NOVARTIS

Clinical Development

CFZ533 (Iscalimab)

Clinical Trial Protocol CCFZ533X2207 / NCT04129528

Investigator- and subject-blinded, randomized, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and efficacy of CFZ533 in pediatric and young adults with new onset type 1 diabetes mellitus (T1DM)

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"CCFZ533X2207".**

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

Tables, Figures, Listings (TFL) details the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification **(**PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Study reference documentation

Final study protocol (version v06) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objectives***
• *To evaluate effects of CFZ533 on pancreatic beta cell function in subjects with new-onset T1DM.*	• Stimulated C-peptide AUC by mixed meal tolerance test (MMTT) after 52 weeks of treatment.
• *To evaluate the safety and tolerability of CFZ533 in subjects with new onset T1DM.*	• Adverse events, safety labs.

1.3.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objectives***
• *To evaluate the pharmacokinetics (PK) of CFZ533 in subjects with new onset T1DM.*	• CFZ533 plasma concentrations at baseline, during treatment (Cmax, Tmax after IV administration, and Ctroughs after SC administration) and follow-up period.
• *To evaluate durability of effects of CFZ533 on pancreatic beta cell function in subjects with new-onset T1DM.*	• Stimulated C-peptide AUC by MMTT at 20 weeks from last dose.
• *To evaluate the treatment effect of CFZ533 on remission or partial remission in subjects with new onset T1DM.*	• Not requiring exogenous insulin therapy with HbA1c <6.5% (remission) or Insulin dose adjusted HbA1c (IDAA1c ≤9.0) or HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day at 52 weeks (partial remission).

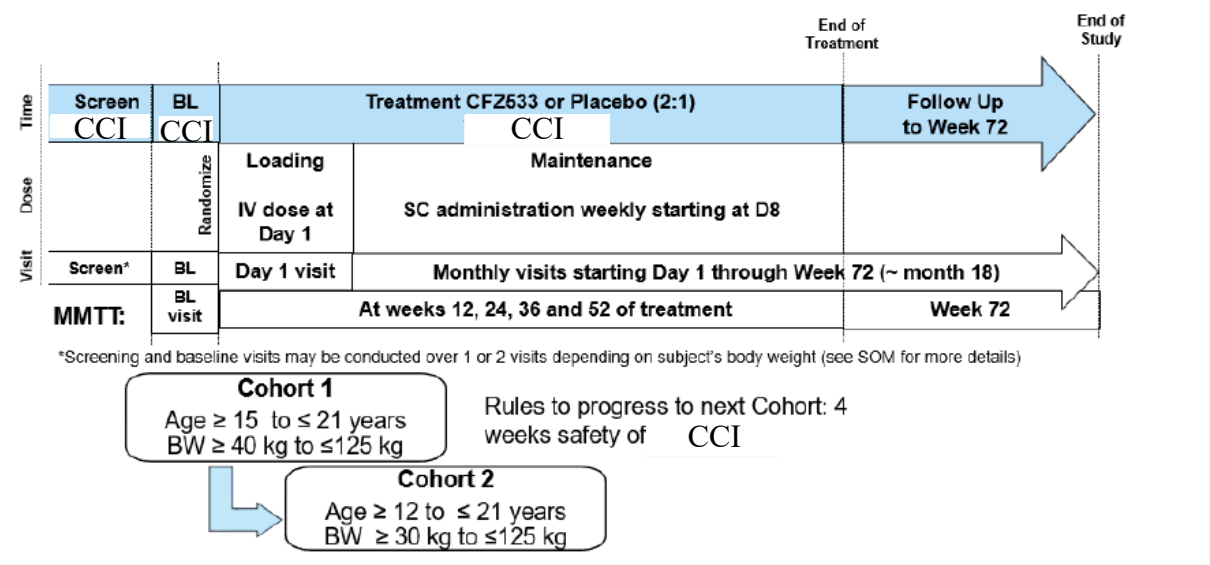
1.4 Study design and treatment

CCFZ533X2207 is a Phase 2, non-confirmatory, investigator- and subject-blinded, randomized, placebo-controlled study to evaluate the safety, tolerability, PK, and efficacy of CFZ533 compared to placebo on preservation of residual pancreatic β-cell function in new onset T1DM pediatric and young adult subjects.

Forty-four subjects aged 12-21 years with weight between 30 to ≤125kg will be enrolled. Two sequential study cohorts (based on age and body weight at screening visit) are planned.

Cohort expansion safety data (adverse events and safety lab) review will initially be based on pooled data at first. Aggregate data by treatment group (i.e. CFZ533 or Placebo) or specific subject(s)' treatment information can be requested if such information is needed as part of the crucial information in safety evaluation.

Figure 1-1 Study design



2 First interpretable results (FIR) and interim analysis report

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3 Interim analyses

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4 Statistical methods

4.1 Data analysis general information

Unless otherwise specified: categorical data will be presented as frequencies (n) and percentages. Continuous data will be presented as n, mean, standard deviation (SD), median, minimum, and maximum.

4.1.1 General definitions

On-treatment assessment/event

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

1. ***pre-treatment period***: from day of subject's informed consent to before date of first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 98 days after date of last administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 98+1 after last administration of study treatment.

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.

4.2 Analysis sets

For subjects whose actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis, except for analyses using the Full analysis set.

The Per-protocol analysis set includes subjects compliant with the protocol and is characterized by the following criteria:

1. Subject received at least 9 months of the randomized treatment,
   a. Within those 9 months, subject received at least 75% of the planned doses.
2. Subject does not have any major protocol violations (See Table 4-1)

The Full analysis set includes all subjects to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The safety analysis set will include all subjects that received any study drug.

The PK (Pharmacokinetics) analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD (Pharmacodynamic) analysis set will include all subjects who received any study drug with at least a baseline or one post-baseline PD assessment.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PP analysis set in case of these PDs:		Exclude subject from **PP** analysis set
Inc04	Deviation from inclusion criterion 4-Evidence of one or more T1D autoantibody(ies): anti-GAD, protein tyrosine, anti-IA-2, anti-ZnT8 and anti-ICA.	
Inc06	Deviation from Inc06-Peak stimulated C-peptide≥0.2 nmol/L after standard liquid MMTT when subject is metabolically stable, at least 2 weeks from diagnosis and within 56 days prior to randomization.	
Exc01	Any other diabetes present except auto immune type 1, by judgement of the investigator.	
Exc18	Ongoing, and up to 2 weeks prior to screening, use of medications that may affect glucose control (e.g., systemic steroids, thiazides, beta blockers).	
Subjects are excluded from PP and PK analysis set in case of these PDs:		Exclude subject from **PP and PK** analysis sets
Exc20	Taking medications prohibited by the protocol	
Subjects are excluded from PP analysis set in case of these PDs:		Exclude subject from **PP** analysis sets
OTH01	Subject potentially unblinded	Exclude only data after the date of unblinding
OTH02	Inv or Site Staff- Unblinded	Exclude only data after the date of unblinding

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

4.2.1 Withdrawal of Informed Consent

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

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

Free CFZ533 concentration in plasma

For each PK sample, the actual recorded sampling time will be captured (CRF). The actual elapsed time since the first dose (with reference to the Dose Reference ID series #1; see Table 8-1 Blood sampling log in the Site Operations Manual) and since the specified dose (with reference to the Dose Reference ID series #2 in Table 8-1 in the SOM) will be calculated.

PK parameters

The following PK parameters will be determined and reported: Ctrough, Ctrough,ss (steady state) and Cmax (.defined as concentration at the end of infusion 1.5 hr after start of infusion). They will be directly derived from the bioanalytical data in tables and listings.

Additional PK parameters (independent Novartis analysis) may be determined if data permit. A dose-independent, model-based analysis considering both IV and SC PK data may be performed as appropriate and will be reported in a separate, standalone modeling and simulation report. During modeling of PK data, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics, will be followed.

5.2 Descriptive analyses

All statistical summaries and plots will be produced by body weight category: ≥30 to <50 kg, ≥50 to ≤125 kg and overall.

CFZ533 plasma concentrations will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, Commercially Confidential Information
Pharmacokinetic parameters will be listed by treatment and subject and summarized by treatment and visit. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

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Arithmetic mean (SD) plasma concentration by time will be plotted on linear-linear and log-linear scale (all treatment groups in the same graph).

Overlaying individual plasma concentration by time profile will be plotted (one graph per treatment group, all subjects in the same graph) on linear-linear and log-linear scale.

Individual plasma concentration by time profile, by subject will be plotted on linear-linear and log-linear scale.

6 Statistical methods for Efficacy

All efficacy analyses will be performed on the full analysis set (FAS).

In case of dose adjustment occurring during the study, subjects will be analyzed under first doses received, censoring any observations post dose adjustment (if any) in statistical models and descriptive summaries.

6.1 Primary objective

The primary objective is to evaluate effects of CFZ533 on pancreatic beta cell function in subjects with new-onset T1DM.

6.1.1 Variables

Normalized stimulated C-peptide AUC, defined by stimulated C-peptide $AUC_{0\text{-}2\ hrs}$ by mixed meal tolerance test (MMTT) after 52 weeks, divided by the actual duration of measurements, is the primary analysis variable. This variable is derived from the blood samples taken for C-peptide determination over the course of 2 hours: at baseline (average of t = -10 and t = 0 C-peptide values), and at 15, 30, 60, 90, and 120 min after completing consumption of the liquid meal. AUC will be calculated by linear trapezoid rule under the stimulated C-peptide concentration curve. At a minimum the baseline and 120 min (first and last) concentrations must be available to compute the AUC. Under linear trapezoid rule, if there are concentration missing for time points between first and last observed time point during the 2 hours window, this part of area under the curve will be covered by the trapezoid constructed by the closest neighboring time points with concentration values. Commercially Confidential Information Actual time between each concentration measurement will be used during the calculation. If the total duration of measurement is >120 minutes, the trapezoid will be truncated at 120 minutes.

Baseline stimulated C-peptide AUC will be derived from the last set of C-peptide values collected before the start of study treatment.

6.1.2 Descriptive analyses

Normalized stimulated C-peptide AUC (Weeks 12, 24, 36 and 52 on treatment and Week 72), its change and percent change from baseline will be listed by treatment, subject and visit. Summary statistics will be provided for raw value, change and percent from baseline by treatment and visit/time and will include mean (arithmetic), SD, CV (arithmetic), median, minimum and maximum. In addition, geometric mean/CV will be provided for raw value.

6.1.2.1 Graphical presentation of results

Geometric mean (80% CI) of normalized stimulated C-peptide AUC and ratio to baseline will be plotted by visit and treatment. Spaghetti plots of normalized stimulated C-peptide AUC and percent change from baseline of all individuals will be given by treatment.

6.1.3 Statistical model, assumptions and hypotheses

The primary statistical analysis will be done using the Full analysis set (treatment policy estimand). As a secondary analysis, the model will be run using the Per Protocol set (hypothetical strategy estimand). For both analyses, all data collected for subjects in the respective analysis sets will be used in the model (e.g. including data after study drug discontinuation). Stimulated C-peptide AUC by the standard MMTT, normalized by the duration of measurements, will be analyzed with a mixed model repeated measures (MMRM) analysis. The natural log of the AUC (Weeks 12, 24, 36 and 52 on treatment) will be the dependent variable in this analysis. Independent variables will include age group (≥12 to <18, ≥18 to 21) treatment, visit, and the treatment by visit interaction.

The natural log of the baseline AUC will be used as a covariate and subject will be used as a random effect. Back transformation (exponential) will be used to obtain the least square geometric mean of each treatment, the ratio of CFZ533 to placebo, the 80% confidence interval of the ratio, and the one-sided p-value of treatment benefit for each time point. The model-based estimated fixed effects and p-values will be presented, along with the overall treatment effect.

Note 1: Any C-peptide AUC collected at a post-baseline unscheduled visit will be assigned to the closest scheduled visit for the model-based analysis; in the case of a tie it will be assigned to the previous visit (e.g. unscheduled collected at Week 30 will be assigned to Visit 24 for the model-based analysis). If a C-peptide AUC is already available at the scheduled visit, the average of the scheduled and unscheduled visit AUC will be used in the model.

Note 2: Week 52 C-peptide AUC which was not actually collected 365 +-15 days after the first dose (i.e. due to it being the EOT assessment for early treatment discontinuation) will not be used for the model-based analysis as a Week 52 assessment, but will be assigned to the closest visit.

6.1.3.1 Model checking procedures

Handling of missing values/censoring/discontinuations

The primary analysis will be based on all subjects in FAS analysis dataset. There will be no imputation for the primary analysis based on mixed model repeated measurements (MMRM) for stimulated C-peptide AUC measurements at various visits, which is valid under the assumption that the missing data are missing at random (MAR).

6.1.3.2 Graphical presentation of results

Model estimated treatment geometric means and ratio between treatment and their 80% CI will be plotted over time, by visit.

6.1.3.3 Sensitivity analyses

If there are reasonable evidence that data may be missing not at random (MNAR), for example there are subjects discontinued study due to lack of efficacy or worsening of disease, alternative statistical model such as pattern mixture models may be used to evaluate the robustness of the primary analysis results.

6.2 Secondary objectives

The secondary objectives of this study are to evaluate the treatment effect of CFZ533 on full or partial remission, and to evaluate durability effects of CFZ533 over time on pancreatic beta cell function.

6.2.1 Variables

- Normalized stimulated C-peptide $AUC_{0\text{-}2\ hrs}$ by MMTT at Week 72.
- Average of Total daily dose of insulin

  Total daily dose of insulin for a given day is the total daily units of insulin (adding insulin pump total basal units per day, insulin pump total bolus units per day and total units insulin injection (syringe) units per day) adjusted per body weight (unit/Kg/24 h). This information will be recorded at the site for at least 3 days and up to 7 days prior to each visit, as available (See Site Operations Manual). The average of total daily units of insulin per day (at each visit) will be calculated.
- Insulin-dose adjusted HbA1c (IDAA1c) (Andersen et al 2014).

  IDAA1C = HbA1C (percent) + 4 × [insulin dose (units per kg per day)].

  If HbA1c is stated in mmol/mol, it can be converted to percent by the following formula: HbA1c % = (HbA1c mmol/mol × 0.0915) + 2.15).
- Remission at 52 weeks defined by meeting any of the below criteria:
  - Full remission defined by HbA1c ≤6.5% (48 mmol/mol) and no exogenous insulin use at 52 weeks.
  - Partial remission defined by Insulin Dose Adjusted HbA1c (IDAA1c) ≤ 9.0 (Mortensen et al 2009)
  - Partial remission defined by HbA1c < 7.0% (53 mmol/mol) and total daily insulin dose <0.5 units per kg per day (Couper and Donaghue 2009).
- The proportion of subjects with detectable C-peptide and time to undetectable C peptide.

  Undetectable C-peptide is defined as all timed values on the MMTT below the LLOQ.
- The proportion of subjects with Peak C-peptide ≥0.2 pmol/mL and time to Peak C-peptide <0.2 pmol/mL (or below LLOQ)
- Rate of decline from baseline C-peptide

  A linear mixed model regression of the log transformed stimulated C-peptide AUC, including baseline assessment, on time expressed in years (time = 1 at Week 52 and 0 at baseline) will be performed. The mixed model will include treatment effect, time by treatment interaction with time as continuous variable and subject as random effect. The estimates of the yearly rate of decline by treatment and their 80% confidence intervals will be obtained after back transformation (exponential) of the estimates of the slopes.

6.2.2 Descriptive analyses

- For stimulated C-peptide AUC by MMTT at Week 72, total daily dose of insulin, insulin-dose adjusted HbA1c, their change and percent from baseline will be summarized by descriptive statistics for each treatment group and each time point (where applicable).

- The proportion of subjects with remission and each of the three components (full remission and two different criteria for partial remission) and subjects with detectable C-peptide will be descriptively summarized for each treatment group and each time point and overall study period.
- Time to undetectable C peptide will be analyzed by Kaplan-Meier methods by treatment group. Estimates of median time to undetectable C peptide and proportion of subjects with detectable C-peptide and their confidence intervals for each treatment group and each time point (where applicable) will be produced. Time to Peak C-peptide<0.2 pmol/mL (or below LLOQ) and proportion of subjects with C-peptide ≥0.2 pmol/mL will be analyzed similarly.

6.2.2.1 Graphical presentation of results

Model-based geometric mean (80% CI) of stimulated C-peptide AUC by MMTT will be plotted by treatment and time point.

Arithmetic mean (80% CI) of insulin-dose adjusted HbA1c and total daily dose of insulin will be plotted by treatment and time point.

Graphical presentation of Kaplan-Meier estimate of proportion of subjects with detectable C-peptide will be plotted by treatment.

6.2.3 Statistical model, assumptions and hypotheses

Normalized stimulated C-peptide AUC by MMTT at Week 72 will be analyzed in the same manner (and using the same model) as the primary objective. C-peptide AUC at all time points up to and including Week 72 will be included. The baseline by visit interaction term may also be considered for this model.

6.2.3.1 Model checking procedures

Model checking procedures for stimulated C-peptide AUC by MMTT at Week 72 will be the same as for primary analysis, refer to Section 6.1.3.1.

6.2.3.2 Graphical presentation of results

Model estimated treatment geometric means for stimulated C-peptide AUC by MMTT at Week 72 and ratio between treatment and their 80% CI will be plotted over time, by visit.

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7 Statistical methods for safety and tolerability data

All subjects within the Safety set will be included in the safety data analysis. Safety outputs will be produced by treatment.

7.1 Variables

Safety variables include adverse events, vital signs (blood pressure [SBP and DBP] and pulse), height and weight, ECG intervals, laboratory measurements (hematology, clinical chemistry, urinalysis, coagulation panel, virology and viral serology for SARS-CoV-2, CMV, EBV, and HSV), as well as subject demographics, baseline characteristics, and treatment information.

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 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).

For all safety data listings (e.g. ECG, lab, vital signs, AEs), data collected during the post-treatment period will be flagged.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

- All data for background (Growth z score, puberty, bone age, tanner stage, HLA) and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group. Growth Z-scores include z-score (SDS) for height, weight and BMI.

Note: HLA data for each allele will be captured in separate columns in the database. For the

analysis, the data should be combined into one record. For example:

Format in database (with a dummy example):

HLA-DRB1 Allele 1	DRB1*03:01
HLA-DQB1 Allele 1	DQB1*02:01
HLA-DQA1 Allele 1	DQA1*03:01
HLA-DRB1 Allele 2	DRB1*04:01
HLA-DQB1 Allele 2	DQB1*03:02
HLA-DQA1 Allele 2	DQA1*05:01

Format transposed for the analysis:

HLA-DRB1 Allele 1	HLA-DRB1 Allele 2	HLA-DQA1 Allele 1	HLA-DQA1 Allele 2	HLA-DQB1 Allele 1	HLA-DQB1 Allele 2
*DRB1*03:01*	*DRB1*04:01*	*DQA1*03:01*	*DQA1*05:01*	*DQB1*02:01*	*DQB1*03:02*

Type 1 diabetes risk associated with HLA haplotypes at baseline will be summarized by treatment with frequency counts and percentages.

Haplotypes associated with T1D are listed in the table (Atkinson and all 2001) below.

Type 1 diabetes risk associated with HLA-DR and HLA-DQ haplotypes

Risk	**HLA**		
	HLA DRB1	HLA DQA1	HLA DQB1
High risk	0401	0301	0302
	0402	0301	0302
	0405	0301	0302
	0301	0501	0201
Moderate risk	0801	0401	0402
	0101	0101	0501
	0901	0301	0303
Weak or moderate	0401	0301	0301
protection	0403	0301	0302
	0701	0201	0201
	1101	0501	0301
Strong protection	1501	0102	0602
	1401	0101	0503
	0701	0201	0303

Relevant medical history including diabetic ketoacidosis at time of diagnosis of T1DM, current medical conditions, any other relevant baseline information will be listed by treatment group and subject.

Treatment

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time. For height, weight and BMI using SDS (z-score) summary statistics for change from baseline by treatment at Week 52 and Week 72 may be provided if enough data allows, otherwise percentiles will be listed.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Listing of all laboratory parameters will be provided in subjects with abnormal values. Summary statistics will be provided by treatment and visit/time. Shift table will be provided.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. Similar information will also be presented by preferred term.

The number and percentage of subjects with adverse events by maximum severity of adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

The number and percentage of subjects with adverse events classified as related to study drug will be tabulated by body system and preferred term with a breakdown by treatment. Similar analysis will be performed for serious adverse events, and adverse events leading to treatment discontinuation.

ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population and prepared internally by Novartis.

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

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

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

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

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7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Pharmacokinetic / pharmacodynamic relationships

The relationship between PK, PD, efficacy or biomarker endpoints may be explored graphically.

Modeling of PK/PD data using a population approach may be performed as appropriate and will be reported if necessary in a separate, standalone modeling and simulation report.

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10 Reference list

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