NOVARTIS

Clinical Development

XXB750

CXXB750B12201 / NCT05562934

A multi-center, randomized, double-blind, parallel-group, 20-week dose-finding study to evaluate efficacy, safety, and tolerability of XXB750 in participants with resistant hypertension

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-Nov-2022	Prior to FPFV	Creation of final version	N/A – First version	NA
26-July-2024	After protocol amendment v02	Update the definition of the period from randomization to EOS (end of study)	Replace “double-blind period” by “randomization period”	Whole document
		Investigational study treatment dose adjustement and/or interruptions are not permitted per protocol	Remove definition and analysis on treatment interruption	Section 2.1.1, 2.4.1
		Gender refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people.	Replace gender by sex	Section 2.2.1
		[redacted]	Categories updated to Positive, Negative, PBL and Missing	Section 2.2.1
		Some analysis may treat “Eastern Europe” and “Western Europe and other” as two region categories	Add the country list for “Eastern Europe” and “Western Europe and other”	Section 2.1.1
		Give accurate description of parameters to be summarized	“sitting” and “cyclic GMP (urine)/urine creatinine” were added	Section 2.3.2
		Anatomical main group is too broad and not informative	Replaced by chemical subgroup	Section 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		No need to summarize the categories of Antiplatelet agents	Remove category list	Section 2.4.2
		Number of anti-hypertensive background medication is expanded	Beta blocker is included as allowed anti-hypertensive background medication	Section 2.4.2
		More reasonable to impute XXB treatment group with lower dose group than simply placebo group	Update imputation rules	Section 2.5.3
		MAR (missing at random) assumption is not applicable to missing data due to death, lost to follow-up or early study discontinuation due to AE	Remove tipping point analysis	Section 2.5.6, 2.6.5
		"observed" has the same meaning as "raw"	Replace "raw" by "observed"	Section 2.5.7, 2.6.2
		Repeated measures ANCOVA may not converge	Use a compound symmetric matrix instead if model does not converge	Section 2.6.2
		Safety lead proposed updated safety topics	Safety topics	Section 2.7
		Safety lead updated required additional analysis	Redundant analysis was removed. Subgroups of interest for each safety topics were clarified	Table 2-3
		Renal and liver function tests in Table 2-3a were moved to Table 2-4 as clinical notable laboratory values	Table 2-3a were merged to Table 2-4	Section 2.7.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		SD will be provided for treatment group comparison on lab parameters	Added formula	Section 2.7.3
		Did not clearly clarify type of BP and position of office BP	Give accurate description of parameters	Table 2-4
		Original wording does not imply table outputs of interest	Categories names and description were changed for ECG	Section 2.7.4.1
		[redacted]	Definition and description were added to SAP accordingly	Seftion 2.7.4.3
		[redacted]	[redacted]	Section 2.12.1
		Severity grading was not mentioned	Severity grading was added	Section 5.2
		Sensitivity analysis was revised	Related references were removed	Section 6
		Model covariate and subgroup of interest were changed	Beta blocker usage (yes, no) was replaced by number of background antihypertensive medication (=3 vs >3)	Section 1.1, 2.2.1, 2.3.2, 2.5, 2.6, 2.11, 2.12
		The second secondary objective was updated	Nocturnal SBP dipping was replaced by average change from baseline at Week 9 and Week 12	Section 1.2, 2.6.2, 3.1.2
		[redacted]	[redacted]	Section 2.12

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			renamed as “individual drug concentration”	
		Analysis on safety endpoints was added	MMRM on rate change in eGFR	Section 2.7.3
		[redacted]	MCP-MOD on urine and plasma cGMP	Section 2.11

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List of abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACEI	Angiotensin Converting Enzyme Inhibitor
ADA	Anti Drug Antibodies
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
ARR	Aldosterone-to-renin Ratio
ATC	Anatomical Therapeutic Chemical classification system
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CCB	Calcium Channel Blocker
CRF	Case Report Form
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
DB	Double-blind
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DMS	Document Management System
ED50	Median Effective Dose
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GMP	Guanosine Monophosphate
GP	Glycoprotein
HDL	High-density Lipoprotein
HLGT	High Level Group Term
HLT	High Level Term
IA	Interim Analyses
IV	Intravenous
LDL	Low-density Lipoprotein
LS	Least Squares
MCP-MOD	Multiple Comparison Procedure-Modeling
mean 24hr DBP	mean 24hr ambulatory diastolic blood pressure
mean 24hr SBP	mean 24hr ambulatory systolic blood pressure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MAR	Missing at Random

MCMC	Markov Chain Monte Carlo
MMRM	Mixed Model for Repeated Measure
MNAR	Missing Not at Random
NMQ	Novartis MedDRA Query
NT-proBNP	N-terminal prohormone B-type Natriuretic Peptide
PD	Pharmacodynamics
PDE-5	Phosphodiesterase-5
PDS	Programming Datasets Specifications
PK	Pharmacokinetics
[redacted]	
PT	Preferred Term
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
q4w	once every 4 weeks
RAN	Randomized set
RAP	Reporting & Analysis Process
RAS	Randomized Analysis Set
RBC	Red Blood Cell
rHTN	Resistant Hypertension
RIS	Run-in Set
SAF	Safety set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCR	Screened set
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMQ	Standard Medical Query
SOC	System Organ Class
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Events
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol for XXB750B12201. The analyses following the SAP below will be used for clinical study reporting purposes.

It is important to note that this version of statistical analysis plan details the statistical methodology for the analyses planned and agreed to at the time of finalization of the XXB750B12201 protocol (Version 02 – protocol amendment).

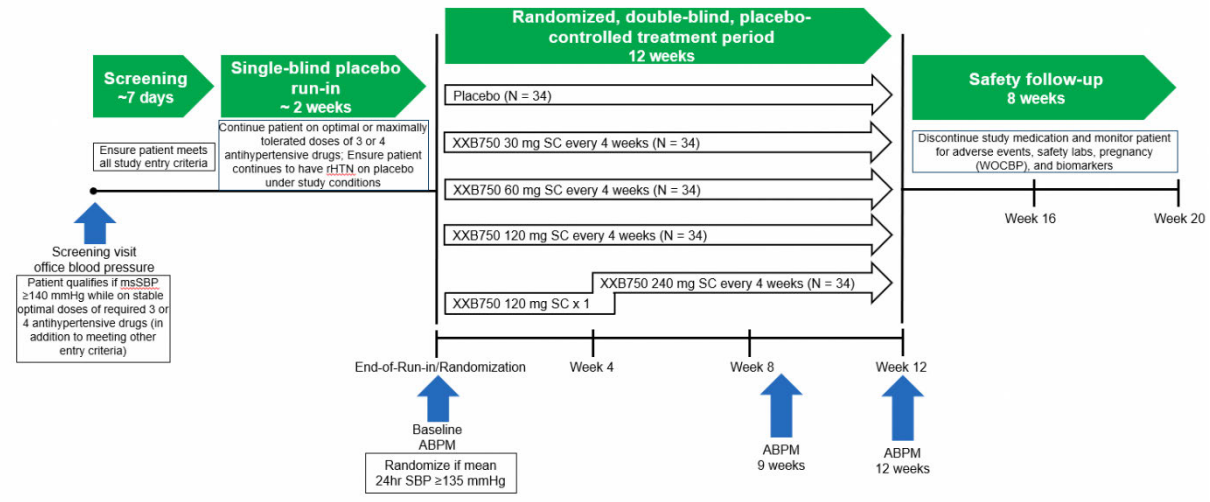
1.1 Study design

Study XXB750B12201 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 study which is comprised of four periods (Figure 1-1):

- A screening period (approximately 7 days)
- A single-blind placebo run-in period lasting approximately 2 weeks
- A 12-week double-blind, placebo-controlled, parallel-group treatment period
- An 8-week safety follow-up period

The study will enroll participants with rHTN defined as participants with uncontrolled BP despite treatment with optimal or maximally tolerated doses of 3 or 4 antihypertensive drugs of different classes, specifically a thiazide/thiazide-like diuretic, an ACEI or an ARB, and a long acting dihydropyridine CCB. The study population will consist of male and female participants 18 years old or older with apparent resistant hypertension as defined in the inclusion and exclusion criteria in the protocol. Approximately 170 participants will be randomized to receive placebo, XXB750 30 mg, 60 mg, 120 mg, or 240 mg SC every 4 weeks, at an overall final ratio of 1:1:1:1:1.

Figure 1-1 Study Design



ABPM = ambulatory blood pressure monitoring; mean 24hr SBP = mean ambulatory systolic blood pressure (based on 24hr ambulatory blood pressure monitoring); msSBP = mean sitting systolic blood pressure (based on office assessment); SC = subcutaneously; WOCBP = women of childbearing potential.

The randomization in this study will be stratified by region (America, Asia except Japan, Japan, Eastern Europe, Western Europe combined with others). The stratification factor will be appropriately accounted for in the planned statistical analysis. At visit 100, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the allowed treatment arms per design (Figure 1-1).

A staggered approach as summarized in Table 1-1 will divide randomized participants into two groups, which will vary in terms of the ratio of allocation to the treatment arms. Please refer to study protocol Section 4.1 for details.

Table 1-1 Overview of staggered enrollment strategy

Treatment arm	Group 1	Group 2 (adjusted*)	Total (adjusted*)
Placebo	n = 17	n = 17	N = 34
XXB750 30mg SC every 4 weeks	n = 17	n = 17	N = 34
XXB750 60mg SC every 4 weeks	n = 17	n = 17	N = 34
XXB750 120mg SC every 4 weeks	n = 17	n = 17	N = 34
XXB750 120mg SC×1 dose, then XXB750 240mg every 4 weeks	n = 0	n = 34 (0*)	N = 34 (0*)
Group Total	N = 68	N = 102 (68*)	N = 170 (136*)

* Adjusted numbers are applicable if DMC recommends against administration of dose level 4 in the Group 2 enrollment.

One interim safety analysis will be conducted when approximately first 40 participants complete at least 5 weeks of double-blind treatment. No alpha adjustment will be made for the interim safety analysis. Interim safety analyses and regular safety data monitorings will be reviewed by the independent data monitoring committee (DMC) as specified in the DMC charter.

The primary analysis will be performed after all participants have completed Week 12 (or discontinued prior to Week 12). A final analysis will be performed after all participants have completed Week 20 (or discontinued prior to Week 20). Formal testing of the primary endpoint with full level alpha of 0.025 (1-sided) will be performed at the primary analysis timepoint.

1.2 Study objectives, endpoints and estimands

Table 1-2 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy and dose-response relationship of XXB750 30 mg SC q4w, 60 mg SC q4w, 120 mg SC q4w, and 240 mg SC q4w compared to placebo in reducing the mean 24hr ambulatory systolic blood	• Change from baseline in mean 24hr SBP at Week 12

Objective(s)	Endpoint(s)
pressure (mean 24hr SBP) from baseline at Week 12.	
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the treatment effect of the highest XXB750 dose versus placebo in reducing the mean 24hr SBP from baseline to Week 12.	• Change from baseline in mean 24hr SBP at Week 12
• To evaluate the treatment effect of the highest XXB750 dose versus placebo in the dosing interval average of ambulatory SBP as assessed by average of mean 24hr SBP measured at week 9 and week 12.	• Average of changes from baseline in mean 24hr SBP at Week 9 and at Week 12
• To evaluate the proportions of participants achieving ambulatory BP control (i.e., mean 24hr SBP < 130 mmHg and mean 24hr DBP < 80 mmHg) with respect to the dose-response relationship of the four XXB750 dose level groups compared to placebo at week 12.	• The proportions of partipicants achieving blood pressure control defined as mean 24hr SBP <130 mmHg and mean 24hr DBP <80 mmHg at Week 12
• To evaluate the safety and tolerability of the XXB750 regimens over 12 weeks of treatment and over the 20-week study period including safety follow-up.	• Adverse events, safety laboratory parameters, and vital signs through end of treatment/study (EOT/EOS)
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

1.2.1 Primary estimand(s)

The primary clinical question of interest is: Is there a dose-response signal with respect to the dose-response relationship of XXB750 30 mg SC q4w, 60 mg SC q4w, 120 mg SC q4w, and 240 mg SC q4w versus placebo in reducing the mean 24hr SBP at Week 12 from randomization in participants with rHTN, regardless of discontinuation from study treatment, regardless of change in the dose of allowed background antihypertensive medications and regardless of receiving prohibited concomitant medication?

The justification for the primary estimand is that it will capture both the effect of the tested treatments and the effect of additional standard concomitant medications, mirroring the conditions in clinical practice.

The primary estimand is described by the following attributes:

1. Population: participants with rHTN receiving allowed concomitant medications defined in study population (study protocol Section 5).
2. Variable: change from baseline in mean 24hr SBP at Week 12.
3. Treatment of interest: the randomized treatments (XXB750 30 mg SC q4w, 60 mg SC q4w, 120 mg SC q4w, 240 mg SC q4w or placebo) with allowed antihypertensive concomitant medications.

Handling of remaining intercurrent events:

1. Discontinuation of study treatment: ignore (treatment policy strategy).
2. Unforeseen change in the dose of allowed concomitant medications: ignore (treatment policy strategy).
3. Receiving prohibited concomitant medication: ignore (treatment policy strategy).

Allowed and prohibited concomitant medications are defined in the programming datasets specifications (PDS). Unforeseen change in the dose of allowed concomitant medications is defined as any change from randomization, including medication switch within the same class or between ACEi and ARB. Intercurrent events will be listed by treatment group.

The summary measure is the difference in variable means between treatments.

Mean 24hr SBP and mean 24hr DBP will be listed by treatment group.

1.2.2 Secondary estimand(s)

Difference between highest XXB750 dose group versus placebo in change from baseline in mean 24-hour SBP at Week 12

The estimand of the first secondary objective in terms of attributes will be the same as described for the primary estimand (Section 1.2.1) except for the treatment of interest, which is restricted to the highest XXB750 dose group and placebo only.

This estimand will further demonstrate the efficacy of XXB750 highest dose group compared with placebo and provide an estimate with a p-value in a hierarchical hypothesis testing procedure with overall type I error control after a dose-response signal is established in the primary objective.

Difference between highest XXB750 dose group versus placebo in average of changes from baseline in mean 24-hour SBP at Week 9 and at Week 12

The estimand of the second secondary objective in terms of attributes are the same as described for the primary estimand (Section 1.2.1) except for (1) the treatment of interest which is restricted to the highest XXB750 dose group and placebo only; and (2) for variable which is average change from baseline in mean 24hr SBP at Week 9 and at Week 12. This estimand will demonstrate the overall efficacy of XXB750 highest dose group compared with placebo in terms of average change from baseline at Week 9 (approximate peak state) and at Week 12 (approximate trough state) and provide an estimate with a p-value in a hierarchical hypothesis testing procedure with overall type I error control after efficacy in primary and first secondary objectives are established.

Dose-response signal and dose-response relationship of XXB750 dose groups versus placebo with respect to the proportion of participants achieving blood pressure (BP) control at Week 12

The third secondary question of interest is: What is dose-response signal and assess the dose-response relationship of XXB750 30 mg SC q4w, 60 mg SC q4w, 120 mg SC q4w, and 240 mg SC q4w versus placebo with respect to the proportion of participants achieving BP control at Week 12 in participants with rHTN without any premature discontinuation from study treatment and without any increase in the dose of allowed background antihypertensive medications nor receiving any prohibited medications.

The key secondary estimand is described by the following attributes:

1. Population: participants with rHTN receiving allowed concomitant medications defined in study population.
2. Variable: participant's achievement of blood pressure control defined as mean 24hr SBP <130 mmHg and mean 24hr DBP <80 mmHg at Week 12.
3. Treatment of interest: the randomized treatment XXB750 30 mg SC q4w, 60 mg SC q4w, 120 mg SC q4w, 240 mg SC q4w or placebo.

Handling of remaining intercurrent events:

1. Discontinuation of study treatment: imputed as not achieving BP control (composite strategy).
2. Unforeseen increase in the dose of allowed concomitant medications: imputed as not achieving BP control (composite strategy).
3. Receiving prohibited concomitant medication: imputed as not achieving BP control (composite strategy).

Allowed and prohibited concomitant medications are defined in the programming datasets specifications (PDS). Unforeseen increase in the dose of allowed concomitant medications is defined as any increase from randomization. Medication switch within the same class or between ACEi and ARB is not considered as unforeseen increase. Intercurrent events will be listed by treatment group.

The summary measure is the difference in proportions between treatments.

Evaluating the safety and tolerability of XXB750 regimens over 12 weeks of treatment and up to 20 weeks of follow-up

Adverse events (AEs) and serious AEs, laboratory parameters and vital signs will be evaluated and summarized in each treatment group for different treatment periods (run-in, randomization period, randomized treatment period and post-treatment safety follow-up). Please refer to Section 2.7 for analysis details.

2 Statistical methods

The following section contains important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Data will be analyzed by Novartis according to the statistical analysis Section 9 of the study protocol using R 4.1.0 and SAS 9.4, unless otherwise specified. Further details on planned statistical analyses and data-driven regression diagnostics will be presented in the following section and in CSR Appendix 16.1.9. Separate analysis plan developed by the external DMC independent statistician will be used for planned interim safety analysis.

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. CIs for the percentage of binary endpoint will be constructed based on the method of Agresti and Caffo (2000). Graphical presentation of summary data will also be provided as applicable.

The randomization in this study will be stratified by region. The stratification factors will be appropriately accounted for in the planned statistical analyses.

Interim safety analysis and regular safety monitoring (approximately every six months) 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 day

For efficacy analysis (based on FAS), study day is defined as the visit/assessment date – randomization date +1 for baseline and post-baseline visits, but defined as the visit/assessment date – randomization date for visits prior to baseline, unless specified otherwise. Study day for randomization date therefore is Day 1 for CSR analyses and reporting purpose. Note that this is different from day numbering in the study protocol assessment Table 1-2 for baseline visit.

For safety analysis (based on SAF), Day 1 is the first double-blind treatment injection date.

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 and placebo as assigned to a participant at randomization.

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. End of treatment (EOT) for participants who complete randomized treatment period is at Visit 170 (Week 12); and for participants who prematurely discontinue randomized treatment is defined as max(the last administration of double-blind study drug + 28 days, treatment disposition date), date of withdrawal of informed consent, or the date of death, whichever occurs first.

Screening period

Screening period begins at Visit 1 until the day before the start of single-blind placebo run-in (Visit 20) or screening disposition date for those who do not qualify to continue.

Single-blind placebo run-in period

The single-blind placebo run-in period is defined as the period between the start of run-in study medication (i.e., date of one injection of placebo matching XXB750, or, Visit 20) until the day before date of randomization or end of run-in visit date for those who do not qualify for randomization.

Randomized treatment period

The randomized treatment period begins at the time of randomization and ends with the max(end of treatment (EOT) disposition, Week 12 EOT visit date). During the randomized treatment period, participants will return for scheduled clinic visits. For all related safety analyses, randomized treatment starts with the first administration of randomized, double-blind study drug.

Safety follow-up period

The safety follow-up period begins one day after max(end of treatment (EOT) disposition, Week 12 EOT visit date), and ends on the date of EOS. For participants whose EOS visit is on/before Week 12 and for those who do not take study treatment at all during randomized treatment period, they should not have safety follow-up period calculated, i.e., start date and end date for safety follow-up should be missing.

Randomization period

The randomization period is the combination of the randomized treatment period and the safety follow-up period.

Study exposure

The study exposure means the exposure for 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 end of run in (Visit 30) or randomization visit (Visit 100) whichever occurs last, or the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to the Visit 30/Visit 100, if Visit 30/Visit 100 measurement is missing.

For OBPM, baseline derivation is based on measurements eligible for analysis, as specified in Section 2.12.1

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 170) or the measurement obtained closest to the EOT visit if the measurement at EOT is missing.

Baseline for run-in period

The placebo run-in baseline is defined as the last available measurement prior to or at time of Visit 20. For some parameters, values may be only collected at screening (Visit 1) and then the placebo run-in baseline will be at screening for these parameters.

Unscheduled visit

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

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 or within 28 days after final study drug administration date for pre-mature permanent treatment discontinuation.

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.

Run-in set (RIS) - All participants who have signed the informed consent and received at least one dose of single-blind run-in medication drug.

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 double-blind 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 double-blind 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 of that treatment or the first treatment received if the randomized/assigned treatment was never received.

[redacted]

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 treatment effects and safety profiling on selected endpoints between the subgroups and the overall population.

In general, subgroups will be defined based on baseline information. In this study, since we have a run-in period to ensure that only participants whose BP remains elevated based on 24hr ABPM per the study entry criteria under study conditions while being treated with the run-in study medication (i.e. one injection of placebo matching XXB750) and optimal or maximally tolerated doses of triple background antihypertensive therapy (a thiazide/thiazide-like diuretic, an ACEI/ARB, and a long-acting dihydropyridine CCB) with good compliance before they can enter the randomized treatment period, we have defined baselines for different periods in Section 2.1. Subgroups will be formed using one of these baselines according to their analysis purposes.

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 presented in the corresponding

sections as appropriate. Antihypertensive background medications taken at randomization will be listed by treatment group.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Background & Demographics / Exposure	Efficacy	Safety
Age groups: (<60 vs. ≥60 years)	Screening (derived)	X	X	X
Age groups: (≤median vs. >median)	Screening (derived)	X	X	X
Sex (male/female)	Screening	X	X	X
Region*	Derived (pooled countries or country), using screening data	X	X	X
eGFR (<60 vs. ≥60 mL/min/1.73m2)	Baseline		X	X
Number of background antihypertensive medications (=3 vs >3) **	Derived at randomization		X	X
Race (Asian and others, Black or African American, White)	Screening	X	X	X
Office SBP groups: (≤median vs. >median)	Baseline		X	X
History of diabetes (Yes, No)	Screening			X
Weight (≤ median vs. > median)	Baseline		X	X
[redacted]	Derived			X

* ***America:*** *USA*

Asia: *China, Taiwan, Japan*

Eastern Europe: *Bulgaria, Czechia, Poland, Slovakia*

Western Europe and other: *Austria, France, Germany, Italy, Spain, UK, Netherlands, Australia*

** If a participant takes both an ACEi medication and an ARB medication at randomization, it is counted as 2 for number of AHM.

[redacted]

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 participants enrolled and completed/failed in run-in will be summarized. The reasons for run-in failures will be provided. The analysis set is RIS.

The number and percentage of randomized participants (RAS) 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 (e.g. COVID related) 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 enrolled in run-in and randomized per region and per country will be presented for the RIS 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

For the run-in period, summary statistics will be provided for the total number of participants pertaining to the Run-in set (RIS) for background and demographic characteristics, disease characteristics, and cardiovascular risk factors for the run-in period 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), sitting office systolic blood pressure (in mmHg), sitting office diastolic blood pressure (in mmHg), sitting pulse (in bpm), cyclic GMP (plasma and urine), cyclic GMP (urine)/urine creatinine, renin concentration, aldosterone, renin/aldosterone ratio, NT-proBNP, urine creatinine, eGFR and dose of antihypertensive background therapy of different classes.
- **Categorical variables**: Age group (<60 years vs. ≥60 years; ≤ median vs. > median), sex, race, ethnicity, region, number of background antihypertensive medications (=3 vs >3), history of diabetes (Yes, No), smoking history (Yes, No), current smokers (Yes, No), alcohol use history (0, >0 to 3, >3 drinks consumed per day in average), prior history of coronary heart disease (Yes, No), eGFR (<60 vs. ≥60 mL/min/1.73m2).

BMI will be calculated as weight (kg) / $height^2$ (m^2) from the measured height and weight at Visit 1 (Screening Visit). Mean and SD of pack year will be summarized for current smokers and participants who have smoking history.

Similarly, for the randomized treatment period, summary statistics will be provided by randomized treatment group and overall for the above mentioned parameters in addition to: 24hr mean SBP (in mmHg), mean nighttime systolic blood pressure (in mmHg), mean daytime systolic blood pressure (in mmHg), 24hr mean DBP(in mmHg), mean nighttime DBP (in mmHg), mean daytime DBP (in mmHg), [redacted] standing office systolic blood pressure (in mmHg), standing office diastolic blood pressure (in mmHg).

The summary will be presented for RIS and FAS, separately.

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 database lock. Medical history will be collected at Visit 1 (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 RIS and for the FAS.

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

2.4.1 Study treatment / compliance

XXB750 dose level 1 (30 mg), dose level 2 (60 mg), dose level 3 (120 mg), and dose level 4 (240 mg) or matching placebo will be administered as SC injection every 4 weeks during the Randomized Treatment Period (Baseline, Week 4 and Week 8).

At Visit 100 participants will be randomly assigned to one of the following five treatment arms targeting a final ratio of 1:1:1:1:1 at the end of the trial.

Placebo SC every 4 weeks for x 3 doses.

XXB750 30 mg SC every 4 weeks x 3 doses (dose level 1).

XXB750 60 mg SC every 4 weeks x 3 doses (dose level 2).

XXB750 120 mg SC every 4 weeks x 3 doses (dose level 3).

XXB750 120 mg SC at the Randomization visit followed by 240 mg SC every 4 weeks for 2 injections beginning 4 weeks after the first dose (dose level 4).

Treatment exposure during the randomized treatment period

The duration of the randomized treatment period exposure is defined as below:

(1) for a participant who completes the randomized treatment period, it is defined as the Week 12 (EOT) visit date – first study drug administration date +1;

(2) for a participant who 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.

The duration of overall randomized treatment exposure 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

The frequency of study treatment administrations will be summarized using descriptive statistics (mean, standard deviation, min, Q1, median, Q3, max) by treatment group. Number and percentage of participants will also be summarized by the number of study treatment administrations, by treatment.

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

- Overall patient-years on-treatment = Sum of duration of treatment exposure (in days) from all participants/ 365.25
- Average patient-years on-treatment = Overall patient-years on-treatment / Number of participants randomized to the treatment

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

Number and percentage of participants with permanent treatment discontinuations will be provided by reason for discontinuation. Time from randomization to permanent study treatment discontinuation will be summarized by treatment group by providing Kaplan-Meier estimate of cumulative rate of permanent treatment 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 database lock will be used.

Prior medications are defined as drugs taken prior to the run-in study medication. Any medication given at least once between the first day of run-in study medication and the last day prior to randomization visit will be a **run-in concomitant 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, run-in, 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 randomized treatment period and safety follow-up period will be summarized based on the SAF. The prior and run-in concomitant medications will be summarized based on RIS and SAF, separately.

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.

- Anti-diabetic drugs
    - Insulins
    - Oral anti-diabetic drugs
    - SGLT-2
- Antiarrhythmic agents
- Anticoagulants
- Antiplatelet agents (excl. Aspirin)
- Aspirin
- Diuretics (Loop/non-loop diuretics, summarized by IV/ oral diuretics)
- Other lipid lowering agents
- Statins
- Anti-hypertensive background therapies
    - ACEI/ARB
    - Long-acting dihydropyridine CCB
    - Thiazide/thiazide-like diuretic
    - Beta Blockers
    - Other
- Vasodilators (e.g. Phosphodiesterase-5 (PDE-5) inhibitors, Nitrates)

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 SUBWAY 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).

Antihypertensive background medication

For participants with two or more dose levels on one antihypertensive background therapy, the mean daily dose 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)

For a participant who switches medication within the same class, total number of days for the medications within the same class should add up to the total number of days in respective period

of interest. For a participant who switches medication between ACEi and ARB, total number of days for the medications within ACEi or ARB should add up to the total number of days in respective period of interest.

Please refer to Section 2.1.1 for the definition of each period. The summary for antihypertensive background therapy will be presented for single-blind placebo run-in period using RIS and randomized treatment period using FAS, separately.

2.5 Analysis supporting primary objective(s)

Please refer to study protocol Section 3 for the primary objective and the corresponding estimand and Section 9 for related statistical analyses. The primary analysis will be performed after all participants have completed Week 12 (or discontinued before Week 12). A final analysis will be performed after all participants have completed Week 20 (or discontinued before Week 20). Formal testing of the primary endpoint with full level alpha of 0.025 (1-sided) will be performed at the primary analysis timepoint.

For mean 24hr blood pressure related measurements, if there are multiple valid assessments at a scheduled visit, then:

- Baseline: the latest valid assessment prior to the study treatment at baseline will be used;
- Week 9 or Week 12: the valid assessment closest to the scheduled visit date will be used.

2.5.1 Primary endpoint(s)

The primary efficacy variable is change from baseline in mean 24hr SBP at Week 12.

Missing values at Week 12 will be imputed as described in Section 2.5.3 and Section 2.5.4. In addition to those mentioned in Section 2.5.3 and Section 2.5.4, invalid assessments defined in the 3rd party vendor manual for 24hr BP, which will be flagged, will also be considered as missing data.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective of determination of a dose-response signal and to characterise the dose-response relationship in XXB750 doses compared to placebo will be evaluated using an optimally weighted contrast test following the Multiple Comparison Procedure-Modeling (MCP-MOD) methodology described in Pinheiro et al. 2006 & Pinheiro et al. 2014.

A candidate model set is defined corresponding to the range of the expected mean response in each of the dose groups. The candidate model set is used to generate a set of optimal contrasts vectors to test the hypothesis of a flat dose-response curve, where XXB750 dose-groups and placebo have the same group mean for the change from baseline. Multiple candidate models correspond to multiple contrast vectors, hence a multiple contrast test is performed based on using the maximum contrast test as a test statistic. A critical value for the maximum contrast test statistic is derived based on the multivariate t distribution, with correlation matrix induced by the correlation of the different contrast test statistics.

Test of the dose response signal

The null hypothesis of a flat dose-response relationship for the change from baseline in mean 24-hour ambulatory systolic blood pressure (mean 24 hr SBP) compared to placebo will be tested at a 1-sided significance level of 2.5% against the alternative hypothesis of a dose-response relationship leading to a significant reduction in the mean 24 hr SBP.

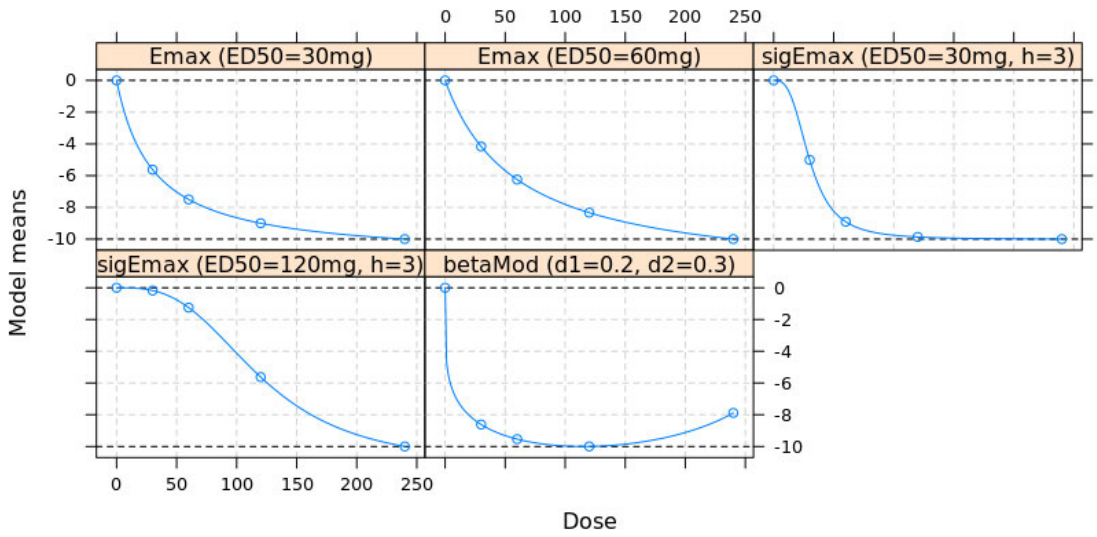
Hence, the following null and alternative hypotheses will be tested:

- $\mathbf{H_{10}}$: there is no dose-response relationship for XXB750 (i.e. the dose response relationship is flat and all XXB750 doses have the same group mean as placebo).
- $\mathbf{H_1}1$: there is a dose-response relationship for XXB750 (i.e. there is more reduction in mean 24hr SBP in XXB750 doses based on the assumed candidate models).

There are five candidate models to capture the shape of the dose-response relationship for XXB750 at Week 12 endpoint, as depicted in Figure 2-1. The candidate models generating the contrast weights are described below:

- Model 1: Emax with ED50 at 30 mg SC q4w
- Model 2: Emax with ED50 at 60 mg SC q4w
- Model 3: Sigmoid Emax with ED50 at 30 mg SC q4w and hill parameter h=3
- Model 4: Sigmoid Emax with ED50 at 120 mg SC q4w and hill parameter h=3
- Model 5: Beta-model with delta1=0.2, delta2=0.3 and scale=288

Figure 2-1 Dose-response curve of candidate models



The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) model with the change from baseline mean 24 hr SBP at Week 12 as response variable, treatment (placebo and XXB750 dose groups), number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia) as factors, and the baseline mean 24 hr SBP as a covariate.

The response variable of the change in mean 24 hr SBP from baseline at Week 12 used in the above ANCOVA model is from an imputed dataset, where missing Week 12 mean 24 hr SBP is imputed using the multiple imputation method as described in Section 2.5.3 and Section 2.5.4. In order to account for the imputation uncertainty, this ANCOVA model will be repeated for each imputed dataset, which results in a set of least squares (LS) mean estimate for all treatment groups and the related covariance matrices. Rubin's rule will be used to combine the multiple sets of LS mean estimates and the related covariance matrices to a single set of LS mean estimates of change of mean 24 hr SBP at Week 12 for all treatment groups and the related covariance matrix.

The optimal contrasts derived from the candidate model sets will be applied to the combined estimated dose means and covariance matrix to obtain t statistics for each candidate model and the common critical value $C_{0.025}$. $C_{0.025}$ is the common critical value derived from the reference multivariate t-distribution with the 5x5 correlation matrix induced by testing the candidate dose response models.

The H_{10} will be rejected and the statistical significance of dose-response in mean 24hr SBP reduction is established if the max(t1, t2,..., t5) $\geq C_{0.025}$.

Test statistics, t1 to t5, with adjusted p-values for each candidate model will be displayed. The analysis is based on participants in FAS.

Model averaging to obtain the dose response

A parametric bootstrap-based model averaging approach will be implemented to obtain the dose response estimates according to the following steps:

1. The parametric bootstrap procedure will draw a sample of changes of mean 24 hr SBP from baseline to Week 12 for all doses (including placebo) from a multivariate normal distribution, with mean and covariance matrix was determined using Rubin's rule, as described earlier. This sample corresponds to the mean response for each dose (including placebo).

2. Model selection will be performed as follows: general dose-response models as specified will be fit to this bootstrap sample, i.e. Emax, Sigmoid Emax and β-model will be fit to mean response data from placebo and XXB750 doses. The best model based on the gAIC criterion will be selected.

3. The dose response estimate will be calculated for each dose group, including placebo, using this selected model. The difference in estimated dose response between each dose and placebo will also be calculated. The target doses of interest will be calculated based on this common model as well.

4. The above procedure (steps 1-3) will be repeated 5,000 times. The mean dose-response estimates by dose group and mean differences of dose-response estimates between each XXB750 dose and placebo, the target doses of interest, as well as their 95% confidence intervals will be calculated based on the quantiles (median, 2.5^{th} and 97.5^{th} percentiles) of these multiple sets of dose-response and target dose estimates generated in step 3.

Dose response results (change with/without placebo substracted and corresponding 95% CI) based on model averaging over all models in the candidate sets as described will be presented.

In addition, estimates (change with/without placebo substracted and corresponding 95% CI) from ANCOVA model mentioned previously using imputed datasets are combined based on Rubin's rule and presented alongside model averaging estimates.

Figure of dose-response shape based on model averaging will also be displayed.

The analysis will be based on all participants in FAS.

2.5.3 Handling of intercurrent events of primary estimand

Intercurrent events for the primary endpoint are defined in Section 1.2.1 and the strategy for handling of intercurrent events in the primary analysis is described below:

1) Discontinuation of study treatment: mean 24hr SBP data collected after discontinuation of study treatment will be used in the analysis (treatment policy strategy).

2) Unforeseen change in the dose of allowed concomitant medications: mean 24hr SBP data collected after unforeseen change in the dose of allowed concomitant medication will be used in the analysis (treatment policy strategy).

3) Receiving prohibited concomitant medication: mean 24hr SBP data collected after receiving prohibited concomitant medication will be used in the analysis (treatment policy strategy).

If missing data for primary endpoint occurs after intercurrent event(s), it will be imputed based on participants with observed endpoint after same type of intercurrent event(s) in the respective treatment group. The assumed treatment effect for participants with missing after intercurrent event(s) is similar as those from the same treatment group who have same type of intercurrent event(s) but have observed data (retrieved dropout). Multiple imputations (MIs) based on the subset of retrieved dropouts (i.e., participants who have intercurrent event(s) but have observed measurements after intercurrent event(s)) are generated, resulting in multiple imputed datasets (100). The imputation model with fully conditional method (FCS) will include longitudinal sequence of mean 24hr SBP data collected at baseline, Week 9 and Week 12 visits, number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia), imputing for each treatment group separately. SAS proc MI FCS statement is used to impute missing values in the following sequence: factor variables in the increasing order of missing frequency, the mean 24hr SBP at baseline, Week 9 and Week 12.

If there is no or very limited participants with observed endpoint after intercurrent event(s) in the respective treatment group, then the missing primary endpoint will be imputed based on the respective treatment group combined with lower dose group(s). If there are still very limited participants with observed endpoint after intercurrent event(s), then missing will be imputed based on those with observed endpoint in the placebo group. Copy reference (CR) will be applied to imputation then.

2.5.4 Handling of missing values not related to intercurrent event

Missing data for the primary endpoint will be imputed using a multiple imputation approach assuming that missingness mechanism can be retrieved from observed data (missing at random (MAR)). MIs (100) of missing Week 12 mean 24hr SBP under MAR assumption are generated, resulting in multiple imputed datasets (100). The imputation model with fully conditional

method (FCS) will include longitudinal sequence of mean 24hr SBP data collected at baseline, Week 9 and Week 12 visits, number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia), imputing for each treatment group separately. SAS proc MI FCS statement is used to impute missing values in the following sequence: factor variables in the increasing order of missing frequency, the mean 24hr SBP at baseline, Week 9 and Week 12.

2.5.5 Multiplicity adjustment

Please refer to Section 2.5.2 for primary analysis of MCP-MOD for multiplicity adjustment with respect to testing for a dose response signal across multiple candidate shapes. The secondary hypotheses included in the order of hierarchical testing procedure are: (1) evaluate and demonstrate treatment effect of highest XXB750 dose group versus placebo in reducing the mean 24hr SBP from baseline to Week 12, (2) evaluate and demonstrate treatment effect of highest XXB750 dose group versus placebo in reducing the average of mean 24hr SBP from baseline to Week 9 and Week 12, and (3) dose-response relationship in terms of proportions of participants achieving BP control among XXB750 dose groups and placebo. The secondary hypotheses will be tested in the order described above and statistical inference will be made only if the primary hypothesis is rejected.

2.5.6 Sensitivity analyses

The primary analysis using retrieved dropouts or missing at random (MAR) approaches for missing values after early treatment/study discontinuation due to adverse event(s) or death may assign values in the XXB750 dose groups that are too favorable. Therefore, a sensitivity analysis will be performed where missing values after early treatment/study discontinuation due to AE or death will be multiply imputed based on results from similar participants in the placebo group. Placebo multiple imputation method will be performed, where participants randomized to XXB750 dose groups are assumed to be similar to placebo treated participants after drop-out. mIs based on the subset of participants in placebo arm are generated, resulting in multiple imputed datasets (100). The imputation model with fully conditional method (FCS) will include longitudinal sequence of mean 24hr SBP data collected at baseline, Week 9 and Week 12 visits, number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia). SAS proc MI FCS statement is used to impute missing values in the following sequence: factor variables in the increasing order of missing frequency, the mean 24hr SBP at baseline, Week 9 and Week 12.

2.5.7 Supplementary analyses

The supportive analyses for the primary analysis results are listed below:

1. Results based on the single best dose response model fit will also be reported.
2. The mixed model for repeated measures (MMRM) analysis of covariance (ANCOVA) with treatment, number of background antihypertensive medications (=3 vs >3), region stratification factor (with Japan combined into Asia), visit (Week 9 or Week 12), and treatment-by-visit as factors, and baseline mean 24hr SBP as a covariate, with a common unstructured covariance matrix among visits will be used. Treatment comparisons at Week

12 will be provided. The analysis will be based on all available data up to Week 12 in the FAS and based on likelihood method with an assumption of missing at random for missing data.

3. In addition to treatment policy strategy to handle the intercurrent events in the primary analysis, a supplemental analysis based on a hypothetical strategy will be also used to handle the intercurrent events. This strategy assumes that premature discontinuations of study treatment, change in the dose of allowed concomitant medication, receiving prohibited concomitant medication or lost to follow-up/discontinue study would not have occurred in the participants. This analysis uses partial data available up to the occurrence of the intercurrent events, and missing data after the intercurrent events will be imputed as based on the pattern of other participants who do not have intercurrent events (missing at random). The imputation steps are same as described in Section 2.5.4 and the newly imputed data will be used in the analysis as described in Section 2.5.2.
4. Analysis based on the while on-treatment strategy to handle the intercurrent of premature discontinuations of study treatment will be performed. This analysis uses the last on-treatment data for efficacy endpoint defined in Section 2.1.1 as the Week 12 assessment and repeat the analysis described in Section 2.5.2. This analysis will only be performed when premature treatment discontinuation occurs in more than 10% of FAS participants.
5. 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. If convergence issue arises, then the subgroup category will be combined with another one for subgroups with more than two categories. Otherwise, subgroup analysis will not be performed. A forest plot will be provided. Please see Section 2.2.1 for subgroup details.

Summary statistics for mean 24hr SBP and change from baseline will be summarized by treatment group for observed and imputed values. Figures will be produced to visually show the observed and the imputed mean changes by visit over 12 weeks randomized treatment period for each treatment group. FAS will be used for the analyses.

2.6 Analysis supporting secondary objectives

The secondary efficacy endpoints are described in Section 2.6.1 and are part of the hierarchical testingstrategy. Analyses related to safety endpoints are described in Section 2.7.

Please refer to Section 2.5 for handling of multiple valid mean 24hr blood pressure assessments at a scheduled visit.

2.6.1 Secondary endpoint(s)

There are three efficacy secondary objectives:

1. Between treatment comparison of XXB750 highest dose versus placebo in reducing the mean 24hr SBP from baseline at Week 12.
2. Between treatment comparison of XXB750 highest dose versus placebo in reducing the average of the mean 24hr SBP from baseline at Week 9 and at Week 12.

3. To determine a dose-response signal and to characterize the dose-response relationship in XXB750 doses and placebo with respect to the proportion of participants achieving BP control at week 12.

2.6.2 Statistical hypothesis, model, and method of analysis

The efficacy variable in secondary objective 1 is the change from baseline at Week 12 in the mean 24hr SBP and will be analyzed using a repeated measures ANCOVA model with treatment, number of background antihypertensive medications (=3 vs >3), region stratification factor (with Japan combined into Asia), visit (Week 9 or Week 12), and treatment-by-visit as factors, and baseline mean 24hr SBP as a covariate, with a common unstructured covariance matrix among visits. The analysis time point for the treatment comparisons is at Week 12. Please refer to Section 1.2.2 and Section 2.5.3 for the intercurrent events and its handling strategy and Section 2.5.4 for handling missing data not related to intercurrent event. The analysis will be run on each of the imputed datasets as described in Section 2.5.2. Overall results, including adjusted mean change at Week 12 within each treatment arm, the difference in mean change at Week 12 between XXB750 dose arm and placebo, its 95% confidence interval (CI), are obtained by applying Rubin's rules on the estimates obtained from imputed datasets.

If the mentioned model above does not converge, the model will be modified by replacing the common unstructured covariance matrix with a compound symmetric matrix between treatment groups and provide the mentioned estimates above.

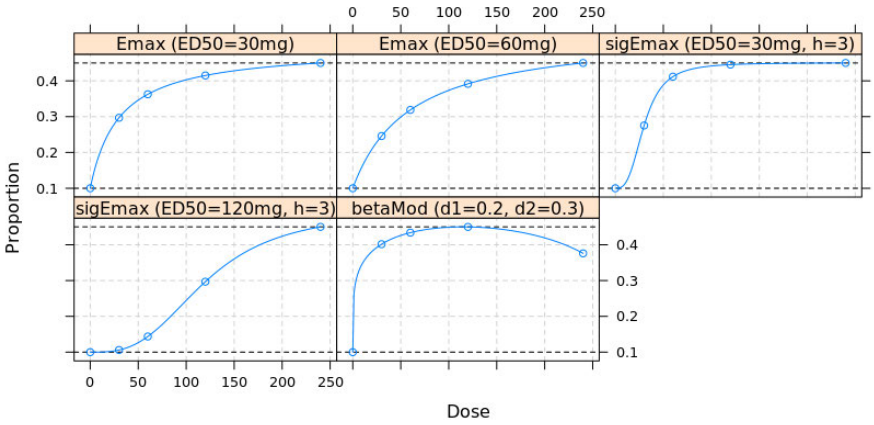
The efficacy variable in secondary objective 2 is the average change from baseline at Week 9 and Week 12 in the mean 24hr SBP and will be analyzed using an analysis of covariance (ANCOVA) model including treatment, number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia) as fixed-effect factors and baseline mean 24hr SBP as covariate. Please refer to Section 1.2.2 and Section 2.5.3 for the intercurrent events and its handling strategy and Section 2.5.4 for handling missing data not related to intercurrent event. The analysis will be run on each of the imputed datasets as described in Section 2.5.2. Overall results, including adjusted mean change at Week 12 within each treatment arm, the difference in mean change at Week 12 between XXB750 dose arm and placebo, its 95% confidence interval (CI), are obtained by applying Rubin's rules on the estimates obtained from imputed datasets.

The efficacy variable in secondary objective 3 is the achievement of BP control by ABPM (i.e., mean 24hr SBP <130 mmHg and 24-hour mean ambulatory diastolic blood pressure (mean 24hr DBP) <80 mmHg) at Week 12.

There are five candidate models to capture the shape of the dose-response relationship for XXB750 with respect to the proportion of participants with BP control at Week 12, as depicted in Figure 2-2. The candidate models generating the contrast weights are described below:

- Model 1: Emax with ED50 at 30 mg SC q4w
- Model 2: Emax with ED50 at 60 mg SC q4w
- Model 3: sigmoid Emax with ED50 at 30 mg SC q4w and hill parameter h=3
- Model 4: sigmoid Emax with ED50 at 120 mg SC q4w and hill parameter h=3
- Model 5: Beta-model with delta1=0.2, delta2=0.3 and scale=288

Figure 2-2 Dose-response curve of candidate models for proportion of participants with BP control



The analysis method of generalized MCP-Mod for binary data is similar as the primary analysis described in Section 2.5.2, but with the response for participant i in treatment k, Y_{ki}, follows a Bernoulli(p_k), where p_k is the probability of participants achieving BP control in treatment group k. And logit(p_k) will be estimated using a logistic regression with treatment (placebo and XXB750 dose groups), number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia) as factors, and the baseline mean 24hr SBP and mean 24hr DBP as covariates. The intercurrent events and corresponding handling strategy are described in Section 1.2.2, and the handling of missing not related to intercurrent events in Section 2.5.2 and Section 2.5.4 so that achievement of BP control will be based on imputed mean 24hr SBP and mean 24hr DBP at Week 12. Participants with intercurrent events will be imputed as not having BP control in the analysis.

Test statistics, t1 to t5, with adjusted p-value for each candidate model will be displayed. The analysis is based on participants in FAS.

Dose response results (proportion with/without placebo subtracted and corresponding 95% CI) based on model averaging over all models in the candidate sets as described in Section 2.5.2 will be presented. In addition, a logistic model will be fitted to the response variable at Week 12 based on imputed datasets with treatment (placebo and XXB750 dose groups), number of background antihypertensive medications (=3 vs >3), and region stratification factor (with Japan combined into Asia) as factors, and the baseline mean 24hr SBP and mean 24hr DBP as covariates. Estimates (proportion with/without placebo subtracted and corresponding 95% CI) from logistic model are combined based on Rubin's rule and presented alongside model averaging estimates. Figure of dose-response shape based on model averaging will also be displayed.

Number and percentage of participants with ambulatory BP control will be summarized by treatment group for observed values. Figures will be produced to visually show the observed ambulatory BP control by visit over 12 weeks randomized treatment period for each treatment group.

The analysis will be based on all participants in FAS.

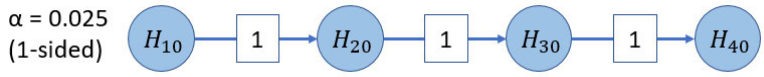
The statistical testing procedure described below will be carried out for the multiple treatment comparisons in the primary and secondary efficacy objectives to ensure that the overall significance level for the multiple hypotheses to be tested is controlled at the one-sided 0.025 level (i.e. two-sided 0.05).

The testing hypotheses associated with secondary efficacy objectives are described below:

- **H_{20}:** No difference in the change of mean 24hr SBP from baseline at Week 12 between highest XXB750 dose versus placebo.
- **H_{30}:** No difference in average change of mean 24hr SBP from baseline at Week 9 and at Week 12 between highest XXB750 dose versus placebo.
- **H_{40}:** There is no dose-response relationship for XXB750 (i.e. the dose response relationship is flat) in terms of proportions of participants achieving blood pressure control at Week 12.

The testing procedure is to be based on the sequentially rejective multiple test procedure pre-specified in controlling overall type I error (Bretz et al 2009) and H_{10} of the primary hypothesis will be initially test first at the one-sided 0.025 significance level. If the primary hypothesis can be rejected, the relocation of its significance level with a weight of 1 to the other hypotheses is specified in Figure 2-3 below. The sequentially rejective multiple test procedure is completed until no more hypothesis can be further rejected.

Figure 2-3 Sequentially rejective multiple testing procedure



2.6.3 Handling of intercurrent events

For Ambulatory BP control, participants with intercurrent events will be imputed as not having BP control. Refer to Section 2.5.3 for other secondary estimands intercurrent event handling.

2.6.4 Handling of missing values not related to intercurrent event

Refer to Section 2.5.4

2.6.5 Sensitivity analyses

The secondary analysis using retrieved dropouts or missing at random (MAR) approaches for missing values after early treatment/study discontinuation due to adverse event(s) or death may assign values in the XXB750 dose groups that are too favorable. Therefore, a sensitivity analysis will be performed where missing values after early treatment/study discontinuation due to AE or death will be multiply imputed based on results from similar participants in the placebo group. Placebo multiple imputation method described in Section 2.5.6 will be performed, where participants randomized to XXB750 dose groups are assumed to be similar to placebo treated participants after drop-out.

2.6.6 Supplementary analyses

The supportive analyses for the secondary analysis results are listed below:

1. Analysis based on the while on-treatment strategy to handle the intercurrent of premature discontinuations of study treatment will be performed. This analysis uses the last on-treatment data defined in Section 2.1.1 as the Week 12 assessment and repeat the analysis described in Section 2.6.2. This analysis will only be performed when premature treatment discontinuation occurs in more than 10% of FAS participants.
2. Subgroup analyses (region and race excluded due to small sample size) will be performed for the first secondary efficacy analysis. The analysis will be done using the analysis specified in Section 2.6.2 at individual subgroup level separately. If convergence issue arises, then the subgroup category will be combined with another one for subgroups with more than two categories. Otherwise, subgroup analysis will not be performed. Please see Section 2.2.1 for subgroup details.

2.7 Safety analyses

For all safety analyses, the safety 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)
- Adverse events of special interest (AESI): Serious hypotension, Serious hypersensitivity reactions, and Serious injection site reactions, Severe tachycardia, Severe acute bradycardia, Serious presyncope/syncope
- Safety topics that are potential risks: Hypotension, Hypersensitivity reactions, Injection site reactions, Tachycardia, Bradycardia, [redacted]
- 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 by the specific treatment period as described in Table 2-2, i.e., AEs that occurred in one of the following periods: (1) run-in period, (2) randomized treatment period , (3) safety follow-up period, and (4) randomization period (randomized treatment period and safety follow-up period).

The analysis will consider all participants in the Run-in set (RIS) for AEs reported during the run-in period and Safety set (SAF) for reported AEs during the randomization period, randomized treatment period and safety follow-up period.

Table 2-2 Allocation of AEs (randomized treatment period and safety follow-up period listed separately from randomization period)

Screening visit (V1)	Placebo run-in (V20-V30)	Randomized treatment (V100-V170)	Safety follow-up (V180-V1999)	Phase AE to be reported in
		* Randomization period		
X				Reported by site from informed consent;
	X			Report AE in Placebo run-in
	X	X2		Report as two separate AEs: One with onset date X for Placebo run-in and one with onset date X2 for Randomized treatment (also randomization period);
	X		X2	Report as two separate AEs: One with onset date X for Placebo run-in and one with onset date X2 for Safety follow-up (also randomization period)
	X	X2, X3		Report as two separate AEs: One with onset date X for Placebo run-in and one for Randomized treatment period (* Randomization period) with corresponding onset date and severity depending on analysis
	X	X2 X3		Report as three separate AEs: One with onset date X for Placebo run-in, One with onset date X2 for Randomized treatment, and one with onset date X3 for Safety follow-up; * One for randomization period with corresponding onset date and severity depending on analysis
	X	X2, X3		Report as two separate AEs: One with onset date X for Placebo run-in and one for Safety follow-up (* Randomization period) with corresponding onset date and severity depending on analysis
	X	Y		Report as two separate AEs: One with onset date X for Placebo run-in and one with onset date Y for Randomized treatment (also randomization period)
	X		Y	Report as two separate AEs: One with onset date X for Placebo run-in and one with onset date Y for Safety follow-up (also randomization period)
	X	Y, Y2		Report as two separate AEs: One with onset date X for Placebo run-in

Screening visit (V1)	Placebo run-in (V20-V30)	Randomized treatment (V100-V170)	Safety follow-up (V180-V1999)	Phase AE to be reported in
		* Randomization period		
				and one for Randomized treatment (* Randomization period) with corresponding onset date and severity depending on analysis;
	X	Y	Y2	Report as three separate AEs: One with onset date X for Placebo run-in, one with onset date Y for Randomized treatment, and one with onset date Y2 for Safety follow-up; * One event for Randomization period with corresponding onset date and severity depending on analysis
	X		Y, Y2	Report as two separate AEs: One with onset date X for Placebo run-in and one for Safety follow-up (* Randomization period) with corresponding onset date and severity depending on analysis;
	X	Y Z		Report as three separate AEs: One with onset date X for Placebo run-in, one with onset date Y for Randomized treatment, and one with onset date Z for Safety follow-up; * One event with onset date Y for Randomization period
	X	Y Z, Z2		Report as three separate AEs: One with onset date X for Placebo run-in, one with onset date Y for Randomized treatment, and one for Safety follow-up with corresponding onset date and severity depending on analysis; * One event with onset date Y for Randomization period
		X		Report one AE X in Randomized treatment period (* Randomization period)
		X, X2		Report as one AE for Randomized treatment (* Randomization period) with corresponding onset date and severity depending on analysis
		X	X2	Report as two separate AEs: One with onset date X for Randomized treatment and one with onset date X2 for Safety follow-up;

Screening visit (V1)	Placebo run-in (V20-V30)	Randomized treatment (V100-V170)	Safety follow-up (V180-V1999)	Phase AE to be reported in
		* Randomization period		
				* One event for Randomization period with corresponding onset date and severity depending on analysis
		X	Y	Report as two separate AEs: One with onset date X for Randomized treatment and one with onset date Y for Safety follow-up; * One event with onset date X for Randomization period
		X	Y, Y2	Report as two separate AEs: One with onset date X for Randomized treatment and one for Safety follow-up with corresponding onset date and severity depending on analysis; * One event with onset date X for Randomization period
			X	Report AE X in safety follow-up period (*Randomization period)
			X, X2	Report as one AE: One for Safety follow-up (*Randomization period) with corresponding onset date and severity depending on analysis
X stands for onset date of AE. Y is the same PT which onsets after the end date of X. Similarly, Z is the same PT which onsets after the end date of Y. X2/Y2/Z2 stands for the same PT but with an increased severity over X/Y/Z respectively X3 stands for the same PT but with an increased severity over X2.				

Treatment emergent adverse events (new or worsened) during a specific period (run-in, randomization, randomized treatment or safety follow-up) are defined as any recorded AE with its start date (recorded or imputed) later than or equal to the start date of the specific period as defined below:

1) Run-in period: injection date of single-blinded placebo.
2) Randomization period: first date of study treatment injection.
3) Randomized treatment period: first date of study treatment injection.
4) Safety follow-up: 1+ max(end of treatment (EOT) disposition, Week 12 EOT visit date)

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 database lock will be used for reporting the study.

Within each reporting period (run-in period, randomized treatment period, safety follow-up period or randomization period, see Table 2-2), the following rules are applicable. If a participant reports more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reports 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, which will be performed for the randomization period and other periods as appropriate, will include all AEs with onset date during the defined 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.

Separate summaries, for each reporting 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 separately in addition to the above analysis. Please see Section 2.7.1.1 for details.

2.7.1.1 Adverse events of special interest (AESI) 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, pertaining 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 "summarize") in the Case Retrieval Strategy (eCRS). The latest version of the eCRS at the time of database lock will be used.

The following standard analyses will be provided for all the listed safety topics ([redacted]):

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

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 pre-defined subgroups (as per Table 2-1)
Tachycardia	ADR Tachycardia [ADR_STD] (NMQ)	Distribution of TEAE by pre-defined subgroups (as per Table 2-1)
Bradycardia	ADR Heart rate decreased [ADR_STD] (NMQ)	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 the following subgroups: a. age <60 vs. ≥60 years b. age ≤median vs. > median c. sex d. region e. race f. history of diabetes g. weight ≤median vs. > median h. [redacted]
Hypersensitivity reactions	(Anaphylactic/anaphylactoid shock conditions (SMQ) OR Anaphylactic reaction (SMQ) OR Hypersensitivity other than administration site reactions [XXB750] (NMQ))	Distribution of TEAE by the following subgroups: a. age <60 vs. ≥60 years b. age ≤median vs. > median c. sex d. region

Safety topic	Definitions	Analysis and additional criteria for characterizing selected AEs
		e. race f. history of diabetes g. weight ≤median vs. > median h. [redacted]
[redacted]	All serious and non-serious TEAE in participants with at least one positive [redacted]	Distribution of TEAE by [redacted] (as per Table 2-1)
Serious hypotension	Only SAE: ADR Hypotension [ADR_STD] (NMQ)	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 the following subgroups: a. age <60 vs. ≥60 years b. age ≤median vs. > median c. sex d. region e. race f. history of diabetes g. weight ≤median vs. > median h. [redacted]
Serious injection site reactions	Only SAE: ADR Injection site reaction [ADR_STD] (NMQ)	Distribution of TEAE by the following subgroups: a. age <60 vs. ≥60 years b. age ≤median vs. > median c. sex d. region e. race f. history of diabetes g. weight ≤median vs. > median h. [redacted]
Severe tachycardia	Only severe AE: ADR Tachycardia [ADR_STD] (NMQ)	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 pre-defined subgroups (as per Table 2-1)
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 pre-defined subgroups (as per Table 2-1)

2.7.2 Deaths

Participants that died during the study period will be reported separately for run-in period, randomization period, randomized treatment period and safety follow-up. 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 while deaths during the run-in period will be reported based on participants in the Run-in set (RIS).

2.7.3 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 both run-in and 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 randomized treatment period and other periods as appropriate.

Table 2-4 Clinically notable laboratory values and vital signs

Parameter	Clinical 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
White blood cell count	value > 100,000 cells/mm^3 (unit equivaleng to 10E6/L) value < 2000 cells/mm^3 (unit equivaleng to 10E6/L)
Platelet count	value < 50,000 platelets/mm^3 (unit equivaleng to 10E6/L)
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

Parameter	Clinical notable criteria
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
Blood pressure increase (mean measurement)	
Mean sitting office SBP (mmHg)	> 180 mmHg
Mean sitting office DBP (mmHg)	> 110 mmHg
Blood pressure decrease (mean measurement)	
1. Mean sitting office SBP (mmHg)	< 110 mmHg
2. Mean sitting office DBP (mmHg)	< 70 mmHg
3. Criteria 1 OR 2	Participants meeting either criterion 1 OR criterion 2
4. ABPM day time mean SBP (mmHg)	< 110 mmHg
5. ABPM day time mean DBP (mmHg)	< 70 mmHg
6. Criteria 4 OR 5	Participants meeting either criterion 4 OR criterion 5
7. ABPM night time mean SBP (mmHg)	< 90 mmHg
8. ABPM night time mean DBP (mmHg)	< 55 mmHg
9. Criteria 7 OR 8	Participants meeting either criterion 7 OR criterion 8
10. ABPM mean 24 hours SBP (mmHg)	< 105 mmHg
11. ABPM mean 24 hours DBP (mmHg)	< 65 mmHg
12. Criteria 10 OR 11	Participants meeting either criterion 10 OR criterion 11
13. Any one criteria	Participants meeting any one of the criteria 1 to 12
Heart rate* increase	
Pulse (bpm)	> 100
Heart rate* decrease	
Pulse (bpm)	1. < 60
	2. < 50
Orthostatic hypotension	

Parameter	Clinical notable criteria
1. Systolic blood pressure (mm Hg) 1 minute after standing	≥ 20 mmHg reduction from corresponding mean measurement in sitting position
2. Diastolic blood pressure (mm Hg) 1 minute after standing	≥ 10 mmHg reduction from corresponding mean measurement in sitting position
3. Systolic blood pressure (mm Hg) 3 minutes after standing	≥ 20 mmHg reduction from corresponding mean measurement in sitting position
4. Diastolic blood pressure (mm Hg) 3 minutes after standing	≥10 mmHg reduction from corresponding mean measurement in sitting position
5. Criteria 1 OR 2	Participants meeting either criterion 1 OR criterion 2
6. Criteria 3 OR 4	Participants meeting either criterion 3 OR criterion 4
7. Criteria 5 OR 6	Participants meeting either criterion 5 OR criterion 6
Liver function tests	
ALT (SGPT) OR AST (SGOT)	1. value > 3 x ULN 2. value > 5 x ULN 3. value > 8 x ULN 4. value > 10 x ULN 5. value > 20 x ULN
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 H''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))

Parameter	Clinical notable criteria
Renal function tests	
eGFR	1. > 25% decrease
	2. > 40% decrease
	3. > 50% decrease
	4. > 30 mL/min/1.73m^2 decrease
	5. Participants meeting any of the criteria 1 to 4 above
Creatinine	1. ≥ 0.3 mg/dL increase
	2. ≥1.5 to ≤ 1.9 x baseline
	3. >1.9 to ≤ 2.9 x baseline
	4. > 2.9 x baseline
	5. ≥ 4.0 mg/dL
	6. Participants meeting either criterion 1 OR 2 above
	7. Participants meeting either criterion 4 OR 5 above
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; ABPM: ambulatory blood pressure measurement; Increases and decreases of parameters as mentioned in the table are from baseline; * Heart Rate: increase or decrease is based on 24hr mean measurement of ABPM.

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 both run-in period, randomized treatment period and 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.

For the rate change in eGFR during randomized treatment period, the eGFR slope will be estimated from a repeated measures ANCOVA model including treatment, number of background antihypertensive medications (=3 vs >3), region, time (when the eGFR is assessed in weeks), and treatment-by-time as fixed effects with random intercept and slope (time) and a common unstructured covariance. The least-square means of slopes for within and between treatment groups, and the corresponding two-sided 95% confidence intervals will be provided.

2.7.4 Other safety data

2.7.4.1 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 randomized treatment period and 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 was not performed/is not available, respectively for that participant, where "Yes" is defined as any one of the abnormality interpretation is checked, "No" is defined as ECG evaluation is performed and none of the abnormality interpretation is reported and "Missing" if ECG evaluation is not performed at the visit.

The analysis will be based on SAF.

2.7.4.2 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 randomized treatment period and 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 of 24 hour blood pressure and heart rate values will be summarized by visit (mean, Q1, median, Q3, standard deviation, min, max) for randomized treatment period and for randomization period.

[redacted]

[redacted]

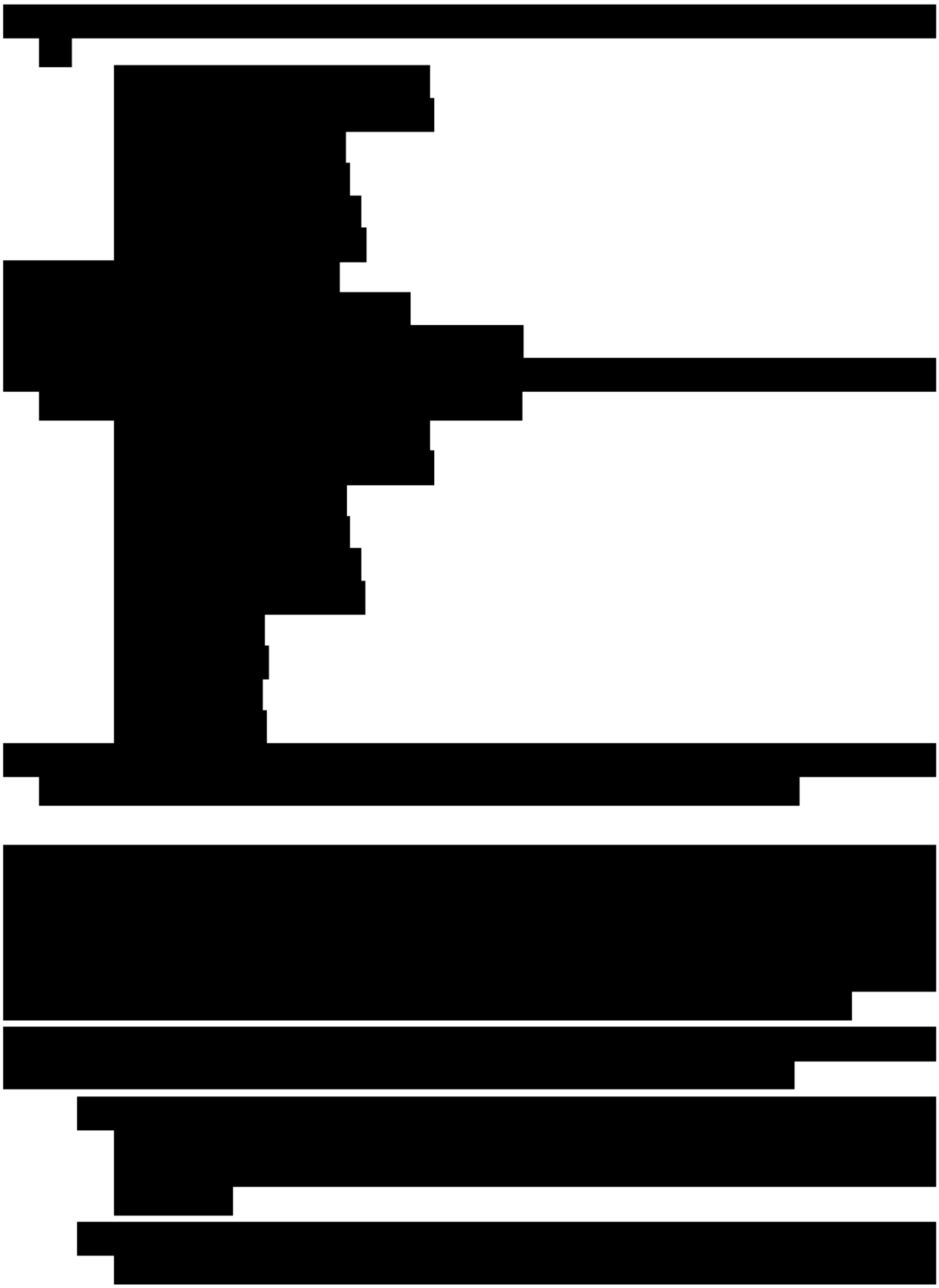
[redacted]

[redacted]

2.10 Patient-reported outcomes

Not applicable.

[redacted]



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2.13 Interim analysis

One interim safety analysis will be conducted when approximately first 40 participants complete at least 5 weeks of double-blind treatment. Regular safety data monitoring is planned as specified in Section 4.6 of protocol. No alpha adjustment will be made for the interim safety analysis and safety data monitoring. Interim safety analysis and safety data monitoring will be performed by an independent statistician who will not be involved in the trial conduct. The results will be reviewed by the independent DMC.

The primary analysis will be performed after all participants have completed Week 12 (or discontinued prior to Week 12). A final analysis will be performed after all participants have completed Week 20 (or discontinued prior to Week 20). Formal testing of the primary endpoint with full level alpha of 0.025 (1-sided) will be performed at the primary analysis timepoint.

3 Sample size calculation

3.1 Primary endpoint(s)

The study is planned to randomize 170 participants including approximately 10% lost to follow-up, allocated in the ratio of 1:1:1:1:1 to placebo, XXB750 30 mg SC q4w, 60 mg SC q4w, XXB750 120 mg SC q4w and XXB750 240 mg SC q4w, respectively.

Assuming a common standard deviation of 12 mmHg for mean 24hr SBP change from baseline and a one-sided 2.5% significance level (with adjustments for multiple comparisons using MCP-MOD), a sample size of 150 participants (30 each in placebo, XXB750 30 SC q4w, XXB750 60 mg SC q4W, and XXB750 120 mg SC q4w, and XXB750 240 mg SC q4w) will provide a minimum power of 92% if the underlying true maximum mean 24hr SBP reduction on XXB750 vs placebo is 10 mmHg.

3.2 Secondary endpoint(s)

Assuming a common standard deviation of 12 mmHg for mean 24hr SBP change from baseline and a one-sided 2.5% significance level, a sample size of 30 participants in placebo and in XXB750 highest dose, respectively, will provide approximately 89% power if the true mean 24hr SBP reduction on XXB750 vs placebo is 10 mmHg.

Secondly, same assumption as first secondary endpoint is used for the average change from baseline in mean 24hr SBP at Week 9 and at Week 12 and a one-sided 2.5% significance level , a sample size of 30 participants in placebo and in XXB750 highest dose, respectively, will provide approximately 89% power if the true mean 24hr SBP reduction on XXB750 vs placebo is 10 mmHg.

Lastly, assuming a one-sided 2.5% significance level (with adjustments for multiple comparisons using MCP-MOD), a sample size of 150 participants (30 each in placebo, XXB750 30 mg SC q4w, XXB750 60 mg SC q4W, XXB750 120 mg SC q4w, and in XXB750 240 mg

SC q4w) will provide a minimum power of 76% if the underlying true BP control achievement in placebo and XXB750 doses range from 10% to 45%, respectively.

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

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 AGB global standard approach. Details will be provided in the study 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 ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications (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 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;
	Not receiving single-blind run-in study medication
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
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

6 References

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