**Revised Clinical Study Protocol**

| | |
|---|---|
| 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

**Sponsor:** AstraZeneca AB, .

**AstraZeneca Research and Development site representative**

_____ _____
Date

Study Delivery Team Leader
AstraZeneca R&D



**The following Amendment(s) and Administrative Changes are included in this revised protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| 1 | | | |
| 2 | | | |

| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
|---|---|---|---|
| | | | |

AstraZeneca

# PROTOCOL SYNOPSIS

## 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

**International Co-ordinating Investigator**

Dr .

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**Study centre(s) and number of patients planned**

In this study it is planned to include approximately 60 randomised patients recruited from around 16 sites in 4 countries. Each site is expected to recruit between 3 to 5 patients.

| Study period | Phase of development |
|---|---|
| Estimated date of first patient enrolled | IIa |
| Estimated date of last patient completed | |

**Objectives**

The primary objective is:

- To evaluate the safety and tolerability of AZD5069 in patients with Chronic Obstructive Pulmonary Disease (COPD)

The secondary objectives are:

- To investigate the pharmacokinetics of AZD5069 in patients with COPD
- To investigate the relationship between appropriate measures of AZD5069 exposure (which may include dose, concentration, $C_{max}$ and/or AUC) and the effect on circulating neutrophils.

The exploratory objectives are:

- To store remaining plasma samples for further potential metabolism and PK investigations
- To collect samples for analysis of blood inflammatory markers, including, but not limited to sVCAM-1, sICAM-1, CRP, SAA and VEGF
- To retain several aliquots of serum for potential future retrospective analysis of mediators relevant to the mechanism of inflammation in COPD (archive sample)
- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5069, and/or susceptibility to COPD, and/or associated biomarkers
- To undertake additional analyses of AZD5069 plasma concentrations and / or exposure versus the safety and clinical parameters, if warranted.
- To investigate leucocyte stability by measuring leucocyte (including neutrophil) counts at approximately 2 hours (local laboratory analysis) and at intervals between receipt of sample and 72 hours (central laboratory analysis) after sample collection.

The exploratory analyses will not be reported in the CSR and will be reported separately.

**Study design**

This is a randomised, double-blind, placebo-controlled, parallel group, multicentre study in patients with moderate to severe COPD (Global Initiative on Obstructive Lung Disease (GOLD) stage II-III) (Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2009. Available from URL: http://www.goldcopd.com.). The study consists of 3 treatment arms. Approximately 60 patients will be randomised to receive one of the following treatments in the fasted state (approximately 20 patients per treatment arm):

- 50 mg AZD5069 twice daily (bd) (100 mg total daily dose)
- 80 mg AZD5069 bd (160 mg total daily dose)
- Placebo to match AZD5069 bd.

The total duration of the study for a patient will be between 7 and 9 weeks, which includes a 4-week treatment period.

Approximately 16 patients, at selected sites, will complete a PK sub-study. The patients will follow the same visit schedule as the main study but 3 of the clinic visits (Visits 2, 4 and 6) will be extended and these patients will remain at site for approximately 5 hours, to allow further PK samples to be obtained. Patients must not take investigational product (AZD5069

or placebo) at home on the morning of Visits 4 and 6. At these extended visits, 5 blood samples (1 pre-dose and approximately 1, 2, 3 and 5 hours post-dose) will be drawn for evaluation of plasma PK. In addition, blood samples (to match PK samples taken pre-dose [Visit 2 only], 1 and 3 hours post-dose) will be drawn for measurement of leukocyte count including circulating neutrophils. Further details can be found in Section 6.6.

There will be an optional pharmacogenetic element to collect samples for possible retrospective analysis. Further details can be found in Appendix D.

**Target patient population**

Male and female patients (females of non-childbearing potential) with moderate to severe COPD aged between 40 to 80 years of age (inclusive).

**Investigational product, dosage and mode of administration**

AZD5069 will be administered as oral capsules at doses of 50 mg or 80 mg bd for 4 weeks.

**Comparator, dosage and mode of administration**

Matching placebo capsules will be administered, orally, bd, for 4 weeks in a blinded fashion.

**Duration of treatment**

Patients who have given their informed consent at Visit 1 will attend a screening visit (Visit 1.1) for study screening procedures. Patients who fulfil the inclusion criteria and none of the exclusion criteria at this visit will enter the run-in period (minimum of 14 days, maximum of 21 days). At Visit 2 eligible patients will be randomised into the 4-week treatment period. Study visits will take place 2 days, 1 week, 2 weeks, 3 weeks and 4 weeks after randomisation (Visits 2.1 to 6). Patients will return to the clinic 1 to 2 weeks after stopping investigational product for a follow up visit (Visit 7). Patients will be asked to fill in a daily diary during the study (Visits 1 to 7). A new diary card will be given to the patient at each clinic visit.

The total duration of the study for a patient will be between 7 to 9 weeks.

**Outcome variable(s):**

Primary variable:

- Safety and tolerability variables
  - Adverse Events (AEs)
  - 12-lead Electrocardiogram (ECG)
  - Physical examination
  - Haematology, clinical chemistry and urinalysis

  - Vital signs and body temperature
  - Pre- and post-bronchodilator lung function tests (Forced Expiratory Volume in 1 second ($FEV_{1)}$, Forced Vital Capacity (FVC), Slow Vital Capacity (SVC), Inspiratory Capacity (IC), Forced Expiratory Flow 25-75% ($FEF_{25-75\%}$))

Secondary variables:

- Pharmacokinetic variables
  - AZD5069 concentration in plasma and resulting PK parameters
- Pharmacodynamic variable
  - Circulating neutrophil count in blood

Exploratory variables:

- Safety variables
  - Neutrophil counts determined at different times post-sample collection
- Pharmacokinetic variables:
  - Potential future pharmacokinetic and metabolic investigations
- Pharmacodynamic variables:
  - Blood inflammatory biomarkers, including, but not limited to sVCAM-1, sICAM-1, CRP, SAA and VEGF
  - Potential future retrospective biomarker investigations of mediators relevant to the mechanism of inflammation in COPD
- Pharmacogenetic- please refer to Appendix D of the Clinical Study Protocol for further details
- To undertake additional analyses of AZD5069 plasma concentrations and / or exposure versus the safety and clinical parameters, if warranted.

**Statistical methods**

No formal statistical hypothesis testing will be performed. The analyses of safety, tolerability, and pharmacokinetic and pharmacodynamic data will involve only descriptive statistics including tables, listings and graphs, as appropriate.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 6.4.1) |
| ALT | Alanine Aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification |
| ATS | American Thoracic Society |
| AUC | Area under the plasma concentration curve from zero to infinity |
| $AUC_{(0-t)}$ | Area under the plasma concentration curve from zero to t hours |
| AZ | AstraZeneca |
| BALF | Bronchoalveolar lavage fluid |
| bd | Twice daily |
| BMI | Body Mass Index |
| CD11b | Cluster of differentiation molecule 11b; Mac-1 |
| $C_{max}$ | Maximum observed plasma concentration |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPD | Clinical Pharmacology and Drug Metabolism Pharmacokinetics |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case Report Form (electronic/paper) |
| CRP | C-Reactive Protein |
| CSA | Clinical Study Agreement |
| CSR | Clinical Study Report |
| CXCR1 | CXC chemokine receptor 1 |
| CXCR2 | CXC chemokine receptor 2 |
| DAE | Discontinuation of Investigational Product due to Adverse Event |
| DMC | Data Management Centre |
| DNA | Deoxyribonucleic acid |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ENA 78 | Epithelial cell-derived neutrophil-activating protein |
| ERS | European Respiratory Society |

| Abbreviation or special term | Explanation |
|---|---|
| $FEF_{25-75\%}$ | Forced Expiratory Flow 25-75% |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| FSH | Follicle stimulating hormone |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCS | Glucocorticosteroids |
| G-CSF | Granulocyte colony stimulating factor |
| GMAD | Global multiple ascending dose |
| GMP | Good Manufacturing Practice |
| GOLD | Global Initiative on Obstructive Lung Disease |
| GRand | Global Randomisation System |
| GROα | Growth related oncogene alpha |
| GSAD | Global single ascending dose |
| hERG | Human ether-a-go-go-related gene |
| HIV | Human Immunodeficiency Virus |
| hsCRP | High sensitivity C-Reactive Protein |
| IATA | International Airline Transportation Association |
| IB | Investigator's Brochure |
| IC | Inspiratory Capacity |
| ICH | International Conference on Harmonisation |
| ICS | Inhaled corticosteroids |
| IL-8 | Interleukin-8 |
| IP | Investigational Product |
| ISF | Investigator Site File |
| IUD | Intra-uterine device |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| L | Litres |
| LABA | Long-Acting β2 Agonist |
| LAMA | Long acting muscarinic antagonist |
| LFT | Liver Function Test |
| LH | Luteinizing hormone |
| LIMS | Laboratory Information Management System |
| LLN | Lower Limit of Normal |
| LLOQ | Lower Limit Of Quantification |
| LOQ | Limit of Quantification |

| Abbreviation or special term | Explanation |
|---|---|
| LPLV | Last Patient Last Visit |
| LPS | Lipopolysaccharide |
| MAD | Multiple ascending dose |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | Millilitre |
| NAG | N-acetyl-beta-D-glucosaminidase |
| NOAEL | No observable adverse effect level |
| OAE | Other Significant Adverse Event (see definition in Section 11.1.1) |
| PD | Pharmacodynamic |
| PgP | Permeability glycoprotein |
| PK | Pharmacokinetic |
| PT | Preferred Term |
| QT | ECG interval measured from beginning of Q wave (or the R wave if Q is missing) to the end of the T wave; the time interval of ventricular depolorisation and repolarisation |
| QTc | QT interval corrected for heart rate |
| QTcF | QT corrected according to Fridericia's formula |
| R&D | Research and Development |
| SAA | Serum Amyloid A |
| SABA | Short Acting β2 Agonist |
| SAD | Singe ascending dose |
| SAE | Serious adverse event (see definition in Section 6.4.2). |
| SAMA | Short acting muscarinic antagonist |
| SD | Standard deviation |
| SDT | Study Delivery Team |
| SDV | Source Data Verified |
| sICAM-1 | Soluble Inter-Cellular Adhesion Molecule-1 |
| SOC | System Organ Class |
| SVC | Slow Vital Capacity |
| sVCAM-1 | Soluble Vascular Cell Adhesion Molecule-1 |
| TB | Tuberculosis |
| $t_{max}$ | Time to $C_{max}$ |
| TS | Translation Science |
| ULN | Upper Limit of Normal |
| VEGF | Vascular endothelial growth factor |
| WBDC | Web Based Data Capture |

# 1. INTRODUCTION

## 1.1 Background

AZD5069 is a small molecule CXCR2 (CXC chemokine receptor 2) antagonist that is proposed to have potential as a novel oral treatment of inflammatory diseases, including Chronic Obstructive Pulmonary Disease (COPD).

CXCR2 is a G-protein coupled receptor expressed on a variety of inflammatory cells (monocytes, macrophages, neutrophils) and epithelium that are believed to be critical in the pathogenesis of COPD. CXCR2 ligands, the chemokines epithelial cell-derived neutrophil-activating protein (ENA 78), growth related oncogene alpha (GROα) and interleukin-8 (IL-8), are produced by macrophages, mast cells and epithelial cells. Levels of IL-8 are elevated in sputum, bronchoalveolar lavage fluid (BALF) (Rutgers et al 2000) and plasma in COPD patients (AZD8309 Investigator's Brochure) (Hageman et al 2003) and correlate with increased neutrophil numbers and reduction in lung function (Perng et al 2004). Levels of GROα have also been shown to be elevated in COPD sputum (Traves et al 2002). IL-8 and GROα are potent inducers of chemotaxis of neutrophils and monocytes in vitro, an effect believed to be due to activation of CXCR2, rather than CXCR1 (CXC chemokine receptor 1), which is selective for IL-8.

A CXCR2 antagonist would be expected to decrease neutrophilic inflammation in the lung as well as sequelae of neutrophilic infiltration such as mucus production and tissue destruction mediated by proteinases released from the neutrophils. Similar beneficial effects would occur through the blocking of CXCR2 mediated influx of monocytes. As a consequence, inhibition of cough, enhanced airway function and decreased air trapping would be anticipated. By decreasing the frequency and intensity of the pulmonary inflammatory response in COPD (chronically and during exacerbations) and by limiting the exposure of lung tissue to proteolytic attack, a CXCR2 antagonist would also be expected to influence the long-term course of the disease.

A CXCR2 antagonist previously studied by AstraZeneca, AZD8309, has been shown to inhibit GROα induced CD11b expression on human neutrophils and to reduce numbers of peripheral blood neutrophils when given orally to healthy subjects. Oral dosing of AZD8309 also reduced neutrophil counts in induced sputum following lipopolysaccharide (LPS) challenge to healthy subjects.

There are a number of CXCR2 receptor antagonists currently in development by other companies. As far as is known the most advanced of these is SCH527123, currently in Phase II clinical trials. Single and multiple ascending dose studies in healthy subjects have shown this compound to have an acceptable safety profile (Khalilieh et al 2007a) (Khalilieh et al 2007b). A dose-related decline in circulating neutrophils was seen, which could be reversed by administration of G-CSF (Khalilieh et al 2007a). No evidence of a cumulative effect was seen with multiple doses (Khalilieh et al 2007b). SCH527123 inhibited

ozone-induced airway neutrophilia in a double-blind controlled study (Holz et al 2010). The compound had no effect on acquired immunity to hepatitis A vaccine (Khalilieh et al 2007c).

Additional relevant information of note is detailed below:

- AZD5069 is a potent reversible antagonist at human CXCR2 and a potent inhibitor of CXCR2-mediated calcium mobilisation, adhesion molecule expression and chemotaxis in human neutrophils in vitro.

- A probe CXCR2 antagonist, AZ10397767, reduced LPS induced neutrophil influx in rat and rabbit lung. In the rabbit, this effect was associated with inhibition of histological indicators of the pulmonary inflammatory response. Since AZ10397767 is a selective CXCR2 antagonist in the rabbit (CXCR2:CXCR1 selectivity 400-fold), its efficacy in this species indicates that, despite the theoretical potential for redundancy of CXCR pathways, CXCR2 antagonism alone is sufficient to substantially reduce a pulmonary inflammatory response.

- Investigation of the position and frequency of polymorphisms in African-American, Caucasian (Western European) and Japanese populations has provided no evidence of common (frequency >5%) polymorphisms in human CXCR2 that would be anticipated to modify interaction of AZD5069 with the receptor.

- Immunocytochemical assessment of lung tissue from human lung resections from normal donors and from patients with COPD ranging from moderate to severe, has shown an increase in CXCR2 expression in COPD.

- AZD5069 demonstrated a high degree (>100-fold) of selectivity and specificity for the human CXCR2 receptor compared with other chemokine receptor subtypes and all other receptor or enzyme targets investigated.

- In safety pharmacology studies, the only observations of particular note were impaired gastric emptying and decreased gastrointestinal motility after single doses of 350 mg/kg in the rat.

- An integrated assessment of results obtained in the IKr channel (human ether-a-go-go-related gene [hERG] expression system) in vitro and in dog QT studies in vivo indicate that AZD5069 has a low potential for QT prolongation.

- In the recently completed global single ascending dose study (GSAD, D3550C00001 study) and global multiple ascending dose study (GMAD, D3550C00007 study), subjects receiving AZD5069 had a positive response in the biomarker assay, ie, it inhibited GROα-induced CD11b expression on neutrophils. This response was more marked as the dose increased.

- In the GSAD study, there were no serious or severe adverse events relating to AZD5069 and no clinically significant laboratory abnormalities, apart from

reductions in circulating neutrophils and total white cell count, which were expected with a CXCR2 antagonist.

- No gastrointestinal adverse events (AEs) of concern were seen in either the GSAD or the GMAD studies.

AZD5069 pharmacokinetics (PK) have been investigated in 3 studies to date in healthy subjects (GSAD, GMAD and Fed/Fasted/Elderly study (D3550C00010)) following single oral doses up to 200 mg and twice a day dosing up to 100 mg AZD5069. AZD5069 generally displayed dose proportional pharmacokinetics, following both single dose and at steady-state over the dose range tested. Steady-state kinetics appears to be attained following 2-3 days of dosing. This is consistent with the mean terminal elimination half-lives of approximately 11 hours seen over the 17.99 to 200 mg dose range, which started at approximately 24 hours post-dose. AZD50698 is absorbed relatively quickly, medium $t_{max}$ ranges from 1-2 hours post-dose, independent of dose. Following peak plasma AZD5069 concentrations ($C_{max}$) plasma AZD5069 concentrations appear to decline in a multi-exponential manner. Over the 8- to 24-hour post-dost period, drug concentrations declined with an elimination half-life of approximately 4 hours, which may potentially be the pharmacologically relevant half-life. Over the dose range investigated, less than 5% of the oral dose was excreted as parent drug in urine following single doses and at steady-state. Preliminary draft data suggests that dosing AZD5069 with a high-fat meal reduced the rate of drug absorption ($C_{max}$) by approximately 50%, $t_{max}$ was later (4 hours compared to 1.5 hours) compared to the fasted state, but did not influence the extent of drug absorption (AUC).

Reductions in blood neutrophil counts and in ex vivo GROa-stimulated CD11b expression on neutrophils in whole blood, appear to be related to plasma drug concentrations of AZD5069, and independent of time (ie, in response to a given plasma concentration of AZD5069, the reduction on blood neutrophils is similar on Day 1 and at steady-state [eg, Day 6 or Day 8]).

## 1.2 Rationale for conducting this study

To date all human studies conducted with AZD5069 have been in healthy volunteers. Healthy volunteers in the Phase I studies have only been treated for up to 7.5 days, following twice daily (bd) dosing, in the GMAD study (D3550C00007). Safety and tolerability information in patients with COPD receiving longer term multiple doses of AZD5069 is required before proceeding into longer term Phase IIb studies. Obtaining safety and tolerability information about 2 doses of AZD5069 will aid dose selection for future studies. This study is planned to provide that information.

AZD5069 is being developed for the prevention and amelioration of exacerbations of COPD. Exacerbations increase in number with increasing GOLD stage (Hurst et al 2010) so GOLD stage 1 patients may not be the most appropriate patient subgroup to study. On the other hand, GOLD stage 4 patients may not have sufficient functional residual capacity to respond to therapy. Because GOLD stage 2 and 3 patients will be the main targets for AZD5069 in future studies, it is necessary to include them in this carefully controlled safety and tolerability study.

## 1.3 Benefit/risk and ethical assessment

It is not expected that patients will derive any clinical benefit from treatment with AZD5069 over a period of one month. Potential risks have been identified through review of the clinical studies so far conducted, the GSAD (D3550C00001) and GMAD (D3550C00007) studies, as well as review of non-clinical animal studies with AZD5069 and of the literature and unpublished information relating to other CXCR2 antagonists. Risks to patients will be minimized by incorporating relevant exposure margins to animal toxicology findings and by regular monitoring.

The most relevant findings observed in the non-clinical studies with AZD5069 with potential relevance to humans were changes in the level of white blood cells. In the initial one-month dog study (20 mg/kg bd), dose-related increases were observed in white blood cells (mostly attributable to neutrophils) from Day 2. In addition, dose-related increases in globulin and C reactive protein (CRP) were noted in all dose groups with increases in CRP being generally highest on Day 2. The second one-month dog study was aimed to define a no observable adverse effect level (NOAEL) for changes in neutrophils and CRP and to understand the speed of onset and recovery from these changes. Increases in both parameters were observed from 24 hours after the first dose in all dogs dosed at 10 mg/kg bd and in individual animals dosed at 0.5 mg/kg bd. Following the cessation of dosing, both parameters returned to baseline levels during the recovery period. A dose level of 0.1 mg/kg bd was determined to be NOAEL for changes in neutrophils and CRP.

The major effect seen to date in the GSAD (D3550C00001) and GMAD (D3550C00007) studies has been a reduction in circulating neutrophils. This was dose-related in the GSAD and GMAD studies, with more subjects having reductions and for longer periods at higher doses. A reduction in neutrophils is an expected effect of a CXCR2 antagonist and was also seen with AZD8309 (see AZD8309 Investigator's Brochure (IB)) and with SCH527123 (Khalilieh et al 2007a), (Khalilieh et al 2007b), (Khalilieh et al 2007c). One subject, dosed with AZD5069 100 mg bd, was withdrawn from the GMAD (D3550C00007) study because of a reduction in circulating neutrophils below the specified limit of 1.0 x $10^9$/L lasting for longer than 48 hours.

The doses to be used in this study have been selected following review of the data from the GSAD (D3550C00001) and GMAD (D3550C00007) and are predicted to minimise the number of subjects with circulating neutrophils remaining below a concentration of 1.0x$10^9$/L for more than 24 hours.

Reductions in neutrophil count may be associated with an increased risk of infections, particularly soft tissue infections. Patients will be regularly monitored by the investigators, including body temperature measurements.

For a more detailed risk benefit assessment of developing a CXCR2 inhibitor for COPD, see the AZD5069 IB.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

The primary objective is to evaluate the safety and tolerability of AZD5069 in patients with COPD. The associated primary outcome variables are shown in Table 1.

**Table 1 Primary objective and outcome variables**

| Objective | Outcome Variables |
|---|---|
| Safety and tolerability of AZD5069 | Adverse Events (AEs) |
| | Electrocardiogram (ECG) |
| | Physical examination |
| | Haematology[a] |
| | Clinical chemistry[a] |
| | Urinalysis[a] |
| | Vital signs |
| | Body temperature |
| | Lung function[b] |

[a] See Section 6.4.5, Table 7 for the full list of parameters to be measured
[b] See Section 6.4.9 for further details of the lung function tests

## 2.2 Secondary objectives

The secondary objectives are:

- To investigate the pharmacokinetics of AZD5069 in patients with COPD
- To investigate the relationship between appropriate measures of AZD5069 exposure (which may include dose, concentration, $C_{max}$ and/or AUC) and the effect on circulating neutrophils

The associated secondary outcome variables are shown in Table 2:

**Table 2 Secondary objectives and outcome variables**

| Objective | Outcome Variables |
|---|---|
| Pharmacokinetics (PK) of AZD5069 in patients with COPD | AZD5069 concentration in plasma and resulting PK parameters |
| Relationship between AZD5069 exposure and the effect on circulating neutrophils | Circulating neutrophil counts in blood and measures of AZD5069 exposure in plasma (which may include dose, concentration, Cmax and/or AUC) |

## 2.3 Exploratory objectives

The exploratory objectives are:

- To store remaining plasma samples for further potential metabolism and PK investigations
- To collect samples for analysis of blood inflammatory markers, including, but not limited to sVCAM-1, sICAM-1, CRP, SAA and VEGF
- To retain several aliquots of serum for potential future retrospective analysis of mediators relevant to the mechanism of inflammation in COPD (archive sample)
- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5069, and/or susceptibility to COPD, and/or associated biomarkers
- To undertake additional analyses of AZD5069 plasma concentrations and / or exposure versus the safety and clinical parameters, if warranted.
- To investigate leucocyte stability by measuring leucocyte (including neutrophil) counts at approximately 2 hours (local laboratory analysis) and at intervals between receipt of sample and 72 hours (central laboratory analysis) after sample collection.

The exploratory analyses will not be reported in the CSR and will be reported separately.

# 3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

## 3.1 Overall study design and flow chart

This is a 4-week, randomised, double-blind, placebo-controlled, parallel group, multicentre study to investigate the safety and tolerability of AZD5069 in patients with moderate to severe

COPD. In the study it is planned to include approximately 60 randomised patients recruited from around 16 sites in 4 countries. Each site is expected to recruit between 3 to 5 patients.

The patient population will be 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 Visit 1.1. The patients must 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 Visit 1.1. See Section 4.1 and Section 4.2 for further details of the eligibility criteria.

Patients who have given their informed consent at Visit 1, will attend a screening visit (Visit 1.1) for study screening procedures. Patients who fulfil the inclusion criteria and none of the exclusion criteria at this visit will enter the run-in period (see Figure 1 for details).

At Visit 2 eligible patients will be randomised into the 4 weeks treatment period to receive one of the following treatments in a 1:1:1 ratio:

- 50 mg AZD5069 bd (100 mg total daily dose)
- 80 mg AZD5069 bd (160 mg total daily dose)
- Placebo to match AZD5069 bd.

Randomisation will be stratified for use of inhaled corticosteroid.

The investigational product will be taken orally twice daily, with doses approximately 12 hours apart. The first dose of investigational product will be taken in the clinic at Visit 2. All other doses will be taken by the patient in accordance with their normal routine, unless the patient is taking part in the pharmacokinetic (PK) sub-study when the morning dose at Visits 4 and 6 should be taken in the clinic after pre-dose assessments. No food should be consumed within the 2 hours prior to the scheduled dose and for one hour after taking the dose. After completion of the treatment period the patients will return to standard COPD therapy, as chosen by the investigator.

Patients will visit the clinic within 2 days of randomisation (Visit 2.1) for an additional sample to measure leucocytes and circulating neutrophils and then after 1 week, 2 weeks and 3 weeks (Visits 3 to 5) on treatment and at the end of treatment (after 4 weeks, Visit 6). The weekly visits (Visits 3, 4, 5 and 6) should be no more than 7 calendar days apart. Patients will be asked to fill in a daily diary during the study (Visits 1 to 7) and will also be provided with an accurate thermometer to record their temperature orally twice daily (morning and evening). A new diary card will be given to the patient at each clinic visit. Clinic staff will also contact patients twice weekly (in addition to clinic visits) via telephone in order to monitor any AEs, assess general health status, ensure that the patients do not have a fever and to ascertain whether an additional clinic visit is required. Patients will return to the clinic 1 to 2 weeks after stopping investigational product for a follow up visit (Visit 7). Due to diurnal variations in lung measurement, it is important that the clinic visits are scheduled so that spirometry

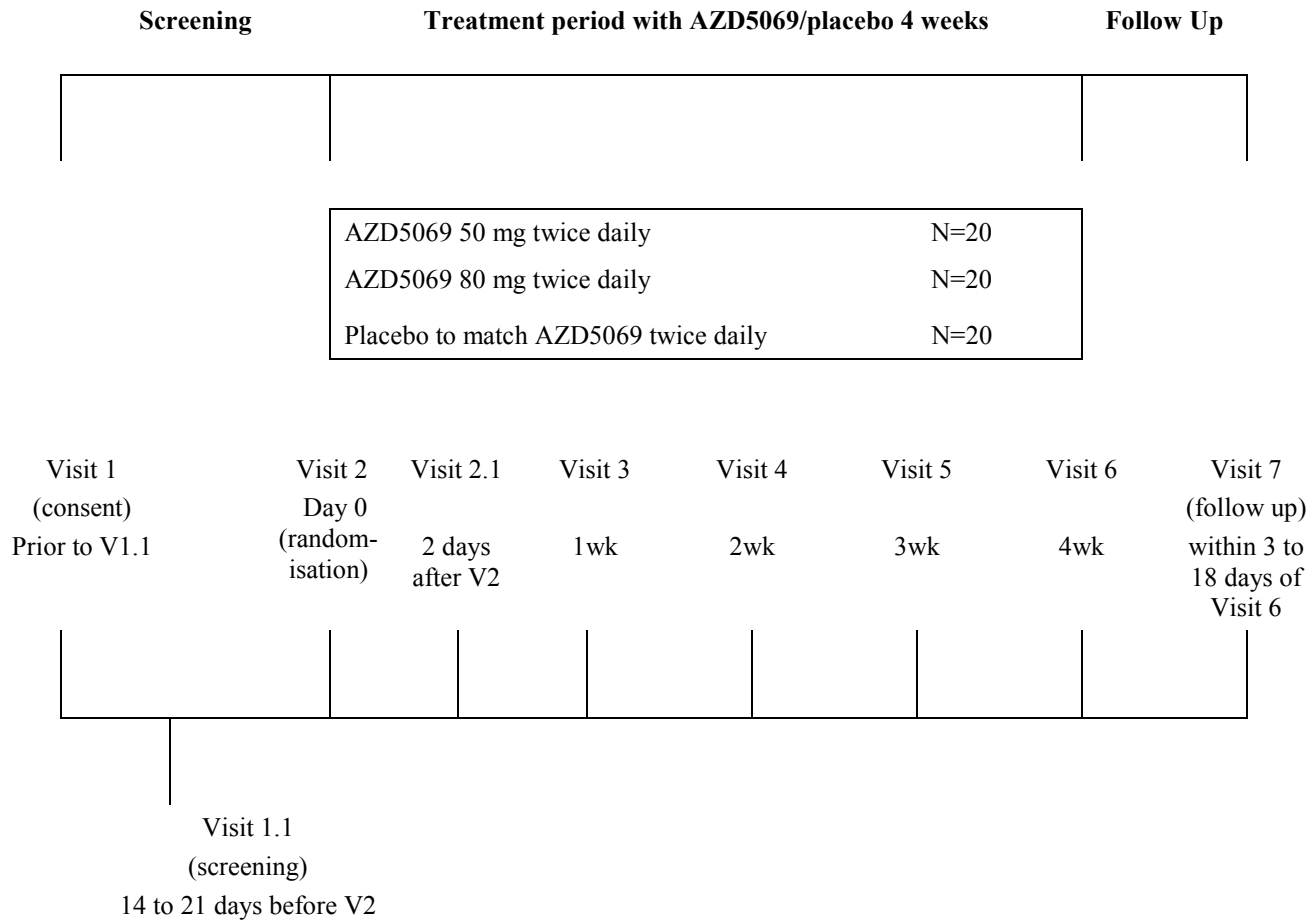
measurement can take place within ±2 hours in relation to the time of the Visit 2 measurement (baseline).

Approximately 16 patients, at selected sites, will complete a PK sub-study. The patients will follow the same visit schedule as the main study but 3 of the clinic visits (Visits 2, 4 and 6) will be extended and the patient will remain at site for approximately 5 hours. At these extended visits, 5 blood samples (1 pre-dose and approximately 1, 2, 3 and 5 hours post-dose) will be drawn for evaluation of plasma PK. In addition, blood samples (to match PK samples taken pre-dose [Visit 2 only], 1 and 3 hours post-dose) will be drawn for measurement of leucocytes including circulating neutrophils. Further details can be found in Section 6.6.

The total duration of the study for a patient will be between 7 to 9 weeks.

There will be an optional pharmacogenetic element to collect samples for possible retrospective analysis to investigate influence of genotypic variation on response, safety, tolerability and PK of AZD5069, and associated biomarkers. Further details can be found in Appendix D.

**Figure 1 Study flow chart**



## Table 3 Table of study assessments

| Study Visit | Visit 1 | Visit 1.1 | Visit 2 | Visit 2.1 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 |
|---|---|---|---|---|---|---|---|---|---|
| Time (No. weeks/days) | Prior to Visit 1.1 | 14 – 21d prior to V2 | Day 0 | Day 2 | 1 week | 2 weeks | 3 weeks | 4 weeks | 3-18d after V6 |
| Detail | Consent | Screening | Start treatment | Interim treatment visit | Interim treatment visit | Interim treatment visit | Interim treatment visit | End of treatment visit | Follow up |
| Written informed consent [a] | ✓ | | | | | | | | |
| Demographics | | ✓ | | | | | | | |
| Medical & surgical history | | ✓ | | | | | | | |
| COPD history | | ✓ | | | | | | | |
| Smoking history | | ✓ | | | | | | | |
| Height | | ✓ | | | | | | | |
| Weight | | ✓ | ✓ | | | | | ✓ | ✓ |
| Concomitant medication | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inclusion/exclusion criteria | ✓ [b] | ✓ [b] | ✓ [b d] | | | | | | |
| Physical examination [c] | | ✓ | ✓ [d] | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Vital signs | | ✓ | ✓ [d] | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Body temperature [e] | | ✓ | ✓ [d] | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Safety bloods (haematology (excluding leucocyte count) & clinical chemistry (including CRP) | | ✓ [f] | ✓ [d, f] | | ✓ [f] | ✓ [f] | ✓ [f] | ✓ [f] | ✓ [f] |
| Urinalysis [g] | | ✓ | ✓ [d] | | ✓ | ✓ | ✓ | ✓ | ✓ |
| LH and FSH (blood) [h] | | ✓ | | | | | | | |
| Urine pregnancy test [i] | | ✓ | ✓ [d] | | | | | | ✓ |
| 12 Lead ECG | | ✓ | ✓ [d] | ✓ | | | | ✓ | ✓ |
| Spirometry [j] | | ✓ | ✓ [d] | | ✓ | ✓ | ✓ | ✓ | ✓ |
| Randomisation | | | ✓ | | | | | | |

## Table 3 Table of study assessments

| Study Visit | Visit 1 | Visit 1.1 | Visit 2 | Visit 2.1 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 |
|---|---|---|---|---|---|---|---|---|---|
| Time (No. weeks/days) | Prior to Visit 1.1 | 14 – 21d prior to V2 | Day 0 | Day 2 | 1 week | 2 weeks | 3 weeks | 4 weeks | 3-18d after V6 |
| Detail | Consent | Screening | Start treatment | Interim treatment visit | Interim treatment visit | Interim treatment visit | Interim treatment visit | End of treatment visit | Follow up |
| PK blood sampling | | | ✓ k l | | | ✓ k l | ✓ k | ✓ k l | |
| Leucocyte count including circulating neutrophils [m] | | ✓ | ✓ k l | ✓ | ✓ | ✓ k l | ✓ k | ✓ k l | ✓ |
| Administer morning dose of investigational product in clinic (only applicable for PK sub study) | | | ✓ | | | ✓ [n] | | ✓ [n] | |
| Dispense study drug | | | ✓ | | | | | | |
| Drug accountability | | | | | ✓ | ✓ | ✓ | ✓ | |
| Blood sample for biomarkers | | | ✓ [d] | | | | | ✓ | |
| Archive blood sample | | | ✓ [d] | | | | | ✓ | |
| Adverse Event Questioning | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Blood sample for Pharmacogenetics | | | ✓ [o] | | | | | | |
| Diary [p] | ✓ → | → | → | → | → | → | → | → | |
| Telephone contact [q] | | | | | ✓ | ✓ | ✓ | ✓ | ✓ |

[a] Informed consent must be obtained prior to any study-related procedures, restrictions or screening assessments. Adequate time must be given between consent and screening according to local requirements

[b] Inclusion and exclusion criteria to be assessed at applicable visits (where relevant at V1, V1.1 and V2)

[c] At Visits 1.1, 6 and 7 a full physical examination is require, at other visits a more brief examination is sufficient (see Section 6.4.6)

[d] Pre-dose assessments

[e] As well as body temperature measured at clinic visits, patients will be provided with an accurate thermometer and should record their oral body temperature twice daily (morning and evening) in their daily diary. Patient-recorded oral body temperature measurements will not be entered into the WBDC system. Patients will be instructed by site staff to contact the clinic if their body temperature increases above 38.1°C and this should be reported as an AE (see Section 6.4).

[f] Haematology analysis at the central laboratory will include leucocyte (and neutrophil) counts as exploratory variables at Visits 1.1, 2, 3, 4, 5, 6 and 7. Each single sample will be repeated analysed at the central laboratory (Quintiles); the first analysis will be upon receipt of the sample and then repeat

analysis at twice daily time intervals eg, at 5.00 pm and 9.00 am until expiry at 72 hours post-sample collection. Exploratory leucocyte measurements taken at the central laboratory are for internal modelling use only and will not be reported in the CSR. Central laboratory leucocyte measurements will also only be available at the end of the study so as not to compromise the study blind.

[g] The following will be assessed as part of the urinalysis dipstick: glucose, protein, blood. In addition, samples will be sent to the central laboratory for urine microscopy and quantitative measurements of total protein, albumin and creatinine if the local dipstick test for protein and/or blood is positive or if the urine sample appears abnormal on macroscopic examination, eg, if it is cloudy

[h] Only for women under 50 years old, to confirm post-menopausal status

[i] All women

[j] Spirometry (lung function assessments) will be performed at the same time of day throughout the study ±2 hours relative to the time at baseline (Visit 2) pre- and 30 minutes post-bronchodilator

[k] On PK days (Visits 2, 4, 5 and 6), blood samples for assessment of plasma PK and circulating leucocytes (including neutrophils) will be collected as far apart as possible (minimum of 90 minutes between samples) and patients should continue to take investigational product as per their normal schedule. Date and time of dose will be recorded in the electronic Case Report Form (eCRF) for Visit 2 and the first PK/leucocyte samples will be collected pre-dose. At Visit 3, 4, 5 and 6 the date and time of dosing on the clinic day and on the previous 2 days will be recorded in the eCRF.

[l] Approximately 16 patients, at selected sites, will complete a PK sub-study. The patients will follow the same visit schedule as the main study but 3 of the clinic visits (Visits 2, 4 and 6) will be extended and the patient will remain at site for approximately 5 hours. Patients must not take investigational product (AZD5069 or placebo) at home on the morning of Visits 4 and 6. At these extended visits, 5 blood samples (pre-dose and then at approximately 1, 2, 3 and 5 hours post-dose) will be drawn for evaluation of plasma PK and blood samples (to match PK samples taken pre-dose [Visit 2 only], 1 and 3 hours post-dose) will be drawn for measurement of circulating leucocytes (including neutrophils). Further details can be found in Section 6.6

[m] Circulating leucocytes counts (including neutrophils) will be analysed at a local laboratory within 2 hours (maximum 4 hours) of sample draw as circulating neutrophils deteriorate rapidly after blood has been taken. In the main study, on PK days, leucocyte counts will be assessed in blood collected at the same time as AZD5069 concentration. In the PK sub-study, 3 leucocyte samples will be taken at Visit 2 and 2 leucocyte samples will be taken at each of Visits 4 and 6 to match the PK samples taken pre-dose (Visit 2 only), 1 and 3 hours post-dose. The leucocyte results from Visit 2-7 (inclusive) will be blinded from the site staff, refer to Section 5.4.1

[n] Patients taking part in the PK sub-study should take their morning dose of study drug (AZD5069 or placebo) in the clinic after pre-dose assessments have been completed

[o] Optional blood sample for retrospective pharmacogenetic exploratory analysis to be taken at Visit 2 or any subsequent visit after randomisation providing the patient has provided separate consent for the pharmacogenetics part of the study

[p] Patients will complete a daily diary card recording date and time of dosing, fasting status, use of concomitant medication, oral body temperature twice daily and any changes in the medical state of the patient. A new diary card will be given to the patient at each clinic visit. The patient should bring their completed diary card to each of their clinic visits for review and discussion with clinical staff. Data on diary cards will not be entered into the eCRF directly but information will be reviewed with clinical staff to enable them to record date and time of dose on selected days in the eCRF and support accurate recording of compliance, concomitant medication and AEs in the medical records and eCRF.

[q] Clinic staff will contact patients twice weekly via telephone in order to monitor any AEs, assess general health status, ensure that the patients are without fever and to ascertain whether an additional clinic visit is required.

## 3.2 Rationale for study design, doses and control groups

The study is being conducted in moderate to severe COPD patients as this is the target population for the study drug. The rationale for the optional pharmacogenetics component of the study in included in Appendix D.

### 3.2.1 Patient population and control groups

The patient population will be males and females of non-childbearing potential aged between 40-80 years (inclusive) with a clinical diagnosis of COPD, with symptoms for more than 1 year prior to Visit 1.1. The patients must 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 value and an $FEV_1$/FVC <70% (both post-bronchodilator) at Visit 1.1.

### 3.2.2 Study design

The study will be randomised, placebo-controlled and double-blind to ensure a robust design and minimise bias, which could compromise the conduct of the study, the recording of data and/or interpretation of the results. As the leucocyte count (including neutrophil data) will potentially be unblinding to site and study personnel, the data will be blinded from Visit 2 to Visit 7. The study includes placebo in parallel with active investigational product doses, to limit the occurrence of conscious and unconscious basis in the conduct of the trial and interpretation of the data. Randomisation will be stratified for use of inhaled corticosteroids and dynamic randomisation methodology will be applied to minimise imbalance across treatment groups.

### 3.2.3 Selection of outcome variables

The end-points chosen as primary variables are those that will assess the safety and tolerability of AZD5069 50 mg and 80 mg, bd in COPD patients.

The end-points chosen as secondary variables are those that will assess the AZD5069 concentration in plasma in COPD patients and the relationship between AZD5069 exposure and circulating neutrophils and will assist in future dose selection.

### 3.2.4 Dose consideration and treatment duration

Two doses of AZD5069, 50 mg and 80 mg, bd, will be administered to COPD patients for 4 weeks.

These doses have been selected based upon established safety and tolerability in the GSAD and GMAD studies, and have been chosen to minimise the risk that patients will have drops in circulating neutrophils below $1.0x10^9$/L for periods longer than 24 hours.

Following 100 mg bd dosing in the GMAD, 1 out of 6 healthy subjects had neutrophil counts which decreased below $1.0x10^9$/L. Based on the PK/PD modelling done from the GSAD data, on 80 mg bd, 15% or less of the healthy subjects dosed would be expected to experience a neutrophil decrease below this limit that persists for more than 24 hours. Therefore this dose was chosen to be near the top of the dose response curve based on systemic neutrophil

decrease, where the large majority of COPD patients (whose neutrophil numbers will be elevated in comparison with healthy volunteers) would be expected to complete 1 month's dosing. 50 mg is a dose where no patients would be expected to withdraw due to decreases in neutrophils, according to the withdrawal criteria.

A treatment period of 4 weeks has been selected as this is considered sufficient to investigate safety and tolerability and will be supported with respect to toxicology.

# 4. PATIENT SELECTION CRITERIA

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 4.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Provision of informed consent prior to any study-specific procedures

2. Male, or female of non-childbearing potential ie, women who are permanently or surgically sterilised or post menopausal.

   Women will be considered post menopausal if they are:

   (i) under 50 years of age and have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range

   or

   (ii) over 50 years old and have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments

   Permanent sterilization is defined as having undergone hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy; bilateral tubal occlusion on its own is not adequate

3. Aged 40 – 80 years inclusive at screening (Visit 1.1)

4. $FEV_1 \geq 30\%$ and $<80\%$ of the predicted normal value post-bronchodilator as assessed at screening (Visit 1.1)

5. $FEV_1$/FVC <70% post-bronchodilator at screening (Visit 1.1)

6. Current or ex-smokers with a smoking history of ≥10 pack years (1 pack year = tobacco consumption corresponding to 20 cigarettes smoked per day for one year) at screening (Visit 1.1)

7. Documented clinical diagnosis of COPD, GOLD stage II - III (according to Global Initiative on Obstructive Lung Disease (GOLD) guidelines) with symptoms for more than 1 year before Visit 1.1

8. COPD patients on a stable treatment regimen, as judged by the Investigator

9. Body mass index (BMI) of 18-30 $kg/m^2$ (inclusive) and a weight of 50-100 kg (inclusive).

Criteria relating specifically to the optional pharmacogenetics component can be found in Appendix D.

## 4.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Any clinically significant disease or disorder (eg, cardiovascular, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the absorption, distribution, metabolism and excretion of drugs

2. Patients with active or latent tuberculosis (TB)

3. Patients with known Human Immunodeficiency Virus (HIV) or who belong to a high-risk group for HIV infection

4. Evidence of serum hepatitis or presence of hepatitis B surface antigen or hepatitis C antibodies

5. Patients with other latent or chronic infections (eg, recurrent sinusitis, urinary tract infection) or at risk of infection (surgery, trauma, significant infection within 90 days before Visit 2, history of skin abscesses or soft tissue infection within 90 days before Visit 2 or, in the opinion of the investigator, patients in regular contact with subjects who have active pulmonary TB [Martineau et al 2007]).

6. Exacerbation of COPD (defined as worsening in COPD requiring treatment with oral or parenteral antibiotics and/or oral or parenteral glucocorticosteroids (GCS) and/or hospitalization-related) which was not resolved within 30 days of Visit 2

7. Clinically significant lower respiratory tract infection not resolved 4 weeks prior to Visit 2, as judged by the investigator

8. Requirement for long term oxygen therapy

9. Patients who have received live or live-attenuated vaccine in the 2 weeks prior to first dosing (Visit 2)

10. Asthma and any current respiratory tract disorder other than COPD, which is considered by the investigator to be clinically significant or may influence the result of the study

11. Disease history suggesting reduced or abnormal immune function other than that related to COPD

12. Any clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, urinalysis, vital signs or ECG at baseline (Visit 1.1), which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study

13. Active malignancy or neoplastic disease in the previous 12 months

14. Alanine aminotransferase (ALT) / aspartate aminotransferase (AST) level ≥1.5 x upper limit of normal (ULN) at screening (Visit 1.1)

15. Neutrophil count below the lower limit of normal (LLN)

16. Abnormal crystals in the urine at Visit 1.1 (if dipstick test for protein and/or blood is positive or if the urine sample appears abnormal on macroscopic examination)

17. Patients who have had a clinically significant illness within 4 weeks before Visit 2 as determined by the investigator

18. Blood donation of more than 500 mL during the previous 12 weeks before Visit 2 and more than 50 mL in the 2 weeks before Visit 2

19. Known or suspected hypersensitivity to the investigational product or any excipients or a compound of the same class

20. Current evidence of drug abuse or significant history of drug abuse as judged by the investigator

21. Current evidence of alcohol abuse or significant history of alcohol abuse as judged by the investigator

22. Participation (defined as administration of at least one dose of an investigational product) in another clinical study within 12 weeks preceding Visit 2

23. Patients who, in the opinion of the investigator, should not participate in the study

24. Previous exposure to AZD5069

25. Scheduled inpatient surgery or hospitalisation during the study

26. Pregnancy or breast-feeding during the study

27. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

28. Previous randomisation in the present study

29. Use of oral or systemic glucocorticosteriods within 30 days prior to Visit 2

30. Concomitant immunosuppressive medication

31. Use of prohibited medications (see Table 6)

32. Patients with serum creatinine, above the upper limit of the reference range at screening (Visit 1.1)

Criteria relating specifically to the optional pharmacogenetics component can be found in Appendix D.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

# 5. STUDY CONDUCT

## 5.1 Restrictions during the study

1. Male patients must abstain from unprotected sex and sperm donation from the time of dosing until 3 months after the last dose.

   Recommended contraception will be double barrier method, ie, male patients must use condoms and, in addition, the female partner should use additional contraception from the time of dosing until 3 months after the last dose. Acceptable methods to be used by female partners include the oral contraceptive pill, hormone implants, intra-uterine devices (IUDs), diaphragms with spermicide.

   Male patients should inform the investigator if their partner becomes pregnant during the study.

2. Patients should observe the following restrictions prior to the clinic lung function tests (Visits 1.1, 2 and 3-7):

   – No strenuous exercise within 2 hours

   – No smoking within 1 hour

   – No large meals within 2 hours

3. Use of disallowed concomitant medication (refer to Section 5.6)

4. Patients should not receive a vaccination during the study

5. Patients should abstain from drugs of abuse throughout the entire study

6. Patients should not donate blood at any time during the study and for 12 weeks following completion of the study

7. Patients must not take part in any other study whilst participating in the current study.

## 5.2 Patient enrolment and randomisation

The Principal Investigator or delegate will:

1. Obtain signed informed consent from the potential patient before any study-specific procedures are performed.

2. Assign potential patient a unique enrolment number (E code), beginning with for example 'E0001001 (EXXXXYYY)' where XXXX reflects the centre number and YYY will be allocated sequentially to enrolled patients at each centre.

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Assign eligible patients a unique randomisation code (patient number). Refer to Section 5.2.1.

If judged appropriate by the Investigator, a patient who initially fails screening may have a repeat enrolment. If a patient is re-enrolled they will be assigned a new E code.

If a patients withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

### 5.2.1 Procedures for randomisation

A dynamic randomisation approach will be applied. Randomisation codes will be generated by the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) provider using minimisation with biased coin assignment method which assigns

patients to treatments in a clinical trial with stratifying factors on which it is desired to achieve balance.

Patients will be assigned to treatment groups using IVRS / IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

Randomisation codes will be assigned to patients who are eligible for randomisation. Randomisation will be stratified for use of inhaled corticosteroids. Patients will be randomly allocated to AZD5069 50 mg bd, AZD5069 80 mg bd or placebo in a 1:1:1 ratio.

Patients who are withdrawn after randomisation will not be replaced.

The randomisation code will be loaded into AstraZeneca Global Randomisation System (GRand).

## 5.3 Procedures for handling patients incorrectly enrolled, randomised or initiated on investigational product

**Patients who fail to meet the inclusion/exclusion criteria** should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are enrolled in error but are not yet randomised the procedures included in the protocol for the discontinuation from the study must be followed.

Where patients that do not meet the selection criteria are incorrectly randomised, incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patients should have their study therapy stopped and be discontinued from the study.

## 5.4 Blinding and procedures for unblinding the study

### 5.4.1 Methods for ensuring blinding

This will be a double-blind study. AZD5069 will be provided as capsules for oral administration and with matching placebo capsules of the same size, weight and colour. Patients in all treatment arms will take the same number of capsules of investigational product or placebo ie, 4 capsules bd.

As the leucocyte count (including neutrophil data) will potentially be unblinding to site and study personnel, the data will be transferred from the local laboratory performing the analysis to the central laboratory. The results for Visit 1.1 will be communicated to the sites, but for all other visits (Visits 2-7) the central laboratory will review the data and notify the site if values are above the ULN or if a patient needs to be recalled for repeat sampling or needs to

be withdrawn from the study. Furthermore, to ensure that the investigator is not unblinded by only patients on active treatment being recalled, a number of patients with a normal leucocyte count will be randomly selected for repeat leucocyte assessments. Full details of the above process are detailed in the laboratory specifications.

Leucocyte (including neutrophil) count measurements performed by the central laboratory to investigate leucocyte stability will not be made available until the end of the study to ensure the study blind is not compromised. These data will also not be made available for blind review.

### 5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

A copy of the randomisation scheme will also be made available to the PK bioanalyst, to enable the analysis of samples from patients who have received active treatment to be prioritised. This documentation will be placed in a secure location until the end of the study.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to the patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 5.5 Treatments

### 5.5.1 Identity of investigational product(s)

The investigational products used in the study are listed in the table below. The capsules will be packaged in blisters containing 64 capsules each, sufficient for 8 days' dosing.

**Table 4 Identity of Investigational Products.**

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| AZD5069 | capsule 20 mg | AstraZeneca AB |
| AZD5069 | capsule 50 mg | AstraZeneca AB |
| Placebo for AZD5069 | capsule | AstraZeneca AB |

### 5.5.2 Doses and treatment regimens

The investigational product will be taken orally twice daily, with doses approximately 12 hours apart (4 capsules in the morning and 4 capsules in the evening). The first dose of investigational product will be taken in the clinic at Visit 2. All other doses will be taken by the patient in accordance with their normal routine, unless the patient is taking part in the PK sub-study when the morning dose at Visits 4 and 6 should be taken in the clinic after pre-dose assessments. No food should be consumed within the 2 hours prior to the scheduled dose and for one hour after taking the dose.

In the event of an abnormal absolute neutrophil count (ANC) or leucocyte count (according to local laboratory measurements), patients should not take more than 4 doses of investigational product from the time of the abnormal blood test. Patients will be informed that they should not take the morning dose of investigational product 2 days after the first abnormal blood test without first obtaining consent from the clinic that it is appropriate to do so.

The patients will receive a box of medication containing 4 blister packs for the whole treatment period at Visit 2.

### 5.5.3 Additional study drug

No additional study drug is used in this study.

### 5.5.4 Labelling

Labels will be produced in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

### 5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the box specifies the appropriate storage.

## 5.6 Concomitant and post-study treatment(s)

### 5.6.1 Medication allowed during the study

Patients can continue with the following existing treatments during the study at a stable dose to be determined by the investigator:

- short acting β2 agonist (SABA)
- short acting muscarinic antagonist (SAMA)
- long acting β2 agonist (LABA), including ultra LABA
- long acting muscarinic antagonist (LAMA)

- inhaled corticosteroids (ICS)
- ICS/LABA combination.

Patients should refrain, if possible, from taking specified medication (as detailed in Table 5) prior to clinic visits where lung function assessments are performed.

Other drugs, including inhaled and oral respiratory medications, are permitted provided the dose is stable for at least 4 weeks prior to screening (Visit 1.1) and throughout the study.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

### 5.6.2 Medication restrictions

Patients should refrain from taking restricted medications prior to clinic visits associated with lung function assessments (Visits 1.1, 2 and 3 to 7).

**Table 5 Restriction of medication during the study**

| Treatments to be restricted | Time limits prior to clinic visit (hours) |
|---|---|
| Short acting β2 agonist (SABA) | 6 |
| Short acting muscarinic antagonist (SAMA) | 8 |
| Long acting β2 agonist (LABA) | 12 |
| Ultra-LABA | 12 |
| Long acting muscarinic antagonist (LAMA) | 12 |
| Oral β2 agonists | 6 |
| Oral β2 agonists slow release formulations | 24 |
| Glucocorticosteroid (GCS)/LABA combination therapy | 12 |
| Ipratropium | 6 |
| Tiotropium | 12 |

### 5.6.3 Disallowed medication

**Table 6 Disallowed medications**

| Treatment to be withdrawn before Visit 2 until completion of the study follow up visit (Visit 7) | Time limits prior to Visit 2 |
|---|---|
| Oral, parenteral and depot parenteral glucocorticosteriods (GCS) | 4 weeks |
| Intramuscular or intra-articular depot steroids | 3 months |
| Antibiotics (systemic and nebulised) | 4 weeks |
| Immunomodulatory agents | 8 weeks |
| Any medication containing ephedrine | 24 hours |
| CYP2B6 substrates<br>Including but not limited to: bupropion, cyclophosphamide, efavirenz, ifosfamide, selegiline, alfentanil, nevirapine, propofol, tamoxifen, valproic acid, artemisinin, pethidine, modafinil, sertraline, thiotepa. | 4 weeks |
| Permeability glycoprotein (PgP) substrates<br>Including but not limited to: quinidine, tacrolimus, ivermectin, colchicines, etoposide, doxorubicin, vinblastine, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, cyclosporin, digoxin | 4 weeks |
| Warfarin or other coumarins | 4 weeks |
| All herbal medications | 3 weeks |

In addition, treatment with any other drug which, in the opinion of the investigator, is likely to compromise patient safety or interfere with the objectives of the study is disallowed from Visit 1 and throughout the study.

## 5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF and the drug accountability/dispensing record.

Investigational product accountability will be performed at Visits 3, 4, 5 and 6. Intake of investigational product will be recorded daily by the patient in their diary cards, this data will

be used by clinic staff to record the date/time of dose and fasting status in the eCRF on the day of clinic visits and the 2 previous days and to support compliance monitoring.

### 5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

The destruction of used and unused study drug should preferably be done by the study site. The study site personnel/AZ monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. If destruction at the study site is not possible, the monitor will be responsible for organising destruction in accordance with local requirements and will account for all received study drugs and return of all unused study drugs.

All certificates of delivery, destruction and return should be signed.

## 5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance to study protocol
- Safety reasons (risk to patients as judged by the investigator and/or AstraZeneca)
- Eligibility criteria not fulfilled
- Patient lost to follow-up

In addition to the above, the Investigator shall discontinue IP in the following situations:

- Development of study-specific withdrawal criteria:
  - Clinically significant lower respiratory tract infection as judged by the investigator
  - Patient has haematological changes which have not recovered on repeat sample taken after 2.30 pm and within 48 hours defined as one or more of:
  - local laboratory confirmed neutrophil count $<1.0 \times 10^9$/L (see below)

- local laboratory confirmed leucocyte count <2.0 x $10^9$/L (see below)
- Patient has hepatic toxicity defined as one or more of:
- confirmed ALT or AST increase >3 x ULN
- confirmed isolated total bilirubin increase >2 x ULN
- confirmed ALT or AST increase >2 x ULN concurrent with an increase in total bilirubin to >1.5 x ULN
- any pattern of liver function test (LFT) abnormalities giving cause for concern in the opinion of the Investigator

  These events must be followed up as appropriate for the patient.
- Confirmed serum creatinine >1.5 x ULN

- COPD exacerbation requiring treatment with antibiotics, and/or systemic glucocorticosteroids, and/or hospitalisation
- Other reasons:
  - Pregnancy (refer to Section 13.3)
  - Treatment code prematurely broken by the investigator
- Death.

AstraZeneca are proposing to discontinue patients from study medication if they have a high likelihood of having a sustained ANC below 1 x $10^9$/L. AstraZeneca have defined "sustained" as a period greater than 24 hours but less than 48 hours. Patients who are found to have an ANC below 1 x $10^9$/L or a leucocyte count below 2 x $10^9$/L (according to local laboratory measurements) at any of their clinic visits will have a repeat blood sample taken in the afternoon of the following day (after 2:30 pm). The second test is in the afternoon because the circulating neutrophil numbers then are naturally higher than in the morning. Neutrophil numbers normally vary in a diurnal pattern, the numbers being lowest at around 8:00 am and highest around 8:00 pm. Diurnal fluctuations in the ANC/leucocyte count are still present in patients who have taken AZD5069.

If on repeat examination, the ANC/leucocyte count stopping criteria are still met, despite the second sample being taken when neutrophil levels are usually higher than in the morning, AZD5069 therapy will be discontinued. This is because AstraZeneca will assume that the ANC/leucocyte count is sustained even though the counts will not have been determined at the highest point of its daily cycle. Site staff should ensure that no patient takes more than 4 doses of study drug from the time of their initial abnormal blood test. Patients will be

informed by site staff (at enrolment and screening) that they should not take the morning dose of the study drug 2 days after the first abnormal blood test without first obtaining consent from the clinic (by telephone on the morning of the third day) that it is appropriate to do so.

Subjects who have missed and/or forgotten more than 3 consecutive doses should be referred to the AstraZeneca Study Physician for assessment as to whether the interruption in the Investigational Product constitutes discontinuation.

If a patient is withdrawn because of low neutrophil counts, the Investigator will monitor the blood count the following day and then at least every other day after that until the neutrophil numbers are within the local laboratory's reference range.

Specific reasons for discontinuing a patient from the genetic research are detailed in Appendix D.

### 5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s).

If a patient discontinues after randomisation, they should be asked to attend the end of treatment visit (Visit 6) and all assessments at Visit 6 should be carried out unless the patient does not wish to do so. The patient should then be asked to attend the follow-up visit (Visit 7). The reason for discontinuation will be recorded in the eCRF. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); diary cards and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 5.9.

## 5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (see Sections 6.4.3 and 6.4.4); diary cards and all study drugs should be returned by the patient.

In the event that a patient cannot return for Visit 6 (eg, because of death, or because they are lost to follow up), this will be recorded in the eCRF. Adverse events will be followed up to the last point of contact.

Withdrawn patients will not be replaced.

# 6. COLLECTION OF STUDY VARIABLES

## 6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator will ensure that data are recorded in the eCRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

The patient will be instructed to maintain a paper diary throughout the study period (Visits 1-7), to record administration of study drug, fasting status, concomitant medications, AEs and twice daily body temperature measurements (orally morning and evening). A new diary card will be given to the patient at each clinic visit. Patient-recorded daily oral body temperature measurements will not be entered onto the WBDC system but if a temperature above 38.1°C is recorded this will be reported as an AE (fever) (see Section 6.4). Data collected on the diary cards will not be entered directly into the eCRF but will be reviewed by site staff to enable entry of dosing information on selected days, concomitant medications and AEs. A copy of the diary cards will be archived at the study site with the source data.

## 6.2 Data collection and enrolment

Investigators should refer to the study plan in Table 3 for a detailed list of study procedures and assessments to be performed at screening and throughout the study period.

At Visit 1 patients will sign the informed consent form prior to any study procedure or restriction being applied and will be assigned a unique enrolment code (see Section 5.2). Patients will then attend the clinic for Visit 1.1 and will be screened and evaluated for eligibility to enter the study. The following assessments will be performed, with data being captured in the eCRF as appropriate:

- Demographic data
- Medical and surgical history
- COPD history
- Smoking history
- Height and weight
- Physical examination
- Vital signs

- Body temperature
- Safety bloods (haematology and clinical chemistry)
- Urinalysis
- Leucocyte count (analysed at local laboratory)
- Pregnancy test for all female patients
- 12-lead ECG
- Pre- and post-bronchodilator $FEV_1$, FVC, SVC, IC and $FEF_{25-75\%}$
- Concomitant medications
- AEs.

In addition to the weekly clinic visits, clinic staff will also contact patients twice weekly via telephone in order to monitor any AEs, assess general health status, ensure that the patients are without fever and to ascertain whether an additional clinic visit is required. The date of the twice weekly telephone contact visits will be recorded on the WBDC system.

### 6.2.1 Follow-up procedures

Investigators should refer to the study plan in Table 3 for a detailed list of study procedures and assessments to be performed at the follow-up visit (Visit 7).

The following assessments will be performed and recorded in the eCRF at this visit:

- Weight
- Concomitant medications
- AEs
- Physical examination
- Vital signs
- Body temperature
- Safety bloods (haematology and clinical chemistry)
- Urinalysis
- Leucocyte count

- Pregnancy test for all female patients
- 12-lead ECG
- Pre- and post-bronchodilator $FEV_1$, FVC, SVC, IC and $FEF_{25-75\%}$.

## 6.3 Efficacy (Not applicable)

Not applicable.

## 6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

### 6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

### 6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

### 6.4.3 Recording of adverse events

**Time period for collection of adverse events**

Adverse Events will be collected from time of signature of informed consent and throughout the treatment period and the follow-up period (until Visit 7 or last study-related contact).

**Follow-up of unresolved adverse events**

Any AEs and laboratory abnormalities that are unresolved at the patient's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Variables**

The following variables will be collected for each AE:

- AE (verbatim)
- the date and time when the AE started and stopped
- maximum intensity
- whether the AE is serious or not
- investigator causality rating against the Investigational Product (yes or no)
- action taken with regard to investigational product
- outcome

The categories of intensity to be used in this study are:

  - mild (awareness of sign or symptom, but easily tolerated)
  - moderate (discomfort sufficient to cause interference with normal activities)
  - severe (incapacitating, with inability to perform normal activities).

In addition, the following variables will be collected for SAEs:

- date and time AE met criteria for serious AE
- date Investigator became aware of serious AE
- AE is serious due to
- date of hospitalisation

- date of discharge
- primary/secondary cause of death
- date of death
- autopsy performed
- causality assessment in relation to study procedure(s)
- causality assessment in relation to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

**Causality collection**

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'.

For SAEs causal relationship will also be assessed for other medication and/or study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

**Adverse Events based on signs and symptoms**

All AEs spontaneously reported by the patient, recorded in a diary card or reported in response to the open question from the study personnel: 'Have you had any health problems since the previous visit?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

**Adverse Events based on examinations and tests**

The results from protocol mandated laboratory tests, ECGs and vital signs will be summarised in the clinical study report.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables should therefore only be reported as AEs if:

- Fulfils any of the SAE criteria. This should be reported as a SAE.
- Reason for discontinuation of treatment with the investigational product. This should be reported as a Discontinuation AE (DAE).
- Investigator decides additional diagnostics and/or treatment is required because he/she considers deterioration of any of the safety variables to be clinically relevant. This should be reported as an AE (note, a repeat test showing the first abnormal result was not valid should not be reported as an AE).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

**Adverse Events related to study procedures or the conduct of the study**

Signs and/or symptoms judged by the investigator to be clearly related to the conduct of the study or study procedures (eg, venepuncture; blood pressure and ECG measurement) are only to be reported as AEs if:

- Fulfils any of the SAE criteria. The should be reported as a SAE.
- Reason for discontinuation of treatment with the investigational product. The should be reported as a Discontinuation AE (DAE).
- Investigator decides additional diagnostics and/or treatment is required because he/she considers deterioration of any of the signs/symptoms/findings is clinically relevant. This should be reported as an AE (note, a repeat test showing the first abnormal result was not valid should not be reported as an AE).

**Symptoms of disease under study**

COPD symptoms or signs, such as cough, dyspnoea, sputum increased and wheeze (or terms considered synonymous with these) will not be recorded as AEs unless:

- the sign or symptom is serious according to the definition of an SAE (see Section 6.4.2), and/or

- the patient discontinues the investigational product due to the signs or symptoms, and/or

- the sign or symptom is new to the patient or not consistent with the patient's pre-existing COPD history (defined as within one year of screening (Visit 1.1)).

COPD exacerbations (see Section 6.4.10) that meet the SAE criteria as defined in Section 6.4.2 should be reported as SAEs.

**Disease progression**

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease.

Events, which are unequivocally due to disease progression, should be reported as an AE during the study.

**AEs with recommended follow-up activities**

Results of abnormal liver function tests should be confirmed with a repeat test (via the central laboratory) as soon as possible, and within 48 hours, and the findings reported in the eCRF. Abnormal liver findings should be reported as AE(s) if in the investigator's judgment they meet the criteria. Abnormal liver function tests and hepatic AEs should be followed up and risk factors, signs and symptoms and diagnostic investigations recorded in the appropriate module provided in the eCRF.

AEs of infection should be followed up and risk factors, signs and symptoms and diagnostic investigations recorded in the appropriate module(s) provided in the eCRF.

### 6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). This includes SAEs occurring during any phase of the study, including run-in and follow-up periods where no investigational product is being given. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs. The AZ representative is required to access the AZ aware module within the WBDC system and trigger the email alert to the AstraZeneca Data Entry Site.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The investigator(s) and other site personnel will access the WBDC system and report SAE information by entering it into the relevant eCRF module. Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone immediately. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug .

### 6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, leucocyte counts and urinalysis will be taken at the times indicated in the Study Plan (Table 3).

Blood samples will be analysed at a central laboratory with the exception of leucocyte counts. Due to rapid degradation of neutrophils, leucocyte counts will be performed promptly in local laboratories within 2 hours (maximum 4 hours) of sample collection. Additional leucocyte (including neutrophil) counts will also be analysed at the central laboratory at intervals between receipt of sample and 72 hours after sampling to investigate leucocyte stability.

Urine will be tested locally using dipsticks. In addition, samples will be sent to the central laboratory for urine microscopy and quantitative measurements of total protein, albumin and creatinine if the local dipstick test for protein and/or blood is positive or if the urine sample appears abnormal on macroscopic examination, eg, if it is cloudy.

The central laboratory will provide all the materials required for blood and urine sampling. Instructions for labelling, storage and shipping will be detailed in the laboratory manual.

The laboratory variables to be measured are outlined in Table 7.

**Table 7 Laboratory parameters**

| Haematology | Clinical Chemistry | Urinalysis |
|---|---|---|
| B-Erythrocytes | S-Creatinine | U-Haemoglobin (dipstick) |
| B-Haemoglobin | S-Bilirubin (total) | U-Protein (dipstick) |
| B-Leucocyte count | S-Alkaline phosphatase | U-Glucose (dipstick) |
| (absolute and differential count including neutrophils, basophils, lymphocytes, monocytes, eosinophils) | S-Aspartate Aminotransferase (AST) | U-Microscopy (if required, refer to Section 6.4.5) |
| B-Platelet count | S-Alanine Aminotransferase (ALT) | U-Albumin (if required, refer to Section 6.4.5) |
| | S-Albumin | U-Total protein (if required, refer to Section 6.4.5) |
| | S-Protein (total) | U-Creatinine (if required, refer to Section 6.4.5) |
| | S-Potassium | |
| | S-Calcium (total) | |
| | S-Sodium | |
| | S-Glucose (non-fasted) | |
| | S-hsCRP | |
| | S-Urate | |
| | S-Urea | |

For blood volume see Section 7.1.

### 6.4.6 Physical examination

As detailed in Table 3, a physical examination will be performed at all visits except Visits 1 and 2.1. The assessment will be performed pre-dose at Visit 2.

At Visits 1.1, 6 and 7 a full physical examination will be performed and the following assessed: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, musculo-skeletal (including spine and extremities), cardiovascular, lungs and abdomen. At other visits, an examination of general appearance, cardiovascular system, lungs and abdomen is sufficient.

Height (screening only) will be measured in centimetres and weight (Visits 1.1, 2, 6 and 7) in kilograms. Measurements should be taken without shoes and using calibrated scales for all measurements. BMI will be calculated from the height and weight.

### 6.4.7 ECG

As detailed in Table 3, a resting 12 lead ECG will be performed at Visits 1.1, 2, 2.1, 6 and 7. The ECG will be recorded pre-dose at Visit 2.

ECGs will be recorded in the supine position after the patient has rested for 10 minutes. Heart rate, QRS duration, PR, RR and QT intervals will be recorded. Overall evaluation of the ECG (normal, abnormal or borderline) should be recorded along with a note of any abnormalities and whether or not they were clinically significant. The original ECG traces must be stored in the patient's record as source data.

### 6.4.8 Vital signs

#### 6.4.8.1 Pulse and blood pressure

Pulse and blood pressure will be measured at Visits 1.1, 2 and 3 to 7 (pre-dose at Visit 2) as detailed in Table 3.

Supine blood pressure and pulse rate will be measured using non invasive equipment after a 10-minute rest on a bed.

#### 6.4.8.2 Body temperature

Body temperature (oral) will be measured in degrees Celsius using an automated thermometer at Visits 1.1, 2 and 3 to 7 (pre-dose at Visit 2) as detailed in Table 3. Body temperature (oral) will also be measured by the patient twice daily (morning and evening) using a thermometer provided and the readings recorded in their daily diary cards.

### 6.4.9 Lung function measurements

Lung function tests will be measured by spirometry at the clinic at Visits 1.1. 2 and 3 to 7 inclusive. The tests being performed are $FEV_1$, FVC, SVC, IC, $FEF_{25-75\%}$, pre- and 30 minutes post-bronchodilator.

The measurements at Visit 2 will be performed pre-dose, and subsequent measurements will be performed at the same time of day throughout the study ±2 hours relative to the time at baseline (Visit 2). A record of the measurements must be made in the patient's notes and results recorded in the eCRF. All printouts should be signed, dated, and marked with study code, enrolment/randomisation code, date and time of measurement and visit number.

The initial assessments should be performed prior to the administration of any bronchodilators and should be performed with the patient in an upright, seated position, having rested for 15 minutes. See Section 5.1 for restrictions around the spirometry tests.

Measurements should be performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines (Miller et al 2005a, Miller et al 2005b). In general:

- An electronic spirometer should be used and the same apparatus used for each patient at the centre

- The centre will be responsible for calibrating and recording the calibration of the spirometer according to the recommendations of the manufacturer. Unless otherwise advised, this should be on a daily basis and where there is a significant fluctuation in temperature or barometric pressure.

  All calibration reports should be signed, dated and filed in the Investigator Site File (ISF). If a calibration report cannot be printed, the results should be documented in writing in the ISF.

- Lung function measurements may be carried out in the morning or in the afternoon; however, lung function measurements should be carried out at the same time of day (±2 hours) for each individual patient throughout the study

- The patient should be sitting with his/her head level and tight clothing should be loosened

- The patient should perform the manoeuvre with a nose clip

- Where possible, 3 repetitions of the manoeuvre should be obtained. However, if the patient becomes too short of breath, a minimum of 2 technically satisfactory manoeuvres is acceptable. Record the highest FVC and $FEV_1$ in the eCRF after examining the data from all acceptable curves, even if the 2 values do not come from the same curve. If the reproducibility criteria cannot be met after 8 manoeuvres, record the highest FVC and $FEV_1$ values in the eCRF.

### 6.4.10 COPD Exacerbations

A COPD exacerbation is defined as worsening in COPD requiring treatment with one or more of the following:

- systemic antibiotics (oral or parenteral)

- systemic GCS (oral or parenteral)

- Emergency Room treatment

- hospitalisation.

The start date is defined as the first day of hospitalisation/emergency room treatment or the first day of systemic GCS or antibiotic treatment. The end date is defined as the last day of hospitalisation/emergency room treatment or the last day of systemic GCS or antibiotic treatment. If the same exacerbation includes both hospitalisation/emergency room treatment and systemic GCS/antibiotic treatment, the start and end dates are the first and last day that either criteria is fulfilled. If hospitalisation was prolonged for reasons other than COPD

exacerbation, then the exacerbation end date should be determined by the Investigator. One day without any criteria for fulfilment of an exacerbation is required to start to count a new exacerbation.

Exacerbations should be recorded as AEs in the eCRF.

Patients who experience a COPD exacerbation should be discontinued from investigational product, refer to Section 5.8.

## 6.5 Patient reported outcomes (PRO)

Patients will be asked to complete a daily diary card recording date and time of dosing, fasting status, use of concomitant medication, body temperature (oral) and any changes in the medical state of the patient throughout the study (Visit 1 to 7).

A new diary card will be given to the patient at each clinic visit. The patient should bring their completed diary card to each of their clinic visits for review and discussion with clinical staff. Data on diary cards will not be entered onto the eCRF directly, but information will be reviewed with clinical staff to enable them to record date and time of dose and fasting status on selected days in the eCRF and support accurate recording of compliance, concomitant medication and AEs in the medical records and eCRF.

## 6.6 Pharmacokinetics

### 6.6.1 Collection of samples

Blood samples for determination of AZD5069 in plasma will be taken at Visits 2, 4, 5 and 6 (refer to Table 3). At each visit 2 blood samples will be collected as far apart as possible with a minimum of 90 minutes between samples. The first sample should be collected pre-dose at Visit 2. At subsequent visits the patient should continue to take investigational product as per their normal schedule and the times of the previous dose and doses on the previous 2 days will be recorded in the eCRF.

Approximately 16 patients, at selected sites, will complete a PK sub-study. At these selected sites, patients will be recruited into the sub-study as a priority until the overall target of 16 patients has been reached; the sites may also concurrently recruit patients into the main study. The randomisation of 16 patients into the sub-study is expected to result in approximately equal number of patients receiving 80 mg, 50 mg and placebo (ie, approximately 10 patients receiving active treatment).

The PK sub-group patients will follow the same visit schedule as the main study but will attend 3 extended clinic visits when the patient will remain at site for approximately 5 hours (Visits 2, 4 and 6). Patients must not take investigational product (AZD5069 or placebo) at home on the morning of Visits 4 and 6. At these extended visits patients should take their morning dose of Investigational Product at the clinic and 5 blood samples (1 pre-dose and at approximately 1, 2, 3 and 5 hours post-dose) will be drawn for evaluation of plasma PK. In addition, at Visit 2 three blood samples and at Visits 4 and 6 two blood samples (to match

PK samples taken pre-dose [Visit 2 only], 1 and 3 hours post-dose) will be drawn for measurement of circulating neutrophils. Each patient will have a cannula inserted into a suitable vein for the withdrawal of the PK samples, and a small volume of blood (approximately 0.5 mL) will be discarded before each sample is taken.

Samples will be collected, labelled, stored and shipped as detailed in Laboratory Manual.

For blood volume see Section 7.1.

### 6.6.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by the appointed bioanalytical laboratory on behalf of AstraZeneca. The laboratory will use a validated method of high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) after protein precipitation. The lower limit of quantification (LLOQ) of AZD5069 in plasma will be 1 nmol/L. Full details of the analytical method used will be described in a separate bioanalytical report.

Plasma samples from patients who were dosed with placebo will not be analysed for AZD5069.

Samples that are outside of the known stability of AZD5069 will not be reported.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

Any remaining plasma samples will be stored for possible further metabolism and pharmacokinetic investigations (Section 7.2.2). Any results from such analyses will be reported separately from the CSR.

## 6.7 Pharmacodynamics

### 6.7.1 Collection of pharmacodynamic markers

#### 6.7.1.1 Circulating neutrophil count

Circulating neutrophil counts (absolute and percentage) will be analysed at local laboratories within 2 hours (maximum 4 hours) of sample collection. Haematology analysis at the central laboratory will include leucocyte (and neutrophil) counts as exploratory variables to be analysed intervals between receipt of sample and 72 hours after sample collection. Samples will be collected, labelled, stored and shipped as detailed the laboratory specifications.

For blood volume see Section 7.1.

#### 6.7.1.2 Biomarker blood sampling

Blood will be taken to generate serum samples for biomarker analysis at Visit 2 (pre-dose) and Visit 6. Analysis will be conducted by a suitably qualified bioanalytical laboratory under guidance of Clinical Pharmacology and DMPK (CPD) or Translation Science (TS) at

AstraZeneca R&D. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

#### 6.7.1.3 Archive sample

Blood will be taken to retain a serum sample for future retrospective analysis of mediators relevant to the mechanism of inflammation in COPD at Visits 2 and 6.

Any results from such analyses will be reported separately from the CSR.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 7.1.

## 6.8 Pharmacogenetics

Please refer to Appendix D. These data will not form part of the CSR.

## 6.9 Health economics (Not applicable)

Not applicable.

# 7. BIOLOGICAL SAMPLING PROCEDURES

## 7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

**Table 8 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Safety | Clinical chemistry (including LH and FSH at Visit 1.1) | 5 | 7 | 35 |
| | Haematology | 2 | 7 | 14 |
| Leucocyte count | | 2 | 12 main study<br>(13 PK sub-study) | 24<br>(26 PK sub-study) |
| Pharmacokinetic | | 4 | 8 main study<br>(17 PK sub-study) | 32<br>(68 PK sub-study) |
| Biomarker blood sample | | 8.5 | 2 | 17 |
| Archive sample | | 8.5 | 2 | 17 |
| Pharmacogenetic | | **9** | 1 | **9** |
| **Total** | | | | **148**<br>(**186** PK sub-study) |

A cannula will be supplied for repeated samples as required and a small volume will be discarded before each sample is taken.

## 7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at AstraZeneca R&D or delegated facility on behalf of AstraZeneca for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report.

### 7.2.1 Safety and/or circulating neutrophil samples

The clinical chemistry, haematology, circulating leucocyte (including neutrophil) count and urinalysis samples will be used up during analysis or disposed of after analysis.

### 7.2.2 Pharmacokinetic samples

Samples will be disposed of after the clinical study report has been finalised, unless retained for future analyses, see below.

Key samples for investigation of long-term stability and/or metabolite identification and/or analysis will be retained at AstraZeneca R&D on behalf of Clinical Pharmacology and DMPK(CPD), AstraZeneca for a maximum of 1 year following the finalisation of the Clinical Study Report. The results from the investigation will not be reported in the clinical study report but separately in a bioanalytical/metabolism report.

### 7.2.3 Pharmacodynamic samples

CRP and SAA samples will be disposed of after the clinical study report has been finalised. All other exploratory biomarker samples, including archive biomarker samples, will be held for up to 15 years after last patient last visit; after this time all samples will be destroyed.

### 7.2.4 Pharmacogenetic samples

Please refer to Appendix D.

## 7.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

## 7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

## 7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

# 8. ETHICAL AND REGULATORY REQUIREMENTS

## 8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided

to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

## 8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the ISF
- Ensure a copy of the signed Informed Consent Form is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## 8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the co-ordinating investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## 8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

# 9. STUDY MANAGEMENT BY ASTRAZENECA

## 9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities

- Determine availability of appropriate patients for the study

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

## 9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and the WBDC system utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)

- Confirm that facilities remain acceptable

- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

### 9.3.1 Source data

Refer to the CSA for location of source data.

## 9.4 Study agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

### 9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

## 9.5 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in and to end by .

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD5069.

# 10. DATA MANAGEMENT BY ASTRAZENECA DATA MANAGEMENT CENTRE

Data management will be performed by AstraZeneca Data Management Centre (DMC) staff.

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data queries will be raised for inconsistent, impossible or missing data. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/queried and updated as needed. The principal investigator will then sign the eCRF electronically. Clean file occurs when all data have been coded, validated, signed by the investigator, locked and declared clean. Any treatment revealing data may thereafter be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Medical coding is done using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and AstraZeneca Drug Dictionary. Adverse events and medical/surgical history will be classified according to the terminology of the latest version MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca DMC.

The DMC will determine the format of third party data and coordinate the flow of data to an external environment or clinical database (if applicable). The DMC will ensure that the data collection tool (for eg, IVRS/IWRS) will be tested / validated as needed. The data collected through third party sources will be obtained and reconciled against study data.

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

For details of genotype data handling refer to Appendix D.

# 11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

## 11.1 Calculation or derivation of safety variable(s)

### 11.1.1 Other significant adverse events (OAE)

During the evaluation of the blinded AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

## 11.2 Calculation or derivation of patient reported outcome variables

No variables will be derived from the diary card data.

## 11.3 Calculation or derivation of pharmacokinetic variables

The PK analyses of the plasma concentration for AZD5069 will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. Due to the sparse PK sampling employed for all but a sub-group of the patients, a population-PK approach will be used to derive the PK parameters, for which a full PK & PK/PD analysis plan will be written and finalised prior to database-lock. Briefly, the PK data from all patients using actual sample times will be used to build a population PK model and the individuals' PK parameters derived from a post-hoc estimation of the model to each individual's data. Where possible, the following PK parameters will be determined for AZD5069:

Maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($t_{max}$), terminal rate constant ($\lambda z$), terminal plasma half-life ($t_{½}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), plasma clearance (CL/F), volume of distribution during terminal phase (Vz/F) and mean residence time (MRT).

For the calculation of PK parameters, plasma concentrations for AZD5069 prior to the first measurable concentration will be taken as zero. Plasma concentrations of AZD5069 below the limit of quantification (LOQ) that occur after the first measurable concentration will be excluded from the analysis. The resulting PK parameters will be estimated based on the whole profile.

## 11.4 Calculation or derivation of pharmacodynamic variable(s)

Circulating neutrophil counts will be assessed in blood samples.

### 11.4.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

The relationship between AZD5069 plasma concentration and the effect on circulating neutrophils in blood will be presented graphically. If appropriate, concentration-effect relationships will be explored using a population-PK/PD approach to link the population-PK model described in Section 11.3 to the neutrophil count data.

Additional analyses of potential relationships between AZD5069 dose, plasma concentration or exposure ($C_{max}$, AUC) and safety or clinical parameters may be performed if required.

## 11.5 Calculation or derivation of pharmacogenetic variables

See Appendix D for information on the pharmacogenetic research.

## 11.6 Calculation or derivation of health economic variables (Not applicable)

Not applicable.

# 12. STATISTICAL METHODS AND SAMPLE SIZE

## 12.1 Description of analysis sets

### 12.1.1 General principles

The analysis of the data will be based on potentially different subsets according to the purpose of analysis, ie, for safety, PK and PD, respectively. The decision regarding validity of data for inclusion in each of the analysis sets will be based on blind review of the data.

The as-treated principle will be applied to all evaluations; ie, patients who received another treatment than the one assigned in the randomisation list will be analysed as belonging to the actual treatment group and not that assigned by randomisation.

### 12.1.2 All subject analysis set

This analysis set comprises all patients screened for the study and will be used for reporting of disposition and screening failures.

### 12.1.3 Safety analysis set

All patients who are randomised into the study and receive at least one dose of randomised investigational product, AZD5069 or placebo, and for whom any post-dose data are available will be included in the safety analysis set.

Throughout the safety analyses, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

### 12.1.4 PK analysis set

The PK analysis set will be based on the safety analysis set. The patients who are in the safety analysis set and provide evaluable PK data appropriate for the evaluation of interest (with no major protocol deviations or violations thought to significantly affect the pharmacokinetics of the drug) will be included in the PK analysis set. It may be that specific data points are not included in this analysis set due to deviations or violations at that specific time. Patients who receive placebo will not be part of the PK analysis set.

### 12.1.5 PD analysis set

The PD analysis set will be based on the safety analysis set. The patients who are in the safety analysis set and provide the evaluable PD data appropriate for the evaluation of interest (with no major protocol deviations or violations thought to significantly affect the PD assessment of the drug) will be included in the PD analysis set. It may be that specific data points are not

included in this analysis set due to deviations or violations at that specific time. Patients who receive placebo will be included in this analysis set.

## 12.2 Methods of statistical analyses

### 12.2.1 General principles

No formal statistical hypothesis testing will be performed.

Data will be presented by actual dose.

No action will be taken to handle missing data unless specified. The summaries of the data will show the number of data points and/or patients included. If a baseline value is missing, then the pre-treatment value taken closest to the scheduled baseline will be used.

A patient who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation.

### 12.2.2 Patient characteristics

Continuous variables will be summarised using descriptive statistics (eg, n, mean, standard deviation (SD), min, median, max) by treatment group. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group.

Demographic data, medical and surgical histories, and physical examination data will be listed for all patients and summarised by treatment group using standard summary statistics.

Concomitant medications will be classified according to the AZ Drug Dictionary, the ATC system and the Committee for Medicinal Products for Human Use (CPMP) route of administration dictionary. All concomitant medications reported at entry and recorded during the study will be listed. Concomitant medications will be summarised by treatment group and ATC code using standard summary statistics, if there are sufficient data. This will be determined during the blind review of the data.

### 12.2.3 Safety and tolerability

Safety data will be summarised based on the safety analysis set.

Continuous variables will be summarised using descriptive statistics (eg, n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group. Graphical presentations will be used as appropriate. Examples may include line graphs showing individual or mean development over time, shift plots showing baseline values on the horizontal axis and post-treatment values on the vertical axis.

Baseline will be the value measured and collected at Visit 2 prior to the first dose. If the measurement is missing, the latest pre-treatment measurement for each parameter will be

taken as baseline. For ECG parameters, vital signs and lung function tests, change from baseline at on- and post- treatment visits will be defined as: visit value-baseline value.

All adverse events will be collected for each patient from the time when informed consent is received until the follow-up visit (Visit 7). Adverse events will be considered as treatment emergent if they start or worsen on or after the first day of dosing, up to the post-study medical examination performed at Visit 7. AEs that occur before dosing will be reported separately. All AEs will be listed for each patient.

Adverse events will be summarised by PT (preferred term) and SOC (System organ class) using MedDRA vocabulary. Adverse events will also be summarised by causality and intensity, and causality and seriousness. Furthermore, listings of serious adverse events and adverse events that led to withdrawal will be made and the number of patients who had any adverse events, serious adverse events, adverse events that led to withdrawal, adverse events with severe intensity, other significant adverse events and deaths will be summarised.

ECG parameters will be summarised for the absolute values at each scheduled assessment, together with the corresponding changes from the baseline values. The QT correction factor will be based on the Fridericia's formula. Further categorical summaries of absolute QT and calculated QTcF values (>450 ms, >480 ms, >500 ms) and change from baseline values in QT and QTcF values (>30 ms, >60 ms) may also be produced.

All laboratory data will be listed. Deviations from extended and standard reference ranges quoted in project reporting ranges, will be explicitly noted on these listings where applicable. For parameters where there are no extended or standard reference ranges the reference range from the local laboratory will be used. Numerical laboratory data will be summarised using standard summary statistics for each treatment group at each visit. The change from baseline value will be similarly summarised. Discrete laboratory data will be summarised showing the number of patients at each level of measurement at each visit by treatment group. Summaries of the number of patients falling outside the reference ranges at each time point will also be provided by treatment group. Separate listings of only those values falling outside these reference ranges will also be produced.

Neutrophil counts will be summarised for the absolute value at each scheduled assessment together with the corresponding changes from the baseline value and the % changes from the baseline value. In addition, the maximum change and maximum % change from the baseline value will be summarised together with the assessment time the maximum changed occurred.

The following plots (please also refer to Section 12.2.6) will also be provided:

- Plots of mean value at each dose level of AZD5069 and placebo against time, symbols indicating dose level - medians will be used instead of means if the data is not normally distributed

- Plots of absolute values vs time (one plot per treatment group per data type showing separate lines for each patient, with a reference line added at the upper reference limit)
- Plots of change from baseline value vs time (one plot per treatment group per data type showing separate lines for each patient)
- Plots of % change from baseline value vs time (one plot per treatment group per data type showing separate lines for each patient).

Additional plots may produced if appropriate.

Pulse, systolic blood pressure, diastolic blood pressure and body temperature will be listed for each patient and summarised over time by treatment group using standard summary statistics. The change from baseline value will be similarly summarised. Summaries of the number of patients falling outside the reference ranges quoted on LDMS_001_0069526 "Standards for Collection and Evaluation of Laboratory and Vital Signs Safety Data in Clinical Studies", at each time point will also be provided by treatment group.

Pre- and post- bronchodilator lung function tests will be listed for each patient and summarised over time by treatment group using standard summary statistics. The change from baseline will be similarly summarised.

### 12.2.4 Pharmacokinetics

Listings and summary statistics for the derived parameters, along with figures will be provided as detailed in the PK/PD analysis plan.

### 12.2.5 Pharmacodynamics

Circulating neutrophils will be summarised using the methods described in Section 12.2.3 and will be based on the safety analysis set. In the unlikely event that the safety analysis set and the PD analysis set are very different, summaries may also be produced based on the PD analysis set. This will be determined at blind review.

### 12.2.6 Pharmacokinetics/Pharmacodynamics

Graphical representation of the data will be detailed in the PK/PD analysis plan.

## 12.3 Determination of sample size

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

## 12.4 Data monitoring committee (Not applicable)

Not applicable.

# 13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

## 13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

In the case of a medical emergency the investigator may contact the Study Delivery Team (SDT) Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca Research and Development site.

| Name | Role in the study | Address & telephone number |
|---|---|---|
| | SDT Leader responsible for the protocol at central R&D site | AstraZeneca R&D |
| | SDT Physician responsible for the protocol at central R&D site | AstraZeneca R&D<br>Bakewell Road |

## 13.2 Overdose

For the purpose of this study an overdose is defined as any dose of investigational product above that which is mandated within the protocol. There is no experience of overdose and no antidote to AZD5069. In cases of known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the overdose eCRF module. If the AE meets the criteria for an SAE, it should also be recorded on the SAE module.
- An overdose without associated symptoms is only reported on the overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

## 13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

### 13.3.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study (refer to Section 4.1). Should a pregnancy still occur, the investigational product should be discontinued immediately, the patient withdrawn from the study and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All initial reports and outcomes of pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 day for fatal and life threatening events or 5 days for all other SAEs, see Section 6.4.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy module in the eCRF is used to report the pregnancy together with a pregnancy fax report page which is sent to Patient Safety when a pregnancy is identified. The Pregnancy Outcome Report is used to report the outcome of the pregnancy. These reports should be sent through to the Data Entry Site within 30 calendar days of the Investigator becoming aware.

### 13.3.2 Paternal exposure

Male patients must refrain from fathering a child during the study and 3 months following the last dose (refer to Section 5.1).

Pregnancy of a patient's partner is not considered to be an adverse event. However, the outcome of any pregnancy occurring from the date of the first dose until 3 months after the last dose must be reported to AstraZeneca **within 5 days** and documented as specified in Section 13.3.1.



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**Clinical Study Protocol Appendix B**

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

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)



## Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

## Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

## Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

# Appendix C
# International Airline Transportation Association (IATA) 6.2 Guidance Document

# LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES



International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

**Clinical Study Protocol Appendix D**

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

# Appendix D
# Pharmacogenetics Research

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation or special term | Explanation |
|---|---|
| COPD | Chronic Obstructive Pulmonary Disease |
| CSR | Clinical Study Report |
| DNA | Deoxyribonucleic acid |
| LIMS | Laboratory information management system |
| PGx | Pharmacogenetics |

# 1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the AZD5069 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD5069. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD5069 but also susceptibility to Chronic Obstructive Pulmonary Disease (COPD) for which AZD5069 may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to COPD and AZD5069.

# 2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5069, and/or susceptibility to COPD, and/or associated biomarkers.

# 3. GENETIC RESEARCH PLAN AND PROCEDURES

## 3.1 Selection of genetic research population

### 3.1.1 Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

### 3.1.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

### 3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant.

- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

### 3.1.4 Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

## 3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Visit 2 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

## 3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA).

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

# 4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

## 4.1 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

## 4.2 Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

# 5. DATA MANAGEMENT

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research will not be reported in the CSR for the main study.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

# 7. LIST OF REFERENCES (NOT APPLICABLE)

Not applicable.