Clinical trial results:
An explorative study to assess the safety, tolerability, and efficacy of AZD4831 in the treatment of pulmonary arterial hypertension (PAH) (MPO-PAH)

Summary

EudraCT number	2020-002788-80
Trial protocol	DE
Global end of trial date	14 March 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	Uni-Koeln-4243

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Universität zu Köln
Sponsor organisation address	Albertus-Magnus-Platz, Köln, Germany, 50923
Public contact	KKS Marburg, Koordinierungszentrum für Klinische Studien (KKS), info@kks.uni-marburg.de
Scientific contact	KKS Marburg, Koordinierungszentrum für Klinische Studien (KKS), info@kks.uni-marburg.de

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	06 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2021
Global end of trial reached?	Yes
Global end of trial date	14 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of 12 weeks of AZD4831 in patients of two groups:
1) Patients with PAH (pre-capillary PH) who are on established therapy (at least 1 targeted PAH drug: ERA, PDE5i/sGC-S, PCA/PRA), and
2) Patients with post-capillary PH

by measuring the change from baseline in pulmonary vascular resistance (PVR).

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	9
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

15 patients have been registered for trail participation.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Treatment with AZD4831

Arm description:

The AZD4831 will be administrated orally over a period of 12 weeks. The dose of study treatment is defined as 5 mg tablet once daily.
Single-arm; no placebo.

Arm type	Experimental
Investigational medicinal product name	AZD4831
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The dose of study treatment is defined as 5 mg tablet once daily over a period of 12 weeks

Number of subjects in period 1	Treatment with AZD4831
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	61		
full range (min-max)	35 to 83	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	10	10	

End points

End points reporting groups

Reporting group title	Treatment with AZD4831

Reporting group description:

The AZD4831 will be administrated orally over a period of 12 weeks. The dose of study treatment is defined as 5 mg tablet once daily.
Single-arm; no placebo.

Subject analysis set title	ITT-Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population is defined as all patients enrolled, regardless of whether they actually received treatment.

Primary: Pulmonary vascular resistance (PVR)

End point title	Pulmonary vascular resistance (PVR)

End point description:

Change from baseline to 12 weeks of treatment in pulmonary vascular resistance (PVR) as assessed by right heart catheterization

End point type	Primary

End point timeframe:

Baseline to 12 weeks

End point values	Treatment with AZD4831	ITT-Analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15[1]	15[2]		
Units: dyn×sec×cm−5				
median (confidence interval 95%)	-2 (-3.5 to 0)	-2 (-3.5 to 0)		

Notes:

[1] - All patients enrolled

[2] - Intention-to-treat set equals per-protocol set

Attachments (see zip file)	Boxplot of PVR (baseline and week 12)/figure_PE.jpg

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Paired Wilcoxon signed-rank test at two-sided significance level 5%; moreover, a corresponding two-sided 95% confidence interval for the median difference is calculated

Comparison groups	Treatment with AZD4831 v ITT-Analysis
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.101
Method	Paired Wilcoxon signed-rank test
Parameter estimate	Median difference (final values)
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	0

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Dec 11 2020-Aug 03 2021	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Patients with symptomatic PAH (WHO-FC II or III) who are on targeted medical therapy with at least one PAH-specific drug	
Reporting group title	Group 2
Reporting group description:	
Patients with post-capillary PH	
Reporting group title	All patients / ITT
Reporting group description:	
The intent-to-treat (ITT) population is defined as all patients enrolled, regardless of whether they actually received treatment.	

Serious adverse events	Group 1	Group 2	All patients / ITT
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	2 / 5 (40.00%)	4 / 15 (26.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	Group 1	Group 2	All patients / ITT
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	2 / 5 (40.00%)	7 / 15 (46.67%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Blood iron decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Atrial fibrillation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Palpitations			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Nervous system disorders			

Syncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Presyncope			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 10 (20.00%)	1 / 5 (20.00%)	3 / 15 (20.00%)
occurrences (all)	2	1	3
Infections and infestations			
Fungal infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 5 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 5 (0.00%)	2 / 15 (13.33%)
occurrences (all)	2	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 5 (20.00%)	1 / 15 (6.67%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 March 2021	An additional group of 5 patients (with post-capillary pulmonary hypertension) should be included to the study and the effect of AZD4831 on the endothelial dysfunction by these patients will be assessed via flow-mediated dilation. Also zymosan stimulation of plasma MPO should be done prior to the freezing of sample.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported