Clinical trial results:
A Randomized, Double Blind, Placebo-controlled, Parallel Group, Multicentre, Phase 2a Study to Assess Target Engagement, Safety and Tolerability of AZD4831 in Patients with Heart Failure with Preserved Ejection Fraction (HFpEF)

Summary

EudraCT number	2018-002895-42
Trial protocol	SE DK FI NL
Global end of trial date	07 May 2020

Results information

Result version number	v1 (current)
This version publication date	23 May 2021
First version publication date	23 May 2021

Trial information

Trial identification

Sponsor protocol code	D6580C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Astraallén, Södertälje, Sweden, 15185
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 18772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 November 2020

Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2020
Global end of trial reached?	Yes
Global end of trial date	07 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of AZD4831 (an MPO inhibitor) on TE, by measuring MPO specific activity in plasma following ex vivo stimulation of fresh blood samples with zymosan, in patients with HFpEF. The study objectives also included evaluation of the safety and tolerability of AZD4831 in patients with HFpEF, and the incidence of Grade 3 maculopapular rash (maculopapular rash is an identified risk for AZD4831), and to assess the effect of AZD4831 on CFVR (as a measure of myocardial microvascular function) and 6MWD, in addition to assessing the PK of AZD4831 after repeated dosing.

Protection of trial subjects:

Visit 4 and 6 may be performed as telephone contacts with the patient, if judged appropriate by investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Sweden: 24
Worldwide total number of subjects	41
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	2
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects may enter a screening period up to 28 days prior to randomization.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD4831

Arm description:

AZD4831 tablets taken orally for for 90 days.

Arm type	Experimental
Investigational medicinal product name	AZD4831
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Arm title	Placebo

Arm description:

Placebo tablets taken orally for 90 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Number of subjects in period 1	AZD4831	Placebo
Started	27	14
Completed	24	9
Not completed	3	5
Subject meets exclusion criteria	-	1
Dosing discontinued due to COVID-19	3	3

Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AZD4831
Reporting group description:	
AZD4831 tablets taken orally for for 90 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets taken orally for 90 days.	

Reporting group values	AZD4831	Placebo	Total
Number of subjects	27	14	41
Age categorical Units: Subjects			
Adults (18-64 years)	1	1	2
From 65-84 years	25	13	38
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	74.8	73.5	
standard deviation	± 6.61	± 6.99	-
Sex: Female, Male Units: participants			
Female	12	7	19
Male	15	7	22
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	27	13	40
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	27	14	41
Unknown or Not Reported	0	0	0
Country Units: Subjects			
Denmark	3	2	5
Netherlands	2	1	3
USA	0	1	1
Finland	5	3	8
Sweden	17	7	24

End points

End points reporting groups	
Reporting group title	AZD4831
Reporting group description:	
AZD4831 tablets taken orally for for 90 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo tablets taken orally for 90 days.	

Primary: The change from baseline in MPO activity in % after AZD4831 treatment.	
End point title	The change from baseline in MPO activity in % after AZD4831 treatment.
End point description:	
To compare the effect of AZD4831 to placebo on target engagement	
End point type	Primary
End point timeframe:	
Measurements on day 0, 10, 30 and 90.	

End point values	AZD4831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	14		
Units: Ratio				
least squares mean (confidence interval 95%)	0.547 (0.379 to 0.790)	2.177 (1.168 to 4.058)		

Statistical analyses

Statistical analysis title	Relative change from baseline to end of treatment
Comparison groups	AZD4831 v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Least Square Means Ratio
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.52

Secondary: Change from baseline in CFVR measured in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE).

End point title	Change from baseline in CFVR measured in the mid-distal segment of the left anterior descending (LAD) coronary artery under adenosine infusion measured by Transthoracic Doppler Echocardiography (TDE).

End point description:

To compare the effect of AZD4831 to placebo on coronary flow velocity reserve (CFVR)

End point type	Secondary

End point timeframe:

Measurement on day 0 and 90.

End point values	AZD4831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Ratio				
least squares mean (confidence interval 95%)	0.975 (0.835 to 1.138)	1.002 (0.747 to 1.344)		

Statistical analyses

Statistical analysis title	Relative change from baseline to end of treatment
Comparison groups	AZD4831 v Placebo
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568
Method	ANCOVA
Parameter estimate	Least Square Means Ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.74

Secondary: Change from baseline in Walking distance

End point title	Change from baseline in Walking distance

End point description:

To compare the effect of AZD4831 to placebo on 6 minutes walking test (6MWT)

End point type	Secondary

End point timeframe:

Measurement on day 0, 30 and 90.

End point values	AZD4831	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	11		
Units: Meters				
least squares mean (confidence interval 95%)	47.4 (20.3 to 74.5)	25.6 (-19.8 to 71.1)		

Statistical analyses

Statistical analysis title	Change from baseline to end of treatment
Comparison groups	AZD4831 v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	21.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.5
upper limit	74.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events will be collected from the time of the first dose throughout the treatment period and including the follow-up period. Serious Adverse Events will be recorded from the time of signing the informed consent form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo tablets taken orally for 90 days.

Reporting group title	AZD4831

Reporting group description:

AZD4831 tablets taken orally for for 90 days.

Serious adverse events	Placebo	AZD4831	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	2 / 27 (7.41%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 14 (7.14%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	AZD4831	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 14 (64.29%)	21 / 27 (77.78%)	
Vascular disorders			
Bleeding varicose vein			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	2	
Peripheral coldness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Hospitalisation			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Infusion site oedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Head injury			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Subcutaneous haematoma			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Investigations			
Blood urea increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Troponin T increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 14 (7.14%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Headache			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 14 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Transient ischaemic attack			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Nausea			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Plicated tongue			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	3 / 27 (11.11%)	
occurrences (all)	1	3	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Arthralgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	4	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 14 (7.14%)	1 / 27 (3.70%)	
occurrences (all)	1	1	

Gingivitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Pyelonephritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2020	Exclusion criteria 1 is updated to decrease eGFR from 45 to 30 ml/min/1.73m2, at screening visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to premature study termination, the statistical assumptions for the study design according to the protocol could not be fulfilled, therefore, no statistical conclusions can be made based efficacy objectives.

Notes: