NOVARTIS

Clinical Development

XXB750

CXXB750A12201 / NCT06142383

A multi-center, randomized, placebo- and active-controlled, parallel-group, 24-week proof of concept and dose-finding study to evaluate efficacy, safety, and tolerability of XXB750 in patients with heart failure

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 1, Final
Release date:	04-Dec-2024
Number of pages:	35

Template Version 6.0, Effective from 23-Nov-2022

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
30-Nov-2023	Prior to FPFV	Creation of final version	N/A - First version	NA
04-Dec-2024	Prior to DBL	Study early termination	Analysis will be done descriptively. No inferential statistical testing or statistical modelling will be implemented.	All sections

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DMS	Document Management System
FAS	Full Analysis Set
IA	Interim Analyses
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol for CXXB750A12201. The analyses following the SAP below will be used for clinical study reporting purposes.

This version of SAP details the statistical methodology for the analyses planned and agreed to at the time of finalization of the CXXB750A12201 (Version 02 – amended protocol dated 23-Feb-2024).

As per the urgent safety communication (9-Aug-2024) followed by Novartis decision dated 26-Sep-2024, study drug was suspended on 9-Aug-2024 and a decision to terminate the study was taken on 26-Sep-2024. Hence, only an abbreviated clinical study report (CSR) will be created for this study.

1.1 Study design

Study CXXB750A12201 is a multicenter, randomized, placebo- and active-controlled, parallel group phase 2 study which is comprised of three periods (Figure 1-1):

- A screening period of approximately 7 days;
- A 16-week parallel-group randomized treatment period on either
  - i) double-blind placebo-controlled treatment (XXB750 vs. placebo) or,
  - ii) open-label treatment (sacubitril/valsartan);
- An 8-week safety follow-up period.

The study will randomize adult participants with LVEF < 50% receiving ACEI/ARB/ARNI and guideline-recommended HF therapies for HFrEF or HFmrEF to three XXB750 target dose levels; a cohort of patients treated with ACEI/ARB before the study will be randomized to be converted to open-label sacubitril/valsartan in place of their pre-study ACEI/ARB. The study will randomize a total of approximately 720 patients. The percentage of patients with LVEF > 40% will be limited to approximately 25% of the total sample.

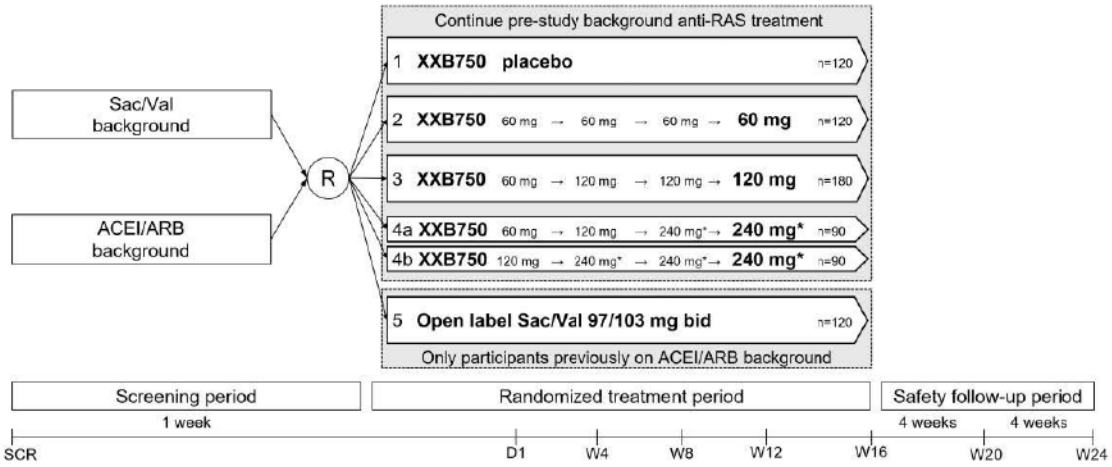
Refer to study protocol Section 6.1.2 for details on the administered doses in the different treatment arms.

A staggered approach to enrollment will be followed in the study protocol. The first group of 300 participants will be randomized to placebo (treatment arm 1), XXB750 60 mg target dose (treatment arm 2), XXB750 120 mg target dose (treatment arm 3), and conversion to sacubitril/valsartan (treatment arm 5). The independent Data Monitoring Committee (DMC) will complete a safety analysis of the XXB750 doses tested and assess if it is safe to allow the dosing of patients with XXB750 planned top dose of 240 mg (i.e., allowing enrollment in arms 4a and 4b as planned). See study protocol Section 4.6 for details on planned interim analyses and adaptive design features.

However, due to safety concerns, an urgent safety communication (9-Aug-2024) was issued to suspend study drug and a decision to terminate the study was taken on 26-Sep-2024. Only first group of participants are available for analysis, including placebo (treatment arm 1), XXB750

60 mg target dose (treatment arm 2), XXB750 120 mg target dose (treatment arm 3), and conversion to sacubitril/valsartan (treatment arm 5).

Figure 1-1 Study design



Sac/Val: Open label sacubitril/valsartan. *May be modified per adaptive design feature of the study (study protocol Section 4.6). Doses of Sac/Val, ACEI or ARB in arms 1-4 equal to dose at randomization.

The primary and final analysis will be performed after all participants have completed their final study visits.

1.2 Study objectives, endpoints and estimands

As per the urgent safety communication notification dated 9-Aug-2024 and Novartis decision dated 26-Sep-2024, the original objectives are no longer applicable due to permanent discontinuation of study treatment and early study termination. No statistical modelling will be done, and no formal statistical hypothesis tests will be performed. Table 1-1 indicates the original planned objectives, endpoints and which of those will be summarized descriptively for the CSR.

Table 1-1 Original objectives and related endpoints

Original objective(s)	Original endpoint(s)	Will be reported in CSR
Primary objective(s)	**Endpoint(s) for primary objective(s)**	
• To evaluate the efficacy and dose-response relationship of three XXB750 target dose levels compared to placebo in reducing NT-proBNP from baseline to Week 16 in symptomatic HF patients with LVEF < 50% treated with standard of care, including ACEI/ARB or sacubitril/valsartan.	• Change in log NT-proBNP from baseline to Week 16	• NT-proBNP

Original objective(s)	Original endpoint(s)	Will be reported in CSR
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**	
• To evaluate the treatment effect of the highest XXB750 target dose level compared to placebo in reducing NT-proBNP from baseline to Week 16 in symptomatic HF patients with LVEF < 50% treated with standard of care, including ACEI/ARB or sacubitril/valsartan.	• Change in log NT-proBNP from baseline to Week 16	• NT-proBNP
• To evaluate the treatment effect of combined two highest XXB750 target dose levels administered in addition to a background of ACEI/ARB versus conversion from ACEI/ARB to sacubitril/valsartan, in reducing NT-proBNP from baseline to Week 16.	• Change in log NT-proBNP from baseline to Week 16	• NT-proBNP
• To evaluate the safety and tolerability of XXB750 up-titration regimens and dose levels.	• Adverse events (incidence and severity, including but not limited to, hypotension, tachycardia, bradycardia, hypersensitivity and injection site reactions), vital signs (blood pressure, pulse), safety laboratory tests, and ECG parameters from baseline to end of study (EOS).	• Adverse events (incidence and severity, including but not limited to, hypotension, tachycardia, bradycardia, hypersensitivity and injection site reactions), vital signs (blood pressure, pulse), safety laboratory tests, and ECG parameters
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**	
• To evaluate the effects of highest XXB750 target dose level compared to placebo in improving a composite hierarchical outcome of : 1) time to all-cause death, 2) number of HF hospitalizations, 3) Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) categorical change, 4) NYHA class change , 5) relative change in NT-proBNP levels between baseline and Week 16.	• Hierarchically ordered composite consisting of: 1) time to all-cause death up to Week 16; 2) number of HF hospitalizations up to Week 16; 3) categorical KCCQ CSS change from baseline to Week 16; 4) NYHA class change from baseline to Week 16; 5) relative change in NT-	•

Original objective(s)	Original endpoint(s)	Will be reported in CSR
	proBNP levels from baseline to Week 16.	
• To evaluate changes in each domain of the KCCQ, including clinical summary score (CSS) and overall summary score (OSS), from baseline to Week 16.	• Change in all domains of the KCCQ from baseline to Week 16.	• KCCQ clinical summary score (CSS) and overall summary score (OSS)
• To evaluate the effects of XXB750 on slowing the rate of decline in estimated glomerular filtration rate (eGFR) from baseline to Week 16.	• Estimated glomerular filtration rate (eGFR) at scheduled assessment visits.	• Estimated glomerular filtration rate (eGFR)
• To evaluate the change in biomarkers related to heart failure, cardiovascular disease and renal function from baseline to Week 8 and to Week 16.	• Change from baseline in biomarkers including, but not limited to, plasma and urine cGMP, urinary cGMP-to-creatinine ratio, urinary albumin-to-creatinine ratio, BNP and hs-Troponin, at Week 8 and Week 16.	• Biomarkers including, but not limited to, plasma and urine cGMP, urinary cGMP-to-creatinine ratio, urinary albumin-to-creatinine ratio, BNP and hs-Troponin
• To evaluate the change in NYHA class and in signs and symptoms of heart failure from baseline to Week 16.	• Change in NYHA class and signs and symptoms of HF from baseline to Week 16.	• NYHA class and signs and symptoms of HF
• To explore the population pharmacokinetic (PK) properties of XXB750 in HF patients.	• Population PK analysis results including mathematic models and parameters.	• Population PK. See Section 2.8 for details.
• To evaluate immunogenicity (IG) of XXB750.	• Detection of immune response markers, including anti-drug antibodies.	• Immune response markers, including anti-drug antibodies. See Section 2.7.5.3 for details.

1.2.1 Primary estimand(s)

Not applicable due to early termination.

1.2.2 Secondary estimand(s)

Not applicable to secondary estimands due to early termination.

Adverse events (AEs) and serious AEs, laboratory parameters and vital signs will be evaluated and summarized in each treatment group for randomization period. Please refer to Section 2.7 for analysis details.

2 Statistical methods

The following sections contain important information on detailed statistical methodology used for clinical study report (CSR) analysis and reporting purposes.

Due to early study termination, the original planned analysis of primary, secondary and exploratory endpoints to demonstrate efficacy and dose range finding are no longer applicable.

2.1 Data analysis general information

Data will be analyzed by Novartis using SAS 9.4, unless otherwise specified. Details on planned statistical analyses and data-driven regression diagnostics (if any) will be presented in the following section and in CSR Appendix 16.1.9.

In general, the continuous variables will be summarized descriptively by presenting n, mean, SD, median, quartiles, minimum and maximum while categorical variables will be summarized by presenting count and percentage of participants in each category.

The randomization in this study will be stratified by region and background medication (ACEI/ARB or sacubitril/valsartan).

Regular safety monitoring (approximately every six months unless otherwise requested by DMC) will be conducted and reviewed by an external DMC as specified in the DMC charter. The relevant DMC analyses will be described in a separate DMC analysis plan and will be executed by an external independent statistician and independent programmers privileged to assess unblinded clinical trial data.

2.1.1 General definitions

Study treatment or drug

In future sections through this document, 'study treatment' or 'study drug' will be used to refer to investigational treatment assigned to a participant. Specifically, for the randomized treatment period, study treatment refers to XXB750 doses, XXB750 placebo, and sacubitril/vasartan as assigned to a participant at randomization.

Due to early termination, only one group of participants initiated, and all analysis will be performed by treatment group within group 1 (i.e., XXB750 placebo, XXB750 60 mg, XXB750 120 mg, and conversion to sacubitril/valsartan).

Date of first or last administration of study drug/treatment

Date of first administration of study drug/treatment refers to the date when the first dose of assigned treatment is administered in randomized treatment period. Date of last administration of study drug/treatment refers to the date when the last dose of assigned treatment is administered in randomized treatment period. For participants who are randomized to XXB750 dose arms or placebo arm, end of treatment (EOT) is at Visit 9998 (Week 16) for participants who complete randomized treatment period; and for participants who prematurely discontinue randomized treatment is defined as max(last administration of double-blind study drug + 28 days, treatment disposition date), date of withdrawal of informed consent, or the date of death,

whichever occurres first. For participants who are randomized to open-label sacubitril/valsartan arm, EOT is defined as the last administration of study drug, date of withdrawal of informed consent, or the date of death, whichever occurrs first.

Screening period

Screening period begins at Visit 10 until the day before the start of randomized treatment period (Visit 101) or screening disposition date for those who do not qualify to continue.

Randomized treatment period

The randomized treatment period begins at the time of randomization and ends with the EOT disposition. During the randomized treatment period, participants will return for scheduled clinic visits. For all safety related analyses randomized treatment starts with the first administration of randomized study drug.

Safety follow-up period

The safety follow-up period begins one day after EOT visit date and ends on the date of EOS.

Randomization period

The randomization period is the combination of the randomized treatment period and the safety follow-up period, unless otherwise specified.

Study exposure

The study exposure means the exposure during the randomization period. The duration of study exposure (days) is defined as the date of end of study minus the date of randomization plus one.

Baseline for randomized treatment period

Only assessments performed prior to first dose of randomized treatment period are considered for baseline. Unless specified otherwise, baseline for the randomized treatment period is defined as the measurement obtained at the randomization visit (Visit 101), or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to the Visit 101, if Visit 101 measurement is missing.

Baseline for randomization period

Randomization period is the total duration of randomized treatment period and the safety follow-up period, therefore, the definition of baseline for randomization period will be the same as the baseline for randomized treatment period.

Baseline for safety follow-up period

Unless otherwise specified, baseline for safety follow-up period is defined as the measurement obtained at the EOT visit (Visit 9998) or the measurement obtained closest to the EOT visit if the measurement at EOT is missing.

Unscheduled visit

Only for the analysis of safety evaluation will unscheduled measurements be taken into account. For efficacy evaluations, measurements from unscheduled visits will generally not be used, unless otherwise specified.

On-treatment data for an efficacy endpoint

In all the analyses planned in this document, on-treatment data refer to data collected while participants are on-study-medication (regardless of treatment interruption) or within 28 days after final study drug administration date for participants randomized to XXB750 and placebo arms; and final study drug amininstration date for particpants randomization to open-label sacubitril/valsartan.

Study day

Study day of any assessment is defined as the date of assessment (event/visit) minus the date of randomization plus one unless specified otherwise.

2.2 Analysis sets

The following analysis sets will be defined for statistical analysis:

Screened Set (SCR) - All participants who signed the informed consent form. The SCR includes only unique screened participants, i.e., in the re-screened participants only the chronologically last screening data is counted.

Randomized Analysis Set (RAS) - All randomized participants who received a randomization number, regardless of receiving trial medication.

Full Analysis Set (FAS) - All participants to whom study treatment has been assigned by randomization and who are not mis-randomized. Mis-randomized participants are those who have not been qualified for randomization, have been inadvertently randomized into the study and did not receive any study medication. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set (SAF) - All randomized participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose/injection of that treatment or the first treatment received if the randomized/assigned treatment was never received.

Per-Protocol Set (PPS) – A subset of the FAS that consisted of 1) participants randomized to XXB750 dose arms or placebo arm who received at least 3 doses/injections as per schedule; and 2) participants randomized to open-label sacubitril/valsartan arm who have been followed for at least 8 weeks post randomization as per schedule. This supplemental efficacy set is to support the efficacy analysis results on key biomarkers of interest.

PK analysis set (PKS) - All randomized participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study XXB750 treatment.

Immunogenicity prevalence set (IPS) includes all participants in the Safety set with a non-missing baseline ADA sample **or** at least one non-missing post-baseline ADA sample.

Immunogenicity incidence set (IIS) includes all participants in the Safety set with a non-missing baseline ADA sample **and** at least one non-missing post-baseline ADA sample.

Rules leading to exclusion from specific analysis sets of participants are provided in Appendix 5.5.

2.2.1 Subgroup of interest

Subgroups will be formed to explore the consistency of efficacy and safety profiling on selected endpoints between the subgroups and the overall population.

In general, subgroups will be defined based on baseline information mentioned in Section 2.1.1.

Subgroups defined for selected endpoints in this study and the ways to derive them are listed in Table 2-1. The details about the subgroup analyses will be described in the corresponding sections as appropriate.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Background & Demographics / Exposure	Efficacy*	Safety
LVEF (≤40% vs. >40%)	Screening	X	X**	X
Type of RAS inhibition (ACEI/ARB, sacubitril/valsartan)	Screening	X	X	X
ADA subgroup*** (Positive, Negative, PBL, Missing)	Derived			X

* Efficacy refers to descriptive analysis for key efficacy biomarkers of interest.

** LVEF (≤40% vs. >40%) subgroup analysis will be performed only for primary endpoint.

*** Defined as positive if ADA screening test at randomization baseline (pre-dose) is negative and the test turns positive at any time post-dose during the study, negative if ADA screening test shows negative at all times during the study, PBL if positive at baseline (pre-dose), and missing otherwise.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of participants screened successfully will be presented. In addition, screen failure participants will be summarized by primary reason for screen failure. For participants who are screened more than once, the information from the last screen will be used in the summary. The analysis is based on the screened set (SCR).

The number and percentage of randomized participants included in different analysis sets (Section 2.2) will be summarized by treatment group. The number and percentage as well as the reasons that participants had been excluded from RAS will be summarized by treatment. The number and percentage of randomized participants (RAS) and those in the full analysis set (FAS) who completed the study, who discontinued the study, and the reasons for discontinuation will be presented by treatment group, respectively.

In addition, the number and percentage of participants with protocol deviations as well as the criteria leading to exclusion from analysis sets will be provided for the participants in randomized set (RAS). Furthermore, the number and percentage of participants randomized per region and per country will be presented for the SCR and the FAS, respectively. All disposition data will also be listed at participant level for randomization period disposition.

2.3.2 Demographics and other baseline characteristics

Summary statistics will be provided for the total number of participants pertaining to the FAS for background and demographic characteristics, disease characteristics, and cardiovascular risk factors for the randomized treatment baseline. The following parameters will be included if applicable:

- **Continuous variables**: Age (in years), weight (in kilogram), height (in centimeter), body mass index (BMI, in kg/m^2), LVEF (%), sitting office systolic blood pressure (in mmHg), sitting office diastolic blood pressure (in mmHg), sitting pulse (in bpm), cyclic GMP (plasma and urine), urinary cGMP-to-creatinine ratio, urinary albumin-to-creatinine ratio, urine creatinine, cyclic GMP (urine)/urine creatinine, NT-proBNP, dose of standard background therapy of ACEI/ARB or sacubitril/valsartan, Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) and overall summary score (OSS), and eGFR ($ml/min/1.73m^2$).
  - **Categorical variables**: Age group (<65 years vs. ≥65 years), sex, race, region, history of diabetes (Yes, No), history of MI (Yes, No), history of hypertension (Yes, No), history of atrial fibrillation/flutter (Yes, No), smoking history (Yes, No), alcohol use history (0, >0 to 3, >3 drinks consumed per day in average), prior history of coronary heart disease (Yes, No), LVEF group (≤40% vs. >40%), NYHA class, etiology of HF (ischemic vs. non-ischemic), category of prior CHF medication, eGFR (< 60 vs. ≥ 60 $ml/min/1.73m^2$).

BMI will be calculated as weight (kg) / $height^2$ (m^2) from the measured height and weight at Visit 10 (Screening Visit).

The summary will be presented for FAS.

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the most updated version of MedDRA dictionary at the time of clinical database lock. Medical history will be collected at Visit 10 (Screening Visit). The number and percentage of participants with each medical condition will be provided by treatment group and system of organ class for the FAS.

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

2.4.1 Study treatment / compliance

Due to early termination, only group 1 was initiated and participants are randomized into one of the following arms targeting a ratio of 1:1:2:1.

- Placebo matching XXB750
- XXB750 60 mg target dose
- XXB750 120 mg target dose
- Sacubitril/valsartan at target doses of 97/103 mg bid (only participants previously treated with ACEI/ARB)

Table 2-2 Study treatment dose levels during randomized treatment epoch

Dose Level	XXB750 arms	Sacubitril/valsartan
0	Placebo or interruption	Interruption
1	XXB750 60 mg	50 (24/26) mg bid
2	XXB750 120 mg	100 (or 49/51) mg bid
3		200 (or 97/103) mg bid

Treatment exposure during the randomized treatment period

The duration of the randomized treatment period exposure for a participant, is defined as follows:

- For participants randomized to XXB750 dose arms or placebo arm:
    - If the participant completes the randomized treatment period, it is defined as the Week 16 (EOT) visit date – first study drug administration date +1;
    - If the participant prematurely discontinues the study treatment, it is defined as min(max(date of last study drug administration + 28 days, treatment disposition date), date of death, date of informed consent withdrawal) – first study drug administration date + 1.
- For a participant randomized to open-label sacubitril/valsartan: min(date of last study drug administration, date of death, date of informed consent withdrawal) – first study drug administration date + 1.

Duration of overall randomized treatment exposure, including temporary interruptions, will be summarized descriptively by treatment group (i.e. n, mean, standard deviation, min, Q1, median, Q3, max) and the number (percentage) of participants within the following duration categories will also be provided:

- < 4 weeks
- ≥ 4 weeks to < 8 weeks
- ≥ 8 weeks to < 12 weeks
- ≥ 12 weeks

Overall patient-weeks on-treatment and average patient-weeks on-treatment will be reported by each treatment group.

- Overall patient-weeks on-treatment = Sum of duration of treatment exposure (in days) from all participants/ 7
- Average patient-weeks on-treatment = Overall patient-weeks on-treatment / Number of participants randomized to the treatment

Number and percentage of participants at each dose level defined in Table 2-2 will also be summarized by the number of study treatment administrations, by visit and treatment.

Average dose will be summarized by treatment group during randomized treatment period and calculated as below:

$$\frac{\sum_{i=0}^{3}(\text{no. of days on dose level i}) \times (\text{dose level i*})}{\sum_{i=0}^{3}(\text{no. of days on dose level i})},$$

where dose level is the dose administered at a visit and number of days will be from the date of injection until the day before next dose administered for XXB750 and placebo treatment groups; and dose level is the total daily dose for open-label sacubitril/valsartan arm.

Dose administration records for randomized treatment period will also be listed at participant level for the participants in safety set.

Number and percentage of participants with permanent treatment discontinuations will be provided by reason for discontinuation.

All these analyses pertaining to treatment exposure during randomized treatment period will be carried out for all participants in Safety set (SAF).

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary, NovDTD which is a modified Novartis internal version of the WHO Drug Dictionary Enhanced (DDE) including the Anatomical Therapeutic Chemical (ATC) code. The latest version at the time of clinical database lock will be used.

Prior medications are defined as drugs taken prior to the study medication. **Randomized treatment concomitant medications** are medications taken at any time during the randomized treatment period and prior to safety follow-up. **Safety follow-up concomitant medications** are those given at least once during safety follow-up period. Prior, randomized treatment period or safety follow-up concomitant medication will be identified based on recorded or imputed start and end dates of taking medication. The rules for imputing incomplete start and end dates are described in Section 5.1.

The concomitant medication information for the randomization period will be summarized based on the SAF. The prior concomitant medications will be summarized based on SCR and SAF, separately. Specifically for concomitant medication summary, the start of randomization period, the start of the period is defined as the first study drug administration date for XXB750 treatment or placebo arm; for open-label Sac/Val arm, the start of the period is defined as 1 day after the first study drug administration date.

Prior and Concomitant medications will be summarized by treatment group. Medications will be presented in alphabetical order by ATC codes and grouped by chemical subgroup (the 4th level of the ATC codes). Tables will also show the overall number and percentage of participants receiving at least one medication of a particular ATC code and at least one drug in a particular chemical subgroup.

The number and percentage of participants on the following classes of background medications during the study will be tabulated by treatment group for FAS and for SAF.

- Aldosterone antagonists
- SGLT-2 inhibitors
- Antiarrhythmics, Class I and III
- Oral anticoagulants
- Antiplatelet agents (including aspirin)
- Beta blockers
- Digitalis glycosides
- Calcium antagonists
- Loop and thiazide or thiazide-like diuretics
- Statins

The search criteria for the classes of medications listed above will be defined in a separate EXCEL sheet with ATC preferred term and WHO drug codes. The EXCEL sheet will be stored in document management/archival system at the RAP level after the content is agreed upon by the Global Program Medical Director or Clinical Head (GPMD/GPCH) and before clinical database lock (CDBL).

Standard background HF medication

Standard background HF medications (or auxiliary medicinal products under EU CTR) in this study are ACEI, ARB and sacubitril/valsartan. The mean daily dose for the background HF medication will be calculated as:

Mean daily dose = [(No. of days on dose level 1)* level 1 daily dose + (No. of days on dose level 2)*level 2 daily dose + … + (No. of days on dose level K)*level K daily dose]/(No. of days in respective period of interest)

Please refer to Section 2.1.1 for the definition of each period. However, for background HF medication summray, the start of randomization period is defined as the first study drug administration date for XXB750 treatment or placebo arm; for open-label Sac/Val arm, the start of the period is defined as 1 day after the first study drug administration date. The summary for standard background HF medications will be presented for randomization period using FAS. For each medication class, the summary table will present the most frequent drug names of interest in the FAS set.

2.5 Analysis supporting primary objective(s)

The primary and final analysis will be performed after all participants have completed their final visits. No formal statistical hypothesis testing nor statistical modelling will be performed.

2.5.1 Primary endpoint(s)

The primary efficacy variable is change in NT-proBNP during randomization period.

2.5.2 Statistical hypothesis, model, and method of analysis

Summaries of absolute values and change from baseline in NT-proBNP by treatment group and visit will be presented using statistics as described in Section 2.1 additionally with geometric mean and corresponding 95% CI. Figures will be produced to visually show the observed mean NT-proBNP level by visit over randomization period for each treatment group.

The FAS and PPS will be used for the above analyses.

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

The missing values will be treated as missing. Unless otherwise stated, missing data will not be imputed for the analysis.

2.5.5 Multiplicity adjustment

Not applicable as no formal statistical hypothese test is planned for primary or secondary objectives.

2.5.6 Sensitivity analyses

No sensitivity analysis will be performed.

2.5.7 Supplementary analyses

Subgroup analyses will be performed for the primary analysis. The analysis will be done using the analysis specified in Section 2.5.2 at individual subgroup level separately. Please see Section 2.2.1 for subgroup details.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

Due to early study termination, the original planned analysis of secondary endpoints to demonstrate efficacy is no longer applicable.

Only group 1 was initiated, which include placebo (treatment arm 1), XXB750 60 mg target dose (treatment arm 2), XXB750 120 mg target dose (treatment arm 3), and conversion to sacubitril/valsartan (treatment arm 5). In addition, as specified in Section 2.5.7, subgroup analysis will provide summary statistics for NT-proBNP during randomization period by treatment group for each type of RAS inhibition (ACEI/ARB, sacubitril/valsartan) at screening.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable due to early termination.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

Not applicable.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

For all safety analyses, the SAF set will be used. All listings, figures and tables will be presented by treatment group.

Safety data to be analyzed are listed as below:

- Adverse events (AE) and Serious Adverse events (SAE)
- Safety topics that are adverse events of special interest (AESI): Serious hypotension, Serious hypersensitivity reactions, Serious injection site reactions, Severe tachycardia, Severe acute bradycardia, and Serious presyncope/syncope
- Safety topics that are potential risks: Hypotension, Hypersensitivity reactions, Injection site reactions, Tachycardia, Bradycardia, Immunogenicity
- Safety topics that are neither AESI nor Potential risks: Renal toxicity and Hepatotoxicity
- Laboratory assessments
- Vital signs, e.g., weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate.

2.7.1 Adverse events (AEs)

Any AE that occurred during the study period will be included in AE summary tables during the randomization period, i.e., consisting of randomized treatment period and safety follow-up period.The analysis will consider all participants in the Safety set (SAF) for reported AEs during the randomization period.

Treatment emergent adverse events (new or worsened) during randomization period are defined as any recorded AE with its start date (recorded or imputed) later than or equal to the start date of the randomization period as defined below:

1) Randomization period: first date of study treatment injection.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug according to the Medical Dictionary for Regulatory Activities (MedDRA). The latest MedDRA version before clinical database lock will be used for reporting the study.

If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Statistical analyses, as appropriate, will include all AEs with onset date during the randomization period and up to the analysis cut-off irrespective of how long after the last day of study treatment they occurred.

The number and percentage of participants reporting any adverse event during each reporting period will be summarized by primary system organ class, preferred term and treatment. The most common adverse events reported (≥ 5% in any group for each preferred term in the SOC-PT table) will be presented in descending frequency according to its incidence in the XXB750 highest dose group starting from the most common event.

Summaries for randomization period will be provided for study medication related adverse events, deaths, serious adverse events, other significant adverse events leading to permanent study discontinuation.

AESI and potential risks will be summarized in addition to the above analysis. Please see Section 2.7.2 for details.

2.7.2 Adverse events of special interest and potential risks

The following specific safety topics will be summarized separately in addition to the above analysis:

- AESI
    - Serious hypotension
    - Serious hypersensitivity reactions
    - Serious injection site reactions
    - Severe tachycardia
    - Severe acute bradycardia
    - Serious presyncope/syncope
- Potential risks:
    - Hypotension
    - Tachycardia
    - Bradycardia
    - Hypersensitivity reactions
    - Injection site reactions

    - Immunogenicity
- Other safety topics
    - Renal toxicity
    - Hepatotoxicity

The sets of terms, pertaning either to MedDRA or to NMQ or to CMQ, that are used to search the database to retrieve cases of interest that relate to the safety topics listed above are stored (or alternatively "summarized") in the Case Retrieval Strategy (eCRS). The latest version of the eCRS at the time of clinical database lock will be used.

The following standard analyses will be provided for all the listed safety topics (excluding Immunogenicity):

- Incidence (absolute and relative frequency) rates in terms of participant regardless of causal relationship to study drug for randomization period, by treatment group.
- Exposure-adjusted incidence rates per 100 patient years regardless of study drug relationship for randomization period, by treatment
- Analysis for time-to-first selected safety topic of interest by treatment group will be performed for randomization period using Kaplan-Meier estimates
- Listing of AEs by participant with AESIs and risk information.

In addition to the above, the analysis specified below will be provided for the safety topics that are listed in Table 2-3.

In the urgent safety communication (9-Aug-2024), it mentions that "the DMC identified an imbalance in the frequency of worsening heart failure events in patients receiving XXB750 in this study". Thus, a further safety topic "Cardiac Failure" will be added in analysis, which is defined as MedDRA SMQ Cardiac Failure (broad).

Table 2-3 AESIs and potential risks with additional analysis

Safety topic	Definitions	Analysis and additional criteria for characterizing selected AEs
Hypotension	Hypotension [STANDARD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Tachycardia	ADR Tachycardia [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Bradycardia	ADR Heart rate decreased [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT

Safety topic	Definitions	Analysis and additional criteria for characterizing selected AEs
		Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Injection site reactions	ADR Injection site reaction [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Hypersensitivity reactions	(Anaphylactic/anaphylactoid shock conditions (SMQ) OR Anaphylactic reaction (SMQ) OR Hypersensitivity other than administration site reactions [XXB750] (NMQ))	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Immunogenicity	All serious and non-serious TEAE in participants with at least one positive ADA test ever	Distribution of TEAE by ADA subgroup (as per Table 2-1)
Serious hypotension	Only SAE: ADR Hypotension [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Serious hypersensitivity reactions	Only SAE: (Anaphylactic/anaphylactoid shock conditions (SMQ) OR Anaphylactic reaction (SMQ) OR Hypersensitivity other than administration site reactions [XXB750] (NMQ))	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Serious injection site reactions	Only SAE: ADR Injection site reaction [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Severe tachycardia	Only severe AE: ADR Tachycardia [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Severe acute bradycardia	Only severe AE: ADR Heart rate decreased [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)

Safety topic	Definitions	Analysis and additional criteria for characterizing selected AEs
Serious presyncope/syncope	Only SAE: ADR Presyncope [ADR_STD] (NMQ) OR ADR Depressed level of consciousness [ADR_STD] (NMQ) OR ADR Loss of consciousness [ADR_STD] (NMQ)	Distribution of TEAE by SOC and PT Distribution of TEAE by pre-defined subgroups (as per Table 2-1)

2.7.3 Deaths

Participants that died during the study randomization period will be reported. Deaths will be summarized by actually received treatment group to present number and percentage of participants that died. In addition, listings will be provided for participants that died.

The analysis will consider all participants in the Safety set (SAF) for reported deaths during the randomization period.

2.7.4 Laboratory data

For each laboratory parameter, evaluations will be summarized by visit and actually received treatment group by presenting summaries (n, mean, standard deviation, median, minimum and maximum) for actual and change from baseline values for randomization period. The summary will be provided separately for biochemistry and hematology laboratory parameters. Central laboratory data will be used for the summaries.

Shift tables based on the standard ranges for each laboratory parameter (biochemistry and hematology) will be provided by treatment group at each visit for the randomization period to present incidence of transitions from a baseline high, normal or low laboratory value to a maximum post-baseline high, normal or low value. In addition to these analyses, laboratory parameter values will be listed for each participant by scheduled assessment visit and treatment group.

The number and percentage of participants with clinically notable laboratory results after baseline will be presented in accordance with Table 2-4, by visit and overall, for randomization period.

Table 2-4 Clinically notable laboratory values and vital signs

Category Parameter (unit)	Clinically notable criteria
Hematology	
Red blood cell count	> 50% increase AND value > ULN > 30% decrease AND value < LLN
Hemoglobin	> 50% increase AND value > ULN either (> 30% decrease AND value < LLN) OR value < 8.0 g/dL
Hematocrit	> 50% increase AND value > ULN > 30% decrease AND value < LLN

Category Parameter (unit)	Clinically notable criteria
White blood cell count	value > 100,000 cells/mm^3 value < 2000 cells/mm^3
Platelet count	value < 50,000 platelets/mm^3
Blood chemistry	
Alkaline phosphatase	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormal
ALT (SGPT)	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormal
AST (SGOT)	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormal
Total bilirubin	value > 3 x ULN if baseline was normal OR value > 3 x baseline if baseline was abnormal
BUN	≥ 50% increase
Creatinine	≥ 50% increase
Potassium	value > 6.0 mmol/L value < 3.0 mmol/L
Chloride	> 115 mEq/L < 90 mEq/L
Calcium	corrected serum calcium > 3.1 mmol/L corrected serum calcium < 1.75 mmol/L
Uric acid	> 50% increase
Plasma glucose	> 25% increase value < 40 mg/dL
Vital signs	
Weight (kg)	Decrease > 7% from baseline Increase > 7% from baseline
Sitting office SBP (mmHg)	> 180 mmHg < 110 mmHg
Sitting office DBP (mmHg)	> 110 mmHg < 70 mmHg
Pulse (bpm)	value > 100 1. value < 60 2. value < 50
Liver function tests	
ALT (SGPT) OR AST (SGOT)	1. value > 3 x ULN 2. value > 5 x ULN 3. value > 8 x ULN 1. value > 10 x ULN 2. value > 20 x ULN

Category Parameter (unit)	Clinically notable criteria
ALT (SGPT) OR AST (SGOT) AND Total bilirubin (TB)	1. ALT or AST > 3 x ULN and TB > 1.5 x ULN
	2. ALT or AST > 3 x ULN and TB > 2 x ULN
	3. ALT or AST > 5 x ULN and TB > 2 x ULN
	4. ALT or AST > 8 x ULN and TB > 2 x ULN
	5. ALT or AST > 10 x ULN and TB > 2 x ULN
	6. ALT or AST > 20 x ULN and TB > 2 x ULN
Alkaline phosphatase	1. > 2 x ULN
	2. > 3 x ULN
	3. > 5 x ULN
Total bilirubin	1. > 1.5 x ULN
	2. > 2 x ULN
	3. > 3 x ULN
Alkaline phosphatase (ALP) AND TB	1. ALP > 3 x ULN AND TB > 2 x ULN
	2. ALP > 5 x ULN AND TB > 2 x ULN
ALT (SGPT) OR AST (SGOT) AND Total bilirubin (TB) AND Alkaline phosphatase (ALP)	1. ALT OR AST > 3 x ULN AND TB > 2 x ULN AND ALP ≤ 2 x ULN
	2. ALT OR AST > 3 x ULN AND TB > 2 x ULN AND ALP ≤ 2 x ULN OR reported Hy's Law case
	3. TB > 3 x ULN AND AST OR ALT ≤ 3 x ULN AND ALP ≤ 1.5 x ULN
	4. ALP > 3 x ULN AND AST AND ALT AND TB are within normal range
Laboratorial and clinical associations	ALT OR AST > 3 x ULN AND (Nausea OR Vomiting OR Fatigue OR General malaise OR Abdominal pain OR (Rash AND Eosinophilia))
Renal function tests	
eGFR	1. ≥ 25% decrease
	2. ≥ 50% decrease
Creatinine	≥ 0.3 mg/dL increase
New onset of proteinuria	Urine protein ≥ 300 mg/dL
New onset of hematuria	Urine hemoglobin ≥ 1 mg/dL

ULN: upper limit of the normal range; LLN: lower limit of the normal range; SBP: systolic blood pressure; DBP: diastolic blood pressure; Increases and decreases of parameters as mentioned in the table are from baseline

Participants with liver function tests (ALT, AST, ALP, Total Bilirubin) and renal-related parameters falling within predefined categories of elevations (new and worsened [i.e., those existent before, and that worsened after, randomization] elevations) will be summarized by treatment group in accordance with Table 2-4 for randomization period. Descriptive summaries

by presenting count and percentage of participants with each type of Liver and Renal event in addition to graphical summaries will be displayed, as applicable.

2.7.5 Other safety data

2.7.5.1 ECG and cardiac imaging data

The following quantitative variables will be summarized: heart rate and QRS duration. Summary statistics for continuous data and number and percentage of participants for categorical data (e.g. interpretation) will be provided by treatment and visit for randomization period.

In addition, shift tables comparing the existence or not of abnormalities (atrial fibrillation, atrial flutter, LBB block, RBB block, left ventricular hypertrophy, paced rhythm, myocardial infarction, 1st degree AV block, 2nd degree AV block, 3rd degree AV block or other) on the ECG at baseline and worst-on study results (during the randomization period) will be provided. The categories Yes, No and Missing will be used to reflect where the abnormality of interest is present, absent or an ECG is not performed/is not available, respectively for that participant.

The analysis will be based on SAF.

2.7.5.2 Vital signs

Vital signs including weight, blood pressure and pulse measures will be summarized by treatment group and scheduled visit with standard summary statistics (mean, Q1, median, Q3, standard deviation, min, max), including changes from randomization baseline. Graphical mean plots with 95% CIs for these vital signs will also be provided. Change from baseline will only be summarized for participants with both baseline and post-baseline values and will be calculated as:

- change from baseline = post-baseline value – baseline value

The number and percentage of participants with clinically notable vital signs after baseline will be presented in accordance with Table 2-4 for randomization period, by visit and overall. The analysis will be based on SAF.

Apart from the above analyses, values for vital signs parameters will also be listed at a participant level by treatment group and visit for all participants in safety set (SAF).

Maximum and minimum post-baseline values will be summarized (mean, Q1, median, Q3, standard deviation, min, max) for blood pressure and pulse measures for randomization period.

2.7.5.3 Immunogenicity

All immunogenicity results including anti-XXB750 antibodies (ADA) will be summarized by treatment group and listed by treatment group, participant, and visit/time. Summary statistics including prevalence and incidence of anti-XXB750 antibodies will be provided by treatment and visit/time. A shift table to summarize the proportion of participants' ADA status change over time from baseline (i.e. participants transitioning from negative to positive or vice versa) will also be provided by treatment group.

Post-Baseline category is defined as positive if ADA screening test turns positive at any time post-dose during randomization period of the study, as negative if ADA screening test is negative at all times post-dose during randomization period of the study, and as undefined otherwise. Treatment-induced ADA-positive sample is defined as ADA-positive sample post-baseline during randomization period with ADA-negative sample at baseline. Treatment-boosted ADA-positive sample is defined as ADA-positive sample post-baseline with titer that is at least the titer fold (i.e. 4-fold) change greater than the ADA-positive baseline titer.

A comparison between the counts and percentages of AE observed in ADA-positive and ADA-negative participants will be performed for each MedDRA PT.

The analysis will be based on immunogenicity prevalence set and incidence set.

2.8 Pharmacokinetic endpoints

Sparse PK samples are collected for population PK analysis. Results will be reported separately. Individual drug concentration will be listed in CSR (Clinical Study Report) for participants in PK sub study.

2.9 PD and PK/PD analyses

See Section 2.11 for PD (excluding NT-proBNP) related analyses. See Sections 2.5 and 2.6 for NT-proBNP related analyses.

2.10 Patient-reported outcomes

See Section 2.12 for Kansas City Cardiomyopathy Questionnaire (KCCQ) related analyses.

2.11 Biomarkers

Biomarkers to be analyzed may include, but are not necessarily limited to: cyclic GMP (plasma and urine), urinary cyclic GMP-to-creatinine ratio, urinary albumin-to-creatinine ratio, BNP and hs-Troponin.

Biomarker data will be summarized by treatment and time point. Descriptive summaries will include n, mean (arithmetic and geometric), SD, minimum, Q1, median, Q3, maximum, geometric mean, and 95% confidence interval of geometric mean. Summary statistics by treatment group will be performed for the baseline values, the post-baseline values, and the change from baseline, with baseline defined as the randomization visit. At each post baseline visit, only participants with a value at both baseline and that post-baseline visit will be included. Missing post-baseline values will not be imputed. Analyses will be based on the Full Analysis Set (FAS) and Per-Protocol Set (PPS).

2.12 Other Exploratory analyses

2.12.1 Exploratory variables

Below are the variables for the exploratory analysis:

1. eGFR during randomization period;

2. Biomarkers (See Section 2.11 for analyses);
3. NYHA class during randomization period ;
4. HF signs and symptoms during randomization period ;
5. Kansas City Cardiomyopathy Questionnaire clinical summary score (CSS) and overall summary score (OSS) during randomization period ;
6. Population PK analysis results including mathematic models and parameters (See Section 2.8 for details);
7. Incidence of anti-XXB750 antibodies (See Section 2.7.5.3 for analyses).

2.12.2 Analysis methods

In general, exploratory variables will be analyzed in the FAS unless specified otherwise. Only descriptive statistics will be provided as appropriate, and no formal statistical hypothesis testing nor statistical modelling will be performed.

For continuous variables, unless otherwise specified, summary tables will be provided by treatment and time point. Summary statistics by treatment group will be performed for the baseline values, the post-baseline values, and the change from baseline, with baseline defined as the randomization visit. At each post baseline visit, only participants with a value at both baseline and that post-baseline visit will be included.

For ordinal variables, unless otherwise specified, shift tables of class change (number and percent of participants) will be provided by treatment group at each visit for the randomization period to present.

2.13 Interim analysis

Regular safety data monitoring was planned as specified in Section 2.1 and study protocol Section 4.6. However, no formal interim analysis has been conducted during the study.

3 Sample size calculation

The study is planned to randomize approximately 720 participants in total, and the following calculation is based on the study design before the early study termination.

3.1 Primary endpoint (s)

For the primary endpoint analysis, 600 participants allocated in the ratio of 2:2:3:3 to placebo, XXB750 60 mg dose level, XXB750 120 mg dose level, and highest XXB750 dose level, respectively.

Assuming a common standard deviation of 0.67 for log NT-proBNP change from baseline and a one-sided 2.5% significance level (with adjustments for multiple comparisons using MCPMOD), a sample size of 600 participants (120 in placebo, 120 in XXB750 60 mg dose level, 180 in XXB750 120 mg dose level, and total of 180 in highest XXB750 dose level) will provide a power of 90% if the underlying true maximum NT-proBNP reduction on XXB750 vs. placebo is 23%.

3.2 Secondary endpoint(s)

A common standard deviation of 0.67 for log NT-proBNP change from baseline and a one-sided 2.5% significance level is assumed for all sample size determinations relating to secondary endpoints.

For the first secondary endpoint, a sample size of 120 participants in placebo and 180 participants in XXB750 optimal dose level, respectively, will provide a minimum power of 90% if the true NT-proBNP reduction on XXB750 vs. placebo is 23%.

For the second secondary endpoint, in participants with ACEI/ARB background medication converted to sacubitril/valsartan, a sample size of 120 participants in a group combining the two highest XXB750 target dose levels and 120 participants in sacubitril/valsartan conversion arm will provide approximately 80% power if the underlying true maximum NT-proBNP reduction with adding XXB750 vs. conversion to sacubitril/valsartan is 22%.

4 Change to protocol specified analyses

Due to early study termination, all analysis will be done descriptively. No inferential statistical testing or statistical modelling will be implemented.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The missing or partially missing start or end dates will be handled/imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications (PDS) document.

5.1.2 AE date imputation

The missing or partially missing AE start or end dates will be handled/imputed using the Novartis AGB global standard approach. Details will be provided in the study PDS document.

5.1.3 Concomitant medication date imputation

The missing or partially missing concomitant medication start or end dates will be handled/imputed using the Novartis AGB global standard approach. Details will be provided in the study PDS document.

5.2 AEs coding/grading

Coding of AE will be done per MedDRA dictionary. The scale of severity grading described in section 8.6.1 of the study protocol will be used.

5.3 Laboratory parameters derivations

Details will be provided in the study PDS document.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Refer to Section 2.5.

5.4.2 Analysis supporting secondary objective(s)

Refer to Section 2.6.

5.5 Rule of exclusion criteria of analysis sets

The following table presents a sample of the rules for participant classification in the analysis sets (Table 5-1).

Table 5-1 Criteria leading to exclusion

Analysis Set	Criteria that cause participants to be excluded
SCR	Not having informed consent;
	Not having disposition page
RIS	Not in SCR;
	Not having disposition page;
RAS	Not randomized
FAS	Not in RAS;
	Mistakenly randomized and no double-blind study drug taken
SAF	Not in RAS;
	No double-blind study drug taken
PPS	Not in FAS;
	Not receiving at least three doses/injection of double-blind study drug;
	Not followed for at least 8 weeks post randomization for open-label arm
PKS	Not randomized;
	Not receiving any study XXB750 treatment;
	No available valid PK concenrtration measurement
IPS	Not in SAF;
	Missing baseline ADA sample and no available post-baseline ADA sample
IIS	Not in SAF;

Analysis Set	Criteria that cause participants to be excluded
	Missing baseline ADA sample or no available post-baseline ADA sample

5.6 KCCQ derivation of scores in each domain

The clinical summary score is a mean of the physical limitation and total symptom scores. The total symptom score is the mean of the symptom frequency and symptom burden scores. Each scale score (the physical limitation, symptom frequency or symptom burden) is calculated as the mean of its item scores and transformed to a 0–100 scale, with higher score indicating higher level of functioning. A score of 100 represents perfect health whereas a score of 0 represents dead. For patients who die, a worst score (score of 0) will be imputed for the clinical summary score at all subsequent scheduled visits after the date of death where the clinical summary score would have been assessed.

Below are the rules each scale score being calculated:

1. Physical Limitation
   - Code responses to each of Questions 1a-f as follows:

Extremely limited = 1

Quite a bit limited = 2

Moderately limited = 3

Slightly limited = 4

Not at all limited = 5

   - Limited for other reasons or did not do = <missing value>

If at least three of Questions 1a-f are not missing, then compute

   - Physical Limitation Score = 100*[(mean of Questions 1a-f actually answered) – 1]/4

Note: references to "means of questions actually answered" imply the following. If there are n questions in a scale, and the subject must answer m to score the scale, but the subject answers only n-i, where n-i >= m, calculate the mean of those questions as

(sum of the responses to those n-i questions) / (n-i)

not

(sum of the responses to those n-i questions) / n

2. Symptom Frequency
   - Code responses to Questions 3, 5, 7 and 9 as follows:

Question 3

Every morning = 1

3 or more times a week but not every day = 2

1-2 times a week = 3

Less than once a week = 4

Never over the past 2 weeks = 5

Questions 5 and 7

All of the time = 1

Several times a day = 2

At least once a day = 3

3 or more times a week but not every day = 4

1-2 times a week = 5

Less than once a week = 6

Never over the past 2 weeks = 7

Question 9

Every night = 1

3 or more times a week but not every day = 2

1-2 times a week = 3

Less than once a week = 4

Never over the past 2 weeks = 5

If at least two of Questions 3, 5, 7 and 9 are not missing, then compute:

S3 = [(Question 3) – 1]/4

S5 = [(Question 5) – 1]/6

S7 = [(Question 7) – 1]/6

S9 = [(Question 9) – 1]/4

Symptom frequency score = 100*(mean of S3, S5, S7 and S9)

3. Symptom burden

- Code responses to each of Questions 4, 6 and 8 as follows:

Extremely bothersome = 1

Quite a bit bothersome = 2

Moderately bothersome = 3

Slightly bothersome = 4

Not at all bothersome = 5

I've had no swelling/fatigue/shortness of breath = 5

If at least one of Questions 4, 6 and 8 is not missing, then compute

Symptom burden score = 100*[(mean of Questions 4, 6 and 8 actually answered) – 1]/4

4. Total symptom score = mean of the following available summary scores:
   - Symptom frequency score
   - Symptom burden score
5. Self-Efficacy score

   If at least one of Questions 10 and 11 is not missing, then compute

   Self-Efficacy score = 100*[(mean of Questions 10 and 11 actually answered) – 1]/4
6. Quality of Life
   - Code responses to Questions 12, 13, 14 as follows:

Question 12

It has extremely limited my enjoyment of life = 1

It has limited my enjoyment of life quite a bit = 2

It has moderately limited my enjoyment of life = 3

It has slightly limited my enjoyment of life = 4

It has not limited my enjoyment of life at all = 5

Question 13

Completely dissatisfied = 1

Mostly dissatisfied = 2

Somewhat satisfied = 3

Mostly satisfied = 4

Completely satisfied = 5

Question 14

I have felt that way all of the time = 1

I have felt that way most of the time = 2

I have occasionally felt that way = 3

I have rarely felt that way = 4

I have never felt that way = 5

If at least one of Questions 12, 13 and 14 is not missing, then compute

Quality of Life = 100*[(mean of Questions 12, 13 and 14 actually answered) – 1]/4

7. Social Limitation

- Code responses to each of Questions 15a-d as follows:

  Extremely limited = 1

  Quite a bit limited = 2

  Moderately limited = 3

  Slightly limited = 4

  Not at all limited = 5

  Limited for other reasons or did not do = <missing value>

If at least two of Questions 15a-d are not missing, then compute

Social Limitation Score = 100*[(mean of Questions 15a-d actually answered) – 1]/4

8. Clinical summary score = mean of the following available summary scores:
   - Physical limitation score
   - Total symptom score
9. Overall summary score = mean of the following available summary scores:
   - Physical limitation score
   - Total symptom score
   - Quality of Life
   - Social Limitation

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.