A randomized, participant and investigator blinded, sponsor open-label, placebo-controlled, single and multiple dose study to investigate the safety and tolerability of XXB750 in heart failure participants with reduced or mildly reduced ejection fraction (HFrEF/HFmrEF)

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To evaluate the safety and tolerability of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Interventional

Summary

ID

NL-OMON53896

Source
ToetsingOnline

Brief title
CXXB750A12101

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym

Chronic heart failure, reduced ejection fraction

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: Chronic heart failure, XXB750

Outcome measures

Primary outcome

To evaluate the safety and tolerability of a XXB750 in adult participants with

chronic stable heart failure with reduced or mildly reduced ejection fraction

(HFrEF/HFmrEF). Endpoints: adverse events, vital signs (blood pressure, pulse),

safety laboratory tests, ECG parameters

Secondary outcome

To evaluate the pharmacokinetics of XXB750 in adult participants with

HFrEF/HFmrEF (XXB750 Tmax, Cmax, AUClast, AUCinf, CL/F, Vz/F, and T1/2)

Study description

Background summary

Heart failure (HF) is a major public health issue characterized by significant mortality, frequent hospitalizations, and poor quality of life, with an overall prevalence that is increasing throughout the world. In the United States (US) alone, over 6 million patients have heart failure (HF), and around half of them have a reduced left ventricular ejection fraction (HFrEF). Heart failure as a primary diagnosis accounts for over 800,000 hospitalizations/year and over $30 billion in costs. Recently, sacubitril-valsartan has been shown to lead to significant improvement in cardiovascular outcomes in patients with HFrEF and

in those with lower-than-normal EF. Treatment with sacubitril/valsartan results in an indirect stimulation of NPR1 by increasing the circulating levels of ANP and BNP through the inhibition of neprilysin, the enzyme responsible for degrading the NPs. Therefore, chronic NPR1 stimulation can represent an effective treatment for chronic HFrEF.

XXB750 is a fully human monoclonal IgG1 antibody agonist of the NPR1. XXB750 has a predicted half-life of ~18 days. The action of XXB750 is specific for NPR1 because XXB750 selectively binds to and activates NPR1, while it does not bind to NPR3 or activate NPR2 in vitro. XXB750 replicates the action of ANP (increasing plasma cGMP, lowering BP and increasing diuresis) in non-clinical pharmacology studies. XXB750 effectively substitutes for ANP in ANP knockout mice, reversing both cardiac hypertrophy and elevations in NT proBNP. XXB750 also increases plasma cGMP and lowers BP in cynomolgus monkeys. In humans, XXB750 has been administered in a Phase 1 study (CXXB750A02101; currently ongoing), and it has shown expected pharmacodynamic effects (cGMP increase, blood pressure lowering) and has been safe and well tolerated at single s.c. doses up to 450 mg in healthy volunteers. These data, together with evidence in humans of the beneficial effects of ANP and other ANP mimetics in heart failure patients, provide a scientific rationale to develop XXB750 for chronic heart failure.

See p. 28 study protocol

Study objective

To evaluate the safety and tolerability of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.

Study design

This is a multi-center, randomized, sponsor open-label, participant and investigator blinded, placebo-controlled, single and multiple dose study to investigate the safety and tolerability of XXB750 in participants with HFrEF/HFmrEF. A screening period of up to 29 days will be used to assess participants' eligibility. This study will consist of 2 cohorts. Cohort 1 will include participants on stable therapies of ACEi/ARB and beta-blockers, in addition to other standard of care medications. Cohort 2 will consist of participants treated with sacubitril/valsartan and beta-blockers, in addition to other standard of care medications.
Approximately 24 eligible participants will be randomized into the study. For Cohort 1, approximately 12 participants will be randomized in a 2:1 ratio to receive a single dose of subcutaneous (s.c) XXB750 120 mg or placebo. For Cohort 2, approximately 12 participants will be randomized in a 3:1 ratio to receive three doses of either s.c. XXB750 or placebo.
Cohort 1: After an initial domiciling period following study drug

administration, participants will be followed for 13 weeks post-dosing for safety, tolerability and PK until the End of Study visit on Day 91. As an additional safety measure, dosing will be conducted in a stepwise approach utilizing sentinel dosing of the first two participants in Cohort 1 (one in placebo, one in XXB750 group).
Cohort 2: After a domiciling period following initial study drug administration of XXB750 120 mg or placebo, participants will be followed for 27 days post-dosing for safety, tolerability and PK. On Day 28, participants will be re-domiciled and receive a matching dose of either 120 mg XXB750 or placebo. Participants will be followed for another 27 days post-dosing for safety and tolerability. On Day 56, participants will be re-domiciled and receive a matching dose of either 240 mg XXB750 or placebo. After the third domiciling period, participants will be followed for 13 weeks post-dosing for safety, tolerability and PK until the End of Study visit on Day 146. As an additional safety measure, up to 4 sentinel participants will be observed and monitored up to the Day 34 visit (approximately at Day 7 following the second dose) to allow for the detection of any safety events before allowing the remainder of the cohort to receive the second dose (120 mg XXB750 or placebo). Similarly, up to 4 sentinel participants will be observed and monitored up to the Day 62 visit (approximately at Day 7 following the third dose) to allow for the detection of any safety events before allowing the remainder of the cohort to receive the third dose (240 mg XXB750 or placebo). Safety monitoring will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), and adverse event monitoring.

See p. 30-33 of study protocol.

Intervention

Treatment with XXB750 or placebo s.c.

Study burden and risks

This is the first time XXB750 is tested in HFrEF/HFmrEF participants; therefore, no benefit has been established in patients with HFrEF/HFmrEF. However, several of the biologic effects of NPR1 agonism are believed to be beneficial in heart failure, such as improved renal function, diuresis, reduction of systemic peripheral resistance, antagonism of the renin-angiotensin system, modulation of the sympathethic tone, and myocardial-specific effects. These effects, might lead to an improvement in the clinical symptoms of HFrEF/HFmrEF during the course of the study following the single and multiple treatment injection(s). These beneficial effects might be transient due to the limited duration of the dose regimens in this study. Measurements of HF symptoms and efficacy biomarkers will be measured throughout this study.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, in-patient unit domiciling period(s) for close safety observation, sentinel dosing, and the study stopping rules.

Potential risks identified in the nonclinical toxicology studies:
- Hypotension and changes in blood volume
- Potential risk associated with immunogenicity
- Potential risk of hypersensitivity reactions
- potential risk of injection site reaction

Discomfort of (smart) blood sampling.

Burden of study visits and domiciling period of 7 days (Cohort 1) or 3 domiciling periods of 3-4 days (Cohort 2)

See p. 40-41 of study protocol.

Contacts

Public
Novartis

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Men or women age 18 to 80 years
• NYHA functional class II-III
• LVEF <= 50%
• Systolic blood pressure (SBP) 110 - 160 mmHg (Cohort 1) or SBP 105 - 160 mmHg (Cohort 2), and heart rate 50 - 90 beats per minute inclusive, at screening
• Cohort 1 only: On stable therapies of ACEi/ARB for at least 4 weeks prior to screening.
• Cohort 2 only: On a stable dose of sacubitril/valsartan for at least 4 weeks prior to screening.
• Treatment with a stable dose of a beta blocker for at least 4 weeks prior to screening, unless contraindicated or not tolerated.

Exclusion criteria

• Acute decompensated heart failure within 3 months prior to screening. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid, or other major cardiovascular surgery, PCI, or carotid angioplasty within the 6 months prior to screening
• Hemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to LV dilatation at screening
• Implantation of a CRT device within 3 months prior to screening or intent to implant a CRT during the study period
• History of severe pulmonary disease (e.g. COPD) requiring chronic supplemental oxygen therapy or pulmonary hypertension requiring pharmacology treatment at Screening
• eGFR <45 mL/min/1.73 m2 at screening
• Cohort 1 only: Treatment with sacubitril/valsartan currently or within 4 weeks from screening
• Cohort 2 only: Treatment with ACEi or ARB currently or within 4 weeks from screening. Valsartan as part of sacubitril/valsartan is not an exclusion.
• BMI >40 kg/m2

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-01-2023
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	XXB750
Generic name:	XXB750

Ethics review

Approved WMO Date:	24-08-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	14-11-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2021-006683-24-NL
ClinicalTrials.gov	NCT05328752

Register	ID
CCMO	NL81962.056.22