



## Clinical trial results:

### A Phase IIa Randomised, Double Blind, Placebo Controlled, Parallel Arm, Multi-Centre Study to Evaluate the Efficacy and Safety of Mitiperstat (AZD4831), for 12-24 Weeks, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2022-002441-18    |
| Trial protocol           | DK ES NL IT BG DE |
| Global end of trial date | 30 October 2024   |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 23 October 2025 |
| First version publication date | 14 August 2025  |
| Version creation reason        |                 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | D6582C00001 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT05492877 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | AstraZeneca AB   |
| Sponsor organisation address | 151 85, Södertälje, Sweden,  |
| Public contact               | Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, information.center@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca Clinical Study Information Center, +1 8772409479, 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                       | 12 May 2025     |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 12 August 2024  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 30 October 2024 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD.

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the

Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements. All participant must meet all inclusion criteria and not meet any exclusion criteria before receiving investigational product. IDMC was formed to monitor potential risk in the study

Background therapy:

Participants need to be on stable regimen of triple therapy or dual therapy for  $\geq 3$  months prior to enrolment (change of inhaler device or change of medication in the same drug class is allowed). Triple therapy may consist of an appropriate combination of ICS + LABA + LAMA. Dual therapy consists of either inhaled ICS + LABA or LABA + LAMA where the treating physician deems the participant unsuitable for ICS (eg, blood eosinophil count  $\leq 100$  cells/ $\mu$ L on 2 separate occasions, or on the basis of previous or perceived risk of significant AEs from ICS-based therapy, such as previous episodes of pneumonia or significant oral candidiasis).

Evidence for comparator:

Not applicable as there was no comparator arm in the study

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 14 November 2022 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Canada: 24         |
| Country: Number of subjects enrolled | United States: 41  |
| Country: Number of subjects enrolled | Bulgaria: 28       |
| Country: Number of subjects enrolled | Poland: 30         |
| Country: Number of subjects enrolled | Türkiye: 20        |
| Country: Number of subjects enrolled | Denmark: 34        |
| Country: Number of subjects enrolled | Italy: 9           |
| Country: Number of subjects enrolled | Netherlands: 7     |
| Country: Number of subjects enrolled | Spain: 31          |
| Country: Number of subjects enrolled | United Kingdom: 52 |
| Country: Number of subjects enrolled | Argentina: 26      |
| Country: Number of subjects enrolled | Mexico: 14         |

|                                      |                  |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | South Africa: 10 |
| Country: Number of subjects enrolled | Germany: 55      |
| Worldwide total number of subjects   | 381              |
| EEA total number of subjects         | 194              |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 158 |
| From 65 to 84 years                       | 223 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 101 centers in 14 countries (Argentina, Bulgaria, Canada, Denmark, Germany, Italy, Mexico, Netherlands, Poland, South Africa, Spain, Turkey, UK and USA).

### Pre-assignment

Screening details:

A total of 381 participants were randomized and received at least one dose of study drug.

### 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, Carer, Data analyst, Assessor |

Blinding implementation details:

Participant was randomised using an interactive web response system to receive either 5mg mitiperstat or placebo. Participants, investigators and the sponsors are blinded with regard to the actual dose information.

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Mitiperstat |

Arm description:

Participants received an oral tablet of mitiperstat 5mg once daily.

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

Dosage and administration details:

5 mg once daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants receive an oral tablet of placebo matched to mitiperstat once daily.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Once daily

| <b>Number of subjects in period 1</b> | Mitiperstat | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 189         | 192     |
| Treated                               | 189         | 192     |
| Completed                             | 165         | 170     |
| Not completed                         | 24          | 22      |
| Adverse event, serious fatal          | 1           | -       |
| Consent withdrawn by subject          | 3           | 7       |
| Physician decision                    | 1           | 2       |
| Adverse event, non-fatal              | 11          | 7       |
| Lost to follow-up                     | 1           | 1       |
| Reason not specified                  | 6           | 4       |
| Protocol deviation                    | 1           | 1       |

## Baseline characteristics

### Reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Mitiperstat |
| Reporting group description:  |             |
| Participants received an oral tablet of mitiperstat 5mg once daily.               |             |
| Reporting group title   | Placebo     |
| Reporting group description:  |             |
| Participants receive an oral tablet of placebo matched to mitiperstat once daily. |             |

| Reporting group values                             | Mitiperstat | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects                                 | 189         | 192     | 381   |
| Age categorical                                    |             |         |       |
| Units: Subjects                                    |             |         |       |
| In utero   | 0           | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0           | 0       | 0     |
| Newborns (0-27 days)                               | 0           | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0           | 0       | 0     |
| Children (2-11 years)                              | 0           | 0       | 0     |
| Adolescents (12-17 years)                          | 0           | 0       | 0     |
| Adults (18-64 years)                               | 75          | 83      | 158   |
| From 65-84 years                                   | 114         | 109     | 223   |
| 85 years and over                                  | 0           | 0       | 0     |
| Age Continuous                                     |             |         |       |
| Units: Years                                       |             |         |       |
| arithmetic mean                                    | 66.2        | 65.7    |       |
| standard deviation                                 | ± 6.65      | ± 7.03  | -     |
| Sex: Female, Male                                  |             |         |       |
| Units:   |             |         |       |
| Female   | 77          | 74      | 151   |
| Male   | 112         | 118     | 230   |
| Ethnicity (NIH/OMB)                                |             |         |       |
| Units: Subjects                                    |             |         |       |
| Hispanic or Latino                                 | 26          | 27      | 53    |
| Not Hispanic or Latino                             | 163         | 165     | 328   |
| Unknown or Not Reported                            | 0           | 0       | 0     |
| Race (NIH/OMB)                                     |             |         |       |
| Units: Subjects                                    |             |         |       |
| American Indian or Alaska Native                   | 1           | 1       | 2     |
| Asian  | 1           | 1       | 2     |
| Native Hawaiian or Other Pacific Islander          | 0           | 0       | 0     |
| Black or African American                          | 2           | 1       | 3     |
| White  | 182         | 183     | 365   |
| More than one race                                 | 0           | 0       | 0     |
| Unknown or Not Reported                            | 3           | 6       | 9     |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Mitiperstat |
| Reporting group description:  |             |
| Participants received an oral tablet of mitiperstat 5mg once daily.               |             |
| Reporting group title   | Placebo     |
| Reporting group description:  |             |
| Participants receive an oral tablet of placebo matched to mitiperstat once daily. |             |

**Primary: To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPD Composite Exacerbation (CompEx) event in patients with moderate to severe COPD.**

|   |  |
|---|--|
| End point title   | To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first COPD Composite Exacerbation (CompEx) event in patients with moderate to severe COPD. |
| End point description:  |  |
| COPDCompEx is a composite endpoint of exacerbations and events defined from participant e-Diaries and peak expiratory flow (PEF). COPDCompEx defined exacerbations as one or more of the following: hospitalization, emergency room visit, treatment with systemic corticosteroids (injected and/or oral), or treatment with antibiotics. Diary COPDCompEx events are defined by threshold and slope criteria being met for $\geq 2$ consecutive days using the following diary and home spirometry variables: overall symptom rating, night-time awakenings due to symptoms, reliever medication use, PEF. COPDCompEx also includes patient withdrawals for treatment failure. The analysis population used was the Full Analysis Set, which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| From baseline to up to 24 weeks   |  |

| End point values                              | Mitiperstat     | Placebo         |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                            | Reporting group | Reporting group |  |  |
| Number of subjects analysed                   | 189             | 192             |  |  |
| Units: Participants                           |                 |                 |  |  |
| Count of Participants with a COPDCompEx event | 125             | 125             |  |  |

### Statistical analyses

|                            |                               |
|----------------------------|-------------------------------|
| Statistical analysis title | Cox proportional hazard model |
| Comparison groups          | Mitiperstat v Placebo         |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 381                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.599 <sup>[1]</sup> |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 1.071                  |
| Confidence interval                     |                        |
| level                                   | 90 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.869                  |
| upper limit                             | 1.32                   |

Notes:

[1] - The p-value was based on a 2-sided log rank test stratified by region

## Secondary: To assess the PK of mitiperstat (AZD4831) in patients with moderate to severe COPD

|                 |   |
|-----------------|---|
| End point title | To assess the PK of mitiperstat (AZD4831) in patients with moderate to severe COPD <sup>[2]</sup> |
|-----------------|---|

End point description:

Measurement of Time to Reach Maximum Plasma Concentration (Tmax) at week 12.

The analysis population used was the PK set which included all participants who had received mitiperstat and had evaluable PK data for mitiperstat, with no important protocol deviations that were thought to have impacted the analysis of the PK data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There is no PK data for placebo arm. There is no PK data at baseline

| End point values              | Mitiperstat          |  |  |  |
|-------------------------------|----------------------|--|--|--|
| Subject group type            | Reporting group      |  |  |  |
| Number of subjects analysed   | 36                   |  |  |  |
| Units: hours                  |                      |  |  |  |
| median (full range (min-max)) | 1.292 (0.42 to 2.92) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: To assess the pharmacokinetics (PK) of mitiperstat (AZD4831) in patients with moderate to severe COPD.

|                 |   |
|-----------------|---|
| End point title | To assess the pharmacokinetics (PK) of mitiperstat (AZD4831) in patients with moderate to severe COPD. <sup>[3]</sup> |
|-----------------|---|

End point description:

Measurement of Maximum Plasma Concentration (Cmax) at week 12.

The analysis population used was the PK set which included all participants who had received mitiperstat



and had evaluable PK data for mitiperstat, with no important protocol deviations that were thought to have impacted the analysis of the PK data.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There is no PK data for placebo arm. There is no PK data at baseline

|   |                      |  |  |  |
|---|----------------------|--|--|--|
| <b>End point values</b>                             | Mitiperstat          |  |  |  |
| Subject group type                                  | Reporting group      |  |  |  |
| Number of subjects analysed                         | 36                   |  |  |  |
| Units: nmol/L                                       |                      |  |  |  |
| geometric mean (geometric coefficient of variation) | 38.786 ( $\pm$ 39.5) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first moderate or severe exacerbation.

|                 |  |
|-----------------|--|
| End point title | To evaluate the effect of mitiperstat (AZD4831) as compared to placebo on the time to first moderate or severe exacerbation. |
|-----------------|--|

End point description:

A COPD exacerbation was considered moderate if it required treatment with systemic corticosteroids and/or antibiotics for at least 3 days or resulted in emergency room visit < 24 hours requiring intensive treatment; and did not result in hospitalization or death.

A COPD exacerbation was considered severe if it resulted in hospitalization (defined as an inpatient admission  $\geq$  24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system) or death due to COPD.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to up to week 24

|  |                 |                 |  |  |
|--|-----------------|-----------------|--|--|
| <b>End point values</b>                          | Mitiperstat     | Placebo         |  |  |
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 189             | 192             |  |  |
| Units: Participants                              |                 |                 |  |  |
| Count of participants with an exacerbation event | 53              | 44              |  |  |

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Cox proportional hazard model |
| Comparison groups                       | Mitiperstat v Placebo         |
| Number of subjects included in analysis | 381                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| Method                                  | Regression, Cox               |
| Parameter estimate                      | Hazard ratio (HR)             |
| Point estimate                          | 1.234                         |
| Confidence interval                     |                               |
| level                                   | 90 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.882                         |
| upper limit                             | 1.726                         |

### **Secondary: To assess the effects of mitiperstat (AZD4831) as compared to placebo on post-bronchodilator (BD) forced expiratory volume in the first second (FEV1) in patients with moderate to severe COPD.**

|                 |   |
|-----------------|---|
| End point title | To assess the effects of mitiperstat (AZD4831) as compared to placebo on post-bronchodilator (BD) forced expiratory volume in the first second (FEV1) in patients with moderate to severe COPD. |
|-----------------|---|

#### End point description:

The mean change from baseline in Post-BD FEV1 at Week 12 was estimated using a repeated measures mixed effects analysis of covariance. Only subjects with non-missing covariates are included in the analysis. FEV1 was measured by spirometry at clinic.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                          |           |
|--------------------------|-----------|
| End point type           | Secondary |
| End point timeframe:     |           |
| From baseline to week 12 |           |

|                                     |                        |                        |  |  |
|-------------------------------------|------------------------|------------------------|--|--|
| <b>End point values</b>             | Mitiperstat            | Placebo                |  |  |
| Subject group type                  | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed         | 130                    | 136                    |  |  |
| Units: Litre                        |                        |                        |  |  |
| least squares mean (standard error) | -0.049 ( $\pm$ 0.0178) | -0.031 ( $\pm$ 0.0175) |  |  |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: To assess the effect of mitiperstat (AZD4831) compared to placebo on respiratory symptoms in patients with moderate to severe COPD - EXACT.**

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|                 |   |
|-----------------|---|
| End point title | To assess the effect of mitiperstat (AZD4831) compared to placebo on respiratory symptoms in patients with moderate to severe COPD - EXACT. |
|-----------------|---|

**End point description:**

Change from baseline in EXAcerbations of Chronic Pulmonary Disease Tool (EXACT) which is a 14-item ePRO instrument developed to assess the frequency, severity and duration of COPD exacerbations. It has a theoretical range of 0 to 100, with higher values indicating a more severe condition. The EXACT will be performed at on-site visits using the e-Diary.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From baseline to week 12 and week 24

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| End point values                    | Mitiperstat     | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 122             | 126             |  |  |
| Units: Units on a scale             |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 12                             | 0.1 (± 0.97)    | -2.4 (± 0.95)   |  |  |
| Week 24                             | -1.9 (± 1.32)   | -3.7 (± 1.36)   |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: To assess the effect of mitiperstat (AZD4831) compared to placebo on respiratory symptoms in patients with moderate to severe COPD - BCSS.**

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|                 |  |
|-----------------|--|
| End point title | To assess the effect of mitiperstat (AZD4831) compared to placebo on respiratory symptoms in patients with moderate to severe COPD - BCSS. |
|-----------------|--|

**End point description:**

Change from baseline to Week 12 and week 24 in mean Breathlessness, Cough and Sputum Scale (BCSS) score is reported. The BCSS was a 3-item daily diary that assesses the severity of the 3 symptoms: breathlessness, sputum, and cough, each on a 5-point Likert scale ranging from 0 (no symptoms) to 4 (severe symptoms). Item scores were summed to yield a total score ranging from 0 to 12; wherein higher total score indicated more severe symptoms. The BCSS was captured each evening via eDiary.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From baseline to week 12 and week 24

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| End point values                    | Mitiperstat     | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 139             | 147             |  |  |
| Units: Units on a scale             |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 12                             | 0.16 (± 0.130)  | 0.15 (± 0.127)  |  |  |
| Week 24                             | 0.11 (± 0.166)  | -0.17 (± 0.172) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: To assess the effect of mitiperstat (AZD4831) compared to placebo in disease impact in patients with moderate to severe COPD.

|                 |   |
|-----------------|---|
| End point title | To assess the effect of mitiperstat (AZD4831) compared to placebo in disease impact in patients with moderate to severe COPD. |
|-----------------|---|

End point description:

Change from baseline to Week 12 and week 24 in cough Visual Analogue Scale (VAS) score is reported. Participants were asked to complete a cough severity VAS (100-point linear scale marked with a horizontal line by the participant, with 0 representing "no cough" and 100 representing "worst cough") that measured subjective assessment by the participant of the prior 24 hrs for severity of cough symptoms. It was completed each evening in the eDiary.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to week 12 and week 24

| End point values                    | Mitiperstat     | Placebo         |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type                  | Reporting group | Reporting group |  |  |
| Number of subjects analysed         | 159             | 165             |  |  |
| Units: Units on a scale             |                 |                 |  |  |
| least squares mean (standard error) |                 |                 |  |  |
| Week 12                             | -1.25 (± 1.183) | -3.05 (± 1.160) |  |  |
| Week 24                             | -2.64 (± 1.540) | -3.48 (± 1.562) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 12 in total COPD Assessment Test (CAT)

|                 |   |
|-----------------|---|
| End point title | Change from baseline to Week 12 in total COPD Assessment Test (CAT) |
|-----------------|---|

End point description:

COPD Assessment Test (CAT) is designed to measure how COPD impacts on a patient's daily life and how this might change over time. It consists of 8 questions that ask the patient to rate items relating to symptoms and impact on quality of life (such as normal activity and sleep). Each question is performed on a 5-point Likert scale from 0 (no symptoms/no impact) to 5 (severe symptoms/impact). The CAT will be completed by participants at on-site visits using the e-Diary.

The analysis population used was the Full Analysis Set (FAS), which included all randomized participants who received at least one dose of study intervention. The 'while on treatment' estimand strategy was followed, meaning that if an intercurrent event occurred, all subsequent data for that subject was excluded from the evaluation.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 12

| End point values                    | Mitiperstat        | Placebo            |  |  |
|-------------------------------------|--------------------|--------------------|--|--|
| Subject group type                  | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed         | 134                | 134                |  |  |
| Units: Units on a scale             |                    |                    |  |  |
| least squares mean (standard error) | -1.2 ( $\pm$ 0.62) | -1.2 ( $\pm$ 0.64) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until the end of the follow-up period

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | AZD4831 |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events  | PLACEBO          | AZD4831           |  |
|---|------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                  |                   |  |
| subjects affected / exposed   | 13 / 192 (6.77%) | 23 / 189 (12.17%) |  |
| number of deaths (all causes)                                       | 0                | 1                 |  |
| number of deaths resulting from adverse events                      | 0                | 1                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                   |  |
| Carcinoid tumour pulmonary  |                  |                   |  |
| subjects affected / exposed   | 1 / 192 (0.52%)  | 0 / 189 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Squamous cell carcinoma   |                  |                   |  |
| subjects affected / exposed   | 1 / 192 (0.52%)  | 1 / 189 (0.53%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Vascular disorders  |                  |                   |  |
| Aortic aneurysm   |                  |                   |  |
| subjects affected / exposed   | 0 / 192 (0.00%)  | 1 / 189 (0.53%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| Cardiac disorders   |                  |                   |  |
| Cardiac failure acute   |                  |                   |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 189 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Atrial fibrillation                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 189 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nervous system disorders                        |                 |                  |  |
| Carotid artery thrombosis                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 189 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal disorders                      |                 |                  |  |
| Constipation                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 192 (0.00%) | 1 / 189 (0.53%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                 |                  |  |
| Chronic obstructive pulmonary disease           |                 |                  |  |
| subjects affected / exposed                     | 5 / 192 (2.60%) | 14 / 189 (7.41%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 1 / 14           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyspnoea  |                 |                  |  |
| subjects affected / exposed                     | 1 / 192 (0.52%) | 0 / 189 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary embolism                              |                 |                  |  |
| subjects affected / exposed                     | 2 / 192 (1.04%) | 0 / 189 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory failure                             |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 0 / 192 (0.00%) | 1 / 189 (0.53%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pulmonary mass  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 192 (0.52%) | 0 / 189 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                                       |                 |                 |  |
| Cholecystitis acute   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 192 (0.00%) | 1 / 189 (0.53%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Portal hypertension   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 192 (0.00%) | 1 / 189 (0.53%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infections and infestations                                   |                 |                 |  |
| Tuberculosis  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 192 (0.52%) | 0 / 189 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Pneumonia   |                 |                 |  |
| subjects affected / exposed                                   | 3 / 192 (1.56%) | 5 / 189 (2.65%) |  |
| occurrences causally related to treatment / all               | 1 / 3           | 1 / 5           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 192 (0.52%) | 0 / 189 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 5 %



| <b>Non-serious adverse events</b>                     | PLACEBO           | AZD4831           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 45 / 192 (23.44%) | 52 / 189 (27.51%) |  |
| Respiratory, thoracic and mediastinal disorders       |                   |                   |  |
| Chronic obstructive pulmonary disease                 |                   |                   |  |
| subjects affected / exposed                           | 36 / 192 (18.75%) | 45 / 189 (23.81%) |  |
| occurrences (all)                                     | 55                | 62                |  |
| Infections and infestations                           |                   |                   |  |
| Nasopharyngitis                                       |                   |                   |  |
| subjects affected / exposed                           | 12 / 192 (6.25%)  | 10 / 189 (5.29%)  |  |
| occurrences (all)                                     | 14                | 10                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 30 June 2022     | Clinical Study Protocol Version 2. Version 1 of the protocol was not published or used. Version 2 was the first version to be submitted to any Health Authority/Ethics committee   |
| 13 January 2023  | Clinical Study Protocol Version 3. Exclusion criterion which excluded participants with a positive diagnostic lateral flow test for SARS-CoV-2 at screening was removed (exclusion criterion 1). Changes were made in response to the requirements of various health authorities. For example, contraceptive requirements. |
| 28 April 2023    | Clinical Study Protocol Version 4. To add the optional substudies which affect only selected sites in selected countries where the substudies will be conducted. A substantial change was made to remove history of treatment with cardiotoxic medications from the list of exclusion criteria (exclusion criterion 22).   |
| 07 December 2023 | Clinical Study Protocol Version 5. To increase the sample size, due to changes in statistical assumptions.   |

Notes:

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### 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.

|   |
|---|
| No significant methodological limitations, protocol deviations or study conduct changes were identified that may have impacted upon the validity or interpretation of the results |
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Notes: