Clinical Study Report Synopsis	
Drug Substance	Mitiperstat (AZD4831)
Study Code	D6582C00001
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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)

Study dates:	First participant screened: 14 Nov 2022 Last participant last visit: 12 August 2024 The analyses presented in this report are based on a clinical data lock date of 30 October 2024
Phase of development:	Therapeutic exploratory (II)
Study Sponsor:	AstraZeneca AB

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study Sites

The study was conducted in 105 sites in 14 countries. The cough substudy was conducted in 61 sites in 8 countries.

Publications

Rosengren et al. Airway myeloperoxidase (MPO) is associated with increased risk of exacerbations in COPD. European Respiratory Journal 2022; 60(suppl 66): 2017.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Estimand description/Endpoints
Primary	
To evaluate the effect of mitiperstat as compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arm. **Endpoint:** time to first COPDCompEx event. **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** Primary estimand: while on treatment – if an intercurrent event occurs before first COPDCompEx event, the participant will be censored at the time of intercurrent event. Supportive estimand: treatment policy (reflects ITT principle) – after intercurrent event participants remain in the study so that the endpoint can be observed. Treatment policy strategy used to estimate the efficacy of mitiperstat in 'real-world' conditions.
Secondary	
To assess the PK of mitiperstat in patients with moderate to severe COPD.	**Population:** all participants who had received at least one dose of mitiperstat, and who had at least one measurable PK sample post dose. **Endpoint:** plasma mitiperstat concentration-time profiles during the intervention and follow-up periods, and PK parameters. **Population level-summary measure:** summary statistics. **Strategy for intercurrent events:** while on treatment.

Objectives	Estimand description/Endpoints
To evaluate the effect of mitiperstat as compared to placebo on the time to first moderate or severe COPD exacerbation.	**Population**: all participants randomised to either active or placebo arms. **Endpoint:** time to first COPD exacerbation event[b] **Population level-summary measure:** hazard ratio. **Strategy for intercurrent events:** while on treatment.
To assess the effects of mitiperstat as compared to placebo on post-BD FEV1 in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in post BD FEV1 after 12 weeks. **Population level-summary measure:** the difference in mean. **Primary estimand:** while on treatment. **Supportive estimand:** treatment policy.
To assess the effect of mitiperstat compared with placebo on respiratory symptoms in patients with moderate to severe COPD.	**Population:** all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in EXACT, BCSS score, and Cough VAS at Week 12 and Week 24. **Population level-summary measure:** the difference in mean. **Strategy for intercurrent events:** while on treatment.
To assess the effect of mitiperstat compared with placebo on disease impact in patients with moderate to severe COPD.	**Population**: all participants randomised to either active or placebo arms. **Endpoint:** change from baseline in Total CAT measured in clinic at Week 12. **Population level-summary measure:** The difference in mean. Proportion of participants with change from baseline of -2 or less. **Strategy for intercurrent events:** while on treatment.

Objectives	Estimand description/Endpoints
Safety	
To assess the safety and tolerability of mitiperstat compared with placebo in patients with moderate to severe COPD.	**Population:** all participants who received at least 1 dose of study intervention (Safety Analysis Set). **Endpoint:** safety and tolerability evaluations using AEs, SAEs, AESI (skin reactions, including maculopapular rash, and infections, including pneumonia), vital sign measures, clinical laboratory assessments (clinical chemistry, haematology, and urinalysis), and ECG. **Population level-summary measure:** descriptive statistics eg, absolute counts and frequencies. **Strategy for intercurrent events:** Safety analysis will not use either the While on Treatment or Treatment policy estimand policy, and will simply include all on study data.

[a] An estimand is a precise description of the treatment effect reflecting the clinical question posed by the study objective. It summarises at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Definition from FDA E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.

[b] COPD Exacerbation: a worsening in the participant's usual COPD symptoms that is beyond normal day-to-day variation, is acute in onset, lasts 2 or more days (or less if the worsening is so rapid and profound that the treating physician judges that intensification of treatment cannot be delayed), may warrant a change in regular medication, and leads to any of the following:

- Use of systemic corticosteroids for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.
- Use of antibiotics to treat COPD exacerbation for at least 3 days.
- An inpatient hospitalisation due to COPD (defined as an inpatient admission ≥ 24 hours in the hospital, an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).
- Admission in emergency department or emergency room due to COPD for < 24 hours requiring intensive treatment.
- An episode of pneumonia.
- Results in death.

Intercurrent events are events occurring after treatment initiation (eg, discontinuation of treatment, switching treatment, terminal events such as death) that affect either the measurement or interpretation of the summary measure (eg, hazard ratio) associated with the clinical question of interest.

This study contains 2 intercurrent events:

- Treatment discontinuation (with the following reasons: SAE, death not due to exacerbation, COVID-19, pneumonia, other).
- Prohibited medication.

AE, adverse event; AESI, adverse events of special interest; BCSS, breathlessness, cough and sputum scale; BD, bronchodilator; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; COPDCompEx, COPD Composite Exacerbations; ECG, electrocardiogram; EXACT, The Exacerbation of Chronic Pulmonary Disease Tool; FEV1, forced expiratory volume in 1 second; ITT, intent-to-treat; PK, pharmacokinetic; SAE, serious adverse event; VAS, visual analogue scale.

For tertiary/exploratory objectives and endpoints, refer to the CSR.

Study Design

This was a Phase IIa, randomised, placebo-controlled, double-blind, parallel-arm, event-driven study to evaluate the efficacy and safety of mitiperstat. It was planned that approximately 677 participants would be screened, and 406 participants would be randomised at approximately 100 sites across 14 countries. This study had 2 treatment arms (mitiperstat and placebo) to allow the efficacy and safety of mitiperstat to be assessed. The participants anticipated to be most likely to benefit from mitiperstat treatment were those at high risk of exacerbations.

The primary objective was to evaluate the effect of mitiperstat compared to placebo on the time to first COPDCompEx event in patients with moderate to severe COPD.

Secondary and exploratory assessments of efficacy included: time to first COPD moderate to severe exacerbation event, post-BD FEV1 at Week 12 compared to Week 1, MPO level and activity in sputum at Week 12 compared to baseline, and symptom scores.

It was planned that enrolment would cease after at least 194 first COPDCompEx events had occurred. At that point, all participants enrolled in the study who had not yet completed SV5 would continue in the study to complete 12 weeks of treatment. For these participants, SV5 and SV7 would be combined into 1 visit. Participants who had already completed 12 weeks of treatment when study enrolment was stopped would attend SV7 as soon as possible, continuing treatment until they do. All participants would attend SV8 14 ± 3 days after SV7/early discontinuation visit.

Four substudies were performed alongside this study: a cough monitoring substudy, Qualitative Study into Acute Worsening Events (Q-SAW) substudy, Study Participant Feedback Questionnaire (SPFQ) substudy, and patient experience interview substudy.

Target Population and Sample Size

Adult participants with confirmed moderate to severe symptomatic COPD (FEV1/FVC < 0.7, ≥ 10 pack-years smoking history, and post-BD FEV1 ≥ 25% predicted) who are at high risk of exacerbations despite being maintained on optimised standard inhaled therapies (triple inhaled therapy [ICS + LABA + LAMA] or ICS + LABA dual therapy or LABA + LAMA dual therapy for participants who were deemed unsuitable for ICS), were recruited.

Investigational Product and Comparator(s): Dosage, Mode of Administration

Participants were randomised 1:1 to treatment with oral mitiperstat 5 mg or oral placebo comparator, in the form of a film-coated tablet to be taken once daily. Mitiperstat and placebo were provided centrally by AstraZeneca and were provided in bottles labelled in accordance with GMP and country regulatory requirements.

Duration of Treatment

The duration of the study for each participant was up to 30 weeks including a 4-week screening period, 12 to 24 weeks of dosing, and 2 weeks of follow up. The maximum duration of treatment was 24 weeks.

Statistical Methods

The null hypothesis was that there is no difference in the time to first COPDCompEx event in mitiperstat 5 mg QD vs placebo. An alternative hypothesis was that there is a difference in the time to first COPDCompEx event.

The study was powered using COPDCompEx, a composite endpoint used to predict treatment effect on moderate and severe exacerbations of COPD. A total of 194 first COPDCompEx events (estimated to require 203 participants per arm) would provide 80% power at the two-sided 10% level of statistical significance to detect a hazard ratio of 0.70 in the mitiperstat arm based on a 24-week first COPDCompEx event risk of 55% assumed in the placebo arm. Since a screen failure rate of 40% was assumed, 677 participants were to be screened to achieve a randomisation of 406 participants.

An administrative interim analysis (IA) was conducted after 136 (70% of the required 194) first COPDCompEx events had occurred. It was to allow an early assessment of efficacy for mitiperstat, according to the decision framework (Frewer et al 2016). No formal statistical test was conducted. The IA assessment was used to guide internal (AstraZeneca) decision making regarding further development of the mitiperstat programme. As a result, no alpha was spent at the IA. The unblinded review committee (URC) was to be set up to review data from this administrative IA on the primary efficacy endpoint.

The data review committee (DRC) conducted an evaluation of safety at the time of the administrative IA, to allow efficacy IA outcome data to be considered should it be required.

Study Population

A total of 673 participants were enrolled in 14 countries: Canada, United States, Bulgaria, Poland, Turkey, Denmark, Germany, Italy, Netherlands, Spain, United Kingdom, Argentina, Mexico, South Africa. Overall, 381 participants were randomised and received study treatment. In total, 48 (12.6%) participants discontinued study treatment.

In the mitiperstat arm, of 189 participants randomised, 165 (87.3%) participants completed the study. In the placebo arm, of 192 participants randomised, 170 (88.5%) participants completed the study. The most common reason for treatment discontinuation in both arms was adverse events, which occurred in 30 (7.9%) participants overall.

There were more males (230 participants [60.4%]) than females (151 participants [39.6%]) in this study, reflecting the global prevalence of COPD by sex. The median age of participants at screening was 66.0 years (range: 48 to 80 years).

Overall, 146 (38.3%) participants were current smokers, with a slightly higher number reported in the mitiperstat arm (79 participants [41.8%]) compared to the placebo arm (67 participants [34.9%]), and 235 (61.7%) participants were former smokers. Median tobacco consumption was 40.0 pack years (range: 10 to 131 pack years).

Medical history among participants was unremarkable. Comorbidities seen were associated with COPD, including hypertension (45.4%), gastro-oesophageal reflux disease (18.4%), type 2 diabetes mellitus (13.6%), hypercholesterolaemia (12.1%), depression (11.8%) and osteoarthritis (10.5%).

Numbers of participants who had received prior medications were similar across treatment arms with 48 (25.4%) participants in the mitiperstat arm and 58 (30.2%) participants in the placebo arm. The most frequently prescribed prior medication among participants in either treatment arm was systemic glucocorticoids (14.4% participants).

Summary of Efficacy Results

- Treatment with mitiperstat compared to placebo did not reduce the risk of time to first COPDCompEx events in participants with moderate to severe COPD ($p = 0.599$).
- The results show a trend towards increasing risk for time to first exacerbations in the mitiperstat arm. The treatment effects reported were in the same direction as the primary endpoint findings (ie, no significant difference in risk between mitiperstat and placebo arms).
- Treatment with mitiperstat had no effect on post-BD FEV1.
- Respiratory symptoms, measured by EXACT (total score), BCSS (total score) cough VAS (average) score and CAT (total) score indicated no improvement with mitiperstat.
- Exploratory endpoints showed that mitiperstat had no effect on spirometry.
- Mitiperstat reduced normalised sputum MPO activity, suggesting target engagement.

Summary of Pharmacokinetic Results

- Following oral administration of mitiperstat at a dose of 5 mg QD, geometric mean C_{max} was 38.786 nmol/L, and absorption of mitiperstat was relatively rapid with T_{max} ranging from approximately 0.5 to 3 hours post-dose.

Summary of Safety Results

Mitiperstat was generally well tolerated. The AEs that were reported in the mitiperstat arm were comparable to those in the placebo arm. No significant laboratory, vital signs, or ECG abnormalities were identified.

However, there were 2 concerning observations, which both negatively affected the benefit-risk ratio of mitiperstat by causing potential harm to the participants. With regard to pneumonia events, according to the DRC charter, the final result for adjudicated events indicates a potential safety signal. Furthermore, there was a trend towards a higher exacerbation rate in participants receiving mitiperstat therapy.

Conclusions

- Mitiperstat did not meet primary or secondary efficacy criteria.
- Mitiperstat was generally well tolerated but there was a trend towards an increased risk of mild to moderate rash and an increased risk of exacerbation events.
- PK and target engagement markers were as anticipated.
- The study was well conducted, recruited beyond the initial target with acceptable participant withdrawal and completed all anticipated substudies.
- No significant methodological limitations, protocol deviations or study conduct changes were identified that may have impacted upon the validity or interpretation of the results.