A Randomised, Double-blind, Placebo-controlled, Multi-center Sequential Phase 2b and Phase 3 Study to Evaluate the Efficacy and Safety of AZD4831 Administered for up to 48 Weeks in Participants with Heart Failure With Left Ventricular Ejection Fraction > 40%

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This study aims to evaluate the effect of AZD4831 on functional improvement and reduction of symptoms in participants with heart failure with left ventricular ejection fraction > 40%. Additionally, the PK and overall safety profile of AZD4831…

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON51637

Source
ToetsingOnline

Brief title
ENDEAVOR

Condition

- Heart failures

Synonym
heartfailure

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: AstraZeneca

Intervention

Keyword: - heart failure, - LVEF > 40%, - MPO inhibitor

Outcome measures

Primary outcome

Part A

KCCQ-TSS change from baseline at 16 weeks compared with placebo

6MWD change from baseline at 16 weeks compared with placebo

Part B

KCCQ-TSS,primary assessment at 24 weeks

6MWD, primary assessment at 24 weeks

Secondary outcome

Part A

• KCCQ-TSS change from baseline at 24 and 48 weeks compared with placebo

• 6MWD change from baseline at 24 and 48 weeks compared with placebo

• NT-proBNP change from baseline at 16, 24 and 48 weeks compared with placebo

• LV-GLS change from baseline at 16 and 24 weeks compared with placebo

• LAVI change from baseline at 16 and 24 weeks compared with placebo

• LVMI change from baseline at 16 and 24 weeks compared with placebo

Concentrations will be summarised by timepoint and dose level.

• hsCRP and IL-6 change from baseline at 16, 24, and 48 weeks compared with placebo

Safety

Safety and tolerability will be evaluated in terms of AEs, Vital signs, Clinical laboratory, and ECG.

Assessments related to AEs will cover:

• Occurrence/Frequency

• Seriousness

• Death

• AEs leading to discontinuation of IMP

• AEoSIs related to skin reactions, including maculopapular rash, and infection

Vital signs parameters include blood pressure, pulse rate, and body temperature; assessments will cover:

• Observed value

• Absolute change from baseline values over time

• Orthostatic blood pressure

A complete list of laboratory parameters is presented in Section 8.2.4; assessments will cover:

• Observed value

• Absolute change from baseline values over time

• Treatment-emergent changes in selected laboratory parameters

Electrocardiogram measurements assessments will cover:

• Investigator evaluation

Part B:

• NT-proBNP, primary assessment at 24 weeks

• hsCRP and IL-6, primary assessment at 24 weeks

Safety

• Occurrence and time to first occurrence of AE, SAE, SAE with outcome death, AE leading to discontinuation of study intervention, possibly related AE as assessed by investigator, possibly related SAE as assessed by investigator.

• Observed laboratory value, change from baseline and time to first treatment emergent abnormality.

• Observed vital sign value, change from baseline, and time to first treatment emergent abnormality.

• Observed ECG abnormalities, change from baseline, and time to first treatment emergent abnormality.

• Occurrence and time to first occurrence of AEoSI categories: skin reactions, including maculopapular rash, and infection.

Study description

Background summary

Chronic HF continues to be a major cause of mortality, hospitalisations, and suboptimal quality of life. Even with the best possible treatment, the 5-year survival rate for HF patients is worse than for most cancers. Heart failure affects 2% of the Western
population, increases to 10% over the age of 65 years, and up to 20% over the age of 75 years. The proportion of the Western population over the age of 65 years is expected to increase to over 30% by year 2050 and the costs of HF to society are expected to triple between years 2010 and 2030. Heart failure is currently broadly divided into three categories based on the systolic function of the left ventricle: (1) HFrEF (LVEF < 40%), (2) HFmrEF (LVEF 40-49%), and (3) HFpEF (LVEF >= 50%). Together, HFmrEF and HFpEF account for 55% of HF cases.

Heart failure with preserved ejection fraction is overrepresented in elderly and in women. Mortality in the community approaches 25% at one year. In a comparison of trial populations, the prognosis in HFpEF is 50-75 deaths and 40-75 HF hospitalisations per 1000 patient-years, whereas in stable coronary disease it is 10-30 deaths and 5-10 hospitalisations per 1000 patient-years and has improved further with modern therapy. Thus, novel interventions for coronary artery disease have little potential, whereas for HFpEF, novel treatment is both a critical unmet need and of great public health impact, if successful.

A novel paradigm for HFpEF pathophysiology states that co-morbidities (renal disease, hypertension, obesity, and diabetes) lead to a global inflammatory state, leading to immune cell recruitment and endothelial and coronary microvascular dysfunction, with distinct pathophysiology different from macrovascular coronary disease. This, in turn, can lead to both extracellular fibrosis and myocardial stiffness and reduced
myocardial nitric oxide bioavailability and cyclic guanosine monophosphate content and impaired myocyte relaxation. Numerous clinical data support this hypothesis.

Multiple lines of evidence suggest that MPO may play a role in atherogenesis in humans and MPO plasma levels predict outcome of cardiovascular disease. In chronic HF, plasma levels of MPO are elevated and also associated with more advanced HF. Additionally, elevated plasma MPO
levels can predict increased adverse clinical outcomes in HF patients. Individuals with inherited low MPO activity were protected from leukocyte activation induced deterioration of vascular function.

Overall, recent evidence suggests that MPO may provide a mechanistic link between inflammation, oxidative stress, vascular dysfunction and impaired cardiac remodelling. It is thus hypothesised that the MPO inhibitor AZD4831 will improve coronary microvascular status as well as systemic endothelial function, leading to improved diastolic function and overall status of HFpEF patients.

Study objective

This study aims to evaluate the effect of AZD4831 on functional improvement and reduction of symptoms in participants with heart failure with left ventricular ejection fraction > 40%. Additionally, the PK and overall safety profile of AZD4831 will be evaluated.

Study design

This is a double-blind (participant, investigator, and sponsor blinded) parallel group treatment study with 3 arms in Part A and 2 arms in Part B.

Intervention

In Part A, participants will undergo a screening period of up to 4 weeks, followed by randomisation across 3 different treatment arms. Eligible participants will be randomised at a 1:1:1 ratio and dosed orally daily. The planned treatment arms are AZD4831 2.5 mg, AZD4831 5 mg, and placebo. Participants will receive either AZD4831 or placebo for 16 weeks and then continue into a safety extension, during which they will receive an additional 32 weeks of the intervention (AZD4831 or placebo, as per their assigned arm during randomisation). A final follow-up visit will occur at 52 weeks from randomisation. In the event that randomisation to the AZD4831 5 mg treatment arm is stopped during the study in either the whole study or in a country or specific ethnic population due to safety, the remaining participants in that cohort would be randomised at a 2:1 ratio to AZD4831 2.5 mg or matching placebo.

In Part B, participants will undergo a screening period of up to 2 weeks, followed by randomisation across 2 treatment arms. Eligible participants will be randomised at a 1:1 (AZD4831:placebo) ratio and dosed orally daily. The planned treatment arms are AZD4831 at the dose selected based on Part A, and placebo. Participants will be treated for 24, 36 or 48 weeks. A final follow-up visit will occur 4 weeks after last treatment (week 24, 36 or 48) visit.

Participants can be randomised only once in the study; therefore, participants who were randomised into Part A cannot be included in Part B.

Study burden and risks

On average, the patient will have to come to the hospital more often than if the patient did not participate in the study. In addition, the following investigations are carried out that sometimes would be performed less often or never:
Physical examination, vital signs, height and weight are measured, orthostatic blood pressure is measured in Part A, EKG, ultrasound, 6-minute walk test,

questionnaires, urine samples, blood samples, possibly a skin biopsy.

In previous studies completed in healthy volunteers, maculopapular rash (reddish rash with flat and raised areas) was identified as a side effect of AZD4831 seen in about 14% (8/59) healthy volunteers given AZD4831 in single and repeated doses. These rashes were seen in healthy volunteers given single doses of 45 mg and above, and at repeated doses of 15 mg and above. These rashes started 7-10 days after starting drug, were considered mild to moderate in severity and generalized (covering bigger portions of the body rather than just a small area or a single body part), and resolved after stopping drug.
In addition, one patient out of 27 on 5mg AZD4831 in a study in patients with heart failure experienced maculopapular rash that was considered severe and generalized. It resolved after treatment with antihistamine (allergy medicine) and steroids (medicine used to decrease inflammation).

There are also potential (possible) risks with AZD4831 that have been identified based on animal studies and how the drug might work:
• Low blood pressure and increased heart rate
• Abnormalities in thyroid function
• Anemia (low red blood cells in the blood)
• Increased incidence of infections
• Agranulocytosis (severely decreased white blood cell count)
These potential risks have been monitored for in previous studies, and safety concerns have not been seen in humans.

Contacts

Public
Astra Zeneca

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A:
1. >= 40 to <= 85 years of age, at the time of signing the informed consent.
2. Documented stable symptomatic HF (New York Heart Association Class II-IV) for at least 1 month at Screening (Visit 1) (transient HF in the setting of an MI does not qualify), with a medical history of typical symptoms of HF and receiving optimal therapy for HF as determined by the health-care physician.
3. LVEF >40% at Screening (Visit 1). All participants will undergo a local echocardiogram at the Screening (Visit 1) with central reading to confirm the LVEF >40% eligibility criteria before randomisation.
4. 6MWD >= 30 meters and <= 400 meters at Screening (Visit 1) and Randomisation (Visit 3). Difference in 6MWD between Screening and Randomisation must be < 50 meters.
5. KCCQ-TSS <= 90 points at Screening (Visit 1) and Randomisation (Visit 3)
6.NT-proBNP >= 250 pg/mL (sinus rhythm) or >= 500 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI <=30 kg/m2.
NT-proBNP >= 200 pg/mL (sinus rhythm) or >= 400 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI > 30 kg/m2.
The ECG performed at Screening should be used for heart rhythm evaluation.
7.At least one of the following:
(a) Structural heart disease, ie, LA enlargement and/or left ventricular hypertrophy at the echocardiogram performed at Screening (Visit 1). Left atrial enlargement is defined by at least 1 of the following: LA width (diameter) >= 3.8 cm or LA length >= 5.0 cm, or LA area >= 20 cm2 or LA volume >= 55 mL or LAVI > 34 mL/m2. Left ventricular hypertrophy is defined by septal thickness or posterior wall thickness >= 1.1 cm or LVMI > 95 g/m2 in women and > 115 g/m2 in men.
(b) Spectral tissue Doppler echocardiography - E/e* ratio (average of septal and lateral) >= 13 at rest at the echocardiogram performed at Screening (Visit 1).
(c) Indirectly estimated elevation of PASP by TRmax velocity > 2.8 m/s (280 cm/s) (PASP >35 mmHg) at the echocardiogram performed at Screening (Visit 1) OR directly measured pulmonary capillary wedge pressure > 15 mmHg at rest within

the past 12 months or > 25 mmHg at exercise documented by right heart catheterisation within 12 months prior to Screening (Visit 1).
(d) HF decompensation within 6 months before Randomisation (Visit 3), defined as hospitalisation for HF or IV diuretic treatment for HF during an urgent, unscheduled visit without hospitalisation.
8.Body mass index >= 18.0 kg/m2 and <= 45.0 kg/m2
9.Male or female of non-childbearing potential.

Part B:
1 Participant must be >= 40 to <= 85 years of age, at the time of signing the informed consent.
2 Documented diagnosis of symptomatic HF (NYHA class II-IV) at Screening (Visit 1), and a medical history of typical symptoms/signs of heart failure >=6 weeks before Screening (Visit 1), and receiving optimal therapy for HF as determined by the health-care physician, with at least intermittent need for diuretic treatment. Symptoms and signs are defined in Appendix G.
3 LVEF >40% and evidence of structural heart disease (ie, left ventricular hypertrophy or left atrial enlargement [1]) documented by the most recent echocardiogram, or cardiac magnetic resonance imaging within the last 12 months prior to Screening (Visit 1). If no echocardiogram is available, it can be performed at Screening (Visit 1).
[1] Structural heart disease, ie, LA enlargement and/or left ventricular hypertrophy at the echocardiogram performed at Screening (Visit 1). Left atrial enlargement is defined by at least 1 of the following: LA width (diameter) >= 3.8 cm or LA length >= 5.0 cm, or LA area >= 20 cm2 or LA volume >= 55 mL or LAVI > 34 mL/m2. Left ventricular hypertrophy is defined by septal thickness or posterior wall thickness >= 1.1 cm or LVMI > 95 g/m2 in women and > 115 g/m2 in men.
4 6MWD >= 30 meters and <= 400 meters at Screening (Visit 1) and Randomisation (Visit 2). Difference in 6MWD between Screening and Randomisation must be < 50 meters.
5 KCCQ-TSS <= 90 points at Screening (Visit 1) and Randomisation (Visit 2).
6 NT-proBNP >= 250 pg/mL (sinus rhythm) or >= 500 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI <= 30 kg/m2.
NT-proBNP >= 200 pg/mL (sinus rhythm) or >= 400 pg/mL (atrial fibrillation/flutter) at Screening (Visit 1) for patients with BMI > 30 kg/m2.
The ECG performed at Screening should be used for heart rhythm evaluation.
7 Body mass index >= 18.0 kg/m2 and <= 45.0 kg/m2 (without rounding the values).
8 Male or female of non-childbearing potential.

Exclusion criteria

Part A:
1 eGFR < 30 mL/min/1.73m2 (Chronic Kidney Disease-Epidemiology Collaboration formula) at Screening (Visit 1).

2. Systolic blood pressure < 90 mmHg or >= 160 mmHg if not on treatment with >= 3 blood pressure lowering medications or >= 180 mmHg irrespective of treatments at Randomisation
3. Heart rate > 110 bpm or < 50 bpm at Randomisation
4. Life expectancy < 3 years due to other reasons than cardiovascular disease.
5. History or ongoing allergy/hypersensitivity reactions to drugs (including but not limited to rash, angioedema, acute urticaria).
6. Presence of any disease or condition rather than HF constituting the main reason for limiting the ability to exercise/reduced exercise capacity
7. Current decompensated HF and/or NT-proBNP > 5000 pg/mL at Screening (Visit 1)
8. Documented history of ejection fraction <= 40%.i.e. HF with recovered ejection fraction. Transient ejection fraction decrease e.g. in the setting of an MI does not apply
9. Any planned cardiovascular procedure (eg, coronary revascularisation, ablation of atrial fibrillation/flutter, valve repair/replacement, aortic aneurysm surgery, etc).
10. Any cardiac event (eg, myocardial infarction, unstable angina), coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial fibrillation/flutter, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to Screening (Visit 1) or between Screening and Randomisation (Visit 3). Patients who underwent a successful atrial fibrillation/flutter cardioversion, can be enrolled in the study after 4 weeks.
14. Hb <110 g/L (male) and <100 g/L (female) or iron-deficiency with/without anaemia requiring ongoing or planned IV iron treatment.
15. Participants with hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH >=10 mIU/mL), or any clinically significant thyroid disease as judged by the investigator.
18. ALT or AST >= 2 × ULN at Screening (Visit 1).
19. Pulmonary arterial hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (ie, requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory support within 12 months prior to Screening (Visit 1).
20. Any active infection requiring oral, intravenous or intramuscular treatment at Screening (Visit 1) and/or at Randomisation (Visit 3).
24. Any concomitant medications known to be a potent CYP3A4 inducers or inhibitors, eg, itraconazole, rifampicin, clarithromycin, or propylthiouracil

Part B:
1 eGFR < 30 mL/min/1.73m2 by Chronic Kidney Disease-Epidemiology Collaboration formula at Screening (Visit 1).
2 Systolic blood pressure < 90 mmHg or >= 160 mmHg if not on treatment with >= 3 BP lowering medications or >= 180 mmHg irrespective of treatments at Randomisation (Visit 2).
3 Heart rate > 110 bpm or < 50 bpm at Randomisation (Visit 2).
4 Life expectancy < 2 years due to other reasons than cardiovascular disease.

5 History or ongoing allergy/hypersensitivity reactions to drugs (including but not limited to rash, angioedema, acute urticaria).
6 Presence of any disease or condition rather than HF constituting the main reason for limiting the ability to exercise/reduced exercise capacity.
7 Current decompensated HF and/or NT-proBNP > 5000 pg/mL at Screening (Visit 1).
8 Documented history of ejection fraction <= 40% (ie, HF with recovered ejection fraction). Transient ejection fraction decrease (eg, in the setting of an MI does not apply).
9 Any planned cardiovascular procedure (eg, coronary revascularisation, ablation of atrial fibrillation/flutter, valve repair/replacement, aortic aneurysm surgery etc).
10 Any cardiac event (eg, myocardial infarction, unstable angina), coronary revascularisation (percutaneous coronary intervention or coronary artery bypass grafting), ablation of atrial fibrillation/flutter, valve repair/replacement, implantation of a cardiac resynchronisation therapy device within 12 weeks prior to Screening (Visit 1) or between Screening (Visit 1) and Randomisation (Visit 2). Patients who underwent a successful atrial fibrillation/flutter cardioversion, can be enrolled in the study after 4 weeks.
13 Hb < 110 g/L (male) and < 100 g/L (female) or iron-deficiency with/without anaemia requiring ongoing or planned IV iron treatment.
14 Participants with hyperthyroidism, uncontrolled hypothyroidism (including but not limited to TSH >=10 mIU/mL), or any clinically significant thyroid disease as judged by the investigator.
17 ALT or AST >= 2 × ULN at Screening (Visit 1).
18 Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD (ie, requiring home oxygen, chronic nebulizer therapy or chronic oral steroid therapy, or hospitalization for exacerbation of COPD requiring ventilatory support within 12 months prior to Screening [Visit 1]).
23 Any concomitant medications known to be a potent CYP3A4 inducers or inhibitors, eg, itraconazole, rifampicin, clarithromycin, or propylthiouracil (refer to Section 6.5 for a list of prohibited and/or restricted medications and treatments).

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):	19-10-2022
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AZD4831
Generic name:	AZD4831

Ethics review

Approved WMO Date:	14-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2022
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	EUCTR2020-005844-47-NL
Other	IND 134026
CCMO	NL81778.056.22

Study results

Date completed:	19-03-2024
Results posted:	30-10-2024
Actual enrolment:	18

First publication
04-09-2024