administration of study treatment to 105 days after date of last actual administration of any study treatment included
3. ***post-treatment period***: starting at day 106 after last administration of study treatment.

Notes: 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 adverse events (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 pre-treatment and post-treatment period will be flagged.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned and who received one dose of study treatment.

Safety Set

The Safety Set includes all participants who received at least one dose of study treatment.

Withdrawal of Informed Consent

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

2.3 Patient 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.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, race, ethnicity) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

Medical history

Medical history and ongoing conditions entered on (e)CRF will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). 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.

Other

All data collected at baseline will be listed.

2.3.1 Patient disposition

Enrollment by center will be summarized for all screened patients using the FAS. The number (%) of enrolled patients included in the FAS will be presented. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number

(%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

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

- Number (%) of patients who are still on-treatment (based on the 'Treatment Disposition' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'Treatment Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'Treatment Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'Treatment Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the Post-treatment follow-up Disposition page);
- Reasons for discontinuation from the post-treatment follow-up (based on Post-treatment follow-up Disposition page);

In addition, disposition of patients with their relationship to the COVID-19 status will be summarized.

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study edit checks specification) for the FAS. In addition, COVID-19 related protocol deviations and issues with potential impact on quality will be summarized.

All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

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. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized.

Subject 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).

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

Cumulative dose

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

The **planned cumulative dose** for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration.

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

For patients who did not take any drug the cumulative dose is by definition equal to zero.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients 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))*4.

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

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

Relative dose intensity (RDI) is defined as follows:

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

DI and RDI will be summarized.

Dose reductions, interruptions

The number of subjects who have dose reductions or interruptions, and the reasons, will be summarized. In addition, their relationship to the COVID-19 status will be summarized.

‘Dose change’, and ‘Dose interrupted’ fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose change and dose interruptions respectively.

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

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

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

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

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 patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

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

2.5 Analysis of the primary objective

The primary objective is to assess the serious adverse events (SAEs) of crizanlizumab in Indian patients with SCD.

2.5.1 Primary endpoint

The primary end point is the frequency, severity and causality of SAEs during the treatment period.

2.5.2 Statistical hypothesis, model, and method of analysis

The number and proportion of patients with at least one SAE will be presented along with the 2-sided 95% confidence interval (CI). SAEs will be summarized by number and percentage of participants having at least one SAE in each primary system organ class (SOC) and for each preferred term. SAE's will be summarized by relationship, leading to treatment discontinuation, leading to dose interruption and leading to fatal outcome.

2.5.3 Handling of missing values/ discontinuations

Not applicable.

2.6 Analysis of the key secondary objective

Not applicable

2.7 Analysis of secondary efficacy objective(s)

Not applicable

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.

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

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

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

dose interruption/adjustment and leading to fatal outcome. In addition, a summary of SAEs with 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, manifestations, risks and complications including death" will be summarized and listed. Summaries for these AEs will be provided 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 / grouping of AEs

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 (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 treatment arm, SOC and PT.

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

The death summaries cover subjects from the Safety Set.

2.8.3 Laboratory data

If the data are available from both central and local laboratories, only central lab results will be reported in the tables and figures for consistency. For those lab parameters collected only in the local laboratories as per protocol, the data from the local laboratories will be reported in the tables and figures. Listings will contain all available patient data from both local and central laboratories.

The summaries will include all assessments available for the lab parameter collected no later than 105 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification 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

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 count 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

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 shift tables to compare baseline to the worst on-treatment value.

2.8.4 Other safety data

2.8.4.1 ECG

Data handling

In case the study requires ECG replicates 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, RR and HR intervals will be obtained locally for each subject during the study. ECG data will be read and interpreted locally.

The number and percentage of subjects with notable ECG values will be presented.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms

  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New value of > 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 and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

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), 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 2-1 below.

Table 2-1 Clinically notable changes in vital signs

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

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

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

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

[2] Fleming S, 2011

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

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

[5] Eldridge L, 2014;

[6] Kou .R, 2009.

The number and percentage of subjects with notable vital sign values (high/low) will be presented.

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

2.8.4.3 Immunogenicity

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

All immunogenicity results and pre-dose PK will be listed by participant and visit/time, and summarized by visit and schedule time point in a table.

2.8.4.4 VOC

In this study, there is no efficacy endpoint, objective or analysis planned. Information about VOCs leading to HC visit is however collected to allow individual patient review and description. All information about VOCs leading to HC visit on treatment will thus be listed.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

PK concentration data for crizanlizumab will be listed as well as summarized by visit and schedule time point in a table.

2.11 Patient-reported outcomes

Not applicable

2.12 Biomarkers

Not applicable

2.13 Other Exploratory analyses

Not applicable

2.14 Interim analysis

Not applicable

3 Sample size calculation

3.1 Primary analysis

This is a descriptive study and no hypothesis testing will be conducted. However the primary endpoint which is the proportion of patients reporting an SAE over the treatment period, will be presented with a 2-sided 95% CI.

In the SUSTAIN study ([CSEG101A2201]), the proportion of patients reporting at least one SAE over the treatment period on Crizanlizumab 5mg/kg was 26%.

Assuming the percentage of patients with at least one serious adverse event in this study in India should be approximately in the range of values previously observed, the half width of the confidence interval is calculated for potential observed proportions of 15, 25 and 35%. With a sample size of 140 patients, the half-width of the confidence interval would vary from +/-5.9 to +/-7.9 if the proportion of patients with SAEs remains between 15 and 35%. This precision is considered appropriate to estimate with enough reliably the safety profile of crizanlizumab in India. The sample size calculation is done in EAST version 6.4.

Table 12-1 Confidence intervals (95%) for different proportions of SAE

Sample Size	Assumed proportion of SAE	Half width of 95% 2-sided CI	Lower 95% 2-sided CI	Upper 95% 2-sided CI
140	0.15	0.059	0.091	0.209
140	0.25	0.072	0.178	0.322
140	0.35	0.079	0.271	0.429

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, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM)

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

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

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY
time (for AE only)	• If AE available day, month and year = day, month and year of study treatment start date then o If AE stop date/time contains a full date/time (time, day, month and year) and AE stop date/time is earlier than study treatment start date/time then set start date/time = DDMONYYYY:00:01. o If Infusion related reaction = "Yes" and "when did the Infusion related reaction start" = "During the infusion" then set start date/time = study treatment start date/time o If Infusion related reaction = "Yes" and "when did the Infusion related reaction start" = "Within 24 hours after the infusion" then set start date/time = study treatment infusion end date/time +01 min of that day of AE o Else set start time = study treatment start time • Otherwise if day, month and year < day, month and year of study treatment start date or if day, month and year > day, month and year of study treatment start date do not impute the AE start time and leave it blank

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

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

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

Any AEs and ConMeds which are continuing will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

5.2 AEs coding/grading

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

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

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per Novartis Internal Guidance on CTC Grading of Lab Parameters version 1.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high 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

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.

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

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

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

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

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

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory 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

Novartis internal CTC grading document:

Internal Guidance on
CTC Grading of Lab P

Novartis Internal Guidance on CTC Grading of Lab Parameters, Version Number: 1.0. Effective Date: 27-Nov-2023

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)..