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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

XXB750

Trial Indication(s)

Heart Failure

Protocol Number

CXXB750A12101

Protocol Title

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)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase 1

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Study Start/End Dates

Study Start Date: May 17, 2022 (Actual)
Primary Completion Date: January 18, 2024 (Actual)
Study Completion Date: January 18, 2024 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was 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 was used to assess participants' eligibility. This study consisted of 2 cohorts. Cohort 1 included participants on stable doses of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Cohort 2 consisted of participants on stable doses of an angiotensin receptor neprilysin inhibitor (sacubitril/valsartan). For Cohort 1, participants were randomized in a 2:1 ratio to receive a single dose of s.c. XXB750 or placebo, and for Cohort 2, participants were randomized in a 3:1 ratio to receive 3 doses of s.c. XXB750 or placebo.

Cohort 1 comprised of a screening period of up to 29 days, a domiciled baseline evaluation (Day -2 and/or Day -1), a single 120 mg s.c. dose of XXB750 or placebo on Day 1 at site, followed by a 5-day domiciling period (total 6 to 7 day domicile from Day -1 or Day -2 through Day 5), and a further five follow-up visits out to 13 weeks post-dose with the End of Study (EOS) visit on Day 91.

Cohort 2 comprised of a screening period of up to 29 days, a domiciled baseline evaluation on Day -1, a 120 mg s.c. dose of XXB750 or placebo on Day 1 at site, followed by a 3-day domiciling period (total 4-day domicile from Day -1 through Day 3). On Day 28, participants received a second dose of either 120 mg XXB750 or placebo and were re-domiciled for 3 days (Day 28 through Day 30). On Day 56, participants received a third dose of either 240 mg XXB750 or placebo and were re-domiciled for 3 days (Day 56 through Day 58). Follow-up visits after each dose occurred out to 21 weeks post dose with the EOS visit on Day 146.

Centers

4 centers in 2 countries: United States(3), Netherlands(1)

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Objectives:

Primary objective

- To evaluate the safety and tolerability of XXB750 in adult participants with chronic stable heart failure with reduced or mildly reduced ejection fraction (HFrEF/HFmrEF)

Secondary objective

- To evaluate the pharmacokinetics of XXB750 in adult participants with HFrEF/HFmrEF

Test Product (s), Dose(s), and Mode(s) of Administration

Study drug and strength	Pharmaceutical Dosage Form	Route of Administration
XXB750 150 mg/1mL	Solution for Injection	s.c. use
Placebo 1mL	Solution for Injection	s.c. use

Statistical Methods

Primary endpoint: All information obtained on adverse events were displayed by cohort, treatment group and participant. The number (and percentage) of participants with treatment emergent adverse events were summarized for each cohort and overall population.

Secondary endpoint: For pharmacokinetic parameters of Cohort 1 and Cohort 2 descriptive summary statistics were calculated.

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Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:

• NYHA functional class II–III

• LVEF ≤ 50% documented at screening

• Systolic blood pressure 110 - 160 mmHg (cohort 1) or 105-160 mmHg (cohort 2), and heart rate between 50-90 beats per minute, inclusive

- Treatment with a stable dose of a beta blocker.
- Cohort 1: Treatment with a stable dose of ACE inhibitor or ARB
- Cohort 2: Treatment with a stable dose of sacubitril/valsartan.

Key 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: Treatment with ACE inhibitor or ARB currently or within 4 weeks from screening

• BMI >40 kg/m2

Other protocol-specific criteria may apply.

Participant Flow Table

Overall Study

	XXB750 Cohort 1	Placebo Cohort 1	XXB750 Cohort 2	Placebo Cohort 2	Total
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses	
Started	8	4	11	4	27
Completed	8	4	9	4	25
Not Completed	0	0	2	0	2
Withdrawal by Subject	0	0	1	0	1
Adverse Event	0	0	1	0	1

Baseline Characteristics

	XXB750 Cohort 1	Placebo Cohort 1	XXB750 Cohort 2	Placebo Cohort 2	Total
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses	
Number of Participants [units: participants]	8	4	11	4	27
Baseline Analysis Population Description					
Age Continuous (units: years) Analysis Population Type: Participants Mean (Full Range)					

	64.9 (50 to 77)	61.8 (56 to 70)	63.5 (51 to 73)	71.5 (64 to 79)	64.9 (50 to 79)
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
Female	2	0	3	2	7
Male	6	4	8	2	20
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)					
American Indian or Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	1	3	0	8
White	4	3	8	4	19
More than one race	0	0	0	0	0
Unknown or Not Reported	0	0	0	0	0

Primary Outcome Result(s)

Number of participants with Adverse Events

Description	To evaluate the safety and tolerability of XXB750 in adult participants with chronic stable heart failure with reduced or mildly reduced ejection fraction (HFrEF/HFmrEF). Adverse events may include abnormal vital signs, safety lab tests, or ECG parameters that induce clinical signs or symptoms, are considered clinically significant or require therapy.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)

Analysis Population Description	Safety analysis set. All participants who received study treatment.

	XXB750 Cohort 1	Placebo Cohort 1	XXB750 Cohort 2	Placebo Cohort 2
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses
Number of Participants Analyzed [units: participants]	8	4	11	4
Number of participants with Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Any Adverse Events	6 (75%)	2 (50%)	7 (63.64%)	3 (75%)
Serious AEs	2 (25%)	0 (%)	3 (27.27%)	0 (%)
AEs leading to discontinuation of study treatment	0 (%)	0 (%)	1 (9.09%)	0 (%)

Secondary Outcome Result(s)

Pharmacokinetics parameters Tmax

Description	To evaluate the pharmacokinetics: Time to maximum concentation (Tmax) parameters of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750

	XXB750 Cohort 1	XXB750 Cohort 2
Arm/Group Description	XXB750, single dose	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	8	11
Pharmacokinetics parameters Tmax (units: hr)	**Median (Full Range)**	**Median (Full Range)**
First dose	323 (94.7 to 650)	147 (143 to 265)
Third dose		168 (74 to 171)

Pharmacokinetics parameters Cmax

Description	To evaluate the pharmacokinetics parameters: Peak plasma concentration (Cmax) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750

	XXB750 Cohort 1	XXB750 Cohort 2
Arm/Group Description	XXB750, single dose	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	8	11
Pharmacokinetics parameters Cmax (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
First dose	8360 ± 3770	9100 ± 3770
Third dose		22700 ± 7300

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Pharmacokinetics parameters AUClast for Cohort 1

Description	To evaluate the pharmacokinetics parameters: Area under the plasma concentration curve (AUClast) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 1
Arm/Group Description	XXB750, single dose
Number of Participants Analyzed [units: participants]	8
Pharmacokinetics parameters AUClast for Cohort 1 (units: hr*ng/mL)	**Mean ± Standard Deviation**
	7360000 ± 4110000

Pharmacokinetics parameters AUCinf for Cohort 1

Description	To evaluate the pharmacokinetics parameters: Area under the curve (AUCinf) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 1
Arm/Group Description	XXB750, single dose
Number of Participants Analyzed [units: participants]	5

Pharmacokinetics parameters AUCinf for Cohort 1 (units: hr*ng/mL)	Mean ± Standard Deviation
	9210000 ± 3750000

Pharmacokinetics parameters Vz/F

Description	To evaluate the pharmacokinetics parameters: Vd/F of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 1	XXB750 Cohort 2
Arm/Group Description	XXB750, single dose	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	8	8
Pharmacokinetics parameters Vz/F (units: mL)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**
First dose	7450 ± 3830	
Third dose		8290 ± 3650

Pharmacokinetics parameters CL/F

Description	To evaluate the pharmacokinetics parameters: (CL/F) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 1	XXB750 Cohort 2
Arm/Group Description	XXB750, single dose	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	5	9
Pharmacokinetics parameters CL/F (units: mL/hr)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
First dose	16.4 ± 10.9	32.2 ± 13.2
Third dose		23.6 ± 10.3

Pharmacokinetics parameters T1/2

Description	To evaluate the pharmacokinetics parameters: (T1/2) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.
Time Frame	91 days (Cohort 1), 146 days (Cohort 2)
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 1	XXB750 Cohort 2
Arm/Group Description	XXB750, single dose	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	5	8
Pharmacokinetics parameters T1/2 (units: hr)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
First dose	333 ± 92.4	
Third dose		275 ± 76.6

Pharmacokinetics parameters AUCtau for Cohort 2

Description	To evaluate the pharmacokinetics parameters: Area under the curve (AUCtau) of XXB750 in adult participants with chronic stable HFrEF/HFmrEF.

Time Frame	146 days
Analysis Population Description	PK analysis set. All participants with at least one available valid PK concentration measurement, who received XXB750.

	XXB750 Cohort 2
Arm/Group Description	XXB750, multiple doses
Number of Participants Analyzed [units: participants]	9
Pharmacokinetics parameters AUCtau for Cohort 2 (units: hr*ng/mL)	**Mean ± Standard Deviation**
First dose	4270000 ± 1590000
Third dose	11600000 ± 3940000

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment up to 91 days (Cohort 1) and 146 days (Cohort 2)
Source Vocabulary for Table Default	MedDRA (26.1)

Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	XXB750 Cohort 1 N = 8	Placebo Cohort 1 N = 4	XXB750 Cohort 2 N = 11	Placebo Cohort 2 N = 4
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses
Total Number Affected	0	0	0	0
Total Number At Risk	8	4	11	4

Serious Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment up to 91 days (Cohort 1) and 146 days (Cohort 2)
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

	XXB750 Cohort 1 N = 8	Placebo Cohort 1 N = 4	XXB750 Cohort 2 N = 11	Placebo Cohort 2 N = 4
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses

Total # Affected by any Serious Adverse Event	2	0	3	0
Total # at Risk by any Serious Adverse Event	8	4	11	4
Cardiac disorders				
Acute myocardial infarction	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Cardiac failure acute	1 (12.50%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Cardiac failure congestive	0 (0.00%)	0 (0.00%)	2 (18.18%)	0 (0.00%)
Gastrointestinal disorders				
Pancreatic cyst	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
General disorders and administration site conditions				
Non-cardiac chest pain	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders				
Haematuria	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events were reported from first dose of study treatment up to 91 days (Cohort 1) and 146 days (Cohort 2)
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	XXB750 Cohort 1 N = 8	Placebo Cohort 1 N = 4	XXB750 Cohort 2 N = 11	Placebo Cohort 2 N = 4
Arm/Group Description	XXB750, single dose	Placebo, single dose	XXB750, multiple doses	Placebo, multiple doses
Total # Affected by any Other Adverse Event	5	2	7	3
Total # at Risk by any Other Adverse Event	8	4	11	4
Blood and lymphatic system disorders				
Iron deficiency anaemia	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac disorders				
Cardiac failure	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Gastrointestinal disorders				
Diarrhoea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nausea	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions				
Oedema peripheral	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders				
Hypertransaminasaemia	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Infections and infestations				
Cellulitis	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)

COVID-19	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Cystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Influenza	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Urinary tract infection	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Skin laceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Investigations				
Blood creatinine increased	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders				
Fluid retention	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypokalaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Musculoskeletal and connective tissue disorders				
Back pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Nervous system disorders				
Dizziness	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Renal and urinary disorders				
Bladder mass	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Haematuria	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)

Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Rales	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders				
Erythema	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders				
Haematoma	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)
Hypotension	2 (25.00%)	1 (25.00%)	0 (0.00%)	1 (25.00%)
Thrombosis	0 (0.00%)	0 (0.00%)	1 (9.09%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

- XXB750 was safe and well tolerated in both single (120 mg) and multiple dose (120 mg, 120 mg, and 240 mg administered every 4 weeks).

Date of Clinical Trial Report

04-Oct-2024