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Novartis Research and Development

Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CXXB750B12201/ NCT05562934

Version Number: 02 (Clean)

Compound: XXB750

Brief Title: An efficacy, safety, tolerability and dose finding study of XXB750 in resistant hypertension patients

Study Phase: II

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): EUDRACT: 2021-005738-41; IND: 147562

Approval Date: 05-Mar-2024 (content final)

Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022

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Amendment 2 (05-Mar-2024)

Amendment rationale

The protocol amendment is issued for the following reasons:

- To clarify the treatment unblinding during primary endpoint and safety analysis, when all participants have completed week 12 or discontinued from the study. During primary analysis, some study team members will be unblinded to the double blinded treatment assignment. However, safety follow up will still be ongoing throughout this period. The amendment provides clarification around the unblinding process.
- Stage 2 of the study will be eliminated as the primary purpose of this study is to evaluate the dose response of different doses of XXB750 vs. placebo and evaluation against an active comparator is out of the scope for the stated objective of the study.
- Updated model averaging method in Section 9.3.2 using bootstrapping samples instead of using imputed datasets because it is a more statistically sound and accepted method.
- Miscellaneous administrative clarifications and the correction of typographical errors throughout the protocol.
- [redacted]

Changes made in the amendment are not expected to have any impact on the target population of the study, the main study objectives, or the scientific integrity of the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underline for insertions.

List of major changes to protocol are below:

- Section 1 Protocol summary updated. Removal of mention of optimal XXB750 dose comparison to 50 mg spironolactone dose and Stage 2 of protocol.
- Section 2.2 Study design update. The “Stage 2 of the protocol” section is removed as it will not be conducted
- [redacted]
- Section 4.1 The "Stage 2 of the protocol” section is removed
- Section 4.6 Adaptive design feature and introduction of Stage 2 of the study is removed.
- Section 6.3.2 Treatment blinding updated to reflect the unblinding plan for the primary analysis.
- Table 6-3 Blinding and unblinding plan - updated to reflect the unblinding plan.
- Section 8.6.2 of the protocol: Wording is incorporated in this section to alert the investigators that all instances of Drug Induced Liver Injury (DILI) are to be reported as SAEs as per the guidance of regulatory authorities.

- Section 9.3.2 Statistical model, hypothesis, and method of analysis; under part "model averaging to obtain the dose response in" is updated to using bootstrapping samples instead of using datasets.
- [redacted]
- Section 9.5.2: Statistical analysis method for proportion of participants achieving BP response is added.
- Appendix 3; Table 10-2: Clarification provided about definition of clinically notable blood chemistry abnormalities in participants with elevated laboratory values at baseline.
- Appendix 5; Table 10-3: Footnote added with respect to DILI reporting requirements

IRBs/IE IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol do not require IRB/IEC approval prior to implementation as it will not have any impact on the conduct of the study and participants.

The changes herein do NOT affect the Informed Consent.

Amendment 1 (07-Jun-2023)

Amendment rationale

The main aim of the CXXB750B12201 study is evaluate the safety and efficacy of various doses of XXB750 in patients with treatment resistant hypertension (rHTN) as defined by various major clinical practice guidelines across the world. Accordingly, the inclusion/ exclusion criteria were chosen with the intent to identify and recruit patients that are reflective of the commonly accepted definition of rHTN, i.e., patients who remain hypertensive despite being treated with maximally tolerated doses of the first three lines of antihypertensive medication classes recommended by international guidelines, specifically a thiazide/thiazide-like diuretic, an ACEI or an ARB, and a long acting dihydropyridine CCB. The protocol also stipulates that patients should be treated with maximally tolerated doses of those medication classes, but also requires specific minimum doses of triple background antihypertensive medications that the patients must be taking to qualify for enrollment. It also disallows use of any other medications for the purpose of treating hypertension, including beta blockers.

However, international guidelines specifically refer to optimal and maximally or best-tolerated doses. Further, experience to date suggests that the incorporation of guideline directed medical therapy into clinical practice varies considerably across regions. Given the subtle differences in local guidelines, it became apparent that clinical practice in some regions is not reflective of some of the stringent criteria set out in the study protocol. As many of the patients have significant other cardiovascular morbidities such as ischemic heart disease, beta blockers are commonly prescribed in these patients and in most instances, these are chosen as drug of choice to serve both the purposes of treating hypertension as well as the comorbidities. Feedback from participating investigators suggests that the doses of background antihypertensive medications considered optimal in individual patients and patient groups differ amongst regions.

A universal protocol mandate requiring all patients to be on a set minimum dose of background antihypertensive medications is proving to be unpragmatic and inconsistent with global clinical practice.

Therefore, in order to ensure enrollment of patients with relevant clinical characteristics into the study and taking into consideration the clinical profile of patients with rHTN across several countries, an amendment to some of the inclusion/exclusion criteria are made in the protocol. These changes will allow for investigators' best clinical judgement taking into account participants' comorbidities in drug and dose selection across countries and yet remain consistent with various international guideline recommendations. Recruitment in study CXXB50B12201 began on 08-Nov-2022 and as of 23-May-2023 39 patients were randomized in the study. None of the changes made in the amendment are expected to have a major impact on the target population intended for the study, the analysis of the objectives, or the scientific integrity of the study. Key changes to the protocol are summarized in the 'changes to the protocol' section.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

List of major changes to protocol are below:

- Section 1.1 Summary section updated to reflect all the major changes of this protocol amendment.
- Table 1-2 Footnote #2 updated to add a pregnancy test assessment in WoCBP prior to randomization.
- Table 1-2 - Screening: updated msSBP from 145 to 140, changed to optimal 3 or 4 antihypertensive drugs; single blind period: changed to optimal or maximum tolerated dose of 3 or 4 antihypertensive drugs.
- Section 3 Multiple updates as the second secondary objective is replaced with "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."
- Section 4.1 and Section 4.2
- Multiple changes to match with the updated inclusion/exclusion criteria
  - Clarified the need to witness intake of the background medication during the visits as well as when to take the medicine during the visits where ABPM is attached.
  - Removed time requirement for rescreening.
- Section 4.1Corrected the error in the total number of enrollment in Group 2 (68 instead of 136).
- Section 5 Study Population - 25% limit of beta blocker treated participants was removed.
- Section 5.2 Updated inclusion criteria 3 to "Apparent rHTN at screening (Visit 1) defined as uncontrolled BP with an office msSBP ≥ 140 mmHg despite treatment with stable (i.e., unchanged for ≥4 weeks), optimal or maximally tolerated doses of three or four antihypertensive drugs of different classes, including an ACEI/ARB, a long-acting dihydropyridine CCB, and a thiazide or thiazide-like diuretic. Refer to Section 10.8 for recommended minimum doses of some commonly prescribed drugs in those classes. Participant with documented intolerance to any doses of CCBs may be eligible if receiving another class of antihypertensive medication at an optimal or maximally tolerated dose. An optimal dose is defined as the highest dose taking into account participant's documented comorbidities and tolerability per investigator's clinical judgment. "
- Section 5.2
  - Updated exclusion criteria 1 to remove minimum SBP requirement at Visit 30.
  - Updated exclusion criteria 5 adding Sacubitril/Valtarsan
  - Updated exclusion criteria 11 to increase mid-arm circumference to 44cm.
  - Updated exclusion criteria 12 "Patients with history of hospitalization for hypertensive emergencies characterized by severe hypertension (usually grade 3) associated with funduscopic changes (flame hemorrhages and/or papilloedema), microangiopathy, disseminated intravascular coagulation, encephalopathy, acute aortic dissection, acute myocardial ischemia, or acute heart failure any time prior to screening or hospitalization for non-emergent/non-urgent uncontrolled hypertension without target organ damage within 3 months prior to screening"

  - Replaced exclusion criteria 13 with "Receiving more than 4 antihypertensive medications."
  - Updated exclusion criteria 22 to specify the acceptable dose of aspirin.
  - Added exclusion criteria 24 "History of hypersensitivity to any of the study drugs, excipients or drugs of similar class."
- Section 5.3, Section 8.1 and Section 10.2.2. Re-screening only after 4 weeks was removed; Clarified participant can be re screened if a fails the initial screening or prior to administration of single blind study medication
- Section 6 - Multiply changes: triple before background medication and specifying LCMS compliance test refers to End of Run in.
- Section 6.3.2 added wording to precise blinded team: pharmacist or delegated qualified personnel
- Section 7.1: Rephrasing change
- Section 8.3.1 Text modified to: ABPM assessment will be performed at Visit 30 (End of Run-in) and after the participant has met office BP criterion (i.e. msSBP < 180 mmHg and msDBP <110 mmHg);Precised: Patients should take their background medications in the clinic witnessed by the investigator or designee (and study medication when applicable) prior to attaching the ABPM device.
- [redacted]
- Section 8.3.3 - typo correction
- Section 9 Multiple updates to statistical section support new secondary objective and other changes related to inclusion of patients receiving 3 or 4 background antihypertensive medications with removal of the limitation on patients receiving beta blockers.
- Section 10.6.1 Updated the units of the cut-off values defining renal events
- Section 10.8 Updated title to "Recommended minimum doses of background medications".
- Section 11 Ref. Guideline on Missing Data in Confirmatory Clinical Trials removed

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the Informed Consent.

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

An efficacy, safety, tolerability and dose finding study of XXB750 in resistant hypertension patients

Purpose

The purpose of this 20-week randomized double-blind study in patients with resistant hypertension (rHTN) is to evaluate the efficacy, safety, and tolerability, of four doses of XXB750 (30 mg, 60 mg, 120 mg and 240 mg) administered once every 4 weeks (q4w) as subcutaneous (SC) injections, compared to placebo. Since all study participants will be patients with rHTN, all study treatments will be given on top of optimal or maximally tolerated background antihypertensive therapy recommended by international guidelines for treatment of HTN (i.e., a thiazide or a thiazide-like diuretic, an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), and a long-acting dihydropyridine calcium channel blocker (CCB).

Study Indication /Medical Condition:

Resistant Hypertension

Treatment type

Biological

Study type

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Primary and secondary objectives, endpoints and estimands

Objectives	Endpoints
Primary	
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 pressure (mean 24hr SBP) from baseline to Week 12.	• Change from baseline in mean 24hr SBP at Week 12

The primary clinical question of interest is: Is there a dose-response signal, and if so, to characterize 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, change in the dose of allowed background antihypertensive medications and receiving prohibited concomitant medication?	
Secondary	
• To evaluate the treatment effect of the highest XXB750 dose versus placebo in reducing the mean 24hr SBP from baseline to Week 12. The estimand of this objective will further demonstrate the efficacy of XX750 highest dose group compared with placebo, regardless of discontinuation from study treatment, change in the dose of allowed background antihypertensive medications and receiving prohibited concomitant medication, 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. • 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 . The estimand of the second secondary objective in terms of attributes are the same as described for the primary estimand (Section 3.1) 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. • To evaluate the proportions of participants achieving BP (Blood Pressure) control by ambulatory blood pressure monitoring - ABPM (i.e., mean 24hr SBP <130 mmHg and 24-hour mean ambulatory diastolic blood pressure (mean 24hr DBP) <80 mmHg) and dose-response relationship in the four XXB750 dose level groups compared to placebo at week 12. The third secondary question of interest is: What is the dose-response signal and 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 patients with rHTN without any premature discontinuation from study treatment	• Change from baseline in mean 24hr SBP at Week 12 • Average of changes from baseline in mean 24hr SBP at Week 9 and at Week 12 • The proportions of participants achieving blood pressure control defined as mean 24hr SBP <130 mmHg and mean 24hr DBP <80 mmHg at Week 12 • Adverse events, safety laboratory parameters, and vital signs through end of treatment/study (EOT/EOS)

and without any unforeseen increase in the dose of allowed background antihypertensive medications nor receiving any prohibited medications. It will provide an estimate with a p-value in a hierarchical hypothesis testing procedure with overall type I error control after previous primary and secondary objectives are demonstrated. • To evaluate the safety and tolerability of the XXB750 regimens over 12 weeks of treatment and over the overall 20 weeks of study duration including safety follow-up.	

Trial Design:

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

- 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, including a thiazide/thiazide-like diuretic, an ACEI or an ARB, and a long acting dihydropyridine CCB. Approximately 170 participants will be randomized to receive placebo, XXB750 30 mg, 60 mg, 120 mg, or 240 mg SC every 4 weeks.

Brief Summary:

XXB750 is a fully human monoclonal antibody with potent NPR1 agonistic activity. NPR1 agonism induces the effects of natriuretic peptides, enhancing Natriuresis, diuresis and vasodilatation. Consistent with its mechanism of action, XXB750 was shown to have a potent blood pressure lowering effect in healthy human volunteers. Study XXB750B12201 aims to evaluate the antihypertensive effect of XXB750 in subjects with resistant hypertension.

Subjects whose blood pressure is not under control despite treatment with triple antihypertensive medications, including an angiotensin converting enzyme blocker or angiotensin receptor blocker, a calcium channel blocker, and a thiazide or thiazide-like diuretic will be recruited into the study. Subjects will receive a single-blind XXB750 placebo injection at the start of the run-in period which lasts for approximately 2 weeks. Subjects whose blood pressure is still not under control at the end of the run-in period despite compliance with triple antihypertensive background treatment (i.e., with mean 24hr systolic blood pressure >135 mmHg) will be randomized to receive one of four dose levels of XXB750 (30 mg, 60 mg, 120 mg, or 240 mg SC Q4W) or placebo Q4W. Overall, a total of approximately 170 participants will be randomized. The study duration is for 20 weeks during which each participant will receive a total of 3 doses of study medication at 4 weekly intervals, i.e., at baseline, 4 weeks, and 8 weeks. Ambulatory blood pressure monitoring will occur at baseline, Week 9, and Week 12 (primary endpoint timepoint). [redacted]

[redacted]. Participants will be followed to monitor their safety for an additional 8 weeks during which time no active study medication will be given.

Each of the first approximately 68 randomized participants will be assigned to receive one of the three lower doses of XXB750 or placebo (17 participants per arm). A DMC will review the safety and tolerability data of those participants when the first 40 participants have completed at least 5 weeks of the study and, contingent upon DMC's findings of their safety and tolerability experience, the highest XXB750 dose of 240 mg will be introduced in the remaining approximately 102 participants.

Study Duration:

20 weeks

Treatment Duration:

12 weeks

Visit Frequency:

Every 1-4 weeks

Treatment of interest

The investigational treatment XXB750/placebo.

Number of Participants:

A total of approximately 170 participants will be randomized into the study.

Key Inclusion criteria

- Male and female participants who are ≥18 years old.
- Signed informed consent prior to participation in the study.
- Apparent rHTN at screening (Visit 1) defined as uncontrolled BP with an office msSBP ≥ 140 mmHg despite treatment with stable (i.e., unchanged for ≥4 weeks), optimal or maximally tolerated doses of three or four antihypertensive drugs of different classes, including an ACEI/ARB, a long-acting dihydropyridine CCB, and a thiazide or thiazide-like diuretic. Refer to Section 10.8 for recommended minimum doses of some commonly prescribed drugs in those classes. Participant with documented intolerance to any doses of CCBs may be eligible if receiving another class of antihypertensive medication at an optimal or maximally tolerated dose. An optimal dose is defined as the highest dose taking into account participant's documented comorbidities and tolerability per investigator's clinical judgment.
- Mean 24hr SBP ≥135 mmHg (measured by ABPM) at the end-of Run-in-Visit (Visit 30) on treatment with optimal or maximally tolerated doses of an ACEI/ARB, a long-acting dihydropyridine CCB (or a suitable alternative in case of intolerance per inclusion criterion above), and a thiazide or thiazide-like diuretic.

Key Exclusion criteria

- Subjects with the following blood pressures at the specified time points:
  - Office msSBP <140 mmHg at Visit 20 OR
  - Office msSBP ≥180 mmHg or office msDBP ≥110 mmHg at the end-of-run-in visit (Visit 30) OR
  - 24h mean SBP >170 mmHg or 24h mean DBP >105mmHg measured by ABPM at the end of the run-in (Visit 30).
- Known history of secondary hypertension (moderate-to-severe obstructive sleep apnea without receiving CPAP therapy (either face mask or nasal device), renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation or other cause of secondary hypertension).
- Estimated GFR <30 mL/min/1.73m^2 using CKD-Epi equation at screening (Visit 1) or at end-of-run-in visit (Visit 30)
- Serum potassium >5.0 mmol/L (or equivalent plasma potassium value) at screening or end-of-run-in visit (Visit 30)
- Current therapy with a mineralocorticoid receptor antagonist (MRA) or sacubitril/valsartan, received an MRA or sacubitril/valsartan within the 4 weeks prior to screening
- Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), high-grade AV block (e.g., Mobitz type II and third-degree AV block in absence of a pacemaker) within 6 months of screening according to investigator's judgement.
- Receiving more than 4 antihypertensive medications

Treatment Groups:

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 12 weeks

XXB750 30 mg SC every 4 weeks for 12 weeks (dose level1)

XXB750 60 mg SC every 4 weeks for 12 weeks (dose level 2)

XXB750 120 mg SC every 4 weeks for 12 weeks (dose level 3)

XXB750 120 mg SC at the Randomization visit followed by 240 mg SC at Week 4 and Week 8 (dose level 4)

Data Monitoring/Other Committee:

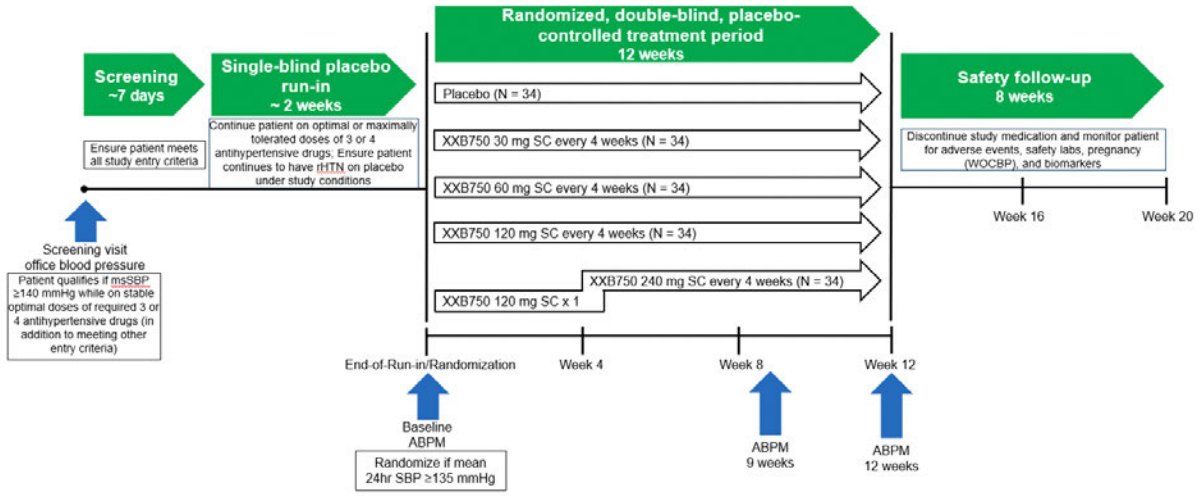
Yes (see Section 10.1.4 Committees Structure)

Key words

Resistant hypertension, randomized, double-blind, dose finding, XXB750.

1.2 Schema

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.

1.3 Schedule of activities (SoA)

The Assessment Schedule (Table 1-2) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the Assessment Schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation or to a change in the timing of the next scheduled visit (if applicable).

Participants who discontinue from study treatment are to complete the end of treatment visit (Visit 170) procedures as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit (Visit 1999) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation

dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	**Screening**	**Placebo Run-in**		**Randomized Treatment**								**Safety Follow-up**	
Visit Name	**Screening**	**Run-In**	**End of Run-in**	**Baseline**	**Week 1 Call**	**Week 2**	**Week 4**	**Week 5 Call**	**Week 8**	**Week 9**	**Week 12 EOT**	**Week 16**	**Week 20 EOS**
Visit Numbers[1]	**1**	**20**	**30**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**1999**
Days	**-21 to -15**	**-14**	**-1 to 0**	**0**	**3**	**14**	**28**	**31**	**56**	**59 to 63**	**84**	**112**	**140**
Informed consent	X												
Demography	X												
Inclusion / Exclusion criteria	X	X	X[2]										
Physical Examination	X	X[3]	X			X[3]	X[3]		X[3]	X[3]	X	X[3]	X
Body Weight			X				X		X		X	X	X
Body Height	X												
Medical history/current medical conditions	X												
Vital Signs/Office BP	X	[redacted]											
[redacted]													
24-hr Ambulatory BP Monitor			X							X	X		
Electrocardiogram (ECG)	X		X								X		X
Pregnancy Test (serum)[5]	X		X								X		X
Pregnancy test (urine)[5]							S		S			S	
Assessment of fertility	S												
Urinalysis	X		X			X	X		X		X	X	X
Urine background medication screening sample collection			X								X		
Laboratory evaluations[6]	X		X			X[7]	X[7]		X[7]		X	X[7]	X
[redacted]													

Period	**Screening**	**Placebo Run-in**		**Randomized Treatment**								**Safety Follow-up**	
Visit Name	**Screening**	**Run-In**	**End of Run-in**	**Baseline**	**Week 1 Call**	**Week 2**	**Week 4**	**Week 5 Call**	**Week 8**	**Week 9**	**Week 12 EOT**	**Week 16**	**Week 20 EOS**
Visit Numbers[1]	**1**	**20**	**30**	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**1999**
Days	**-21 to -15**	**-14**	**-1 to 0**	**0**	**3**	**14**	**28**	**31**	**56**	**59 to 63**	**84**	**112**	**140**
[redacted]													
IWRS/IRT Randomization				X									
IWRS/IRT Registration	X	X	X			X	X		X	X	X	X	X
Study drug dispensation/administration		X		X			X		X				
Background medication compliance		S	S	S		S	S		S		S		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Study period completion information			X								X		X

Period	Screening	Placebo Run-in		Randomized Treatment								Safety Follow-up	
Visit Name	Screening	Run-In	End of Run-in	Baseline	Week 1 Call	Week 2	Week 4	Week 5 Call	Week 8	Week 9	Week 12 EOT	Week 16	Week 20 EOS
Visit Numbers[1]	1	20	30	100	110	120	130	140	150	160	170	180	1999
Days	-21 to -15	-14	-1 to 0	0	3	14	28	31	56	59 to 63	84	112	140

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Only the entry criteria related to 24-hr ABPM, potassium, eGFR, pregnancy testing in WoCBP, and/or compliance with background treatment as applicable per Section 4.1.
[3] Short physical examination.
[redacted].
[5] Only in women of childbearing potential (as described in Section 8.4.5).
[6] Samples must be taken prior to administration of study drug.
[7] Abbreviated safety lab, as defined in Section 8.4.4
[redacted]

2 Introduction

2.1 Study rationale

The design features of this phase 2 trial are intended to support its purpose as stated in Study Design (Section 4). The results of this study will help describe the dose-response relationship of XXB750 and how it compares in its safety and efficacy to placebo. In addition, this study will provide needed insight on XXB750 dose(s) to be studied further in the development program in patients with rHTN.

2.2 Background

Hypertension (HTN) is a key risk factor for heart disease and strokes across the world contributing significantly to cardiovascular (CV) mortality and morbidity and other end organ damage such as retinopathy and nephropathy. Data from the National Health and Nutrition Examination Survey (NHANES) and the International Society of Hypertension suggest that an estimated 50% of deaths from coronary heart disease (CHD) and stroke were attributable to HTN (Lawes et al 2008, Ford 2011). Hypertension is also a leading cause contributing to a third of incident end-stage renal disease (ESRD) among patients with kidney disease (Johansen et al 2021).

The prevalence of HTN is rising globally due to ageing of the population and increases in lifestyle risk factors, such as unhealthy diets, obesity and lack of physical activity. It is estimated that more than 30% of the world's adult population has hypertension and its prevalence seems to continue to increase in the low and middle income countries (Mills et al 2016). Despite it being one of the most important modifiable risk factors of cardiovascular morbidity and mortality, control of HTN in a substantial proportion of patients remains inadequate. It is estimated that nearly half the patients with HTN do not have adequate blood pressure control (Whelton et al 2018). Consequently, the use of multiple antihypertensive medications from different therapeutic classes is not uncommon in treating HTN. Several payor and patient-related factors appear to contribute to inadequate control of blood pressure in hypertensive patients, including excessive reliance on monotherapy, reluctance to increase drug doses or to add more antihypertensive drugs, non-adherence to prescribed medication, drug side effects, and the cost of medications (Elliott 2008).

Despite of the availability of many effective antihypertensive medications with several mechanisms of action, a significant proportion of hypertensive patients experience treatment resistant HTN (rHTN). Based on population studies, this category of hypertension affects approximately 12% to 15% of patients treated for HTN (Egan et al 2011, Persell 2011, Tanner et al 2013) and approaches a prevalence of 20% in clinic-based studies (de la Sierra et al 2011, Egan et al 2013, Borghi et al 2016, Thomas et al 2016). Resistant HTN has been formally defined by international medical societies as blood pressure that remains above goal despite the concurrent use of three antihypertensive agents of different classes at optimal or maximally tolerated doses. Generally, these antihypertensive classes include a long-acting calcium channel blocker (CCB), an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme inhibitor (ACEI), and a diuretic

(Whelton et al 2018, Carey et al 2018). Resistant HTN is often associated with chronic kidney disease (CKD), black race, diabetes, obesity, and atherosclerotic disease, as well as older age (Williams et al 2018). Patients with rHTN are at a particularly high risk of experiencing adverse cardiorenal outcomes compared to other hypertensive patients. Compared to patients with controlled HTN, patients with rHTN are 27% more likely to experience the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or all-cause death and 47% more likely to experience (cardiovascular) death (multivariate-adjusted model) (Smith et al 2014). Moreover, rHTN patients are 32% more likely to reach ESRD than other hypertensive patients (Sim et al 2015).

International guidelines recommend spironolactone 25-50 mg per day for the treatment of patients with rHTN (on top of background antihypertensive therapy that includes a thiazide/thiazide-like diuretic, an ACEI or an ARB, and a long-acting dihydropyridine CCB). This is based on the results of randomized clinical trials, such as ASPIRANT and PATHWAY-2 (Václavík et al 2011, Williams et al 2015). The PATHWAY-2 trial demonstrated that spironolactone dosed at 25-50 mg per day was more effective than the beta blocker bisoprolol dosed at 5-10 mg per day and the alpha blocker doxazosin dosed at 4-8 mg per day (Williams et al 2015). However, spironolactone is not well tolerated in many patients due to a significantly increased risk of hyperkalemia or hormonal abnormalities that cause gynecomastia, erectile dysfunction or menstrual disorders (Williams et al 2018). This is particularly relevant for patients on background therapy of renin-aldosterone-angiotensin system (RAAS) blockers or in patients who have reduced glomerular filtration rates (GFR) associated with CKD or diabetes mellitus, which are all conditions that are commonly present in rHTN patients (Whelton et al 2018). Thus, while beta blockers and alpha blockers can be used in place of spironolactone as they have been shown to have antihypertensive efficacy in rHTN (Williams et al 2015), they are significantly less efficacious than spironolactone. Nonetheless, the use of these therapeutic classes is limited by increased risks of metabolic abnormalities, fatigue, and bradycardia (particularly at higher doses) and orthostatic hypotension. Hydralazine and minoxidil, which are direct vasodilators, have been used in rHTN, but they may cause significant tachycardia and fluid retention. Thus, regardless of which currently available therapeutic drug class is used to treat this complicated subgroup of hypertensive patients, adverse effects and worsening of the significant polypharmacy that rHTN patients already experience limit compliance with treatment, thereby limiting its success in maintaining lower blood pressure in those patients. Thus, there remains a significant unmet need for developing new classes of antihypertensive medications with improved efficacy over the existing therapeutic modalities, preferably minimizing the impact on the polypharmacy in these patients or perhaps even reversing it.

One physiological system that contributes to blood pressure maintenance is the natriuretic peptide (NP) system. It is an endocrine, autocrine and paracrine system, consisting primarily of three genetically distinct, but structurally related peptides including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Natriuretic peptides interact with three different types of NP receptors, NPR-1, (or NPR-A), NPR-2 (or NPR-B), and NPR-3 (or NPR-C). ANP and BNP activate the transmembrane guanylyl cyclase, NPR-1 whereas CNP activates NPR-2. Both receptors catalyze the synthesis of cyclic guanosine monophosphate (cGMP), which mediates most known effects of natriuretic peptides, including vasodilatation, natriuresis, and diuresis. NPR-3 clears natriuretic peptides from the circulation

through receptor-mediated internalization and degradation (Potter et al 2009). Binding of ANP or BNP to NPR1 activates membrane bound particulate guanylate cyclase and stimulates intracellular cGMP- dependent second messenger signaling cascade, which mediates their physiological actions. ANP and BNP play a pivotal role in the maintenance of blood pressure (BP) and intravascular volume. The action on BP effects is likely to be via the regulation of vascular tone, caused by a direct relaxation effect of NPs on vascular smooth muscle cells. Furthermore, NPs help to regulate BP by suppressing the RAAS, reducing sympathetic tone and inhibiting secretion of the vasoconstrictor endothelin-1 (ET-1) (Nishikimi et al 2006). Therefore, augmentation of NP system can be a potential therapeutic target in the management of hypertensive patients.

One mechanism that has been used to upregulate the NP system to lower BP is via the inhibition of neprilysin (also known as neutral endopeptidase 24.11; NEP), an enzyme that breaks down NPs with greater affinity for metabolizing ANP. Exploiting this mechanism in lowering blood pressure necessitates the simultaneous inhibition of the activity of angiotensin II because neprilysin also metabolizes this potent vasoconstrictor. Two therapeutic classes have been investigated in lowering blood pressure by simultaneously inhibiting neprilysin and the activity of angiotensin II: vasopeptidase inhibitors and angiotensin receptor neprilysin inhibitors (ARNIs). Omapatrilat was a vasopeptidase inhibitor which was found to be effective in lowering blood pressure by simultaneously inhibiting ACE and neprilysin. However, this compound resulted in unacceptably high rates of severe angioedema, particularly in African-American patients, a potentially life-threatening adverse effect, because it also inhibited aminopeptidase-P, which, along with ACE and neprilysin, is responsible for metabolism of bradykinin, the key vasoactive peptide thought to be the culprit in angioedema (Kostis et al 2004). As a result, omapatrilat was not approved by regulators despite its efficacy.

Although neprilysin inhibition is an innovative mechanism to lower BP via NP system modulation, it has several drawbacks that may limit its efficacy and use in rHTN. First, neprilysin inhibition blocks only one pathway of NP degradation; other NP degradation pathways, including via insulin-degradation enzyme, exist and limit the effectiveness of this pharmacological pathway. Second, currently available neprilysin inhibitors cannot be administered alone and must be combined with angiotensin receptor blockade to counteract the reduced metabolism of angiotensin II, thereby exposing the patient to potential side effects of two medications instead of one. Finally, because neprilysin inhibitors increase bradykinin levels, they cannot be co-administered with ACEIs, which also increase bradykinin levels, as combined use of these two therapeutic classes may lead to an unacceptably high risk of angioedema. Consequently, switching from an ACEi to an ARNI (or vice versa) require an ACEI/ARNI-free washout of at least 36 hours between stopping one medication and initiating the other. Thus, new modalities to modulate the NP system are needed to exploit its potential more fully and more effectively to safely lower BP in rHTN patients.

One way to efficiently modulate the NP system is by direct NPR-1 agonism. This mechanism has the advantage of specificity. It also does not interfere with the metabolism of bradykinin, and, therefore, is unlikely to increase the incidence of angioedema. Unlike neprilysin inhibition, directly activating NPR-1 does not require co-administration of other medications to counteract off-target effects, which provides much more flexibility in treating patients. In a recently published first-in-human study, the NPR-1 agonist M-atrial natriuretic peptide (MANP), an

analog of human ANP, was shown to increase cGMP levels and natriuresis and to lower aldosterone levels and BP when administered subcutaneously (SC) to hypertensive patients (Chen et al 2021). Although, most of its effect dissipated within 24 hours, the demonstrated effects of MANP in this study provide proof-of-concept for NPR-1 agonism as a potentially effective modality in reducing blood pressure in hypertensive patients.

XXB750 is a long-acting fully human monoclonal IgG1 antibody agonist of NPR-1 with a half-life of approximately [redacted] in humans (Section 4.3). The prolonged half-life allows for once-a-month SC dosing compared to daily dosing of other antihypertensive agents and earlier analogs of ANP. Pre-clinical studies with XXB750 have shown 15-20 mmHg SBP reduction in normal rats and normal monkeys and ~80 mmHg SBP reduction in hypertensive rats. In the ongoing first-in-human (FIH) study in healthy volunteers, XXB750 has been administered as a single SC injection at doses up to 240 mg. XXB750 resulted in plasma cGMP elevations and BP lowering effect up to a placebo-adjusted maximum SBP reduction of ~18 mmHg at peak effect with the 240 mg dose. Cyclic GMP and BP effects trended back to pre-dose values over the weeks after dosing but were still present 4 weeks post-dose (see Section 4.3 and the Investigator Brochure for details on preliminary results from the FIH study).

Given its mechanism of action, its long half-life, its significant BP lowering effects seen in its preclinical trials as well as in healthy volunteers, XXB750 promises to be an innovative and important therapeutic option in the management of patients with rHTN by overcoming several challenges including the hormonal and metabolic side effects of spironolactone and other currently available therapeutics. Moreover, with its expected once monthly SC administration regimen, XXB750 may offer a significant advantage by improving medication adherence in this population in which polypharmacy is common.

The current study is a phase 2 study which aims to establish proof-of-concept of blood pressure lowering by NPR1 agonism using XXB750, identify its optimal dose(s) to study in phase 3, and to characterize its benefit-risk profile in patients with rHTN..

2.3 Benefit/Risk assessment

All study participants are expected to benefit from intensive monitoring of their blood pressure and overall health while receiving the optimal or maximally tolerated triple background antihypertensive therapy for their rHTN. Eighty percent of participants are planned to be treated with an additional antihypertensive agent (XXB750) in an effort to better control their blood pressure. The remaining participants will be treated with placebo and the duration of their treatment with placebo will be kept to a minimum, to accomplish the scientific purpose of the study. Nonetheless, the extent of this potential benefit is unknown at this time and is the primary reason for conducting this study.

As all participants are required to continue with their existing background antihypertensive medications the risk of developing severe uncontrolled hypertension during the study is expected to be minimal. Participants with a baseline office systolic blood pressure of SBP >180 mmHg are excluded from the study. Participants who develop severe uncontrolled hypertension during the study and whose SBP remains or who develop SBP >180 mmHg will be withdrawn from the study and will be managed using conventional therapies. In addition to minimize the risk due to uncontrolled hypertension participants who have experienced any significant

cardiovascular events, subjects with a history of myocardial infarction, stroke or coronary interventions, and hospitalization for hypertension crisis within the 12 months prior to study entry will be excluded from the study.

Except for the small proportion of participants randomized to the placebo cohort (approximately 34 subjects) a significant majority of the study participants will receive additional antihypertensive therapy during the course of the study which may be associated with medication specific adverse events. Use of multiple (typically > 5) medications (polypharmacy) increases the risk for potential adverse events and biochemical abnormalities. Participants in this study will be required to be on optimal or maximally tolerated doses of ACEi /ARB along with a calcium channel blocker and thiazide / thiazide-like diuretic. As the subjects are required to be on stable and optimal or maximally tolerated doses of the triple background antihypertensive therapy prior to study entry, the risk of renal and biochemical abnormalities is expected to be low. However participants will be monitored closely during the study for potential renal dysfunction and electrolyte abnormalities. Changes to the background medications and other supportive measures will be implemented as necessary. Recruitment into the study will be restricted to participants with eGFR (estimated Glomerular Filtration Rate) > 30 mL/min and serum Potassium < 5.0 mmol/l to minimize the risk to participants.

XXB750 is expected to be a potent BP lowering agent and given its long half-life the BP lowering effect may be significant and sustained for a long period of time. A dose proportional blood pressure lowering response was observed in healthy volunteer study with XXB750. In particular the response to the 240 mg dose was clearly separated from the 120 mg q4w dose and the magnitude of SBP decrease reached up to 20 mmHg at its peak. While this is a highly desirable effect in most hypertensive patients who are resistant to treatment, to ensure participants tolerate the study medication without any significant adverse experiences, participants will be closely monitored during the study. To minimize the risk of hypotension in the study population, the highest study dose will be introduced in a staggered fashion. The first cohort of participants will receive 30 mg, 60 mg, 120 mg of XXB750 q4w or placebo. A Data Monitoring Committee (DMC) will evaluate the safety and tolerability of these doses and the 240 mg q4w dose will only be introduced if it was deemed safe to do so by the DMC.

Participants are encouraged to report any adverse events to the site between clinic visits immediately. Participants will be contacted after one week following the first dose administration and following dose escalation via a scheduled telephone call to ensure tolerability and inquire about their general wellbeing. [redacted] Should it be considered necessary, investigators may make changes to the background medications to manage symptomatic hypotension. Subjects whose symptoms and blood pressure cannot be managed by adjustments to background medications will be discontinued from the study and will be managed appropriately with open label local standard of care therapies.

XXB750 is a fully human monoclonal antibody and is not expected to elicit any significant immune response in study participants. [redacted]

Participation in the study and undergoing routine study procedures may cause discomfort associated with sample collection and study drug administration. XXB750 will be administered as single 1.6 mL subcutaneous injection to the study participants. While injection site reaction is a potential local adverse event, subcutaneous injections are well tolerated in the single ascending dose study. Therefore, the risk to the participants in this study is expected to be minimal. Participants will be monitored closely for local injection site reactions and through adverse event collection. Blood samples will be taken on multiple occasions during the course of the study which may be associated with bleeding or bruising and rarely fainting and infection. However, such events are very rare and the risk to the participants in this study is expected to be minimal.

Women of child-bearing potential will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study. In general, the levels of a mAb in semen are expected to be low, and therefore the subsequent levels in female partner would be negligible. Based on this principle, the probability that XXB750 would cause teratogenicity is very low. Therefore, no restrictions will be placed on male participants with regard to sexual activity or condom use.

Given the close monitoring, criteria for participant selection and the known safety and tolerability profile of the drug in human volunteers it is considered that overall potential benefits outweigh the risks for participants in this study.

3 Objectives, endpoints, and estimands

Table 3-1 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 pressure (mean 24hr SBP) from baseline at Week 12.	• Change from baseline in mean 24hr SBP 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 participants achieving blood pressure control defined as mean 24hr SBP <130 mmHg and mean 24hr DBP <80 mmHg at Week 12

Objective(s)	Endpoint(s)
• 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]

3.1 Primary estimands

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 (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).

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

3.2 Secondary estimands

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 3.1) 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 3.1) 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 patients 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 (Section 5).
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).

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, randomized treatment period and post-treatment safety follow-up). Please refer to Section 9.4.2 for analysis details.

4 Study design

4.1 Overall 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 patients 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. 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. The overall design of the study is depicted in Figure 1-1.

A staggered approach to enrollment will be followed in this protocol. As summarized in Table 4-1, the randomized participant sample will be divided into two groups, which will vary in terms of the ratio of allocation to the treatment arms. Group 1 will consist of approximately 68 participants who will be randomized to either placebo, XXB750 30 mg SC every 4 weeks (dose level 1), XXB750 60 mg SC every 4 weeks (dose level 2), or XXB750 120 mg SC every 4 weeks (dose level 3) in a 1:1:1:1 ratio. The Data Monitoring Committee (DMC) will review the safety data of the Group 1 participants when approximately 40 participants have completed at least the first 5 weeks of randomized treatment. If the safety profile of XXB750 dose levels 1, 2 and 3 is deemed acceptable by the DMC, Group 2 enrolment will start upon full completion of Group 1 enrollment. Group 2 will consist of approximately 102 participants who will be randomized to either placebo, XXB750 dose level 1, XXB750 dose level 2, XXB750 dose level 3, or XXB750 120 mg SC for one injection followed by 240 mg SC every 4 weeks for two injections beginning 4 weeks after the first dose (dose level 4) in a 1:1:1:1:2 ratio. All participants will be followed for 8 additional weeks after end of dosing of the study medications to monitor their safety.

In the event that the DMC recommends that participants should not be exposed to XXB750 240 mg dose, the study will continue without it, and dose level 4 will be eliminated from the study. In this case, the Group 2 enrollment will consist of approximately 68 participants randomized to either placebo, XXB750 dose level 1, XXB750 dose level 2, or XXB750 dose level 3 in a 1:1:1:1 ratio.

Table 4-1 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

Treatment arm	**Group 1**	**Group 2 (adjusted*)**	**Total (adjusted*)**
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 x 1 dose, then XXB750 240mg every 4 weeks	n = 0	n = 34 (0*)	N = 34 (0*)
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.			

Refer to Section 1.2 Schema for study design figure.

The following is an overview of the study procedure plan. All office visits should be conducted at approximately the same time throughout the study, which should be approximately between 07:00am and 11:00am. The participant should be instructed not to take any of the background antihypertensive therapy medications prior to the scheduled office visit, but bring their antihypertensive medications to the study site so they can take them after all of the office study assessments are complete witnessed by the investigator or designee . At clinic visits when re ABPM assessment is scheduled, patients should not take their triple background antihypertensive medications until after all office assessments are complete and immediately before attaching the ABPM device.

Screening

The purpose of the Screening Period, which begins at Visit 1 and continues for approximately one week, is to assess participants' eligibility to continue into the run-in period of the study. During the Screening Visit, participants will be asked to review and provide informed consent prior to undergoing any screening procedures. After signing the informed consent form (ICF), inclusion and exclusion criteria will be assessed to verify the study candidate’s eligibility for enrollment into the study. This will include assessment of blood pressure in the investigator’s office and stability of ongoing regimens of background antihypertensive therapy. Every effort should be made to maintain patients at the highest tolerated doses of the background antihypertensive therapy components which include ACEI/ARB, long acting CCB and a thiazide diuretic. If the participant is not taking maximum doses of these medications per their local approved label or local guidelines, the investigator must provide a qualifying reason for that in the participant’s electronic case report form (eCRF. Protocol-specified biochemical criteria will be assessed using a central laboratory. The participant will continue his/her therapy, including his/her antihypertensive medications with no change during the Screening Period. Once the participant’s Screening central lab results become available, he/she will be informed by the investigator or his/her designee of whether he/she is eligible to continue in the study. Only participants who meet all the inclusion criteria and none of the exclusion criteria will be asked to return to Visit 20 to begin the Run-in Period. Per the investigator’s discretion, participants who have failed the screening period (screen failures) or have failed prior to administration of single blind study treatment are allowed to be rescreened once,.

Single-blind placebo Run-in

The purpose of the single-blind placebo Run-in Period is to ensure that only participants whose blood pressure 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 a thiazide or thiazide-like diuretic, an ACEI/ARB, and a long-acting dihydropyridine CCB with good compliance, are randomized into the study and enter the Double-blind Period.

Upon entering the Run-in Period (Visit 20) the investigator will review with the participant all his/her medications to ensure that he/she is continuing to take them as prescribed and the participant's office msSBP remains ≥140 mmHg. Among other procedures, the participant will be administered a single-blind injection of placebo matching XXB750. The investigator will emphasize the importance of maintaining good adherence with the background antihypertensive therapy, which are to be taken at the optimal or maximally tolerated dose throughout the Run-in Period. [redacted]

The participant will return to the site for end of Run-in visit approximately 2 weeks later (Visit 30) to be evaluated for eligibility for randomization. Among other study procedures, compliance with the background antihypertensive therapy regimen and tolerability to it will be assessed by interviewing the participant. A urine sample will be obtained and biobanked to screen for background antihypertensive therapy medication intake in the future. A blood sample will be collected to assess the participant's potassium level and eGFR. [redacted] If the participant is assessed by the investigator to be compliant with the background antihypertensive therapy and tolerated it, , the participant will undergo ABPM for 24 hours while continuing to take his/her background antihypertensive therapy. If the participant's (1) mean 24hr SBP is found to be ≥135 mmHg, (2) had a serum potassium level ≤5.0 mmol/L, (3) and eGFR ≥30 ml/min/1.73m2, and (4) a negative pregnancy test in WoCBP the participant will be considered to have successfully completed the Run-in Period, Visit 30 would be considered complete and the participant will be deemed eligible for randomization into the study.

If the participant does not meet any of the conditions and qualifications listed above, he/she will be deemed ineligible for randomization and will be run-in failed.

During the Run-in period, it may be necessary to bring the participant to the site 24-72 hours before the scheduled visit to perform certain study assessments (e.g., safety laboratory blood sampling for central laboratory assessment, ABPM) to ensure results are received in time for the scheduled visit. A local laboratory can be used to assess key safety parameters for the purposes of qualifying participant for randomization; a blood sample will still have to be collected and sent for analysis at the central laboratory in this situation.

Please refer to Section 5.2 for additional blood pressure-related and other exclusion criteria that should be assessed throughout the run-in period.

Double-blind Randomized Treatment

The purpose of the Double-blind Randomized Treatment period is to investigate the efficacy and safety of the study treatments in reducing blood pressure when administered on top of optimal or maximally tolerated doses of triple background antihypertensive therapy that the participant was taking at the end of the Run-in Period.

Participants who successfully complete the Run-in Period will complete the procedures of Visit 100 as indicated in Table 1-2 and be randomized into one of the treatment arms per study design (Figure 1-1). The participant will receive the first dose of the blinded study medications on the day of Visit 100.

The double-blind treatment period will consist of 8 scheduled office or phone visits. The timing and the list of the study assessments of each visit can be found in Table 1-2 (Assessment schedule) and detailed in Section 8. For the entire duration of the double-blind treatment period, every attempt should be made so that the participant will continue to take the randomized, double-blind study medication in addition to the background antihypertensive therapy at the doses taken prior and during the Run-in Period with no changes. Also, addition of new antihypertensive medications or increases in the doses of the background antihypertensive therapy are strictly prohibited during the double-blind treatment period. If the participant experiences symptomatic hypotension that the investigator believes necessitates modifications to the participant's background antihypertensive therapy, please refer to Appendix 7 (Section 10.7) for more instructions on how to manage this adverse event.

Modifications to the protocol-specified double-blind study medication regimens are strictly prohibited. Participants who discontinue study medication prematurely should continue to attend study visits and undergo all study procedures as planned. Thus, discontinuation of study medication does not imply discontinuation from the study as a whole, unless the participant withdraws his/her consent for participation.

Post-randomization 24hr ABPM will be performed on all participants at Visit 160 (Week 9) and Visit 170 (Week 12/EOT). [redacted]

Throughout the Double-blind treatment period participants will undergo safety [redacted] assessments as well as [redacted] per the schedule shown in Table 1-2.

Safety follow-up

Because XXB750 has a relatively long half-life and might be detectable in the blood for approximately 90 days after the last dose administration, the Safety Follow-up Period is included in the study design to monitor the safety of participants and to ensure they safely transition off the study medication. After completing the procedures of Visit 170, i.e., the final visit of the Double-Blind Treatment Period, the investigator will monitor the participant's health

status and blood pressure to determine the need for modification of the participant's medication regimen. At this point, the investigator may make any modifications to the participant's medication regimen he/she deems necessary, including changes to the participant's background antihypertensive therapy regimen. Two study visits will be conducted to collect safety, [redacted] assessments and to monitor the participant's blood pressure and overall health status (i.e., Visit 180 at Week 16 and Visit 1999 at Week 20). [redacted]

Participants who prematurely discontinue the double-blind study medication will also be required to attend Visits 180 and 1999 to complete the safety follow-up procedures, which will occur 8 and 12 weeks after the last dose administration of XXB750 or its matching placebo.

Remote procedures

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed at a remote location.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

The remote procedures may be offered in certain countries and sites as determined by Novartis based on national and local regulations.

The off-site healthcare professionals may be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals that are not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff may perform certain procedures remotely using tele-visits.

4.2 Scientific rationale for study design

Rationale for study design

This is a randomized, double-blind, placebo-controlled study. This general design minimizes the systematic bias that may be introduced into many aspects of trial conduct based on knowledge of the assigned treatment, including how participants are selected, how the treatments are assigned, how the study is conducted, how participants behave and how investigators conduct the trial and collect the data. Also, the randomized nature of the design maximizes the chances of enrolling participants with similar baseline characteristics in all treatment groups. As a result, this design maximizes the chances of producing reliable, internally and externally valid results to support sound conclusions about the efficacy and safety of the experimental treatment (i.e., XXB750 in this study). A multicenter setting has been chosen to ensure adequate recruitment and enrollment into the study and to include an internationally representative sample that accounts for regional and local differences in practice norms.

The 12-week duration of the double-blind treatment period is sufficient to examine the BP lowering effect of each dose of XXB750 as compared to placebo. It is expected that after 4-6 weeks of study treatment, the full BP lowering effect would have been reached in all treatment groups.

Limited safety data are currently available for XXB750 and it would be prudent to dose the medication cautiously in participants until more is learned about its side effect profile. To help guard the safety of study participants, a staggered enrollment approach is utilized in the early part of the study (Section 4.1, Table 4-1). Participants will be exposed to the highest dose of XXB750 only after the independent DMC evaluates early safety data of the three lower XXB750 doses and deems their safety profile to be acceptable. Moreover, participants assigned to the highest dose level of XXB750 (240 mg) will first be dosed with 120 mg and then up titrated to 240 mg four weeks later to reach the target dose. This gradual up-titration is expected to help avoid potential tolerability issues related to the top XXB750 dose.

Target study population

The protocol utilizes a rigorous process and entry criteria to ensure that only participants who truly have rHTN are randomized into the study. All major international guidelines for the diagnosis and treatment of hypertension define rHTN based on two key aspects of the patient's blood pressure status: (1) treatment with three or more antihypertensives (one of which should be a diuretic) given at optimal or maximally tolerated doses, and (2) patient continues to present with blood pressure above the target values (Whelton et al 2018, Williams et al 2018, Unger et al 2020).

The current study requires all participants to be treated with optimal or maximally tolerated doses of a thiazide or thiazide-like diuretic, an ACEI or an ARB, and a long-acting dihydropyridine CCB, which are the three therapeutic classes of choice recommended by international guidelines for treating most hypertensive patients. These three classes of antihypertensives are commonly available and exploit different complementary mechanisms for lowering BP. Per international guidelines for diagnosis and treatment of hypertension, patients treated with optimal or maximally tolerated doses of medications from these three therapeutic classes and remain with uncontrolled blood pressure are considered to have rHTN (Williams et al 2018).

International guidelines differ in the blood pressure measurement values used to define hypertension and in the way they categorize it. However, they all agree that office msSBP ≥140 mmHg is considered hypertension that should be treated to lower the risk of cardiovascular outcomes (Whelton et al 2018, Williams et al 2018, Unger et al 2020). In this study, participants will be required to have an office msSBP ≥ 140 mmHg at Screening to qualify for inclusion. These initial SBP inclusion criteria are in line with international guidelines definition of hypertension, while allowing a small margin of BP lowering that can occur during the Single-blind Placebo Run-in Period and still remain within the definition of uncontrolled hypertension. In addition, at the end of the Single-blind placebo Run-in Period participants must have a mean 24hr SBP ≥135 mmHg based on ABPM, a BP monitoring procedure that can rule out white coat hypertension. This is above international guidelines for ABPM-based definition of hypertension (mean 24hr SBP ≥130 mmHg) (Unger et al 2020), as it is expected to allow for a primary endpoint baseline value that will help to more clearly demonstrate the differences in

efficacy among the various tested XXB750 dose levels, as well as the placebo. Thus, the entry criteria ensure that the intended population of rHTN is enrolled in this study based on the most recent international hypertension guidelines and maximize the chances of observing clear differences in the efficacy of the different treatment arms on the primary endpoint, while minimizing the screening and run-in failure rates.

Rationale for run in

Once participants qualify for the trial based on office BP measurement and other entry criteria, they will enter the Run-in Period in which they will be administered a placebo injection. This study medication will be administered in addition to their guideline-recommended pre-study optimal or maximally tolerated doses of triple background antihypertensive therapy. [redacted] At the end of the Run-in Period, participants must qualify for randomization by demonstrating that they remain hypertensive based on ABPM. Thus, the rationale for the Run-in Period is to exclude participants who may have uncontrolled blood pressure due to reasons unrelated to true rHTN, such as poor compliance with prescribed antihypertensive regimen and white coat hypertension, as well as those who may have clinically important BP responses to placebo. This ensures that only participants with true rHTN under study conditions will be randomized and the study sample will not be contaminated with participants who are not part of the intended target population.

Rationale for ABPM

The primary endpoint of this study is change from baseline in mean 24hr SBP based on ABPM. Ambulatory blood pressure monitoring is the method of choice for measuring blood pressure changes with new antihypertensive drugs as it allows an assessment of the effect of the drug over a 24-hour period, thereby also allowing for more granular BP assessments during the daytime, and the nighttime. It is considered to be a reference standard and is recommended by both the American and European guidelines for the evaluations of persons with hypertension (Whelton et al 2018, Williams et al 2018) for confirmation of a diagnosis of hypertension. Compared to office-based BP measurements, ABPM has better sensitivity and specificity as a diagnostic tool (Hodgkinson et al 2011). Ambulatory blood pressure monitoring also provides important information regarding the effects of activities of daily living on BP as well as changes in BP during wakefulness and sleep. In addition, multiple assessments can be obtained over a 24hr period which provides a robust assessment of the changes in BP during the day compared to single point estimates of office BP measurements on drug therapies. Both systolic and diastolic BP readings will be collected over a 24hr period; however, changes in mean 24hr SBP will be assessed as the primary endpoint in the study.

[redacted]

[redacted]

4.2.1 Participant input into design

Not Applicable

4.3 Justification for dose

Doses of XXB750 and administration regimen were selected based on the safety, tolerability, and pharmacodynamic profile observed in preliminary data from the first-in-human trial of XXB750 (Study CXXB750A02101). This is an ongoing study investigating the safety, tolerability, [redacted] and pharmacodynamics of single SC doses of XXB750 ranging from 1 mg to 600 mg. At the time of this protocol writing, XXB750 has been administered in healthy volunteers at doses of 1 mg, 3 mg, 10 mg, 30 mg, 60 mg, 120 mg, and 240 mg. There was no observed distinguishable effect on plasma cGMP or BP at doses of 1 mg, 3 mg, and 10 mg and placebo injection. XXB750 showed cGMP elevation and BP lowering effect at doses of 30 mg, 60 mg, 120 mg and 240 mg, which appeared to be greater than the effect of a placebo injection. For these doses, maximum plasma cGMP elevation was achieved at day 2 post-dose, and the BP lowering was slow and progressive, and achieved maximum effect by day 3. Placebo-adjusted maximum office SBP lowering at day 3 was approximately10-13 mmHg in the 30 mg, 60 mg, and 120 mg cohorts, and ~18 mmHg in the 240 mg cohort. The BPs showed a gradual return towards pre-dose values over the following weeks. At day 28 post-dose, plasma cGMP was lower than peak effect but still elevated at 30, 60, 120 and 240 mg dose compared to placebo, and the BP lowering effect was less pronounced than at peak, but still present in the 120 mg and 240 dose cohorts (SBP change from baseline of ~7 mmHg and ~5 mmHg, respectively). Given the sustained cGMP elevation and BP lowering and acceptable safety and tolerability profile, the 30 mg, the 60 mg, 120 mg, and 240 mg doses have been selected to be tested in this study to further investigate efficacy and safety of XXB750 in rHTN patients, and to support its use in subsequent studies as a once every 4 weeks SC administration regimen.

For more information about Study CXXB750A02101, please refer to the Investigator's Brochure.

4.3.1 Rationale for choice of background therapy

The current study requires all participants to be treated with optimal or maximally tolerated doses of a thiazide or thiazide-like diuretic, an ACEI or an ARB, and a long-acting dihydropyridine CCB, which are the three therapeutic classes recommended by international guidelines for treating with no heart failure, status-post myocardial infarction, angina, or any other need for heart rate control. These three classes of antihypertensives are commonly available and exploit different complementary mechanisms for lowering blood pressure. Per international guidelines for diagnosis and treatment of hypertension, patients treated with

optimal or maximally tolerated doses of medications from these three therapeutic classes and remain with uncontrolled blood pressure are considered to have rHTN (Williams et al 2018).

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The primary objective of the study is to assess the true BP lowering effect of various doses of XXB750. Therefore, placebo is chosen as the primary comparator in Stage 1 of this study as it serves as a good reference standard without any relevant pharmacological activity in the disease under study. Placebo as a comparator allows for better characterization of BP lowering responses of various doses of the study drug and for evaluation of the dose-response relationship. Since it is widely known that some patients may show a favorable response to treatment with placebo in clinical trials, a placebo-adjusted evaluation of treatment response still provides a clearer assessment of response as opposed to active comparators which have varying degrees of pharmacological effects in the population under study. Hence placebo will be the primary comparator to assess drug dose response in this study. From a safety perspective, the use of placebo as a control allows for the least possible confounded interpretation of the nature, the causality and the rate of adverse events observed in the overall study population.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

A staggered approach is planned to generate safety data in the target rHTN population with the three lower doses of XXB750 before enrolling participants to receive the highest dose. The staggered enrollment will follow the strategy outlined in Section 4.1 Table 4-1. In this strategy, 17 participants will be exposed to each of the lower doses of XXB750 (dose level 1, dose level 2 and dose level 3), and 17 participants will be exposed to placebo. The DMC will conduct an interim safety analysis on data of approximately 40 participants who complete at least 5 weeks of double-blind treatment. If the safety profile of the 3 lower XXB750 doses is acceptable, approximately 102 additional participants will be randomized and exposed to study medications (17 on XXB750 dose levels 1, 2, 3 and placebo and 34 participants on XXB750 dose level 4).

In addition to the planned early interim safety analysis, there will be safety data reviews conducted regularly by the DMC. Refer to Section 10.1.4 for more information about the role of the DMC in this study.

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). Please see Section 9.8 for more details.

4.7 End of study definition

Study completion is defined as when the last participant completes Week 20/EOS visit assessments as defined in Section 1.3 of the protocol.

5 Study population

The study population will consist of male and female participants 18 years old or older with apparent resistant hypertension as defined in the inclusion criteria. A total of approximately 170 participants will be randomized into this dose-response finding study.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Male and female participants who are ≥ 18 years old.
2. Signed informed consent prior to participation in the study.
3. Apparent rHTN at screening (Visit 1) defined as uncontrolled BP with an office msSBP ≥ 140 mmHg despite treatment with stable (i.e., unchanged for ≥4 weeks), optimal or maximally tolerated doses of three or four antihypertensive drugs of different classes, including an ACEI/ARB, a long-acting dihydropyridine CCB, and a thiazide or thiazide-like diuretic. Participant with documented intolerance to any doses of CCBs may be eligible if receiving another class of antihypertensive medication at an optimal or maximally tolerated dose (referred to as triple background antihypertensive therapy. An optimal dose is defined as the highest dose taking in to account participant's documented comorbidities and tolerability per investigator's clinical judgment. Refer to Section 10.8 for recommended minimum doses of some commonly prescribed ACEI/ARBs, long acting dihydropyridine calcium channel blockers and thiazide diuretics.
4. Mean 24hr SBP ≥135 mmHg (measured by ABPM) at the end-of Run-in-Visit (Visit 30) on treatment with optimal or maximally tolerated doses of an ACEI/ARB, a long-acting dihydropyridine CCB (or a suitable alternative in case of intolerance per inclusion criterion above), and a thiazide or thiazide-like diuretic.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Subjects with the following blood pressures at the specified time points are not eligible to participate in the study:
   a. Office msSBP <140 mmHg at Visit 20 OR
   b. Office msSBP ≥180 mmHg or office msDBP ≥110 mmHg at the end-of-run-in visit (Visit 30) OR
   c. 24h mean SBP >170 mmHg or 24h mean DBP >105mmHg measured by ABPM at the end of the run-in (Visit 30).
2. Known history of secondary hypertension (moderate-to-severe obstructive sleep apnea without receiving CPAP therapy (either face mask or nasal device), renovascular hypertension, primary aldosteronism, pheochromocytoma, Cushing syndrome, aortic coarctation or other cause of secondary hypertension).

3. Estimated GFR <30 mL/min/1.73m^2 using CKD-Epi equation at screening (Visit 1) or at end-of-run-in visit (Visit 30).
4. Serum potassium >5.0 mmol/L (or equivalent plasma potassium value) at screening or end-of-run-in visit (Visit 30).
5. Current therapy with a mineralocorticoid receptor antagonist (MRA) or sacubitril/valsartan or received an MRA or sacubitril/valsartan within the 4 weeks prior to screening.
6. Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma HbA1c ≥9%)
7. Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), high-grade AV block (e.g., Mobitz type II and third-degree AV block in absence of a pacemaker) within 6 months of screening according to investigator's judgement.
8. Chronic non-paroxysmal atrial fibrillation.
9. Acute myocardial infarction (AMI) or unstable angina, or any history of ischemic or hemorrhagic stroke within 12 months of screening; or any percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) within 12 months of screening
10. History of a renal denervation procedure.
11. Mid-arm circumference ≥ 44 cm. The cuff should snugly fit on the arm without the margins of cuff overhanging arm musculature.
12. Patients with history of hospitalization for hypertensive emergencies characterized by severe hypertension (usually grade 3) associated with funduscopic changes (flame haemorrhages and/or papilloedema), microangiopathy, disseminated intravascular coagulation, encephalopathy, acute aortic dissection, acute myocardial ischaemia, or acute heart failure any time prior to screening or hospitalization for non-emergent/non-urgent uncontrolled hypertension without target organ damage within 3 months prior to screening.
13. Receiving more than 4 antihypertensive medications.
14. Night shift workers.
15. History of presence of any other disease where the life expectancy is less than 3 years.
16. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 3 years, regardless of whether there is evidence of local recurrence or metastases.
17. Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), or bilirubin >1.5 mg/dl at Visit 1.
18. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
19. History of drug abuse or alcohol dependency.
20. Lacking the ability to comprehend or follow instructions, or for any reason in the opinion of the investigator, a participant that would be unlikely or unable to comply with study protocol.
21. Concurrent enrollment in any other investigational drug or device trial (participation in non-interventional registries is acceptable).
22. Requiring prolonged/regular use of NSAIDs except for prophylactic use of low dose aspirin up to 325 mg QD or other prohibited medications during the study (i.e., required use for longer than 1 week).

23. Pregnant, nursing or planning to become pregnant (documented negative pregnancy test required within a maximum of 7 days prior to enrollment of all women of childbearing potential). Documentation of highly effective contraception is also required for women of childbearing potential (see below).

    Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping medication. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptom-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral, (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age-appropriate history of vasomotor symptoms). Women are considered not of childbearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

24. History of hypersensitivity to any of the study drugs, excipients or drugs of similar class.

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and, therefore, does not enter into the Run-in Period of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (including clinical laboratory results if available), eligibility criteria, and any serious adverse event (SAE).

The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. Screening laboratory assessments will also be collected and entered into the clinical database. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event (SAE) during the screening period (see Section 8.6.3 for SAE reporting details). If the participant fails to be randomized, the IWRT (Interactive Web Response Technology)/IRT (Interactive Response Technology) must be notified within 2 days of the screen fail that the participant will not be randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated per the investigator's discretion to confirm the participant's eligibility for continuing in the study. If the repeat value remains outside of the specified range, the participant must be screen failed.

Individuals who do not meet the criteria for participation in this study (screen failure) will have one opportunity to be re-screened again for this study.

5.3.1 Replacement policy

Not applicable.

5.3.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant signs the ICF and is screened. This Participant No. is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened.

The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant number available.

A new ICF will need to be signed if the Investigator chooses to rescreen the participant after he/she has screen failed, and the participant will be assigned a new Participant number.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

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). Table 6-1 lists the investigational agents used in the study, including the control drug.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
XXB750 150 mg/mL	Concentration for solution for injection	Subcutaneous	Open label patient specific, Vials	Sponsor (global)
Placebo 0 mg/mL	Solution for injection	Subcutaneous	Open label patient specific, Vials	Sponsor (global)

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Treatment arms/group

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 at Week 4 and Week 8 (dose level 4).

6.1.3 Treatment duration

The planned duration of treatment is 12 weeks per participant. Participants may be discontinued from treatment earlier due to unacceptable adverse events, disease progression and/or if treatment is discontinued at the discretion of the investigator or the participant. Following the conclusion of the 12-week Randomized Treatment Period, participants will enter an 8-week Safety Follow-up Period in which participants may be treated at the discretion of the investigator taking into account that their blood pressure may still be affected by the study treatment for some time after its discontinuation, especially those who were randomized to XXB750.

6.1.4 Medical devices

Not Applicable

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section. It will contain XXB750 or placebo in vials for preparation by unblinded pharmacist or other qualified study site personnel.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to use in preparing the XXB750/matching placebo injectable dose for the participant by contacting the IRT and obtaining the medication number(s) of the required vial(s). Unblinded qualified and properly trained members of the study team at the site will prepare the study drug injection in a blinded way for study staff for injection. Immediately before dispensing the medication kit injection to the site personnel in charge of injecting the participant, site personnel preparing the study medication or his/her designee will detach the outer part of the label from the packaging of the vial(s) used for preparing the study medication dose and affix it to the source document. The instructions of how to prepare the injections of XXB750 and its matching placebo will be provided in a separate pharmacist manual.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP (Investigational Medicinal Product) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant’s home remains under the accountability of the Investigator.

Supply, preparation, IRT registration, dispensation and return of IMP will be described in Pharmacist Manual.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff (blinded or unblinded, as applicable) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. The Investigator must provide accountability also for locally sourced materials used for administration (e.g. i.v. syringes).

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

The treatment for administration will be handled and shipped in line with the pharmacy manual and required procedures for shipping.

6.2.2 Handling of other treatment

Components of the background antihypertensive therapy, which includes the thiazide or thiazide-like diuretic, the ACEI/ARB, and the long-acting dihydropyridine CCB that the participant was taking since screening will be monitored. Those medications will be monitored for compliance through whole duration of the study by asking participant about compliance and by obtaining urine samples for future chemical adherence testing as required.

6.2.3 Instruction for prescribing and taking study treatment

Table 6-2 shows how the study medications should be prescribed at each dispensing visit.

During the Single-blind Run-in Period participants will receive a single SC injection of placebo matching XXB750 in a single blinded fashion to ensure that the participant is unaware of the content of the medication.

A double-blind design is employed during the Randomized Treatment Period. Per Table 6-2, at every dispensing visit of the Randomized Treatment period all participants will receive a SC injection of XXB750/matching placebo according to the participant's randomized treatment assignment. Only the unblinded pharmacist or other qualified site personnel in charge of preparing the study medication will be aware of the contents of the dispensed/administered study medication. Refer to Section 6.2 for more details regarding the preparation of the study medications for dispensing.

Table 6-2 Study Drug/Control Drug

Visit	**Medication**	***Dose***	***Frequency and/or Regimen***
20	Placebo	n/a	SC once
100	XXB750	30 mg/60 mg/120 mg/matching placebo	SC once
130 and 150	XXB750	30 mg/60 mg/120 mg/240 mg/matching placebo	SC every 4 weeks for two doses

The XXB750/matching placebo injections will be administered subcutaneously to participants by a qualified study site team member at the site in the upper arm. All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

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). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by region. The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

For information on treatment assignments, randomization, participant numbering please refer to Section 5.3

6.3.2 Treatment blinding

Participants, investigator staff, and persons performing the assessments, will remain blinded to the identity of the treatment from the time of randomization until final database lock. Since the primary analysis is planned when all participants have completed the 12-week randomized, double-blind, placebo-controlled period, Novartis study team members will be blinded from time of randomization until the primary analysis database lock. The study side site pharmacist/nurse or other designated qualified site personnel who prepares the study drug and the unblinded CRA will remain unblinded.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the unblinded participant should be discontinued from the study treatment.

[redacted]

The following methods will be used to maintain the blind:

1. Randomization data will be kept strictly confidential until database lock for the primary analysis and will not be accessible by anyone else involved in the study with the following exceptions:
   - an independent analysis team that needs to prepare safety and efficacy interim and safety monitoring analysis reports for the DMC,
   - [redacted]
   - unblinded pharmacist/nurse or other designated qualified site personnel at study site and unblinded CRA monitoring the sites.

These personnel will not be involved in any other trial activities.

2. The identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, and odor. All

XXB750/matching placebo injections will be prepared such that they will all have the same injection volumes regardless of dose to maintain the blinding. Blinded label supply (also mention respective drug name) will be provided at sites to the unblinded site pharmacist or other designated qualified site personnel in order to prepare study drug and to conceal treatment code from participants and the investigator staff administering the study injections/dispending the study medications and performing the assessments.

[redacted]

At the time of safety review/interim analysis for design adaptation, the DMC will review unblinded safety/interim reports created by an independent analysis team. More details about the DMC review process and how unblinding data will be handled in the context of DMC reviews will be provided in the DMC charter.

Table 6-3 provides an overview of various key study personnel and their extent of unblinding.

Table 6-3 Blinding and unblinding plan

Role	Time or Event				
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis/ dose escalation/ safety review conducted by DMC	Primary analysis
Participants	B	B	B	B	B
Site Staff	B	B	B	B	B
Unblinded site staff, e.g. pharmacy staff	B	UI	B	B	B
Global Clinical Supply	UG	UG	UG	UG	UI
Randomization Office	UI	UI	UI	UI	UI
Unblinded Sponsor staff, e.g. for study treatment re-supply,	UG	UG	UG	UG	UI
Unblinded Pharmacovigilance Sponsor staff	B	B	UI	B	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	UI	UI	UI	UI	UI
Independent Statistician/statistical programmer/ data analysts (e.g. [redacted])/ unblinded monitor(s)	UI	UI	UI	UI	UI
Sponsor CTT	B	B	B	B	UI

Role	**Time or Event**				
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis/ dose escalation/ safety review conducted by DMC	Primary analysis
All other Sponsor staff not identified above (i.e. project team, management & decision boards, support functions)	B	B	UI	B	UI
B Complete blinded UG Unblinded at the group level (i.e has access to unblinded group level summary results, but not to the individual participant treatment codes) UI Unblinded to individual participant treatment codes					

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

In case of emergency unblinding, the participant should be discontinued from study treatment and continue with the study visits as scheduled without study medication administration.

6.4 Study treatment compliance

The investigator must promote adherence to treatment by instructing the participant to take the antihypertensive background therapy exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study results. This information

should be captured in the source document at each visit. All administered study treatment must be recorded in the Drug Accountability Log.

Injections of XXB750/matching placebo will be administered at the site. Study medication administration and compliance information must be captured in the source document, the appropriate CRF/s and in the Drug Accountability Log.

Adherence to the background antihypertensive therapy medications may be evaluated using urine drug screen by LCMS at end of run-in and Week 12 (EOT) post-randomization.

[redacted]

6.4.1 Recommended treatment of potential anticipated adverse events

Recommendations for handling hypertension and hypotension are described in Section 6.5.3 and Section 10.7, respectively.

Recommendations for handling Liver events are described in Section 10.5.1

Recommendations for handling potential drug induced liver injury (DILI) cases are described in Section 6.5.4.1

Recommendations for handling Renal events are described in Section 10.6.1

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.5 Dose modification

6.5.1 Dose escalation guidelines

Participants randomized into XXB750 dose level 4, will start at dose level 3 and will be up titrated at the Visit 130 (week 4 visit) to dose level 4.

6.5.1.1 Starting dose

Participants will be randomized to XXB750 dose level 1, dose level 2, dose level 3, dose level 4 or matching placebo. Participants randomized to XXB750 dose level 4 will start at dose level 3 and will be force up-titrated to dose level 4 at Visit 130 (week 4 visit).

6.5.1.2 Provisional dose levels

Table 6-4 XXB750 dose levels evaluated during this trial

Dose levels	Monthly dose	Increment from previous dose
1	30 mg	NA
2	60 mg	100%
3	120 mg	100%
4	240 mg	100%

6.5.2 Definitions of dose limiting toxicities (DLTs)

Not Applicable

6.5.3 Dose modifications

Except for force up-titration of study medications outlined in Section 6.5.1.1, Investigational study treatment dose adjustments and/or interruptions are not permitted. Participants who are considered to be intolerant to study medications should discontinue study treatment.

Safety criteria determining dose interruption or discontinuation based on liver or renal events are listed in Appendix 5 (Section 10.5) and Appendix 6 (Section 10.6), respectively. Deviations from mandatory dose interruptions and/or reductions are not allowed.

If the participant experiences severe hypertension (defined as SBP >180 mmHg confirmed by 3 readings 5 minutes apart), consider discontinuing all study medication and starting the subject on open label treatment accompanied by monitoring of BP as per local standard of care until the doses of the new medications are stable and BP is under control.

Dose modifications of background therapy

Dose adjustments of any component(s) of the background antihypertensive therapy medications and study medication due to hypotension are listed in Section 10.7.

6.5.4 Follow-up for toxicities

Refer to Appendix 5 (Section 10.5) for the follow-up of liver events and Appendix 6 (Section 10.6) for the follow-up of renal events.

6.5.4.1 Follow up on potential drug-induced liver injury (DILI) cases

Transaminase increases combined with total bilirubin increases may be indicative of potentially severe DILI and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline level] OR [AST or ALT > 300 U/L] (whichever occurs first) combined with [total bilirubin > 2 x baseline level AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/ International normalized ratio

(INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended. Refer to Section 10.5.1 for further guidance.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography [ERCP]) as appropriate, to rule out an extrahepatic cause of cholestasis.

Table 6-5. provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed liver function test (LFT) abnormalities.

Table 6-5 Diagnostic assessments to determine alternative causes of observed LFT abnormalities

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	• Cæruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin
MCV: mean corpuscular volume; ERCP: Endoscopic retrograde cholangiopancreatography; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus; CMV: cytomegalovirus; EBV: Epstein Barr virus; CD-transferrin: carbohydrate-deficient transferrin; MRI: magnetic resonance imaging; HBsAg: Hepatitis B virus surface antigen; HSV: Herpes simplex virus	

Other causes should also be considered based upon participants' medical history such as hyperthyroidism (causing thyrotoxic hepatitis where T3, T4, thyroid-stimulating hormone [TSH] should be tested), CV disease (causing ischemic hepatitis where an ECG could be performed, and the history of prior hypotensive episodes should be inquired), and Type 1 diabetes mellitus (causing glycogenic hepatitis).

[redacted].

Following the appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e. >50% likely), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant" and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed-up with the outcome clearly documented.

6.5.5 Retreatment criteria

Not Applicable

6.6 Continued access to study treatment after the end of the study

After the end of study continued care should be provided to the participant by the Investigator and/or referring physician as per the local Standard of Care.

6.6.1 Post trial access

No post-trial access program is planned for this trial. Participants who complete or prematurely discontinue participation in this trial will switch to Standard of Care treatment.

6.7 Treatment of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as required according to the pharmacodynamic and pharmacokinetic characteristics of the drug concerned.
- Obtain a plasma sample for PK analysis within 6 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.
- Follow the recommendations of the local label about overdose in case this involves any component of the background therapy

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment

errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study. The participant should be instructed and encouraged to report any new medications/therapies s/he takes at any point in the study.

Dose modifications of beta blockers and prostate-specific alpha blockers in patients taking these drugs for non-hypertension indications or benign prostatic hypertrophy, respectively, should be avoided until the completion of the Double-blind Treatment period.

Triple background antihypertensive therapy

As described in earlier sections of the protocol, all participants will receive the study medication on top of the optimal or maximally tolerated doses of their antihypertensive triple background therapy, which includes a thiazide/thiazide-like diuretic, an ACEI/ARB, and a long-acting dihydropyridine CCB Although participants will enter the run-in based on their optimal or maximally tolerated pre-study triple background and any other antihypertensive therapy they were taking for at least 4 weeks prior to screening, they may still experience adverse events (AEs) related to one or more of its components as they begin to take these medications under study conditions. This may be due to improved compliance, placebo effect, or other reasons. If, per the clinical judgment of the investigator, these AEs could be relieved by modifying the dose of the appropriate component of the background antihypertensive therapy during the run-in, the participant should not be randomized. Once the participants are randomized, every effort should be made to avoid dose modifications of the background antihypertensive therapy components for the 12-week duration of the Randomized Treatment Period, unless absolutely necessary to manage hypotension. Up titration of antihypertensive background therapy is not allowed.

If the participant experiences AEs of hypotension and non-pharmacological interventions were not effective in relieving these AEs, thereby necessitating a modification in the component(s) of the antihypertensive background therapy, please refer to Section 10.7 for instructions on the steps to be taken.

If the investigator decides that, as a last resort for treating the participant it is required to increase the doses of background antihypertensive therapy or to add other antihypertensive medications to a participant's regimen at some point during the 12-week Randomized Treatment Period, an

End of Treatment Visit will be conducted, including a 24-hr ABPM procedure. After that, the study medications can be terminated to allow for introduction of open label antihypertensive therapy according to local standard of care. The participant will continue to attend all remaining study visits as scheduled until the end of the study.

Patients should not take their background antihypertensive medications on the day of clinic visits. Instead they should bring them to the clinic and take them at the appropriate time witnessed by the study staff.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the participant is receiving study medication due to the increased possibility of the occurrence of hypotension.

Neseritide and intravenous (IV) nitrates

The concomitant administration of XXB750 with neseritide and IV nitrates has not been studied. In the event a study participant requires the concomitant administration of neseritide and/or IV nitrates with the study medications, the investigator should consider starting them at a low dose or a slow infusion rate while monitoring the participant's BP carefully.

6.8.2 Prohibited medication

Use of the treatments displayed in Table 6-6 are not allowed after start of single-blind placebo Run-in Period.

Table 6-6 Prohibited medication

Medication	Prohibition period	Action taken
Any antihypertensive treatment that is not part of the antihypertensive background therapy, including any new ACEi inhibitors, ARBs, DRIs, CCBs, or thiazide/thiazide-like diuretics or potassium-sparing diuretics, MRAs, β-blockers`, non-prostate-specific α-blockers, centrally acting agents, vasodilators, etc	Run-in and Double-blind Periods until Week 12 (while on study medication); any time within 48 hours prior to any study visit.	If use of prohibited medication can not be stopped, permanently discontinue study drug.
Sacubitril/valsartan	Run-in and Double-blind Periods until Week 12 (while on study medication)	Temporarily discontinue study drug if sacubitril/valsartan must be taken, and resume study treatment as soon as possible and as judged by the Investigator.
NSAIDs (prophylactic use of low dose aspirin up to 325 mg QD; paracetamol/acetaminophen are allowed*)	Use for greater than 3 consecutive days in the Run-in or 5 consecutive days in the Double-blind until Week 12 (while on study medication)	NSAIDs should be discontinued immediately and site personnel must be notified.

Medication	Prohibition period	Action taken
Sympathomimetic drugs, such as pseudoephedrine, phenylephrine, and other ephedrine derivatives, often found in oral/nasal decongestants, diet aids, attention deficit hyperactivity disorder**	>3 days per week during the Run-in and Randomized Treatment Period; any time within 48 hours prior to any study visit.	Discontinue the prohibited medication as soon as possible. If not possible, discontinue the study medication.
*Administration of paracetamol/acetaminophen (no more than 650 mg in a single dose and no more than 1300 mg per day) or topical NSAID preparations is acceptable but must be documented. **Regular use of bronchodilators for asthma/COPD is acceptable but must be documented.		

6.8.3 Rescue medicine

After completing the Double-Blind Treatment Period when the double-blind medication will be discontinued, the investigator will monitor the participant's health status and blood pressure to determine the need for modification of the participant's medication regimen. At this point, the investigator may make any modifications to the participant's medication regimen he/she deems necessary, including changes to the participant's antihypertensive regimen.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Participants who develop severe uncontrolled hypertension during the study and whose SBP remains >180 mmHg.
- Any situation in which continued study participation might result in an unacceptable safety risk to the participant. This includes adverse events, liver (Section 10.5) and renal (Section 10.6) events as described in the corresponding sections, as well as intolerance to investigational study drugs.
- Following emergency unblinding

The reasons for discontinuation from study treatment must be collected.

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in Section 1.3 Schedule of Assessment.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment all efforts should be made to continue follow-up as per study design; at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consented and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (may include, but are not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study.
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data.
- Discontinuation of study treatment development in rHTN.
- Changes in XXB750 development program that renders continuation of the study unnecessary.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. Participants should be invited for EOT visit and Investigator should ensure the participant will be appropriately switched into Standard of Care therapy. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis (depending on local regulation) will be responsible for

informing IRBs (Institutional Review Board) /IECs (Independent Ethics Committee) of the early termination of the trial.

8 Study Assessments and Procedures

The Assessment Schedule (Table 1-2) lists all the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 1-2) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Unscheduled visits can be performed by the site at the discretion of the investigator, in order to perform a safety evaluation or to retry assessments which were not completed at scheduled visits.

Visit 100 will be considered the reference visit for all study visits during the Randomized Treatment Period and Safety Follow-up Period. Regardless of the occurrence of any unscheduled visits, scheduled visits should be performed within the specified timeframe in relation to Visit 100 as outlined in Table 1-2. If a visit is completed earlier than scheduled or postponed, it should not result in the next visit being brought forward or postponed.

Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible and continue to attend any visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, when all the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and any adverse events and concomitant medications not previously reported must be recorded on the CRF.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

8.1 Screening

Once the participant has signed the informed consent form, the participant may enter the screening period.

An initial screening period can last approximately 7 days. Upon verification of eligibility inclusion/exclusion criteria, the participant will enter the Run-in Period. The Run-in Period will last up to approximately 2 weeks.

Participants who successfully complete the Run-in Period will be randomized and enter the Randomized Treatment Period and receive 3 months of study treatment.

Participants can be re-screened once if she/he fails initial screening.

In the case where a safety laboratory assessment at screening is outside of the allowed range specified in the entry criteria, a single retest to address any transient issues is allowed per the investigator's clinical decision.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographics: full date (only if required and permitted) or year of birth or age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to assess the degree of diversity of the study population as required by Health Authorities and to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics.

All prescription medications, over-the-counter drugs and significant non-drug therapies used before the start of the study must be documented. See the protocol Section 6.8 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy assessments

8.3.1 Ambulatory blood pressure monitoring

The first 24-hour ABPM assessment will be performed at Visit 30 (End of Run-in) and after the participant has met office BP criteria (i.e. msSBP < 180 mmHg and msDBP <110 mmHg). The second and third ABPM assessments will be performed at weeks 9 and week 12 (visit 160 and visit 170/EOT respectively), or earlier in the case of premature permanent discontinuation of blinded study drugs. ABPM assessments may be repeated at any of the visits listed above if there is a quality control finding.

ABPM Procedures

Patients should take their background medications in the clinic witnessed by the investigator or designee (and study medication when applicable) prior to attaching the ABPM device. The ABPM device should be attached to the non-dominant arm of the participant. The application/verification procedures consist of taking several readings using manual prompts to verify that the ABPM device is functioning properly and that no error codes are obtained during the application process. The verification process is not intended for comparison to the clinic reading but rather for confirming that the unit is working properly before prompting the 24-hour period to begin. Following the completion of the verification readings, the investigator or his/her staff would prompt an additional reading to identify the “Beginning of Test” time.

The ABPM unit will be automatically set to measure and record BP every 20 minutes during the day and every 30 minutes during the night.

At the completion of each ABPM assessment, the site staff will transmit the recording using a secure electronic process to a central lab where it will be assessed against a quality assurance (QA) algorithm designed specifically for this study. The QA algorithm will apply quality control specifications to determine the validity of the ABPM assessment within the 24hr period of interest. These specifications are outlined in the ABPM reference manual. A report will be transmitted to the site with the results of the ABPM assessments to indicate whether the recording was valid. It will also provide some key summary data, including mean 24hr SBP/mean 24hr DBP, mean daytime SBP/DBP, and other relevant data. A complete listing and definitions of the quality control criteria are outlined in the ABPM reference manual. If the report does not meet the study specific quality control criteria, at the investigator's discretion, the participant will be requested to complete a repeat monitoring period prior to beginning the next phase of the study.

[redacted]

[redacted]

8.3.4 Appropriateness of efficacy assessments

The efficacy of an antihypertensive drug is generally assessed by blood pressure change before and after starting the treatment with the drug. Blood pressure can be measured with automated devices for 24-hour BP monitoring and/or office BP measurement. The methodology for BP measurement and efficacy variables described in this protocol are appropriate and in line with guidelines for the treatment of hypertension and the evaluation of antihypertensive agents per international health authorities.

8.4 Safety assessments

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

Physical examinations will be performed by the investigator or his/her designee who are qualified to do so per local regulations/standards. A complete physical examination will include the examination of the general appearance, vital signs (blood pressure [SBP and DBP] and pulse), skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, the vascular, and the neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of the general appearance and vital signs (blood pressure [SBP and DBP] and pulse). Refer to Table 1-2 for details of the type and frequency of the physical examination.

Information about all physical examinations performed must be included in the source documentation at the study site. Clinically relevant findings that are present before signing informed consent must be recorded on the appropriate CRF page that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs include BP and pulse measurements. [redacted]

8.4.3 Electrocardiograms

Local 12 lead ECGs will be collected at Visits 1, 30, 170 and 1999.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECGs appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.4 Clinical safety laboratory tests

Safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits or as deemed appropriate by the investigator in the course of study conduct. Moreover, if it will minimize the inconvenience to the subject, local laboratories may be used to assess eGFR and potassium levels at the end of run-in visit to assess the subject's eligibility for randomization more quickly. In such case, an additional blood sample will be obtained at the same time to send to the central laboratory; results of the central laboratory need not confirm the results of the local laboratory. Results of local laboratory assessments should be recorded in the appropriate CRF along with their corresponding reference range. Clinically notable laboratory findings are defined in Section 10.3.1 Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. Investigator may repeat safety tests once if results are unexpectedly out-of-range per his/her clinical judgement.

Table 8-2 lists the clinical safety laboratory tests performed during the study. The tests with an asterisk (*) beside their names are part of the abbreviated panel of clinical safety laboratory tests.

Table 8-2 Clinical safety laboratory tests

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Differential (% Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), hemoglobin A1C

Test Category	Test Name
Chemistry	Albumin*, Alkaline phosphatase*, ALT* , AST* , Gamma-glutamyl-transferase (GGT)*, Lactate dehydrogenase (LDH), Calcium*, Magnesium, Phosphate, Chloride, Sodium*, Potassium*, Creatinine*, Creatine kinase*, Direct Bilirubin*, Total Bilirubin, Fasting Lipid Panel (Total Cholesterol, LDL Cholesterol, High-density lipoprotein [HDL] Cholesterol, Triglycerides), Total Protein, Blood urea nitrogen (BUN)*, eGFR*, Uric Acid, Amylase, Lipase, Glucose (random)
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel* (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time/INR*
Pregnancy Test	Serum / Urine pregnancy test
* test is part of the abbreviated panel of clinical safety laboratory tests	

8.4.5 Pregnancy testing

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

All pre-menopausal women who are not surgically sterile will undergo pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Serum pregnancy testing with beta-human chorionic gonadotropin (β-hCG) must be done at screening, at visit 30 (before randomization), Visit 170 (EOT) and Visit 1999 (EOS). Urine pregnancy test should be performed at Visits 130, 150 and 180. In case the urine pregnancy test is positive, the participant must contact and report to the investigator immediately. A positive urine pregnancy test must be confirmed with a serum pregnancy test. If the latter is also positive, the participant must be discontinued from study treatment.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test may be used at home as described above.

In general, the levels of a mAb like XXB750 in semen are expected to be low; therefore, the subsequent levels in female partner would be negligible. Based on this principle, the probability that XXB750 would cause teratogenicity is very low. Therefore, no restrictions will be placed on male participants with regard to sexual activity or condom use.

Assessments of fertility

Assessment of fertility must be performed at Screening. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy

2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle-stimulating hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening or baseline.

8.4.6 Other safety evaluations

8.4.6.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-1 and Table 10-3 in Section 10.5.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-3 and Table 10-5 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-4 and Table 10-5. Repeat liver chemistry tests (i.e., ALT, AST, total bilirubin (TBL), PT/INR, Alkaline phosphatase [ALP] and GGT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.

If a liver AE is reported that corresponds to these liver events, an assessment of the causal role of each study medication in the origin of the liver AE must be provided.

The following actions should be considered:

- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment, Section 7.1), if appropriate
- Hospitalization of the participant if appropriate

As well, the follow-up actions described in Section 6.5.4.1 should be performed. All follow-up information and findings from consultations and procedures must be recorded as appropriate in the CRFs.

8.4.6.2 Renal safety monitoring

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Section 10.6.1.

[redacted]

8.4.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population. [redacted]

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AE (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered

by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The severity grade, as follows:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken with study treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued at least until Visit 1999 or until 3 months after the last dose of injectable study drug, whichever is longer.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 10.3.

After an AE is reported by the Investigator, Novartis may require additional information from the investigator on that AE.

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that

do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

Treatment-emergent elevations in AST or ALT (>3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until End of Study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events. (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE (electronic Serious Adverse Event) with paper backup (as further detailed in the CRF Completion Guideline). Serious Adverse Event Report Form: all applicable sections of the form must be completed in order to provide a clinically thorough report. SAE reported after the EOS visit must be collected and reported to Novartis using the paper SAE form provided to the site.

Screen failures

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Run-in or Baseline failures

SAEs collected between the time the participant has provided informed consent until time that participant is determined to be a run-in failure or a baseline failure must be reported to Novartis.

Randomized participants

SAEs occurring between the time the participant has provided informed consent until either EOS visit or until 3 months after the last dose of injectable study drug (whichever is longer) must be reported to Novartis. Any SAE experienced by participants who discontinue study treatment prematurely but remain in the study for follow-up, should continue to be reported until either EOS visit or until 3 months after the last dose of injectable study drug (whichever is longer).

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the EOS visit or after 3 months after the last dose of injectable study drug (whichever is longer) should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Any female participant that becomes pregnant after signing the informed consent remain in the study and continue to attend scheduled study visits unless they withdraw informed consent

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same

form and should include an assessment of the possible relationship to the study treatment with any pregnancy outcome.

Any SAE experienced during pregnancy must be reported. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery. Post-natal follow-up should occur at 1, 3 and 12 months after delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

No disease-related events not qualifying as AEs or SAEs are specified in this study

8.6.6 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events which are of scientific and medical interest specific to Novartis's product or program, for which ongoing monitoring may be appropriate. Such events may require further investigation in order to characterize and understand them. AESI are defined on the basis of potential safety risks for the product, class effects, and data from preclinical studies. The following are currently defined as AESI for XXB750 in this study: serious hypotension (i.e., meeting any of the seriousness criteria listed in Section 8.6.2), serious hypersensitivity reactions (including, but not limited to, allergic reactions, anaphylaxis or anaphylactoid reactions, cytokine release syndrome, serum sickness or serum sickness-like reactions), serious injection site reactions, severe tachycardia, severe acute bradycardia and serious presyncope/syncope.

[redacted]

[redacted]

[redacted]

8.10 Health economics OR Medical resource utilization and health economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9 Statistical considerations

9.1 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.

9.2 Statistical analyses

9.2.1 General considerations

Data analyses are described in Section 9 of the study protocol with more details available in statistical analysis plan (SAP).

Unless specified otherwise, baseline 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.

All efficacy analyses will be based on FAS and all safety analyses will be based on SAF unless specified otherwise. In descriptive summaries, continuous variables will be summarized using n, mean, standard deviation (SD), median, minimum, 25th percentile (Q1), 75th percentile (Q3), and maximum; categorical variables will be summarized using frequency and percentage.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease history and standard background medications will be summarized descriptively by treatment group for the FAS and RAS.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group and overall.

9.2.3 Treatments

The duration of exposure in day(s) will be summarized by means of descriptive statistics and treatment group using the safety set. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by treatment group.

Number and percentage of participants on different antihypertensive medications as well as the doses will be summarized by treatment at baseline, Week 4, Week 8 and Week 12 during the randomized treatment period, and at Week 16 and Week 20 during safety follow-up period. The FAS and SAF will be used for these analyses.

9.3 Primary endpoint(s)/estimand(s) analysis

Primary estimands are described in Section 3.1. The primary endpoint and statistical analysis will be described in this Section.

9.3.1 Definition of primary endpoint(s)

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

Missing values at Week 12 will be imputed as described in Section 9.3.3 and Section 9.3.4.

9.3.2 Statistical model, hypothesis, and method of analysis

The primary objective of determination of a dose-response signal and to characterize 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 weights for the calculation of optimal contrasts between the responses in the studied dose groups and the placebo group. A statistical test comparing all doses in the different dose groups simultaneously to the placebo is used, hence a multiplicity adjustment is applied that accounts for the multiple possible dose response behavior considered. A critical value is derived from a multivariate t-distribution using the correlation matrix induced by the correlations between the weights corresponding to the candidate sets as well as the correlation between the tests of shapes in the dosing groups to the placebo group.

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:

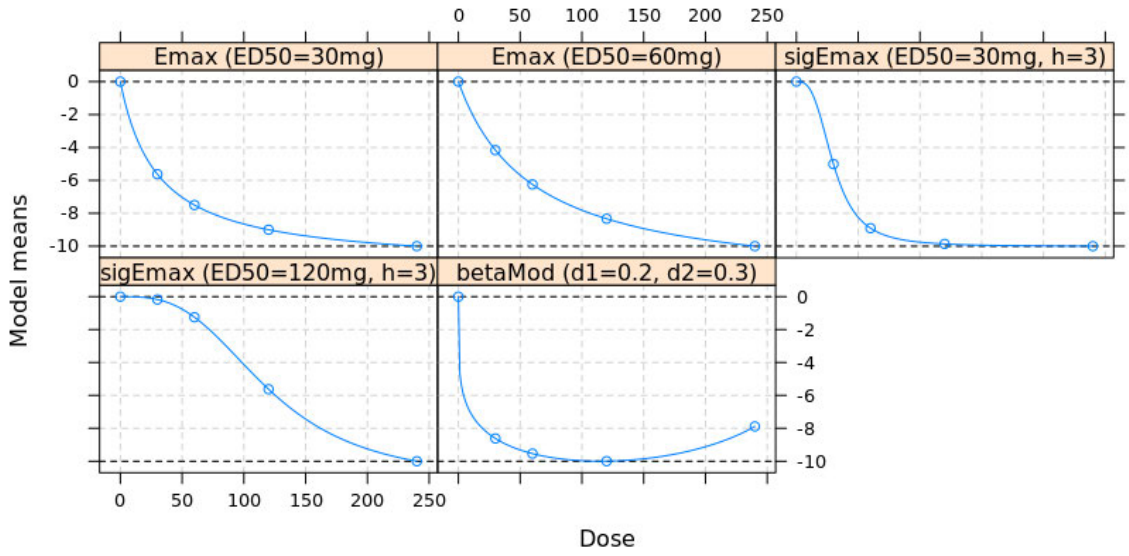
- $\mathbf{H_{10}}$: there is no dose-response relationship for XXB750 (i.e. all dose groups have the same response mean as the placebo group).
- $\mathbf{H_{11}}$: there is a dose-response relationship for XXB750 (i.e. at least one dose-groups has a response mean different from the placebo group).

There are five candidate models to capture the shape of the dose-response relationship for XXB750 at Week 12 endpoint, as depicted in Figure 9-1. 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 9-1 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 antihypertensive medications (3 or >3), and region 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 9.3.3 and Section 9.3.4. 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 test the candidate dose response models with respect to comparing all XXB750 dose groups to placebo.

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) $\geq C_{0.025}$.

Model averaging to obtain the dose response

A parametric bootstrap-based model averaging approach (Pinheiro et al 2014) 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.
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, 2.5th and 97.5th percentiles) of these multiple sets of dose-response and target dose estimates generated in step 3. In addition, the bootstrapping model-based medians over the range from 0 mg (placebo) to 240 mg with 95% point-wise confidence interval (2.5^{th} and 97.5^{th} percentiles) will be displayed in a figure.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

Intercurrent events for the primary endpoint are defined in Section 3.1 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. If there is no or very limited participants with observed endpoint after intercurrent event(s) in the respective treatment group, then missing 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.

9.3.4 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)). The imputation model will include the longitudinal sequence of mean 24hr SBP data collected at baseline, Week 9 and Week 12 visits, number of background antihypertensive medications (3 or >3), region, and other baseline variables as appropriate, imputing for each treatment group separately.

The full detailed information about the multiple imputation algorithms will be specified in a separate statistical analysis plan.

9.3.5 Multiplicity adjustment (if applicable)

Please refer to Section 9.3.2 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.

9.3.6 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 patients 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.

9.3.7 Supplementary analysis

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 measure (MMRM) analysis of covariance (ANCOVA) with treatment, number of background antihypertensive medications (3 or >3), region, 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 9.3.4 and the newly imputed data will be used in the analysis as described in Section 9.3.2.
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 data taken at the end of treatment visit as the Week 12 assessment and repeat the analysis described in Section 9.3.2.
5. Subgroup analyses will be performed for the primary analysis. The analysis will be done using the analysis specified in Section 9.3.2 at individual subgroup level separately. Please see Section 9.7 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 raw and the imputed mean changes by visit over 12 weeks randomized treatment epoch for each treatment group. FAS will be used for the analyses.

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary efficacy endpoints are described in Section 9.4.1 and are part of the hierarchical testing strategy. Analyses related to safety endpoints are described in Section 9.4.2.

9.4.1 Efficacy endpoints

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.

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 or >3), region, 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 3.2 and Section 9.3.3 for the intercurrent events and its handling strategy and Section 9.3.4 for handling missing data not related to intercurrent event. The analysis will be run on each of the imputed datasets as

described in Section 9.3.2. Overall results are obtained by applying Rubin's rules on the estimates obtained from imputed datasets.

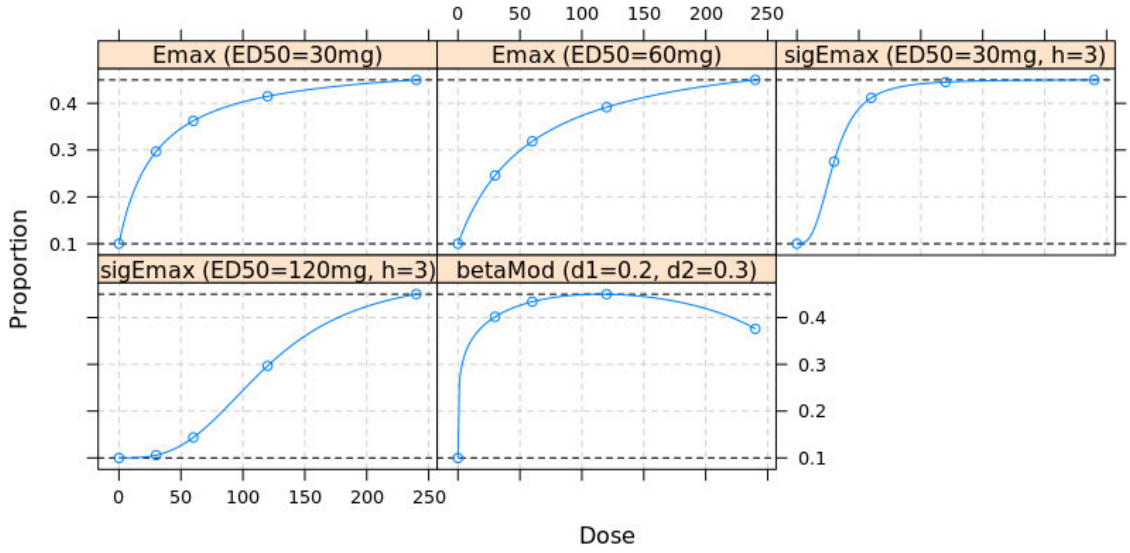
The efficacy variable in secondary objective 2 is the average change from baseline at Week 9 and Week 12 in the mean 24hr SBP and will be analyzed using an analysis of covariance (ANCOVA) model including treatment, number of background antihypertensive medications (3 or >3), and region as fixed-effect factors and baseline mean 24hr SBP as covariate. Within treatment and between treatment comparisons will be provided. Please refer to Section 3.2 and Section 9.3.3 for the intercurrent events and its handling strategy and Section 9.3.4 for handling missing data not related to intercurrent event. The analysis will be run on each of the imputed datasets as described in Section 9.3.2. Overall results 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 9-2. 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 9-2 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 9.3.2, 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 or >3), and region 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 3.2, and the handling of missing not related to intercurrent events in Section 9.3.2 and Section 9.3.4 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.

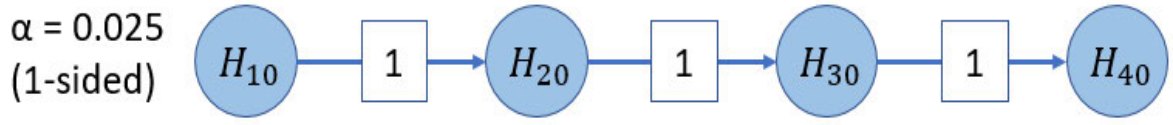
The statistical testing procedure described below will be carried out for the multiple treatment comparisons in the primary and secondary efficacy objectives to ensure that the overall significance level for the multiple hypotheses to be tested is controlled at the one-sided 0.025 level (i.e. two-sided 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. all dose groups have the same response as the placebo group) 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 9-3 below. The sequentially rejective multiple test procedure is completed until no more hypothesis can be further rejected.

Figure 9-3 Sequentially rejective multiple testing procedure



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

9.4.2 Safety endpoints

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

Adverse events

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

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation, and adverse events leading to dose adjustment.

The number (and proportion) of participants with adverse events of special interest and related to potential risks (as per the Investigator's Brochure) will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

More details on the analysis of AE will be described in the Statistical Analysis Plan (SAP).

Vital signs

Summary statistics will be provided by treatment and visit for all vital signs, as well as for the proportion of participants presenting with clinically notable abnormal values. Graphical displays of the values of selected vital signs over time may be provided by treatment group.

More details on the analysis of vital signs will be described in the Statistical Analysis Plan (SAP).

12-lead ECG

A standard 12 lead ECG will be performed at Visit 1, visit 30, visit 170 and visit 1999. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study and subject number, date, and kept in the source documents at the study site. Clinically significant abnormalities

should also be recorded on the Medical History/AE CRF page. Summary statistics for continuous data and number and percentage of participants for categorical data (e.g. interpretation) will be provided by treatment and visit.

More details on the analysis of ECG parameters will be described in the SAP.

Clinical laboratory evaluations

Laboratory data collected during the study will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), summary statistics of raw data and change from baseline. The number of participants meeting pre-defined clinically notably laboratory values and percent changes will also be summarized.

For the rate change in eGFR, the eGFR slope will be estimated from a repeated measures ANCOVA model including treatment, number of background antihypertensive medications (3 or >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.

More details on the analysis of clinical laboratory parameters will be described in the SAP.

[redacted]

[redacted]

[redacted]

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[redacted].

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- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

9.6 (Other) Safety analyses

Please refer to statistical analysis plan for details.

9.7 Other analyses

Subgroup analyses

The subgroups of interest for primary endpoint and selected secondary endpoints include but are not limited to:

- Age (<60, >=60 years)
- Age (<=median, > median)
- Sex (male, female)
- Region
- Number of background antihypertensive medications (3, >3)
- eGFR (<60, >=60 mL/min/1.73m^2)

Please refer to statistical analysis plan for details.

9.8 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. 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.

9.9 Sample size determination

9.9.1 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.

9.9.2 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.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, Investigational directions for use (IDFU), and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required,

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority.

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative. Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant’s agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB) and Core Data Sheet for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or

an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- Optional Genetics Consent to provide a sample for [redacted]

The study includes an optional sub studies/ [redacted] which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments [redacted] will in no way affect the participant's ability to join the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

The study will have support of a Data Monitoring Committee and an Executive Committee.

10.1.4.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site Investigators participating in the study. The DMC will assess at defined intervals the progress of the clinical trial, safety data, and critical efficacy variables as needed and recommend to Novartis whether to continue, modify, or terminate the trial.

Specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between Novartis and the DMC.

10.1.4.2 Executive Committee

The Executive Committee (EC) will be established comprising of outside experts, i.e., not being members of the DMC and Novartis representatives from the Clinical Trial Team.

The EC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The EC will review protocol amendments as appropriate. Together with the Clinical Trial Team, the EC will also develop recommendations for publications of study results including authorship rules.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g. risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-

enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC (Electronic Data Capture) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO-Contract Research Organization) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in monitoring guidelines.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information,

observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
ACEi	Angiotensin Converting Enzyme Inhibitor
[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANCOVA	Analysis of covariance
ANP	Atrial Natriuretic Peptide
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BNP	B-type natriuretic peptide
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CCB	Calcium Channel Blocker
cGMP	cyclic guanosine monophosphate
CKD	Chronic Kidney Disease
CMV	cytomegalovirus
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
EBV	Epstein Barr virus
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
ESRD	End-Stage Renal Disease
FAS	Full Analytical Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
[redacted]	[redacted]
hr	Hour
HSV	Herpes simplex virus
HTN	Hypertension
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

[redacted]	
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous (IV)
IWRS	Interactive Web Response System
LCMS	Liquid Chromatography tandem Mass Spectrometry
LFT	Liver function test
MAR	Missing at random
MCP-MOD	Multiple Comparison Procedure- Modeling
mg	milligram(s)
mL	milliliter(s)
MRA	Mineralocorticoid Receptor Antagonist
msDBP	mean sitting Diastolic Blood Pressure
msSBP	mean sitting Systolic Blood Pressure
mwSBP	mean weekly Systolic Blood Pressure
NP	Natriuretic Peptide
NPR	Natriuretic peptide receptor
NSAID	Non-Steroidal Anti-Inflammatory Drug
PDE-5	Phosphodiesterase-5
PK	Pharmacokinetic(s)
PT	prothrombin time
q4w	once every 4 weeks
QA	Quality Assurance
RAAS	Renin Aldosterone Angiotensin System
RAS	Randomized Analysis Set
rHTN	Resistant Hypertension
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SCR	Screened Set
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
ULN	upper limit of normal

10.2.2 Definitions

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.

Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening or prior to administration of single blind study medication and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Clinically notable laboratory abnormalities for selected tests performed by Central Laboratory (based on: 1) proportional or absolute changes from baseline; 2) the limit of the normal range established by the Central Laboratory; 3) cut-off values used to define Grade 3 as established by the Common Terminology Criteria for Adverse Events [CTCAE] (CTCAE) v 5.0 or higher)

Hematology

Table 10-1 Clinically notable hematology abnormalities

Parameter	Shift	Criteria
Red blood cell count	Increase	> 50% increase AND value > ULN
	Decrease	> 30% decrease AND value < LLN
Hemoglobin	Increase	> 50% increase AND value > ULN
	Decrease	either (> 30% decrease AND value < LLN) OR value < 8.0 g/dL
Hematocrit	Increase	> 50% increase AND value > ULN
	Decrease	> 30% decrease AND value < LLN
White blood cell count	Increase	value > 100,000 cells/mm^3
	Decrease	value < 2000 cells/mm^3
Platelet count	Decrease	value < 50,000 platelets/mm^3
ULN: upper limit of the normal range; LLN: lower limit of the normal range		

Blood chemistry

Table 10-2 Clinically notable blood chemistry abnormalities

Parameter	Shift	Criteria
Alkaline phosphatase	Increase	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormally high.
ALT (SGPT)	Increase	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormally high.
AST (SGOT)	Increase	value > 5 x ULN if baseline was normal OR value > 5 x baseline if baseline was abnormally high.
Total bilirubin	Increase	value > 3 x ULN if baseline was normal OR value > 3 x baseline if baseline was abnormally high.
BUN	Increase	≥ 50% increase
Creatinine	Increase	≥ 50% increase
Potassium	Increase	value > 6.0 mmol/L
	Decrease	value < 3.0 mmol/L
Chloride	Increase	> 115 mEq/L
	Decrease	< 90 mEq/L

Parameter	**Shift**	**Criteria**
Calcium	Increase	corrected serum calcium > 3.1 mmol/L
	Decrease	corrected serum calcium < 1.75 mmol/L
Uric acid	Increase	> 50% increase
Plasma glucose	Increase	> 25% increase
	Decrease	value < 40 mg/dL
ULN: upper limit of the normal range		

Along with investigators, the clinical trial team from Novartis will receive alerts for clinically notable values via fax/e-portal (or appropriate means agreed with central labs and Novartis).

10.4 Appendix 4: Participant Engagement

Not applicable.

10.5 Appendix 5: Liver safety monitoring

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-3 Liver event and laboratory trigger definitions

	Definition/ threshold
If ALT or AST normal at baseline	
Liver laboratory triggers	*· 3 x ULN < ALT or AST ≤ 5 x ULN* *· TBL > ULN**
Liver events	*· ALT or AST > 5 × ULN* *· ALP > 2 × ULN (in the absence of known bone pathology)* *· Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)* *· ALT or AST > 3 × ULN AND (TBL > 2 x ULN OR INR > 1.5)* *· Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)†* *· Any clinical event of jaundice (or equivalent term)* *· ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia* *· Any adverse event potentially indicative of a liver toxicity*
If ALT or AST elevated at baseline:	
Liver laboratory triggers	*· ALT or AST > 2 x baseline or > 200 U/L (whichever occurs first)* *· TBL > ULN**
Liver events	*· ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first)* *· (ALT or AST > 2 × baseline or > 200 U/L [whichever occurs first]) AND (TBL > 2 x ULN OR INR > 1.5)* *· ALT or AST > 5 × ULN* *· ALP > 2 × ULN (in the absence of known bone pathology)* *· Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome)* *· Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)* *· Any clinical event of jaundice (or equivalent term)* *· (ALT or AST > 2 × baseline or > 200 U/L [whichever occurs first]) accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia* *· Any adverse event potentially indicative of a liver toxicity*
* Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines † Please, consult Section 8.6.2 on reporting requirements of potential Hy's Law cases	

Table 10-4 Follow-up requirements for liver triggers (based on ALT, AST and TBL values)

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **No change to study treatment** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **Interrupt study drug** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms. · Initiate close monitoring and workup for competing etiologies. · Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 200 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 200 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-5 Follow-up requirements for liver laboratory triggers based on isolated elevations in TBL

Criterion	***Actions required***	***Follow-up monitoring***
Total Bilirubin (isolated)		
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation. Treat alternative causes according to local institutional guidelines	As shown below according to the degree of elevation
>1.5 – 3.0 x ULN	· *Maintain treatment* · *Repeat LFTs within 48-72 hours*	*Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline*
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	· *Interrupt treatment* · *Repeat LFT within 48-72 hours* · *Hospitalize if clinically appropriate* · *Establish causality* · *Record the AE and contributing factors (e.g. concomitant medications, medical history, lab test) in the appropriate CRF*	*Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT)* *Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)*
> 10 x ULN	· *Discontinue the study treatment immediately after all other alternative causes are ruled out* · *Record the AE and contributing factors (e.g. concomitant medications, medical history, lab test) in the appropriate CRF*	*Monitor ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at investigator discretion)*
Any AE potentially indicative of a liver toxicity	· *Consider study treatment interruption or discontinuation* · *Hospitalization if clinically appropriate* · *Establish causality* · *Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF*	*Investigator discretion*

10.6 Appendix 6: Renal safety monitoring

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-6 Renal event criteria and corresponding actions to be taken upon their occurrence

Renal event	Actions
Confirmed serum creatinine increase of 25 – 49% from baseline	• Consider causes and possible interventions • Follow-up within 2-5 days
Confirmed serum creatinine increase ≥ 50% from baseline (corresponds to KDIGO criterion for acute kidney injury)	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 300 mg/dl OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin and serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset of hematuria ≥ 1 mg/dl on urine dipstick	• Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess serum creatinine • Exclude infection, trauma, bleeding from the distal urinary tract or bladder, menstruation • Consider bleeding disorder

FOLLOW-UP OF RENAL EVENTS

Assess, document and record in CRF:

- Urine dipstick and sediment microscopy evidence of drug-induced nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells
- Blood pressure and body weight
- Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid
- Urine output

Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF

Monitor participant regularly (frequency at investigator's discretion) until:

- Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr)

or

- Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
- Analysis of urine markers in samples collected over the course of the DIN event

10.7 Appendix 7: Managing hypotension

Investigators should monitor BP closely and review [redacted] where available to identify episodes of symptomatic hypotension at each clinic visit. All episodes of symptomatic hypotension should be reported as adverse events. [redacted]

As a general guidance the following events require action:

- Persistent symptomatic hypotension regardless of blood pressure readings
- [redacted]
- [redacted]
- [redacted]

Ensure the participant's hydration status is adequate and that there is no other clinical reason for hypotension that may need attention.

If appropriate, adjust any non background antihypertensive concomitant medications potentially contributing to hypotension (e.g., tricyclics, hypnotic sedatives, beta blockers for non-CV disorders, etc.) and increase sodium intake by favoring salty foods.

If the above interventions do not resolve the hypotension AE, adjust the doses of one or more background medicines as necessary depending on participant's tolerability profile and laboratory assessments. Investigator should exercise best clinical judgement based on laboratory assessments, volume status and any other clinical considerations in individual subjects.

[redacted].

If hypotension persists and no further action can be taken with background therapy, the study drug should be withdrawn. No down titration of study drug dose is allowed.

XXB may increase the risk of prolonged hypotension in case of acute hemorrhage or hypovolemia. Subjects should be managed with appropriate fluid replacement and should be carefully monitored for hemodynamic stability. There is no antidote to XXB available at this time. Diuretics, RAS blockers, and CCBs may be stopped and resumed when hypotension is resolved.

10.8 Appendix 8: Recommended minimum doses of background medication

Table 10-7, Table 10-8, Table 10-9, Table 10-10 list the minimum doses of commonly prescribed thiazide/thiazide-like diuretics, long-acting dihydropyridine CCBs, ACEIs, and ARBs the participant is recommended be on .

If the participant is not receiving the maximum dose per locally approved label and/or treatment guideline, the reason for that must be properly documented in the participant's eCRF.

Table 10-7 Thiazide or thiazide-like diuretics

Medication name	Minimum daily dose
Chlorthalidone	12.5 mg
Hydrochlorothiazide	25 mg
Metolazone	2.5 mg (or 0.5 mg SR)
Indapamide	2.5 mg (or 1.25 mg XL)
Bendroflumethiazide	2.5 mg
Hydroflumethiazide	25 mg
Trichlormethiazide	2 mg
Xipamide	20 mg
Potassium sparing diuretics (excluding MRAs such as spironolactone and eplerenone) either in combination or in addition to Thiazide / thiazide like diuretics are allowed.	

Table 10-8 Long-acting dihydropyridine calcium channel blockers (CCBs)

Drug name	Minimum daily dose
Amlodipine	5 mg
Nifedipine (extended release)	60 mg
Felodipine (extended release)	5 mg
Lercanidipine	20 mg
Nitrendipine	20 mg OD (long acting)

Table 10-9 Angiotensin converting enzyme inhibitors

Drug name	Minimum daily dose
Benazepril	20 mg
Captopril	100 mg (50 mg BID)
Cilazapril	5 mg
Enalapril	20 mg
Fosinopril	40 mg
Imidapril	10 mg
Lisinopril	20 mg
Moxepril	15 mg
Perindopril	4 mg
Quinapril	20 mg
Ramipril	10 mg
Trandolapril	4 mg
Zofenopril	60 mg

Table 10-10 Angiotensin receptor blockers

Drug name	Minimum daily dose
Losartan	100 mg
Candesartan	16 mg
Eprosartan	600 mg
Irbesartan	150 mg
Telmisartan	40 mg
Olmesartan	20 mg
Azilsartan medoximil	40 mg
Valsartan	160 mg

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References are available upon request

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