AstraZeneca

**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD5069 |
| Study Code | D3550C00002 |
| Edition Number | 1 |
| Date | |

# A 4-Week, Double-blind, Placebo-controlled, Randomised, Parallel Group, Multicentre, Phase IIa Study to Investigate the Safety and Tolerability of AZD5069 as Oral Capsules in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease

**Study dates:** First patient enrolled: 22 November 2010
Last patient completed: 22 March 2011

**Phase of development:** Therapeutic exploratory (IIa)

**International Co-ordinating Investigator:**

**Sponsor's Responsible Medical Officer:**

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centre(s)

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

**Table S1 Primary and secondary objectives and outcome variables**

| Objectives | Outcome variables | Type |
|---|---|---|
| **Primary** | **Primary** | |
| Safety and tolerability of AZD5069. | Adverse Events (AEs), Electrocardiogram (ECG), Physical examination, Haematology, Clinical chemistry, Urinalysis, Vital signs, Body temperature, Lung function. | Safety |
| **Secondary** | **Secondary** | |
| Pharmacokinetics (PK) of AZD5069 in patients with COPD. | AZD5069 concentration in plasma and resulting PK parameters. | PK |
| Relationship between AZD5069 exposure and the effect on circulating neutrophils. | Circulating neutrophil counts in blood and measures of AZD5069 exposure in plasma. | PK/PD |

PD: pharmacodynamic

## Study design

This was a 4-week randomised, double-blind, placebo controlled, parallel group, multicentre Phase IIa study to evaluate the safety and tolerability of AZD5069 (50 and 80 mg bd) in patients with COPD.

## Target patient population and sample size

The patient population included males and females (females of non-childbearing potential) aged between 40-80 years (inclusive) with a clinical diagnosis of moderate to severe COPD with symptoms for at least 1 year prior to the screening visit. The patients were to be current or previous smokers with a smoking history of at least 10 pack years and have an $FEV_1$ ≥30% and <80% of predicted normal values and a $FEV_1$/FVC <70% (both post-bronchodilator) at screening visit.

Formal sample size calculations were not performed for this study, since no formal statistical hypothesis testing was to be performed. A sample size of 60 is considered adequate to investigate short-term safety and tolerability in this patient population.

## Investigational product and comparator(s): dosage, mode of administration and batch numbers

**Table S2 Investigational products and comparator**

| Investigational product | Dosage form and strength | Manufacturer | Material identity number | Batch number(s) |
|---|---|---|---|---|
| AZD5069 | 20 mg capsule | AstraZeneca | D1000125 | 10-002480AZ |
| AZD5069 | 50 mg capsule | AstraZeneca | D1000126 | 10-003546AZ |
| Placebo to AZD5069 | Capsule | AstraZeneca | D0800211 | 08-001091AZ |

The investigational product was to be taken orally twice daily, with doses approximately 12 hours apart (4 capsules in the morning and 4 capsules in the evening):

- AZD5069 50 mg bd - 1 x 50 mg capsule and 3 x placebo capsules
- AZD5069 80 mg bd - 4 x 20 mg capsules
- Placebo bd - 4 x placebo capsules

All capsules were the same size.

## Duration of treatment

The total duration of the study for a patient was 7 to 9 weeks; the treatment period was 4 weeks (28 days).

## Statistical methods

All safety data are reported using the safety analysis set and summarised descriptively by treatment received. All AEs and SAEs occurring at any time during the study are listed, indicating whether they occurred during the treatment period, or post-treatment. All post-dose AEs and SAEs (defined as those starting on or after the first dose of AZD5069 or placebo and including post-treatment AEs collected during follow-up) are summarised by frequency and percentage. AEs and SAEs are coded according to a medical dictionary for regulatory activities (MedDRA, Version 13.1) and are categorised in terms of intensity and causality. Physical examination data, laboratory data, ECG and vital signs data and lung function data are summarised descriptively and in relation to relevant reference ranges. Box-plots and shift plots have been produced as appropriate.

Plasma concentrations are summarised descriptively based on actual time. Windowing rules have been applied to actual time and any samples taken outside these windows are not included in the summaries. Plasma concentrations versus time profiles have been produced along with corresponding profiles of arithmetic mean ± SD. Derived PK parameters are summarised descriptively. Exposure parameters have been obtained using the individual post-hoc estimates of the population PK model parameters.

Circulating neutrophil count, change and percentage change from baseline are summarised descriptively. In addition, maximum reduction and maximum % reduction are summarised descriptively, along with the visit that the maximum reduction occurred at. Windowing rules have been applied when determining this visit. Plots of individual and mean absolute values over time have been produced.

**Patient population**

The first patient was enrolled on 22 November 2010 and the last patient completed the study on 22 March 2011. One hundred and nine patients were enrolled and 87 were randomised and received investigational product. Eighty-six patients completed the study; 1 patient in the placebo group voluntarily discontinued from the study after 3 days of study treatment and did not complete Visit 6 and 7. Of those who completed the study, 25 (86.2%), 24 (80.0%) and 25 (89.3%) patients in the placebo, AZD5069 50 and 80 mg groups, respectively, completed treatment.

The treatment groups were reasonably well balanced for demographic and respiratory disease characteristics. The mean (SD) age of patients was 64 (7.4) years (range: 46 to 78 years); 69% were male and all were White; patient weight, height and BMI were unremarkable. Overall, the mean duration of COPD was 8 years (0[1] to 24 years) with a mean smoking history of 37 pack-years; ~47% were current smokers and ~53% ex-smokers). Baseline lung function was balanced across the treatment groups with a mean percent predicted $FEV_1$ 56% and $FEV_1$/FVC (%) ~53%. The mean (SD) time since the last exacerbation prior to screening (for patients with evaluable data) was 12 (12.3) months; when these date were evaluated by the following categories: ≤12 months and >12 months, there were 48 (62%) and 29 (38%) patients, respectively.

**Summary of pharmacokinetic results**

In general, the PK in COPD patients was characterised by fairly rapid absorption with $t_{max}$ occurring at approximately 1.5 hours after dose and a short effective half-life of approximately 3 hours. The geometric mean exposure to AZD5069 in terms of $C_{max}$ was 2570 nmol/L and 3190 nmol/L for the 50 and the 80 mg bid dose, respectively. For $AUC_{(0-24)}$, the geometric mean exposure to AZD5069 was 30500 nmol*h/L and 37800 nmol*h/L for the 50 and the 80 mg bid dose, respectively. The exposure in terms of $C_{max}$ and $AUC_{(0-24)}$ increased less than in proportion to the dose. The expected increase in systemic exposure from 50 to 80 mg was 60%, but the observed increase was only 24% for both $C_{max}$ and $AUC_{(0-24)}$.

Overall variability in exposure in terms of $C_{max}$ and $AUC_{(0-24)}$ was high with a geometric coefficient of variation of approximately 100%.

[1] Patient E0901006 (AZD5069 80 mg group) was diagnosed with COPD on 04 October 2010, ~4 months prior to randomisation (Appendices 12.2.2.1 and 12.2.4.2). The patient's data was not excluded from any of the analyses.

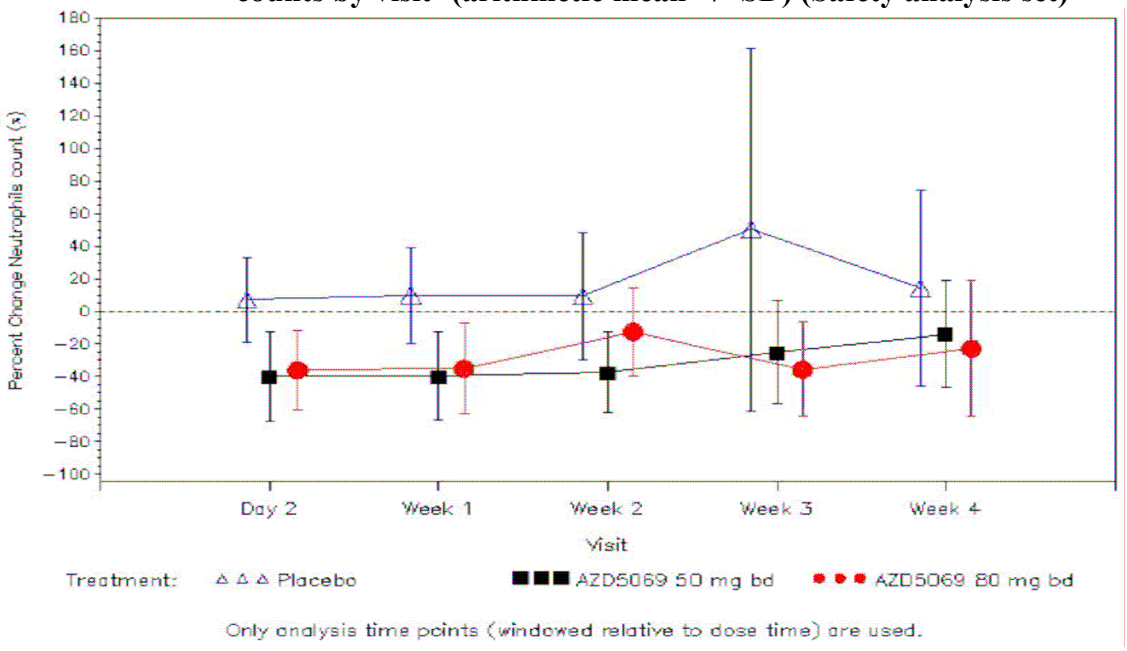
## Summary of pharmacodynamic results

All values, unless otherwise indicated, refer to morning pre-dose samples.

In both AZD5069 groups, the percentage change from baseline in circulating neutrophils showed a mean decrease in counts at each visit (Figure S1). In the AZD5069 50 mg group, a mean % decrease in counts of approximately -40% was seen from Day 2 (first day of dosing) through to Week 2. Thereafter, mean counts were increased from those observed at earlier visits but remained below the baseline mean. In the AZD5069 80 mg group, a mean % decrease in counts of approximately -35% was seen on Day 2 and Week 1. At Week 2, the mean count was increased from those observed at earlier visits but remained below the baseline mean (-12.5%). Thereafter, mean counts decreased from those observed at Week 2 to -35.6 and -22.7% at Weeks 3 and 4, respectively. A similar pattern was observed 1-hour post-dose; too few patients contributed data 2- and 3-hours post-dose to allow meaningful interpretation of the results. There was no evidence of dose dependency for the change from baseline in pre-dose circulating neutrophil counts, by visit, between the AZD5069 groups (Figure S1).

The percentage change from baseline in pre-dose circulating neutrophil counts in the placebo group showed no decrease in mean counts at each visit (Figure S1).

**Figure S1** **Percentage change from baseline in pre-dose[a] circulating neutrophil counts by visit[b] (arithmetic mean +/- SD) (Safety analysis set)**




a Pre the first dose in the morning.

b At Week 3 (placebo group), the percentage change from baseline in pre-dose circulating neutrophil counts had increased to ~40%. Two patients with low baseline counts largely drove this result. The baseline counts for patients E0904005 and E0903001 (Visit 2 – Day 1) were 1.45 and 1.39 x $10^9$/L, respectively (local laboratory). At the Week 3 visit, patient E0904005 had a count of 7.23 x $10^9$/L representing a 398.6% increase from baseline and patient E0903001 had a count of 4.67 x $10^9$/L representing a 236.0% increase from baseline.

**Summary of pharmacokinetic/pharmacodynamic relationships**

Overall, there is a trend towards decreasing neutrophils with increasing systemic exposure, although the variability is high.

**Summary of safety results (primary objective)**

A high proportion of the patients in each treatment group completed study treatment as planned with 86.2, 80.0 and 89.3% patients in the placebo, AZD5069 50 and 80 mg groups, respectively. The mean number of days on treatment was similar across the treatment groups with 27, 25 and 27 days in the placebo, AZD5069 50 and 80 mg groups, respectively.

(i) Adverse events

The number of patients with AEs was similar across each treatment group with 9 (31.0%), 10 (33.3%) and 6 (21.4%) in the placebo and AZD5069 50 and 80 mg groups, respectively. There were no AEs with fatal outcome during the study and 2 non-fatal SAEs (AZD5069 50 mg [1: atrial fibrillation] and AZD5069 80 mg [1: chronic obstructive pulmonary disease; exacerbation of]). The incidence of AEs leading to discontinuation of placebo/AZD5069 was slightly higher in the AZD5069 50 mg group vs. the other groups with 3 (10.3%), 5 (16.7%) and 2 (7.1%) patients in the placebo and AZD5069 50 and 80 mg groups, respectively. With the exception of neutrophil count decreased, all other AEs that lead to discontinuation of investigational product occurred at a single incidence within any group. Neutrophil count decreased was reported in 3 (10.0%) patients in the AZD5069 50 mg group vs. 1 (3.6%) in AZD5069 80 mg group; there were no reports of neutrophil count decreased in the placebo group. No OAEs were identified in any treatment group.

The most commonly reported AE in any group was nasopharyngitis with 4 (13.3%) patients in the AZD5069 50 mg group vs. 2 (6.9%) in the placebo group; there were no reports of nasopharyngitis in the AZD5069 80 mg group. Neutrophil count decreased was reported in 0 (-), 3 (10.0%) and 1 (3.6%) patients in the placebo, AZD5069 50 and 80 mg groups, respectively. There were few AEs of diarrhoea, pyrexia and COPD (*exacerbation*) with 1 (3.4%), 2 (6.7%) and 0 (-), 2 (6.9%), 1 (3.3%) and 0 (-), and 0 (-), 2 (6.7%) and 1 (3.6%) patients, respectively, in the placebo, AZD5069 50 and 80 mg groups, respectively. Otherwise, AEs were typically reported at single incidences overall.

(ii) ECG

There were no important differences across the treatment groups for the overall evaluation of ECG at each visit; the overall evaluation was typically unchanged from baseline.

(iii) Physical examination

A shift table comparing baseline to the last observation on treatment for physical examination showed only 1 patient (AZD5069 80 mg group) with a new or aggravated assessment (examination variable: lymph nodes); all other patients were either normal or if abnormal, were unchanged from baseline.

(iv) Laboratory

The pattern of change in individual patients in both AZD5069 groups was for a decrease in leucocyte counts with the majority of cases occurring within the minimum and maximum boundaries of the AstraZeneca reference ranges. There were no instances of leucocyte counts below the level at which study treatment was to be discontinued ($2.0 \times 10^9$/L).

For neutrophil counts, the pattern of change in individual patients in both AZD5069 groups was similar to that seen for leucocyte counts ie, there was a decrease in neutrophil counts with the majority of cases occurring within the minimum and maximum boundaries of the AstraZeneca reference ranges. There were instances of neutrophil counts decreasing to below the level at which study treatment was to be discontinued ($1.0 \times 10^9$/L) and in 4 cases (AZD5069 50 mg [3] and 80 mg [1]), the patient discontinued treatment due to an AE of 'Neutrophil counts decreased'. Otherwise, there were no clinically important abnormalities in haematology that could be related to treatment with AZD5069.

Overall, there were no clinically important abnormalities in clinical chemistry that could be related to treatment with AZD5069.

There was no apparent change from baseline (screening visit) in urinalysis data at any scheduled visit in any treatment group or any important differences across the groups in the results obtained.

(v) Vital signs: BP, pulse rate, body temperature

In the placebo group, mean (SD) SBP at baseline was 128 (14.5) mmHg. Post-baseline, the change in SBP showed a mean increase of 1 to 4 mmHg during the treatment period. At follow-up, the mean (SD) change from baseline in SBP was 2 (8.7) mmHg.

The mean (SD) SBP at baseline in the AZD5069 50 mg group was 133 (14.5) mmHg. Post-baseline, the change in SBP showed a mean reduction during Weeks 1 and 2 of -4 and -3 mmHg, respectively. Thereafter, the mean change from baseline in SBP during Weeks 3 and 4 was 0 and -0, respectively. At follow-up, the mean (SD) change from baseline was -3 (12.0) mmHg. In the AZD5069 80 mg group, mean (SD) SBP at baseline was 132 (12.5) mmHg. Post-baseline, the change in SBP showed a mean reduction during Weeks 1, 2, 3 and 4 of -1, -3, -5 and -3 mmHg, respectively. At follow-up, the mean (SD) change from baseline was -2 (12.9) mmHg. The pattern of change for DBP in each treatment group was similar to SBP.

In the placebo group, mean (SD) pulse rate at baseline was 72 (9.1) bpm. Post-baseline, the change in pulse rate during the treatment period showed a mean increase of 1 to 4 bpm. At follow-up, the mean (SD) change from baseline in pulse rate was 1 (7.5) bpm.

The mean (SD) pulse rate at baseline in the AZD5069 50 mg group was 72 (10.3) bpm. Post-baseline, the mean change in pulse rate during the treatment period was similar to that seen in the placebo group, -1 to 3 bpm. At follow-up, the mean (SD) change from baseline was 2 (10.7) bpm. In the AZD5069 80 mg group, mean (SD) pulse rate at baseline was 73 (10.4) bpm. Post-baseline, the change in pulse rate showed a mean increase during Weeks 1, 2, 3 and 4 of 5, 1, 2 and 3 bpm, respectively. At follow-up, the mean (SD) change from baseline was 0 (7.2) bpm.

There was no apparent change from baseline in oral temperature (°C) at any scheduled visit in any treatment group or any important differences across the groups in the results obtained.

(vi) Lung function

The results obtained from the lung function variables (pre- and post-bronchodilator $FEV_1$, FVC, SVC, IC and $FEF_{25-75\%}$) were unremarkable.

**Conclusion(s)**