NOVARTIS

Clinical Development

LTP001

CLTP001A12201E1 / NCT05764265

An open-label extension study to investigate efficacy, safety and tolerability of LTP001 in participants with pulmonary arterial hypertension

Statistical Analysis Plan (SAP)

Author:

Document type: SAP Documentation

Document status: Final

Release date: 22-Feb-2023

Number of pages: 23

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Template Version 4.0, Effective from 23-Apr-2021

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
22-Feb-2023	Prior to DB lock	Creation of final version	N/A - First version	NA

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List of abbreviations

AE	Adverse Event
BP	Bood pressure
CCI	[redacted]
CRF	Case Report Form
CSR	Clinical Study Report
DBL	Database lock
DMS	Document Management System
ECG	Electrocardiogram
EOS	End of Study
EOT	End of treatment
FAC	fractional area change
IA	Interim Analyses
LLOQ	Lower limit f quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
CCI	[redacted]
NT-proBNP	the N-terminal fragment of the prohormone B-type natriuetic peptide
OLE	the open label extension
PAH	pulmonary arterial hypertension
PK	Pharmacokinetics
CCI	[redacted]
CCI	[redacted]
CCI	[redacted]
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
RV S'	peak velocity of excursion
RVF	right ventricular function
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SMQ	Standardized MedDRA Query
TAPSE	tricuspid annular plane systolic excursion
TASV	tricuspid annular systolic velocity
TFLs	Tables, Figures, Listings
TS	Trial Statistician
TP	Trial Programmer
TTCW	Time to Clinical Worsening
ULOQ	Upper limit of quantification

1 Introduction

The Reporting and Analysis documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CLTP001A12201E1".

This Statistical Analysis Plan (SAP) has been developed in accordance with Clinical Trial Protocol CLTP001A12201E1 (Protocol Version 01, released on 30-Jan-2023), and describes the implementation of the statistical analysis planned in the protocol.

1.1 Study design

This is a non-randomized, open-label extension study over 52 weeks with LTP001 without a control treatment arm. Participants will be presented the opportunity to consider the extension study at the End of Treatment (EOT) visit (Week 25) of the parent study CLTP001A12201. The investigator will assess if the participant will continue by verifying that the participant has completed the parent study as planned. Moreover, at the EOT the investigator will determine the eligibility for the extension study (i.e. that none of the treatment discontinuation criteria were met and that the assessments at the EOT of the parent efficacy study were completed according to the parent protocol). The patient may directly continue into the extension study. If the patient does not directly continue in the extension study, the time between the end of treatment assessments in the parent study and the enrollment in the extension study i.e. during the transition period should be kept to a minimum (it should not exceed 14 days).

In case of a direct transition into the extension study after the end of treatment visit in the parent study, as not all assessment results will be available (e.g. the central lab assessments) at the same day the investigator will re-assess/reconfirm the eligibility as soon as outstanding results are received.

The safety and efficacy of LTP001 will be checked at the following visits: Weeks 5, 13, 26, 39 and 52, as specified in the Assessment Schedule. Safety and tolerability assessments will take place at each visit. RHC will be performed at week 26 and 6MWT and echocardiography will be assessed at Weeks 26 and 52. PAH-SYMPACT and emPHasis-10 will be collected for 7 day intervals with the seventh day of collection occurring within the allotted visit window for all Treatment visits (Weeks 5, 13, 26, 39 and 52). Participants will have safety follow-up phone calls at Weeks 9 and 17, and may be invited for safety assessment at site if deemed necessary. The PI may exercise their discretion in which safety assessments are required at these optional safety follow-up visits. Following the end of treatment period, participants will have one safety follow-up phone call approximately 30 days after the end of treatment visit at Week 52. The duration of the extension study is currently restricted to 52 weeks, but the study may be prolonged (via an amendment to the protocol) if the LTP001 development program in PAH continues and the benefit/risk assessment remains favorable for the patient population studied. The safety and efficacy profile of LTP001 that is observed in this extension study as well as the parent study, CLTP001A12201, will determine continuation of the extension study.

Please refer to Figure 1-1 for study design figure.

Figure 1-1 Study Schema

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the long term safety of LTP001 in participants with pulmonary arterial hypertension (PAH).	• AEs, SAEs, vital signs, ECGs, safety laboratory measurements
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the effect of LTP001 on hemodynamic parameters derived from RHC including PVR, RA pressures, mean PA pressure, PCWP, CO, SVR.	• Change from baseline at week 26 for each parameter
• To assess the effect of LTP001 on the 6MWD	• Change in 6MWD from baseline over time
• To assess the effect of LTP001 on measurements of right ventricular function (RVF) in participants with PAH	• Change from baseline in tricuspid annular plane systolic excursion (TAPSE) by echocardiography Change from baseline in tricuspid annular systolic velocity (TASV) by echocardiography Change from baseline of peak velocity of excursion (RV S') by echocardiography

Objective(s)	Endpoint(s)
	Change from baseline in fractional area change (FAC) by echocardiography
• To assess the impact of LTP001 on patient reported outcomes (PRO) in participants with PAH.	• Change from baseline in EmPHasis-10 and PAH-SYMPACT
• To assess the impact of LTP001 on Time to Clinical Worsening (TTCW) in participants with PAH.	• Death • Hospital stay (≥ 24 h) due to worsening of PAH. Worsening of PAH is defined by the following right heart failure related signs and symptoms: syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites • Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy • Initiation of parenteral prostanoid therapy, chronic oxygen therapy, or any other PAH-specific therapies or need for increase of diuretics for more than 4 weeks due to worsening of PAH • Disease progression (switch in modified New York Heart Association/WHO FC by at least one grade) • Significant drop in 6MWD (15% from baseline or more) due to PAH-worsening
• To assess the impact of LTP001 on the N-terminal fragment of the prohormone B-type natriuetic peptide (NT-proBNP).	• N-terminal fragment of the prohormone B-type natriuetic peptide
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

1.2.1 Primary estimand(s)

Not applicable

2 Statistical methods

A Clinical Study Report (CSR) will be prepared following the completion of the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis Trial Statistician (TS) and Trial Programmer (TP). SAS version 9.4 or higher (SAS Institute, Cary NC) or later software will be used to perform all data analyses and to generate tables, figures, and listings.

Two change from baseline values will be reported for all the analyzed parameters planed in this document for this study:

- Change from baseline of the parent study (LTP001A12201, prior to the treatment start on Day 1)
- Change from baseline of the current extension study (LTP001A12201E1, parent study week 25)

The comparisons of these two change from baseline values and the treatment group difference within each change from baseline value will be reported.

2.1.1 General definitions

Investigational treatment will be LTP001.

Date of first administration of study treatment (Day 1) will be defined as the date of the first actual administration of LTP001.

Date of last administration of study treatment will be defined as the date of the last actual administration of LTP001.

Two ***Baselines*** will be defined as the following:

Baseline of the Parent study: the Day 1 assessment of study LTP001A12201. If this datum is not available, the last pre-dosing assessment will be considered.

Baseline of the Extension study: Week 25 visit from LTP001A12201. If this datum is not available, the last pre-dosing assessment for this study (LTP001A12201E1) will be considered.***Study day*** will be defined as the number of days since the date of first dose of study treatment (LTP001 or placebo). The date of first dose of study treatment will be defined as ***Day 1*** and the day prior to first dose of will be defined as ***Day -1***. Therefore, for a particular date, study day will be calculated as follows:

for dates on or after the date of first dose of study treatment,

Study day = Assessment date – Date of first dose administration + 1

The on-treatment period lasts from the date of first administration of study treatment to the End of Study (EOS) visit or the date of last randomized dose if EOS visit is not available. The EOS visit is a follow-up visit that is approximately 30 days after the date of the last actual administration of investigational treatment. For participants who will be enrolled into the open label extension (OLE) study, their EOS visits will be skipped.

2.2 Analysis sets

For all analysis sets, participants will be analyzed according to the study treatment(s) received. The safety analysis set will include all participants that received any study treatment.

The PD analysis set will include all participants who received study treatment and had no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as Table 2-1.

Table 2-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from Safety analysis in case of these PDs:		**Exclude subject from Safety analysis set**
INCL01	Subject withdrew consent but continue to receive study medication	Y
Subjects are excluded from PD analysis in case of these PDs:		**Exclude subject from PD analysis sets**
INCL01	Subject withdrew consent but continued to receive study medication	Y

Protocol deviations mentioned above, and analysis sets will be reviewed in the data review meeting to decide inclusion or exclusion of participant(s) from analyses sets. Decisions regarding the exclusion of participants and/or participant data from analyses will be made prior to final database lock (DBL).

2.2.1 Subgroup of interest

Not applicable

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and baseline characteristics of all patients in the extension study will be summarized for the safety population.

2.3.1 Patient disposition

A summary table will be presented including the number and percentage of participants

- Who completed the study
- Who discontinued from study (overall and by the primary reason for discontinuation)

A listing of all participants excluded from any analysis sets will be provided with reasons for exclusion (i.e., including both protocol and non-protocol deviations).

2.3.2 Demographics and other baseline characteristics

Demographics and other extension study baseline data that will be assessed will be summarized descriptively utilizing the safety set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Participant demographics will include age, gender, race, ethnicity & BMI.

Relevant medical history and current medical conditions at the baseline will be listed by participant.

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

The Safety set will be used for treatment related summaries. Categorical data will be summarized as frequencies and percentages. For continuous data, N, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

2.4.1 Study treatment / compliance

The study medication (LTP001 [redacted] mg) will be taken daily over 52 weeks at approximately the same time each day [redacted].

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information will be captured in the source document at each visit. All study treatment dispensed and returned will be recorded in the Drug Accountability Log.

Remote treatment administration compliance will be assessed by the off-site healthcare professional and information provided to the Investigator and/or study personnel.

Pill counts (including counts of dispensed/returned pills) will be listed by participants, and visits, with relevant information about compliance provided by the participant if data is available.

The duration of exposure (in weeks) will be summarized by means of descriptive statistics using the safety set.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system.

2.5 Analysis supporting primary objective(s)

The primary aim of the study is to assess the long-term safety of LTP001 in participants with PAH.

2.5.1 Primary endpoint(s)

Safety assessment will include AEs, SAEs, vital signs, ECGs, and safety laboratory measurements.

Adverse events (AEs)

All Adverse events in the extension study will be summarized and listed. Also, all study emergent AEs in both the parent study and extension study will be summarized.

Consistent with the parent study CLTP001A12201 definitions, AEs starting after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term will be classified as a treatment emergent AE. The definition of the on treatment period is defined in Section 2.1.1. The following treatment emergent adverse events summaries will be produced:

- by primary system organ class and preferred term
- by primary system organ class, preferred term and maximum severity
- by Standardized MedDRA Query (SMQ) and preferred term.

The number and percentage of participants with adverse events will be summarized.

Separate summaries will be provided for study medication related adverse events, serious adverse events, other significant adverse events leading to discontinuation. In case of sparse events in any of these categories occur, only a listing will be provided if deemed adequate.

The number and percentage of deaths, including on-treatment and post-treatment deaths, will be summarized and listed.

Adverse events of special interest/grouping of AEs is not defined in this study.

Vital signs

Vital signs will include the collection of otic or oral body temperature (recorded in °C), blood pressure (BP) and pulse measurements.

All vital signs data will be listed by participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics (including N, mean, SD, minimum, median, maximum) of vital signs and changes from baseline will be provided by visit/time. Graphical presentations (e.g., boxplots) of vital signs will be provided by visit/time.

Electrocardiogram (ECG)

All ECG data, including PR, QRS, QT, QTcF and RR, will be listed by participant and visit/time, and abnormalities will be flagged. Summary statistics and graphical presentations (e.g. boxplots) will be provided by visit/time.

Categorical Analysis of QTcF (Fridericia's formula) interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT or QTc intervals or changes from baseline will be presented. The number and percentage of participants with clinical notable QTcF will be summarized by visit. A listing of these participants will be provided. The clinical notable criteria for QTcF (Fridericia's formula) are indicated in Table 2-2.

Table 2-2 Clinical notable criteria for QTcF (Fridericia's formula)

ECG parameter (unit)	Clinically notable range
Notable value considering newly occurring or worsening cases	
QTcF (msec)	> 500
QTcF (msec)	> 480 if normal at baseline
QTcF (msec)	> 450
Notable change from baseline	
QTcF (msec)	> 60
QTcF (msec)	> 30

Laboratory data

All laboratory data will be listed by participant and visit/time and if normal ranges are available, abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Descriptive statistics (N, mean, SD, minimum, median, and maximum) summarizing continuous laboratory results of clinical chemistry, hematology, urinalysis, and changes from baseline by visit/time will be provided. Graphical presentations (e.g., boxplots) will be provided by visit/time.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

2.5.2 Statistical hypothesis, model, and method of analysis

The long-term safety of LTP001 will be evaluated in this extension study.

All analyses will be based on frequency counts and summary statistics. No statistical models will be used.

The primary analysis population will be the Safety analysis set.

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

Detailed imputation rules are listed in Section 5.1. No additional imputation will be applied to the missing data.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary objectives of the study include assessing the effect of LTP001 on 6MWD, hemodynamic parameters derived from Right Heart Catheterization (RHC), the measurements of right ventricular function (RVF), time to clinical worsening (TTCW), and N-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP).

2.6.1.1 Efficacy and/or pharmacodynamic endpoints(s)

All analyses will be conducted using PD analysis set.

Change from baseline for efficacy endpoints will be descriptively summarized by visit/time for treatment group assigned in the parent study, and overall. Two baseline measurements will be generated as per Section 2.1.1. Graphs (e.g., spaghetti plot) will be provided to show individual time courses of parameters for the extension study together with the parent study.

Additionally, two changes from baseline values for efficacy endpoints will be descriptively summarized by visit/time for treatment group assigned in the parent study, and overall with the following comparisons:

a) Short-term (change from baseline of extension study) vs. long-term (change from baseline of the parent study) treatment effect (For both treatment and placebo groups assigned in the parent study).

b) the treatment group difference (assigned in the parent study) within each change from baseline value.

6MWD

This measures how many meters a person can walk in 6 minutes. It includes total distance walked (6MWD), the number and duration of any stops in 6 minutes. Test performed at baseline and at visits on Day 176 and 358 will be used for analysis.

Descriptive statistics (N, mean, SD, CV% mean, geometric mean, CV% geometric mean, median, min, and max) summarizing 6MWD parameters and their changes from baseline will be summarized by visit/time for treatment group assigned in the parent study and overall.

Panels of individual spaghetti plots over time/visit for treatment group assigned in the parent study and overall for each 6MWD parameter will be provided.

All 6MWD parameters will be listed by participant, and visit and if ranges are available, abnormalities will be flagged.

RHC

The RHC is performed to assess several hemodynamic parameters when the patient is in a stable hemodynamic rest state (as demonstrated by three consecutive cardiac output measurements with 10% of each other). The measurement is taken at baseline and at visit on Day 176. The assessed hemodynamic parameters include:

- PVR
- right atrial (RA) pressure
- mean pulmonary artery pressure (mPAP)
- pulmonary capillary wedge pressure (PCWP)
- systolic and diastolic blood pressure (RV pressures)
- heart rate (HR)
- cardiac output (CO)
- systemic vascular resistance (SVR)
- mixed venous blood gas measurement

Descriptive statistics (N, mean, SD, CV% mean, geometric mean, CV% geometric mean, median, min, and max) summarizing RHC parameters and their changes from baseline will be summarized by visit/time for treatment group assigned in the parent study and overall.

Panels of individual spaghetti plots over time/visit for treatment group assigned in the parent study and overall for each RHC parameter will be provided.

All RHC parameters will be listed by participant, and visit and if ranges are available, abnormalities will be flagged.

Echocardiography/RVF

The echocardiography is performed to assess the impact of study drug on right heart structure and function. All echocardiography images will be centrally read by an imaging vendor. The measurement is taken at baseline and at visit on Day 176 and 358.

The assessed echocardiography parameters include:

- Tricuspid annular plane systolic excursion (TAPSE)
- Tricuspid annular systolic velocity (TASV)
- Peak velocity of excursion (RV S´)

- Fractional area change (FAC)

Descriptive statistics (N, mean, SD, CV% mean, geometric mean, CV% geometric mean, median, min, and max) summarizing echocardiography parameters and their changes from baseline will be summarized by visit/time for treatment group assigned in the parent study and overall.

Panels of individual spaghetti plots over time/visit for treatment group assigned in the parent study and overall for each echocardiography parameter will be provided.

All echocardiography parameters will be listed by participant, and visit and if ranges are available, abnormalities will be flagged.

Time to clinical worsening (TTCW)

TTCW will be defined as time to any of the following events

- Death
- Hospital stay (≥ 24 h) due to worsening of PAH. Worsening of PAH is defined by the following right heart failure related signs and symptoms: syncope or near syncope, cyanosis, increase of breathlessness, clinically relevant deterioration of exercise capacity, decrease of oxygen saturation, increased peripheral edema, hepatomegaly, and ascites
- Worsening of PAH resulting in need for lung transplantation or balloon atrial septostomy
- Initiation of parenteral prostanoid therapy, chronic oxygen therapy, or any other PAH-specific therapies or need for increase of diuretics for more than 4 weeks due to worsening of PAH
- Disease progression (switch in modified New York Heart Association/WHO FC by at least one grade)
- Significant drop in 6MWD (15% from baseline or more) due to PAH-worsening

Time to clinical worsening will be analyzed using survival models (i.e., Kaplan-Meier, cox regression) if adequate number of events occur during the study to characterize the survival curve. Participants without the event will be considered as censored at the end of the time at risk. The hazard ratio between the treatment group assigned in the parent study and the corresponding 80% confidence intervals will be computed using the appropriate method. If there is no adequate number of events, the number (and percentage) of participants with clinical worsening will be summarized by treatment group assigned in the parent study and overall.

NT-proBNP

Descriptive statistics (N, mean, SD, CV% mean, geometric mean, CV% geometric mean, median, min, and max) summarizing N-terminal fragment of the prohormone B-type natriuretic peptide , NT-proBNP (visits on Day 29, 85, 176, 267 and 358) and its changes from baseline will be summarized by visit/time for treatment group assigned in the parent study and overall.

Spaghetti plot over time/visit will be provided. And the endpoint will be listed by participant, and visit and if ranges are available, abnormalities will be flagged.

Change from baseline for efficacy endpoints will be descriptively summarized by visit/time for treatment group assigned in the parent study, and overall. The baseline measurement for the extension will be the baseline measurement taken during the parent study CLTP001A12201. Graphs (e.g., spaghetti plot) will be provided to show individual time courses of parameters for the extension study together with the parent study.

Additionally, changes from baseline for efficacy endpoints will be descriptively summarized by visit/time for treatment group assigned in the parent study, and overall using a different baseline strategy: participants receiving LTP001 in the parent study will use the baseline of parent study as the baseline; participants switching from placebo in parent study to LTP001 in extension study will use the baseline of extension study as the baseline.

2.6.1.2 Patient reported outcomes

All analyses will be conducted using PD analysis set.

PROs (emPHasis-10 and PAH-SYMPACT scores) that will be taken at Day 29, 85, 176, 267, and 358 will be summarized as the original scores, as well as change from baseline, by time/visit. The baseline measurement for the extension study will be the baseline measurement of the parent study CLTP001A12201. Missing data may be imputed using a last observation carried forward approach (LOCF) as necessary.

2.6.2 Statistical hypothesis, model, and method of analysis

Most analyses will be conducted descriptively using summary statistics and visualization of the time course for each endpoints using graphical presentations (e.g. spaghetti plots). statistical models may be used when data allows for TTCW. Detailed method of analyses are specified under each endpoint in Section 2.6.1.1.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

See each endpoint in Section 2.6.1. If not specified, missing data will not be imputed.

2.6.5 Sensitivity analyses

For the analysis of 6MWT, missing measurement will be assumed MAR. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

Refer to Section 2.5 for details.

2.8 Pharmacokinetic endpoints

Pharmacokinetic parameters are not evaluated in this extension study.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Borg score

For the Borg score component, the participant will answer questions on a scale of one to ten to determine the participant's shortness of breath during the 6MWT. Larger score indicates higher breathing difficulty.

The Borg score and change from baseline will be summarized by visit and treatment group assigned in the parent study on the PD analysis set.

emPHasis-10 and PAH-SYMPACT

Refer to Section 2.6.1.2 for details.

2.11 CCI

CCI

- CCI [redacted]

[redacted]

2.12 CCI

CCI [redacted]

2.13 Other Exploratory analyses

CCI [redacted]

2.14 Interim analysis

Not applicable.

3 Sample size calculation

Not applicable.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation of missing/partial start or end study drug date. If missing, the time of study end date will be imputed to 00:00:00.

5.1.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, then the imputed end date should be set to the earliest of the study end date, 31DECYYYY or date of death.
- If the AE end date day is missing, then the imputed end date should be set to the earliest of the study end date, last day of the month or date of death.
- If AE year is missing or AE is ongoing, then the end date will not be imputed.

Rules for imputing the AE start date:

1. If imputing end dates, then this should be done prior to calculating imputed start dates.

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date, then AE start reference date = min(informed consent date, earliest visit date).
- Otherwise, AE start reference date = treatment start date.

Impute AE start date:

- If the AE start date year value is missing, then the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, then the imputed AE start date is set to NULL.
- If the AE start date year value is less than the treatment start date year value, then the AE started before treatment. Therefore:
  - If AE month is missing, then the imputed AE start date is set to the mid-year point (01JulYYYY).
  - Otherwise, if AE month is not missing, then the imputed AE start date is set to the mid-month point (15MONYYYY).
- If the AE start date year value is greater than the treatment start date year value, then the AE started after treatment. Therefore:
  - If the AE month is missing, then the imputed AE start date is set to the year start point (01JanYYYY).
  - Otherwise, if the AE month is not missing, then the imputed AE start date is set to the later of month start point (01MONYYYY) or AE start reference date + 1 day.
- If the AE start date year value is equal to the treatment start date year value:
  - If the AE month is missing, then the imputed AE start date is set to the AE reference start date + 1 day.
  - If the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
  - Otherwise, if the AE month is equal to the treatment start date month or greater than the treatment start date month, then the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date (including on-going records):

a) If imputing end dates, this should be done prior to calculating imputed start dates.
b) When the medication is ongoing at the end of the study, no numeric end date is derived.
c) If the end date is completely missing no numeric end date is derived.

1. If CM end day is missing and CM month/year are non-missing, then impute CM date as the minimum of study end date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing, then impute CM date as the minimum of study end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the complete CM start date, use the complete CM start date as the imputed CM end date.

Rules for imputing the CM start date:

- If imputing end dates, then this should be done prior to calculating imputed start dates.
  - If the CM start date year value is missing, then the imputed CM start date is set to one day prior to *Treatment start date (TR01SDT)*.
  - If the CM start date year value is less than the *Treatment start date (TR01SDT)* year value, then the CM started before treatment. Therefore;
  - If the CM month is missing, then the imputed CM start date is set to the mid-year point (01JulYYYY).
  - Else if the CM month is not missing, then the imputed CM start date is set to the mid-month point (15MONYYYY).
- If the CM start date year value is greater than the *Treatment start date (TR01SDT)* year value, the CM started after treatment. Therefore;
  - If the CM month is missing, then the imputed CM start date is set to the year start point (01JanYYYY).
  - Else if the CM month is not missing, then the imputed CM start date is set to the month start point (01MONYYYY).
- If the CM start date year value is equal to the *Treatment start date (TR01SDT)* year value;
  - And the CM month is missing or the CM month is equal to the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to one day prior *Treatment start date (TR01SDT)*.
  - Else if the CM month is less than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the mid-month point (15MONYYYY).
  - Else if the CM month is greater than the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the complete (imputed) CM end date, then imputed CM start date should be set to the complete (imputed) CM end date.

If there is no end date and ongoing check is not ticked, the CM will be considered as ongoing and included in the summary table.

5.2 AEs coding/grading

The MedDRA version which will be available at the time of database lock, will be used for the coding purpose of the adverse events.

5.3 Laboratory parameters derivations

The following table shows the direction of interest when analyzing worst case values in form of maximum and/or minimum post-baseline values. If the direction of interest is given as "High" the maximum value will be calculated and used as worst value, if the direction is given as "Low" the minimum value will be taken, and if it is given as "Low and high", both the minimum value and the maximum value will be calculated and presented in summary tables.

Table 5-1 Directions of interest for worst case value for laboratory parameters

Laboratory Parameter	Direction of interest for worst case value
A. Hematology	
Hemoglobin	Low
Hematocrit	Low
Erythrocytes	Low
WBC	Low and high
Basophils	High
Eosinophils	High
Lymphocytes	Low and high
Monocytes	High
Neutrophils	Low and high
Platelets	Low and high

B. Chemistry	
Albumin	Low
Alkaline Phosphatase	High
ALT/SGPT	High
AST/SGOT	High
Bilirubin Total	High
Blood Urea Nitrogen (BUN)	High
Creatinine	High
Gamma GT	High

Potassium	Low and high
Magnesium	Low and high
Calcium	Low and high
LDH	High
Phosphorus	Low and high
Sodium	Low and high
CRP	High
Fibrinogen	High
HbA1c	Low and high

5.4 Statistical models

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Refer to Table 2-1 for details.

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.