# 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<br>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<br>Units: years | | | |
| median | 61 | | |
| full range (min-max) | 35 to 83 | - | |
| Gender categorical<br>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