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

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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....

Ethical review	Approved WMO
Status	Completed
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON53418

Source
ToetsingOnline

Brief title
CXXB750B12201

Condition

- Vascular hypertensive disorders

Synonym
Resistant Hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: Dose finding, Resistant Hypertension, XXB750

Outcome measures

Primary outcome

Change from baseline in mean 24hr SBP at Week 12 (dose-response relationship)

Secondary outcome

• Change from baseline in mean 24hr SBP at Week 12

• Average of changes from baseline ion 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)

Study description

Background summary

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). 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. 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). 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. One way to efficiently modulate the NP system is by direct NPR-1 agonism. XXB750 is a long-acting fully human monoclonal IgG1 antibody agonist of NPR-1 with a half-life of approximately 16 days 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.

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.

See protocol page 18-21.

Study objective

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.

See protocol page 18.

Study 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

Approximately 170 participants will be randomized to receive placebo, XXB750 30 mg, 60 mg, 120 mg, or 240 mg SC every 4 weeks.

A staggered approach to enrollment will be followed in this protocol. The randomized participant sample will be divided into two groups:
- 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.
- 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.

See study protocol page 27-31 (and figure 1.1).

Intervention

During the Single-blind Run-in Period participants will receive a single SC injection of placebo matching XXB750 in a single blinded fashion

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).

See page 40-41 of the study protocol.

Study burden and risks

All study participants are expected to benefit from intensive monitoring of their blood pressure and overall health while receiving the 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.

Based on the results from previous studies performed in healthy volunteers, the laboratory and in animals, as well as on known risks of other drugs that have characteristics similar to XXB750, the possible risks or side effects of the study treatment may include:
• Reduced blood pressure, with or without symptoms, such as dizziness, light-headedness or fainting
• Heart rate becoming faster or slower than usual
• Allergic reactions to XXB750, including serious, potentially life-threatening allergic reactions
• Itching, pain, redness, skin rash, swelling of the skin at the site of the study medication injection

Burden due to study visits and procedures:
• The risk of collecting blood may include fainting, pain and /or bruising. Rarely, these may be a small blood clot or infection at the site of the needle puncture.
• Discomfort from 24-hour blood pressure measurement (mostly at night).

See p. 21-23 of the study protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Male and female participants who are >=18 years old.
• 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.
• 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.

Exclusion criteria

• 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).
• 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/1.73m2 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 sacaubitril/valsartan, received an MRA or sacaubitril/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.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	15-03-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	XXB750

Generic name:	XXB750

Ethics review

Approved WMO Date:	29-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2023
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	05-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-005738-41-NL
ClinicalTrials.gov	NCT05562934
CCMO	NL82328.018.22