**Amended Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | AZD9668 |
| Study Code | D0520C000010 |
| Edition Number | 2 |
| Date | [redacted] |

# A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28 Day Oral Administration of AZD9668 in Patients with Bronchiectasis

**Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden**

**AstraZeneca Research and Development site representative**

[redacted] Date

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

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
|---|---|---|---|
| 1 | | | |
| 2 | [redacted] | | |

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

# PROTOCOL SYNOPSIS

## A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28 Day Oral Administration of AZD9668 in Patients with Bronchiectasis

**International Co-ordinating Investigator**

[redacted]

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

It is planned to enrol approximately 60 patients, in order to randomise 40 patients. This study will be conducted in Canada (approximately 6 centres) and UK (approximately 4 centres), with 2-6 patients being randomised per site. Additional sites in Europe will be considered as required.

This study has an optional pharmacogenetic research element which will be detailed in Appendix D

| **Study period** | | **Phase of development** |
|---|---|---|
| Estimated date of first subject enrolled | [redacted] | Phase II |
| Estimated date of last subject completed | [redacted] | |

**Objectives**

The Primary Objective is:

To investigate whether AZD9668 shows evidence of efficacy in bronchiectasis patients by investigation of:

- Absolute and percentage neutrophil cell count in the sputum
- Signs and symptoms of bronchiectasis (including effects on quality of life)

The Secondary Objectives are:

- To investigate the effect of AZD9668 on Neutrophil Elastase (NE) activity in sputum
- To investigate the effect of AZD9668 on other inflammatory markers in sputum
- To investigate the effect of AZD9668 on inflammatory markers in blood
- To investigate the safety and tolerability of 28 days' dosing with AZD9668 in bronchiectasis patients
- To confirm AZD9668 exposure in plasma and in spontaneously produced sputum
- To investigate the effect of AZD9668 on urine desmosine (marker of tissue degradation)

The Exploratory Objectives are:

- To investigate the effect of AZD9668 on other markers of tissue degradation
- To investigate the effect of AZD9668 on markers of mucus hyper-secretion
- To collect samples for possible retrospective pharmacogenetics analysis to investigate the influence of genotype on pharmacokinetics (and pharmacodynamic response where appropriate). This will not form part of the Clinical Study Report (CSR).

**Study design**

This is a randomised, double-blind placebo-controlled, parallel group study in patients with bronchiectasis. Forty patients will be randomised to treatment at a ratio of 1:1 (AZD9668:placebo). Patients who complete the study, will be required to attend 10 visits, some of which may be undertaken in their own home.

There will be an optional pharmacogenetics element to collect samples that may be used for the possible retrospective analysis to investigate the influence of genotype on pharmacokinetics (and pharmacodynamic response, where appropriate). Further details can be found in Appendix D.

**Target patient population**

Male and female (non child bearing potential) patients between 18 and 80 years, with a clinical diagnosis of idiopathic or post-infective bronchiectasis as confirmed by historical high resolution computerised tomography (HRCT) or bronchogram.

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

AZD9668 will be administered orally as a dose of 60 mg (2 x 30mg tablets) twice a day (b.i.d) for 28 days.

**Comparator, dosage and mode of administration**

Matching placebo tablets will be administered orally, two tablets, twice a day (b.i.d) for 28 days

**Duration of treatment**

Treatment will continue for 28 days unless any of the discontinuation criteria are met.

**Outcome variable(s):**

**Primary variables**

- Sputum neutrophils:
  - Absolute and percentage neutrophil cell count
- Signs and symptoms of bronchiectasis:
  - Bronkotest © diary card data
  - Weight of 24 hour sputum collection (pre-treatment versus end of treatment)
  - Quality of life as assessed by St George's Respiratory Questionnaire
  - Lung function tests: (Forced expiratory volume in one second [$FEV_1$], Slow vital capacity [SVC], Forced vital capacity [FVC], forced expiratory flow between 25 and 75% of forced vital capacity [FEF25-75])

**Secondary variables**

- Safety variables
  - vital signs, ECG, haematology, clinical chemistry, urinalysis, sputum culture, reported adverse events.
- Pharmacokinetic variables
  - AZD9668 concentration in plasma and sputum
- Pharmacodynamic variables
  - NE activity in sputum (subject to the availability of validated assay)

- Other inflammatory markers in sputum, including, but not limited to (and subject to the availability of validated assays): TNF-α, IL-8, LTB-4, IL-6, IL-1β, RANTES, MCP-1

- Blood inflammatory markers, including, but not limited to (and subject to the availability of validated assays): differential cell count [absolute and percentage neutrophils], TNF-α, IL-8, high sensitivity CRP, Amyloid-A, IL-6, IL-1β

- Urine desmosine (marker of tissue degradation)

- **Exploratory variables**

- Plasma desmosine and sputum hydroxyproline (markers of tissue degradation)

- MUC5AC in sputum (marker of sputum hyper secretion)

Subject to the availability of validated assays.

- Retrospective pharmacogenetic analysis to investigate the influence of genotype on the pharmacokinetics of AZD9668 (and pharmacodynamic response where appropriate). Further details can be found in Appendix D.

**Statistical methods**

The primary outcome variables will be compared between AZD9668 and placebo using an analysis of variance model with fixed factors treatment and country (or centre) and using baseline as a covariate. As the study is exploratory in nature, a p-value of <0.1 will be considered significant. A 2-sided 90% confidence interval will be constructed for the treatment difference and p-values given. For variables with a skewed distribution, data may be log-transformed prior to analysis or a non-parametric test (Wilcoxon rank sum) used instead. The primary outcome variable analyses will be carried out on the Efficacy Analysis Set.

All other data will be summarised and listed.

There will not be an interim analysis for this study.

Pharmacokinetic analyses will be carried out by, or under the guidance of, the [redacted] group within AstraZeneca

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 7.3.1) |
| ALT | Alanine aminotransferase |
| AMOS | Astra Zeneca database |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification of Drug |
| AUC | Area under the plasma concentration time curve from time zero to infinity |
| $AUC_{(0-24)}$ | AUC from time zero to 24 hours post-dose |
| $AUC_{(0-24),ss}$ | $AUC_{(0-24)}$ at steady state |
| AZ | AstraZeneca |
| BAL | Bronchoalveolar lavage |
| b.i.d | Twice daily dosing (latin) |
| CL/F | Apparent plasma clearance following oral drug administration |
| $CL/F_{,ss}$ | CL/F at steady state |
| $CL_R$ | Renal clearance |
| $CL_{R,ss}$ | $CL_R$ at steady state |
| $C_{max}$ | Observed peak or maximum plasma concentration following drug administration |
| $C_{max,ss}$ | $C_{max}$ at steady state |
| CRR | Clinical Research Region |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPK | Creatinine phosphokinase |
| CPMP | Committee for Proprietary Medicinal Products |
| CRF | Case report form |
| CRP | C-reactive protein |
| CSR | Clinical study report |
| CYP | Cytochrome P450 |
| DAE | Discontinuation due to Adverse Event |
| DMP | Data management plan |
| DMPK | Drug metabolism and pharmacokinetics |

| Abbreviation or special term | Explanation |
|---|---|
| DNA | Deoxyribonucleic acid |
| DQF | Data query form |
| ECG | Electrocardiogram |
| Ecode | Enrolment code |
| EDTA | Ethylenediamine tetra-acetic acid |
| EU | European union |
| $Fe_{(0-48)}$ (%) | Percentage of the dose excreted as unchanged parent in the urine from time zero to 48 hours |
| $Fe_{(0-48),ss}$ (%) | $Fe_{(0-48)}$ (%) at steady state |
| FEF25-75 | forced expiratory flow between 25 and 75% of forced vital capacity |
| $FEV_1$ | Forced expiratory volume in the first second |
| FSH | Follicle-stimulating hormone |
| FVC | Forced vital capacity |
| GARNET | Global application for reconciliation and narrative transcription |
| GCP | Good Clinical Practice |
| GGT | Gamma-glutamyltransferase |
| GMP | Good Medical Practice |
| GRand | Global randomisation system |
| hCG | Human chorionic gonadotropin |
| HELC | AstraZeneca Human Exposure Limits Committee |
| HIV | Human immunodeficiency virus |
| HRCT | High Resolution Computerised Tomography |
| IB | Investigator brochure |
| ICH | International Conference on Harmonisation |
| ICS | Inhaled corticosteroids |
| IL-1β | Interleukin 1 beta |
| IL-6 | Interleukin 6 |
| IL-8 | Interleukin 8 |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| IP | Investigational product |
| LABA | Long-acting β agonists |

| Abbreviation or special term | Explanation |
|---|---|
| LAMA | Long-acting muscarinic antagonist |
| LDH | Lactate dehydrogenase |
| LFT | Liver function test(s) |
| LIMS | Laboratory information management system |
| LLN | Lower limit of normal |
| LLOQ | Lower Limit of Quantification |
| $LTB_4$ | Leukotriene B4 |
| MAD | Multiple ascending dose |
| MC | Marketing Company |
| MCH | Mean cell haemoglobin |
| MCHC | Mean cell haemoglobin concentration |
| MCP-1 | Monocyte chemoattractant protein |
| MCV | Mean cell volume |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MID | Minimal clinically important difference |
| MUC5AC | Mucin 5AC |
| NCR | No carbon required |
| NE | Neutrophil Elastase |
| NOAEL | No observed adverse effect level |
| NOEL | No observed effect level |
| OAE | Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 12.2.4 |
| pCRF | Paper CRF |
| PD | Pharmacodynamic(s) |
| PEF | Peak Expiratory flow |
| PK | Pharmacokinetic(s) |
| PoP | Proof of principle |
| prn | *Pro re nata* (latin) – "As and when required" |
| PRO | Patient reported outcome |
| QT | ECG interval measured from the beginning of the Q wave (or the R wave if Q is missing) to the end of the T wave; the time interval of ventricular depolarisation and repolarisation |

| Abbreviation or special term | Explanation |
|---|---|
| QTc | Corrected QT |
| R&D | Research and development |
| RAMOS | Remote AMOS |
| RANTES | Regulated on activation, normal T cell expressed and secreted |
| RV | Residual Volume |
| SABA | Short-acting β agonists |
| SAD | Single ascending dose |
| SAE | Serious adverse event (see definition in Section 7.3.2). |
| SAMA | Short-acting muscarinic antagonist |
| SAP | Statistical analysis plan |
| S-CPK-MB | Serum creatinine phosphokinase, muscle and brain |
| SD | Standard deviation |
| SGRQ-C | St Georges Respiratory Questionnaire for COPD patients |
| SOP | Standard operating procedure |
| SVC | Slow Vital Capacity |
| $t_{1/2}$ | Half-life |
| $t_{1/2,ss}$ | Half-life at steady-state |
| $T_4$ | Thyroxine |
| $t_{max}$ | Time to reach observed peak or maximum concentration following drug administration |
| $t_{max, ss}$ | $t_{max}$ at steady state |
| TNFα | Tumour necrosis factor alpha |
| TSH | Thyroid stimulating hormone |
| UK | United Kingdom |
| ULN | Upper limit of normal |
| UV | Ultraviolet |
| $V_z/F$ | Apparent terminal volume of distribution following extra-vascular dosing |
| $V_z/F_{,ss}$ | $V_z/F$ at steady state |
| WBDC | Web Based Data Capture |
| WHO | World health organisation |

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

## 1.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) 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 7.3.4**

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at AZR&D [redacted]

| **Name** | **Role in the study** | **Address & telephone number** |
|---|---|---|
| [redacted] | Study Delivery Team Leader responsible for the protocol at central R&D site | [redacted]<br>Telephone: [redacted] |
| [redacted] | SDT Physician responsible for the protocol at central R&D site | [redacted]<br>Telephone: [redacted]<br>Mobile: [redacted] |
| *State local contact persons below* | | |
| | | |
| | | |

## 1.2 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 specific antidote to AZD9668; in cases of overdose, appropriate supportive measures should be undertaken.

The Clinical Study Overdose Report Form will be used in this study:

- An Overdose with associated SAEs is recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF only.
- An Overdose with associated non-serious AEs is recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF and on the separate AZ "Clinical Study Overdose Report Form".
- An Overdose without associated symptoms is only reported on the separate AZ "Clinical Study Overdose Report Form"

The clinical study overdose report form should be sent through to the appropriate Patient Safety Data Entry Site (DES) within 30 days of the Investigator becoming aware.

## 1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

### 1.3.1 Maternal exposure

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. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must 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 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 appropriate Patient Safety Data Entry Site (DES) within 30 calendar days.

The Pregnancy Outcome Report, SOP-330-G T02 is used in this study.

The Pregnancy Outcome Report, part 1, is used to report the pregnancy and the Pregnancy Outcome Report, part 2, is used to report the outcome of the pregnancy. These reports should be sent through to the appropriate Patient Safety Data Entry Site (DES) within 30 days of the Investigator becoming aware.

### 1.3.2 Paternal exposure

The outcomes of any conception occurring from the date of the first dose until 3 months after the last dose must be followed up and documented.

Male patients must refrain from fathering a child during the study and **three** months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

Pregnancy of the patients partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

# 2. INTRODUCTION

## 2.1 Background

AZD9668 is a potent, oral, selective, reversible inhibitor of human neutrophil elastase (NE). It is primarily being developed as a possible therapeutic agent both for symptomatic treatment as well as disease modification in COPD.

NE is a serine protease found in high levels in neutrophils. NE is able to degrade extracellular matrix and proteins leading to long-term destruction of the lung parenchyma. Inhibition of neutrophil elastase therefore has the potential to inhibit this proteolytic destruction raising the possibility of disease modification. A number of clinical and experimental observations indicate that NE plays a pivotal role in COPD, which renders this enzyme a compelling target for drug discovery. Overall, the findings from these studies suggest that an NE inhibitor can be expected to have a beneficial effect on the inflammation, mucus hyper-secretion and matrix degradation characteristic of COPD (Smith et al 2001, Ohbayashi 2002) and thereby provide a therapeutic benefit in terms of symptom control as well as slowing the progressive decline in lung function, both in stable disease and during exacerbations. It could also be of benefit in other airway diseases characterised by neutrophilic inflammation such as bronchiectasis and cystic fibrosis.

Orally administered AZD9668 produced a dose-dependent inhibition of human NE-induced lung haemorrhage in the mouse. Mice exposed to cigarette smoke and treated with AZD9668 showed a significant reduction in total number of cells and neutrophils and IL1-β, compared to vehicle treated smoke exposed mice, indicating the possibility of inhibiting endogenously released NE with this drug.

AZD9668 was well tolerated in rat and dog toxicity studies. In a dog 28-day toxicity study minor haematological abnormalities and a slight QT-prolongation (9%) at a high dose was observed. These however occurred at plasma levels clearly above the expected human exposure range. Mutagenicity tests indicated that AZD9668 does not pose a significant genotoxicity risk.

A first administration to man, Phase I, randomised, double blind, placebo-controlled, 2-part study to assess the safety and tolerability, and pharmacokinetics of single and multiple oral doses of AZD9668 in healthy volunteers has been completed. In the single ascending dose part of the study, AZD9668 was administered at doses of 2 mg, 10 mg, 30 mg, 60 mg, 120 mg and 150 mg with 36 patients receiving the active drug and 12 patients receiving the placebo. In the multiple ascending dose part of the study the drug was given in doses of 30 mg, 70 mg and 120 mg once daily for 8 days with 18 patients receiving the active drug and 9 the placebo. Overall, AZD9668 was well tolerated except for the occurrence of headaches at the highest doses tested. No laboratory abnormalities of any concern or QT prolongation were noted in any of the patients. The PK data from this study is detailed in Section 4.2.

A further safety and tolerability study of AZD9668 in Caucasian and Japanese healthy volunteers, at doses of up to 70 mg b.i.d has been conducted, and a study of tolerability of AZD9668 in COPD patients at a dose of 60 mg b.i.d. has been initiated. Emerging PK and safety data from the Caucasian/Japanese healthy volunteers study give no concern to proceed to studies with b.i.d. dosing in patient groups with this drug.

Details of pre-clinical and clinical pharmacology, toxicity and safety and tolerability of AZD9668 are given in the Investigators Brochure (IB).

The current study is a proof-of-principle (PoP) study in patients with bronchiectasis to see if it is possible to demonstrate that AZD9668 inhibits NE activity and some of its downstream effects. Bronchiectasis is a pathological description of a progressive and debilitating disease in which airways become permanently dilated as the result of inflammatory-related destruction of structural components of the bronchial wall (Barker 2002). As in COPD the airway inflammation in bronchiectasis is characterised by neutrophilic inflammation. Bronchiectasis is chosen as an “exaggerated model” of COPD (see Section 2.3), as NE levels in the sputum are consistently higher in this condition than in stable COPD.

AstraZeneca may perform genetic research in the AZD9668 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD9668. Collection of DNA samples from populations with well described clinical characteristics may aid in the identification of future drug targets and projects to validate identified targets. Further details of the optional pharmacogenetic component of this study can be found in Appendix D.

## 2.2 Research hypothesis

The research hypothesis is that the neutrophil elastase inhibitor AZD9668 shows an effect on the inflammatory markers and signs and symptoms (including quality of life) in patients with bronchiectasis and is safe and well tolerated when given orally at a dose of 60 mg b.i.d. for 28 days.

## 2.3 Rationale for conducting this study

AZD9668 is primarily being developed as a treatment for COPD. So far it has been found to be safe and well tolerated in healthy volunteers. In order to determine if a neutrophil elastase

inhibitor has potential benefit as a treatment for COPD, a one-month study in patients with bronchiectasis is planned, as an "exaggerated model" of COPD for this target mechanism.

COPD and bronchiectasis share many features; both are characterised by a primarily neutrophilic inflammation, both exhibit varying degrees of fixed airway obstruction, and both experience acute infective exacerbations. There is considerable overlap between the conditions: surveys have shown that 30% of COPD patients diagnosed in general practice, and 50% seen in hospital clinics, have some degree of bronchiectasis on high resolution computerised tomography (HRCT) scanning. In both conditions increased levels of NE activity are seen in the sputum or bronchoalveolar lavage (BAL), but the levels are considerably higher in bronchiectasis, giving a larger window to show a pharmacodynamic effect of an NE inhibitor. Hence, this condition is considered a suitable 'exaggerated model' of COPD, which could be used in PoP studies with an opportunity to see greater changes in biomarkers and clinical parameters such as sputum colour and volume. In addition, it might also make it possible to demonstrate an effect of NE inhibition with a smaller number of patients, than if the study was conducted in patients with COPD. Although a 2-week study would be expected to be sufficient to demonstrate changes in NE activity, a 4-week study offers an increased likelihood of observing changes in clinical outcomes.

## 2.4 Benefit/risk and ethical assessment

Patients with COPD are the target population for the NE inhibitor AZD9668. The main purpose of this study is to establish the proof-of-principle that the neutrophil elastase inhibitor AZD9668 shows some effect on the inflammatory markers and signs and symptoms in patients with bronchiectasis, so that one could proceed with confidence to longer-term proof-of-concept studies in COPD patients. It is also intended to obtain further safety/tolerability data prior to proof-of-concept and dose finding studies in COPD patients.

A detailed assessment of the overall risk/benefit of developing a NE inhibitor in COPD is given in the IB. COPD presents an area of high unmet medical need, and there is considerable evidence to indicate that NE presents a compelling target for drug development. In this study bronchiectasis is chosen as an "exaggerated model" of COPD with regard to neutrophilic inflammation and NE activity mediated changes, so that proof that an NE inhibitor is effective in patients can be established in principle, by exposing a fewer number of patients than if the study was conducted in patients with stable COPD. Furthermore, the study could show that a NE inhibitor could be useful in bronchiectasis *per se.*

So far, safety/tolerability and PK data are available in healthy volunteers up to 150 mg as a single dose and up to 120 mg daily for 8 days, and 70 mg b.i.d. as multiple doses. Detail of the PK and the rationale for choosing a dose of 60 mg b.i.d. for this study are detailed in Section 4.2 and the IB.

To mitigate the risks identified in the pre-clinical toxicology studies, haematological and biochemical parameters including evidence for haemolysis will continue to be monitored. Although no significant QT abnormalities were observed in the healthy volunteers studies, patients with a prolonged $QT_c$ value will not be entered into this study. Also, only patients

with normal renal function and normal haematological parameters will be entered into the study.

For an overall risk benefit assessment of developing a NE inhibitor in COPD, see the Investigator's Brochure.

# 3. STUDY OBJECTIVES

## 3.1 Primary objective

The primary objective is to investigate whether AZD9668 shows evidence of efficacy in bronchiectasis patients by investigation of:

- Absolute and percentage neutrophil cell count in the sputum
- Signs and symptoms of bronchiectasis (including effects on quality of life)

The associated primary outcome variables can be found in Table 1.

**Table 1 Primary outcome variables**

| Outcome Variables | Description |
|---|---|
| Absolute and percentage neutrophil cell count in sputum | Absolute cell count will be performed and sputum cytospin slides will be produced for assessment of differential cell count |
| Bronkotest © diary card | The Bronkotest © diary card will be completed by patients from enrolment until follow up visit, to capture signs and symptoms of their bronchiectasis |
| 24 hour sputum collection weight | Patients will be asked to collect sputum for a 24 hour period on 2 occasions during the study |
| St George's Respiratory Questionnaire | The quality of life questionnaire "St George's Respiratory Questionnaire for COPD patients" (SGRQ-C) will be completed pre treatment and at the end of the treatment period |
| Lung function tests | The following lung function tests will be assessed at clinic visits 1, 2, 4 and 5. SVC (slow vital capacity), FEV1(forced expiratory volume in 1 second), FVC (forced vital capacity), forced expiratory flow between 25 and 75% of forced vital capacity (FEF25-75) |

## 3.2 Secondary objectives

The Secondary Objectives are:

- To investigate the effect of AZD9668 on Neutrophil Elastase (NE) activity in sputum
- To investigate the effect of AZD9668 on other inflammatory markers in sputum
- To investigate the effect of AZD9668 on inflammatory markers in blood
- To investigate the safety and tolerability of 28 days' dosing with AZD9668 in bronchiectasis patients
- To confirm AZD9668 exposure in plasma and in spontaneously produced sputum
- To investigate the effect of AZD9668 on urine desmosine (marker of tissue degradation)

The associated outcome variables are detailed in Table 2. The markers assayed will be dependent on the availability of validated methods.

**Table 2 Secondary outcome variables**

| Outcome variables | Description |
|---|---|
| NE activity in sputum | Spontaneous sputum collections will be processed according to the laboratory manual and aliquots will be collected for NE activity |
| Inflammatory markers in sputum | Spontaneous sputum collections will be processed according to the laboratory manual and aliquots will be collected for assessment of the following markers (including, but not limited to) –<br>TNF-α, IL-8, LTB-4, IL-6, IL-1β, RANTES, MCP-1 |
| Inflammatory markers in blood | Blood samples will be collected for assessment of the following markers (including, but not limited to) -<br>Absolute and percentage differential cell count, TNF-α, IL-8, high sensitivity CRP, Amyloid-A, IL-6, IL-1β |
| Safety and tolerability of AZD9668 | Vital signs, ECG, haematology, clinical chemistry, urinalysis, sputum culture, reported adverse events |
| Pharmacokinetic parameters (plasma and sputum) | Concentration of AZD9668 in plasma and sputum |

**Table 2 Secondary outcome variables**

| Outcome variables | Description |
|---|---|
| Tissue degradation markers | Urine desmosine will be measured from the 24 hour urine collections |

## 3.3 Exploratory objectives

The Exploratory Objectives are:

- To investigate the effect of AZD9668 on other markers of tissue degradation (plasma desmosine and sputum hydroxyproline)
- To investigate the effect of AZD9668 on markers of mucus hyper-secretion (MUC5AC in sputum)
- To collect samples for possible retrospective pharmacogenetics analysis to investigate the influence of genotype on pharmacokinetics (and pharmacodynamic response where appropriate). This will not form part of the Clinical Study Report (CSR).

# 4. STUDY PLAN AND PROCEDURES

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

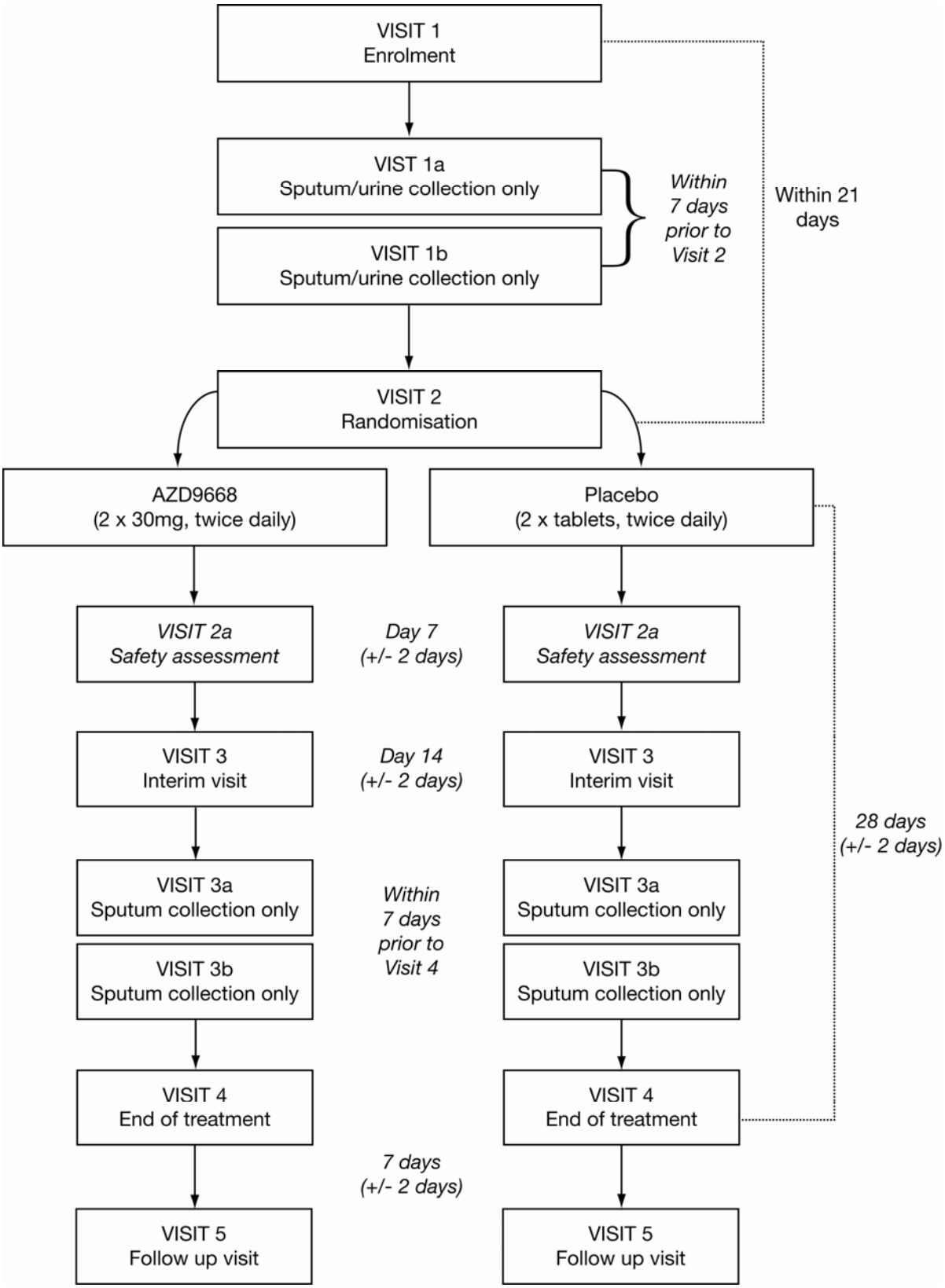
## 4.1 Overall study design and flow chart

This is a randomised, double-blind placebo-controlled, parallel group study in 40 randomised patients with Bronchiectasis. It is planned to perform this study in approximately 10 centres across 2 countries; Canada (approximately 6 sites) and UK (approximately 4 sites) with each site randomising 2-6 patients during the study. Additional sites in Europe will be considered as required.

After patients have provided informed consent, they will be enrolled into the study. Patients who complete the study, will be required to attend 10 visits, some of which may be undertaken in their own home. The overall study design is outlined in Figure 1.

Patients will be randomised (1:1) at Visit 2, to receive either AZD9668 or placebo. They will be given sufficient tablets to allow dosing, 60 mg (b.i.d), until Visit 3 (14 days +/-2 days). At Visit 3, the remaining study drug will be dispensed. This will be sufficient to allow 60 mg b.i.d dosing until Visit 4 (day 28 +/-2 days).

**Figure 1 Study design**



Full details of the study assessments taking place at each visit are outlined in Table 3.

Patients should be informed that they should fast on the morning of Visits 2 and 4.

They should also with-hold their morning dose of medication on Visit 4 as it will be taken at clinic following the pre-dose assessments (as outlined in Table 3) and also at Visit 3a and Visit 3b, they should perform their sputum collections prior to taking their study medication.

Specific details of timing of sputum collections and subsequent analyses are outlined in Table 4.

**Table 3 Table of study assessments**

| **Study Visit** | **1** | **1a** | **1b** | **2** | **2a** | **3** | **3a** | **3b** | **4** | **5** [l] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Timing** | Day -21 to Day -8 | Within 7 days of Visit 2 [a] | Within 7 days of Visit 2 [a] | Day 1 | Day 7 (±2 days) | Day 14 (±2 days) | Within 7 days of Visit 4 [a] | Within 7 days of Visit 4 [a] | Day 28 (±2 days) | 7 days (±2 days) after Visit 4 |
| **Detail** | **Enrolment** | **Sputum/ Urine** | **Sputum/ Urine** | **Start of treatment** | **Interim visit** | **Interim visit** | **Sputum** | **Sputum** | **End of treatment** | **Follow up visit** |
| Written informed consent[b] | ✓ | | | | | | | | | |
| Demographics | ✓ | | | | | | | | | |
| Physical examination | ✓ | | | | | | | | | ✓ |
| Medical/surgical history | ✓ | | | | | | | | | |
| Dispense study drugs | | | | ✓ | | ✓ | | | | |
| Safety bloods | ✓[d] | | | ✓[c] | ✓ | ✓ | | | ✓[c] | ✓ |
| Urinalysis | ✓ | | | ✓[c] | | ✓ | | | ✓[c] | ✓ |
| Inclusion/exclusion criteria | ✓ | | | ✓[c] | | | | | | |
| Lung function tests | ✓ | | | ✓[c] | | | | | ✓[c] | ✓ |
| Vital signs | ✓ | | | ✓[e] | | ✓ | | | ✓[e] | ✓ |
| ECG | ✓ | | | ✓[e] | | ✓ | | | ✓[e] | ✓ |
| Drug accountability | | | | | | ✓ | | | ✓ | |
| Bronkotest© diary card [f] | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |

**Table 3 Table of study assessments**

| **Study Visit** | **1** | **1a** | **1b** | **2** | **2a** | **3** | **3a** | **3b** | **4** | **5** [l] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Timing** | Day -21 to Day -8 | Within 7 days of Visit 2 [a] | Within 7 days of Visit 2 [a] | Day 1 | Day 7 (±2 days) | Day 14 (±2 days) | Within 7 days of Visit 4 [a] | Within 7 days of Visit 4 [a] | Day 28 (±2 days) | 7 days (±2 days) after Visit 4 |
| **Detail** | **Enrolment** | **Sputum/ Urine** | **Sputum/ Urine** | **Start of treatment** | **Interim visit** | **Interim visit** | **Sputum** | **Sputum** | **End of treatment** | **Follow up visit** |
| Concomitant medications recorded | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Adverse event questioning | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Pharmacogenetics blood sampling[g] | | | | ✓ | | | | | | |
| Return 24 hr urine collection (for desmosine)[h] | | ✓[h] | ✓[h] | | | | | | ✓[h] | |
| Return 24 hr sputum collection (for weight)[h] | | ✓[h] | ✓[h] | | | | | | ✓[h] | |
| Randomisation (AZD9668/placebo) | | | | ✓ | | | | | | |
| Waking sputum sample [i,j] | | ✓[c] | ✓[c] | ✓[c] | | | ✓[c] | ✓[c] | ✓[c] | |
| 2 hr sputum collection [i,j] | | ✓ | ✓ | ✓[c] | | | ✓[c] | ✓[c] | ✓[c] | |
| 1 to 2 hr post-dose sputum sample [j] | | | | | | | | | ✓ | |

**Table 3 Table of study assessments**

| **Study Visit** | **1** | **1a** | **1b** | **2** | **2a** | **3** | **3a** | **3b** | **4** | **5** [l] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Timing** | Day -21 to Day -8 | Within 7 days of Visit 2 [a] | Within 7 days of Visit 2 [a] | Day 1 | Day 7 (±2 days) | Day 14 (±2 days) | Within 7 days of Visit 4 [a] | Within 7 days of Visit 4 [a] | Day 28 (±2 days) | 7 days (±2 days) after Visit 4 |
| **Detail** | **Enrolment** | **Sputum/ Urine** | **Sputum/ Urine** | **Start of treatment** | **Interim visit** | **Interim visit** | **Sputum** | **Sputum** | **End of treatment** | **Follow up visit** |
| Quantitative sputum culture | | | | ✓ [m] | | | | | | ✓ |
| AZD9668 PK sample (blood) | | | | ✓ [e] | | | | | ✓ [e] | |
| Blood sampling for pharmacodynamic markers [k] | | | | ✓ [c] | | | | | ✓ [c] | |
| St George's Respiratory Questionnaire | | | | ✓ | | | | | ✓ | |

[a] Visit 1a should occur at least 24 hours before Visit 1b.
[b] The informed consent should be signed before any study-related procedures, restrictions or screening assessments are performed.
[c] Pre-dose
[d] To include measurement of FSH (menopausal status) and hCG (pregnancy test) in serum for female patients at Visit 1.
[e] Pre-dose and 1-2 hours post dose .
[f] Issued at Visit 1 and patient should be instructed to bring it to each clinic visit, for review by site staff. The diary card should be completed daily until termination from the study.
[g] Sample should be taken any point after randomisation.
[h] Patients should be instructed to start 24 hour collection on rising the day before their scheduled visit. They should collect all sputum/urine for the 24 hour period leading to either Visit 1a **or** Visit 1b and Visit 4.
[i] After collecting the waking sputum sample in one pot, patients should collect another sample (of at least 1 to 2 g sputum) in another pot, over a maximum of 2 hours. Immediately after finishing collection of the 2 hour sample, all sputum samples should be taken directly to the clinic or dispatched directly to the local sputum processing lab (dependent on the clinic appointment time and/or patient's preference).
[j] Details of all analytes measured in these spontaneous sputum samples can be found in Table 4 .

[k] Plasma and serum samples will be collected. See Section 7.6.2.
[l] If the patient discontinues after randomisation they should be asked to attend for Visit 5.
[m] The aliquot for the quantitative sputum culture will be taken from the waking sample at Visit 2.

**Table 4 Spontaneous sputum sample summary**

| Timing of sample<br><br>Analysis | Visit 1 | Visit 1a | Visit 1b | Visit 2 (pre dose) | Visit 2a | Visit 3 | Visit 3a | Visit 3b | Visit 4 (pre dose) | Visit 4 (1-2 hours post dose) | Visit 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Cytospin production | | ✓[b] | ✓[b] | ✓[b] | | | ✓[b] | ✓[b] | ✓[b] | ✓ | |
| AZD9668 sputum concentration | | | | ✓[b] | | | | | ✓[b] | ✓ | |
| Aliquots for pharmacodynamic marker (including inflammatory and mucus hyper-secretion markers) | | ✓[b] | ✓[b] | ✓[b] | | | ✓[b] | ✓[b] | ✓[b] | ✓[a] | |
| Quantitative sputum culture | | | | ✓[c] | | | | | | | ✓[c] |

[a] Aliquot for NE activity only
[b] Waking sputum sample and 2 hour sputum collection
[c] Waking sample only

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

The rationale for conducting this study in patients with bronchiectasis and the rationale for dosing up to 28 days are given in Section 2.3. A parallel group rather than a cross over design is considered more appropriate, as the possible duration of effect is uncertain and therefore a carry-over cannot be completely eliminated. The rationale for dose selection is given below.

The first-in-man, two-part, single and multiple ascending dose (SAD and MAD) study of AZD9668 in healthy volunteers (D0520C00001) is now complete and the reporting phase is underway. In the SAD part of the study the doses that have been safely administered were 2, 10, 30, 60, 120 and 150 mg. Dose escalation was stopped because the exposure limits set by the internal AstraZeneca Human Exposure Limits Committee (HELC) were reached. These limits (i.e. $AUC_{(0-24h)}$ and $C_{max}$ of 18 μM.h and 2.5 μM, respectively) were set following a review of the data obtained in the 1-month toxicology studies in the rat and dog and have been based upon the exposures at the no observed adverse effect level (NOAEL) in rat (370 mg/kg), corrected for the differences in plasma protein binding between the species. The NOAEL in the rat has been used because the free exposures at this dose are lower than those obtained in the dog at the no observed effect level (NOEL) dose. In the MAD part of the study the doses that have been safely administered were 30, 70 and 120 mg once a day for a total of 8 days.

Following single dose administration of AZD9668 (2 - 150 mg) absorption was rapid, median $t_{max}$ ranged from 1 to 2 hours. The geometric mean CL/F ranged from 15.4 to 21.6 L/h and the geometric mean $V_z/F$ ranged from 157 to 334 L. The geometric mean terminal half-life of AZD9668 ranged from 5.04 to 14.99 h. The CL/F, $V_z/F$ and $t_{1/2}$ appeared to be independent of dose. The exposure ($C_{max}$ and AUC) increased proportionally with dose between doses of 10 mg and 150 mg.

AZD9668 is renally eliminated and renal clearance ($CL_R$) and the percentage of the dose excreted as unchanged AZD9668 in the urine over 48 h ($F_{e(0-48)}$ (%)) appeared to be independent of dose. The geometric mean $CL_R$ ranged from 5.83 L/h to 6.98 L/h, and the range of the geometric mean $F_{e(0-48)}$ (%) was 31.6% to 40.0%.

Following multiple dose administration of AZD9668 (30 mg, 70 mg and 120 mg, once a day for 8 days), absorption was similar following single and multiple dosing; the median $t_{max}$ and $t_{max,ss}$ was 1 hour for all dose groups. The geometric mean $CL/F_{,ss}$ was 14.7, 14.8 and 19.4 L/h and the geometric mean $V_z/F_{,ss}$ was 191L, 218 and 245L, respectively. The geometric mean $t_{1/2,ss}$ was 9.04 hours, 10.24 hours and 8.73 hours, respectively, and there was no evidence for time or dose dependent change in PK. There was no evidence of accumulation upon multiple dosing to steady state.

AZD9668 is renally eliminated and renal clearance at steady state ($CL_{R,ss}$) and the percentage of the dose excreted as unchanged AZD9668 in the urine at steady state over 48 hours ($F_{e\,(0-48),ss}$ (% dose)) appeared to be independent of dose. The geometric mean $CL_{R,ss}$ was 5.29 L/h, 5.70 L/h and 5.83 L/h, and the geometric mean $F_{e(0-48),ss}$ (% dose) was 38.8%, 40.9% and 31.6%, respectively.

Administration of AZD9668 after consumption of a high fat meal resulted in a reduction in the rate of absorption (median $t_{max}$ was 4 h, 3 h and 4 h for 30 mg, 70 mg and 120 mg, respectively). The $C_{max}$ was reduced by 22 %, 31 % and 22 % and the $AUC_{(0\text{-}24h)}$ was slightly reduced, by 8%, 5% and 5% for 30 mg, 70 mg and 120 mg, respectively. Thus consumption of the food reduced the rate but had relatively little effect on the overall extent of absorption.

A population PK model of the PK data from the SAD and MAD study has been developed and was used to estimate the mean population PK parameters of AZD9668 with the associated variability and to assess the affect of consumption of a high fat breakfast on the PK of AZD9668. A dose of 60 mg twice a day has been selected as the dose for the current study. This dose has been chosen as a dose that is predicted to achieve trough steady state therapeutic plasma concentrations of 19 nM (predicted from an in vivo mouse acute lung injury model) in all patients, whilst ensuring that the predicted geometric mean $C_{max,ss}$ and $AUC_{(0\text{-}24h),ss}$ are below the HELC limits. The estimated margins to the HELC limits in the fasted state are 2.6 and 1.4 for $C_{max,ss}$ and $AUC_{(0\text{-}24h),ss}$, respectively.

From the population PK modelling it was identified that the bioavailability of AZD9668 was approximately 90% of that when it was administered in the fasted state. This did not however have any impact upon the dose selection for the subsequent studies therefore it is not necessary for the patients to restrict food around administration of their doses.

All doses will be administered with approximately 100 mL water. There is no requirement to restrict food consumption before or immediately after administration of AZD9668 except for the morning dose on Days 1 and 28 (Visits 2 and 4, respectively) where an ECG is being performed around $t_{max}$.

Rationale for the optional pharmacogenetics component of the study is included in Appendix D.

# 5. PATIENT SELECTION CRITERIA

Patient population should be selected without bias.

Investigator(s) must keep a record of patients who entered pre-trial screening but were never enrolled eg, patient screening log. Each patient must 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.

## 5.1 Inclusion criteria

For inclusion in the study patients must fulfil the following criteria.

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

2. Male, or female of non-child bearing potential (defined as amenorrhoeic for 12 months and follicle stimulating hormone (FSH) plasma concentration within the post-menopausal range as defined by the laboratory) or surgically sterile (defined as having undergone bilateral oophrectomy and/or hysterectomy; tubal ligation on its own is not adequate), between 18 and 80 years

3. Have a clinical diagnosis of idiopathic or post infective bronchiectasis as diagnosed with a historical high resolution computerised tomography (HRCT) or bronchogram

4. Be sputum producers with a history of chronic expectoration on most days of most weeks of the year. Patients should have a history of spontaneously producing an average of 3 ml or more sputum on a daily basis and should be able to provide at least 2 of the 3 required baseline sputum samples

5. Have normal laboratory values at Visit 1, unless the investigator considers an abnormality to be clinically irrelevant

## 5.2 Exclusion criteria

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

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

2. Previous randomization of treatment in the present study

3. 'Participation (defined as administration of at least one dose of investigational product) in another clinical study within 12 weeks of Visit 1.

4. Bronchiectasis associated with a generalised immunodeficiency disorder, where manifestations other than bronchiectasis predominate

5. Concomitant diagnosis of significant pulmonary disease other than bronchiectasis or COPD, including symptomatic asthma and allergic bronchopulmonary aspergillosis

6. An $FEV_1$ of <30% of predicted normal at Visit 1

7. Any ECG abnormalityat Visit 1 (including a QTc interval of >450 msec for males and >470 msec for females, or any arrhythmia) which in the opinion of the investigator may put the patient at risk or interfere with study assessments.

8. An acute exacerbation (defined as an increase in respiratory symptoms requiring hospitalisation and/or a course of oral glucocorticosteroids and/or antibiotics, either prescribed or self administered); or acute respiratory infection (upper or lower) requiring oral steroids or antibiotics in the 6 weeks prior to Visit 2

9. Other acute infections requiring treatment in the 4 weeks prior to Visit 2

10. Use of prohibited medications as detailed in Section 6.5

11. A past history of or current clinical or laboratory evidence of renal disease, or a calculated creatinine clearance (Cockcroft-Gault formula) of ≤70 ml/min at Visit 1

12. Any other clinical disease or disorder (including insulin dependent diabetes) 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. History of excessive alcohol consumption or chronic alcohol induced disease

14. Donation of >1350 mL of blood in the 12 months or 500 mL of blood in the 3 months before the end of the study

15. Suspected or known risk of the patient transmitting HIV, Hepatitis B or C

16. Scheduled in patient surgery or hospitalisation during the course of the study

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

## 5.3 Procedures for handling incorrectly included patients

**Patients that do not meet the inclusion/exclusion criteria for a study should not, under any circumstances, be enrolled into the study – there can be no exceptions to this rule**.

Where patients that do not meet the study criteria are enrolled in error, incorrectly randomised, or where patients subsequently fail to meet the criteria for the study post enrolment, the procedures included in the protocol for the discontinuation of such patients must be followed. These procedures must be included in the protocol and must take into consideration ethical and safety factors and how these patients will be treated in the analyses.

Once the error is identified a discussion must occur between the AZ Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from the study. The AZ Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their randomised therapy stopped and be discontinued from the study.

## 5.4 Withdrawal of patients

### 5.4.1 Criteria for discontinuation from the study

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient are:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Risk to patients as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrectly enrolled patients
- Patient lost to follow-up
- Non-compliance to study medication (compliance rate of ≤80% following drug accountability at Visit 3)
- Change in QTc >60 msec from baseline value or QTc >500 msec, confirmed by repeat ECG
- Withdrawal of informed consent to the use of biological samples **collected as an integral part of the study**, see Section 8.5
- An ALT / AST level ≥ 3xULN (confirmed on repeat sample) or any pattern of liver function test (LFT) abnormalities giving Investigator or AZ cause for concern
- Evidence of haemolysis as evidenced by the following:

  – Reticulocyte count of over 5%, **and**

  At least two of the following:

  – a drop in haemoglobin below 10.5 g/dL

  – decrease of 25% in haptoglobin. (The value post-dose to be compared with the average of two pre-dose values. The value should also be 15% below LLN).

  – increase of 25% in unconjugated bilirubin or lactate dehydrogenase (LDH). (The value post-dose to be compared with the average of two pre-dose values. The value should also be 15% above ULN).

- A platelet count of below 80 x $10^9$/L confirmed by a repeat test (in the absence of obvious platelet clumping in a peripheral blood film).

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

- Withdrawal of consent for genetics research. A patient may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study described in this protocol. Voluntary discontinuation by the patient will not prejudice further treatment.

### 5.4.2 Procedures for discontinuation of a patient from the study

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 7.3.3 and 7.3.4*);* diary cards and study drug should be returned by the patient.

If a patient discontinues they should be asked to attend the follow up visit (Visit 5).

# 6. STUDY CONDUCT

## 6.1 Restrictions during the study

1. Use of disallowed concomitant medication (refer to Section 6.5).

2. Patients should not donate blood at any time during the study or for 3 months following completion of the study

3. Patients should fast from the midnight (00:00) prior to dosing until 2 hours post-dose on clinic days where ECGs are being performed, ie, Days 1 (Visit 2) and 28 (Visit 4). Water is allowed up to 1 hour before drug administration and will be allowed from 2 hours after drug administration.

4. Patients should abstain from taking part in any other study, whilst participating in this study.

5. Male patients should abstain from unprotected sex and sperm donation from date of consent until 3 months after last dosing. Recommended contraception will be double barrier method, ie, condom and in addition, the female partner to use a reliable contraceptive method, or they must refrain from sexual intercourse for the same time period.

6. There is no evidence from clinical experience to date that AZD9668 is capable of inducing photosensitivity. However until further studies are concluded, patients should be advised not to sunbathe or use sunbeds or U-V lamps, and to limit exposure to sunlight as much as practicable during dosing and for 1 week after last dose of study medication.

## 6.2 Patient enrolment and randomization

The principal investigator 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, beginning with "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 5.1 and 5.2

4. Assign eligible patient unique randomization code (patient number), beginning with "001".

Randomisation codes will be computer generated by AstraZeneca R&D using the AstraZeneca Global Randomisation System (GRand). Patients who are withdrawn for any reason other than adverse events will be replaced as the aim is to achieve 40 evaluable patients. Randomization numbers should not be re-used.

Randomization codes will be assigned strictly sequentially as patients are eligible for randomization (Visit 2).

If a patient discontinues participation in the study, then his/her enrolment/randomization code cannot be reused.

If patients have discontinued after randomisation into the study then they cannot re-enter into the study.

### 6.2.1 Procedures for randomization

Biostatistics will be responsible for producing the randomisation code in GRand. There will be no formal stratification.

## 6.3 Blinding and procedures for unblinding the study

### 6.3.1 Methods for ensuring blinding

AZD9668 will be provided as a tablet for oral administration and with a matching placebo. Tablets of AZD9668 will be provided in the strength of 30 mg.

### 6.3.2 Methods for unblinding the study

Code break envelopes will be sent to site with drug supplies.

Individual treatment codes, indicating the treatment randomization for each randomised patient, will be available to the investigator(s) or pharmacists at the study centre.

A copy of the randomisation scheme will also be made available to the analyst of AZD9668 in sputum and the PK plasma analyst, 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.

A copy of the treatment codes will also be supplied to the Scottish poisons bureau (for use in the event of an out of hours medical emergency in the UK) and the Canadian patient safety group (for use in the event of an out of hours medical emergency in Canada).

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. If the treatment code is broken then the investigator(s) must document and report to AstraZeneca.

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.

There is no planned interim analysis.

## 6.4 Treatments

### 6.4.1 Identity of investigational product(s)

**Table 5 Identity of investigational products**

| Investigational product | Dosage form and strength | Manufacturer | Formulation number * |
|---|---|---|---|
| AZD9668 | Tablet 30 mg | AstraZeneca R&D, [redacted] | 1756 / H 2029-01-01 |
| Placebo AZD9668 | Tablet | AstraZeneca R&D, [redacted] | P1756 / H 2030-01-01 |

* The batch number will be detailed in the CSR (Clinical Study Report)

The composition of the tablets is 30 mg AZD9668 (corresponding to 39.5 mg AZD9668 tosylate).

Excipients: cellulose microcrystalline, calcium hydrogen phosphate dihydrate, crospovidone, sodium laurilsulfate, sodium stearyl fumarate.

The drug product consists of white to off white, plain oblong, biconvex tablet. The nominal tablet weight is 400 mg.

Placebo tablets to match AZD9668 tablets contain the following excipients: cellulose microcrystalline and sodium stearyl fumarate.

Tablets will be supplied (at Visit 2 then again at Visit 3) in bottles containing 72 tablets, which is sufficient for 14 days+/-2 days dosing b.i.d plus overage.

### 6.4.2 Doses and treatment regimens

Patients will be advised to fast from midnight (00:00) prior to Visit 2 (Day 1) where they will be randomised to receive either AZD9668 tablets 60 mg or placebo tablets (using a 1:1 randomisation scheme) orally twice daily for 28 days (±2 days). The first dose will be administered, with 100mL water, in the clinic in the morning of Day 1.

The patients will be issued with sufficient tablets to allow self-dosing until Visit 3.

At Visit 3 (Day 14 ±2 days) patients will attend the clinic in the morning. There is no requirement to withhold their morning dose.

The patients will be issued with sufficient tablets to allow self-dosing until Visit 4.

At Visit 4 (Day 28 ±2 days) patients will be advised to fast from midnight (00:00) and attend the clinic in the morning, having withheld taking their dose of study medication for that day. Patients will take their last dose(s) of study medication in the clinic with 100mL water. There will only be one dose administered on this final day.

There is no requirement for the patients to fast around dosing at any other point during the study.

### 6.4.3 Additional study drug

No additional study drug will be provided for this study.

### 6.4.4 Labelling

The packaging and labelling will be performed by [redacted] All supplies and labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

The labels will fulfil GMP Annex 13 requirements for labelling.

The bottles will be labelled with a two-panel label. One part of the label will be permanently affixed to the bottle and the other part will be a peel-off part for insertion into the CRF at the time of administration.

The boxes, containing 2 bottles, will be labelled with a single-panel label without tear-off part.

The label will include at least the following information:

- Name of sponsor (AstraZeneca)
- Study drug(s) dosage form, route of administration and quantity of dosage units

- Study code
- Enrolment code or Randomisation code
- Directions for use
- Expires end
- For clinical trial use only
- Keep out of the reach of children

### 6.4.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. The investigational product label on the bottle and boxes of study drug specifies the appropriate storage requirements.

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

Patients are allowed to continue long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), LABA/ICS (inhaled corticosteroids) combinations unchanged throughout the study if they are already on these.

They would only need to withhold LAMA/LABA for 12 hours, short-acting beta agonists (SABA) for 6 hours and short acting muscarinic antagonists (SAMA) for 8 hours before their pulmonary function tests. After they have had the test they could take their normal dose of the medication.

In addition, the following treatments are not allowed:

- Use of oral corticosteroids in the 8 weeks prior to Visit 2 and throughout the study (N.B. use of inhaled corticosteroids is allowed)
- Use of non-prophylactic antibiotics, systemic or nebuliser, in the 4 weeks prior to Visit 2 and throughout the study (N.B. prophylactic use is allowed)
- Treatment with immunomodulatory agents within 8 weeks prior to Visit 2 and throughout the study

As AZD9668 is a CYP2C9 inhibitor, the following drugs which are CYP2C9 substrates, will not be allowed throughout the dosing period (ie, Visit 2 - 4):

- Anti-diabetics/hypoglycaemics
- Anti epileptics/anticonvulsives
- Warfarin

- Fluvastatin
- Celecoxib
- High dose, continuous NSAIDs; documented PRN use is allowed. Ibuprofen is permitted only at low to medium doses (<20 mg/kg/day)
- Torsemide
- Amitryptiline
- Fluoxetine

Any other drugs including inhaled and oral respiratory drugs could be allowed provided their doses have been stable for at least 4 weeks before enrolment and the doses remain unchanged throughout the study. SABA and/or SAMA may be taken as needed for symptomatic control of breathlessness.

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

Please refer to 6.1 for other restrictions during the study.

## 6.6 Treatment compliance

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the Case Report Forms.

Drug accountability will be performed at Visits 3 and 4 to assess compliance. Compliance of ≤80% will be considered unacceptable.

### 6.6.1 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 drugs dispensed and returned.

Site personnel will account for all unused drugs and for appropriate destruction. Certificates of delivery, destruction and return must be signed.

# 7. COLLECTION OF STUDY VARIABLES

## 7.1 Recording of data

The investigator will ensure that all data collected in the study are provided to AstraZeneca. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the paper Case Report Form and according to any instructions provided.

Patients will be asked to complete their Bronkotest © diary card on a daily basis, and will be required to bring it along to each scheduled clinic study visit where study staff at site will review it for completeness and provide feedback and guidance on it's completion where necessary.

## 7.2 Screening and demography procedures

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.

Patients should have provided signed informed consent prior to any study procedure or restriction being applied.

At Visit 1, patients will be screened and evaluated for eligibility to enter the study. The following assessments will be performed, with data being captured in the pCRF:

- Demography (Date of birth, sex, race)
- Vital signs (Blood pressure and pulse)
- Height and weight
- Surgical and medical history (including nicotine and alcohol use)
- Physical examination
- Concomitant medications
- Safety blood samples (Haematology and Clinical Chemistry) and a mid stream urine sample for urinalysis
- FSH and hCG measurement will be included in the Visit 1 safety analysis for female patients
- A 12 lead ECG
- Lung function tests ($FEV_1$, SVC, FVC, FEF25-75)

Patients will also be provided with their Bronkotest © diary card and instructed on how to complete it.

### 7.2.1 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 5). The following assessments will be performed and recorded in the pCRF at this visit:

- Physical examination

- Safety blood samples (Haematology and Clinical Chemistry) and a mid stream urine sample for urinalysis
- Lung function tests ($FEV_1$, SVC, FVC, FEF25-75)
- Vital signs (Blood pressure and pulse)
- A 12 lead ECG
- Concomitant medications
- Adverse event questioning

In addition, the patients will return their completed Bronkotest © diary card and their spontaneous sputum collection for quantative bacterial culture as detailed in Section 7.3.9.1.

## 7.3 Safety

It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

### 7.3.1 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

### 7.3.2 Definitions of serious adverse event

A serious adverse event 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 reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and is reported in an expedited manner. Any organism, virus or infectious particle (for example prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

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

### 7.3.3 Recording of adverse events

Adverse Events will be collected from enrolment (Visit 1) throughout the treatment period and including the follow-up period (up to Visit 5).

**Variables**

The following variables will be recorded in the CRF for each AE; description of the AE, the date and time (if available) when the AE started and stopped, intensity, whether the AE is serious or not, causality rating (yes or no), action taken with regard to investigational product, AE caused patient to discontinue study and outcome.

- 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)

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 7.3.2. 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.

The Investigator will assess causal relationship between Investigational Product and Adverse Events, 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.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect will be classified as no reasonable possibility.

For SAEs causal relationship will also be assessed for other medication and/or study procedure. 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 or reported in response to the open question from the study personnel: *"Have you had any health problems since the last time you were asked"*, or revealed by observation will be collected and recorded in the CRF. 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.

The investigator should review the diary card information to assess if any data constitutes an adverse event (see definition in Section 7.3.1) and should be recorded in the pCRF.

**Adverse Events based on examinations and tests**

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. 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.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

**Follow-up of unresolved adverse events**

Any AEs 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 CRF. 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.

### 7.3.4 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). All SAEs will be recorded in the CRF. SAEs will be recorded from the time of informed consent.

The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

For studies in countries implementing the EU Clinical Trials Directive, informing Ethics Committees and Regulatory Authorities will be performed by AstraZeneca. If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it.

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 appropriate AstraZeneca representatives of any follow-up information on a previously reported SAE immediately but no later than the end of the next **business day** of when he or she becomes aware of it.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

If the Clinical Study Serious Adverse Event Report Form is used, then the Investigators or other site personnel fax on the same day the completed form and any other relevant supporting documentation (eg, ECG, laboratory results, autopsy report) and relevant CRF modules to the AstraZeneca representative.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the appropriate AstraZeneca clinical drug safety data entry site within **one business day** for fatal and life threatening events and within **five calendar** days for other SAEs. If the report arrives late in the day, it can be sent the following morning. If the report arrives during a weekend or public holiday, the information is forwarded as early as possible on the first business day following the weekend or holiday. The clock start date is then the next business day.

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

### 7.3.5 Laboratory safety assessment

The laboratory parameters to be collected at the scheduled clinic visits are outlined in Table 6.

Blood samples will be analysed at a central laboratory.

Urinalysis will be performed locally at the study site.

The central laboratory will provide all the materials required for blood and urine sampling. Instructions for labeling, storage and shipping will be detailed in the laboratory manual. The central laboratory will also provide up to date reference ranges throughout the study for the management of patient safety.

Clinically relevant deviations from the reference range in the lab values will be handled as outlined in Section 7.3.3.

For blood volumes see Section 8.1.

**Table 6 Laboratory Parameters**

| Haematology (Blood) | Clinical Chemistry (Serum) | Urinalysis (Urine) |
|---|---|---|
| Haemoglobin | Creatinine | Protein |
| Erythrocyte count | Total bilirubin [d] | Glucose |
| Haematocrit | Alkaline phosphatase | Haemoglobin |
| Mean Cell Volume (MCV) | Aspartate aminotransferase (AST) | |
| Mean Cell Haemoglobin (MCH) | Alanine aminotransferase (ALT) | |
| Mean Cell Haemoglobin Concentration (MCHC) | Albumin | |
| Platelet count | Potassium | |
| Leucocyte count (absolute and percentage including Neutrophil, lymphocyte, monocyte, eosinophil and basophil counts) | Calcium, total | |
| Reticulocyte count | Sodium | |
| | Cholesterol | |
| | Triglycerides | |
| | Urea | |
| | Gamma Glutamyltransferase (GGT) | |
| | Creatinine phosphokinase (CPK) [a] | |
| | Lactate dehydrogenase (LDH) | |
| | Glucose | |
| | Free thyroxine (T4) [b] | |
| | Thyroid stimulating hormone (TSH) [b] | |
| | Haptoglobin | |
| | Follicle stimulating hormone (FSH) [c] | |
| | hCG [c] | |

[a] If elevated, S-CPK-MB will be analysed (will not be databased)
[b] Included at Visit 1 only
[c] Included at Visit 1 for female patients only
[d] If elevated, unconjugated bilirubin will be analysed (will not be databased)

### 7.3.6 Physical examination

As detailed in Table 3, a physical examination will be performed at both Visit 1 and 5 by a medically qualified person.

### 7.3.7 ECG

At Visits 1, 2, 3, 4 and 5, a resting 12 lead ECG will be performed as detailed in Table 3. The ECG will be performed at site according to local procedure.

ECGs will be recorded in the supine position after the patient has rested for 10 minutes. Only overall evaluation by the investigator will be captured in the pCRF. Any abnormalities (including QTc values) should be reviewed by a cardiologist or appropriately qualified physician.

### 7.3.8 Vital signs

Vital signs (pulse and blood pressure) will be measured at Visits 1, 2, 3, 4 and 5 as detailed in Table 3. After a 5 minute rest in the sitting position, pulse and blood pressure will recorded using non invasive equipment.

### 7.3.9 Other safety assessments

#### 7.3.9.1 Sputum culture

At Visit 5, patients will be asked to bring their first sputum collection of the morning to the clinic to be sent for quantitative bacterial sputum culture (performed locally). At Visit 2, an aliquot will be taken out of the waking sample for quantitative bacterial culture.

## 7.4 Efficacy

The efficacy variables for this study are detailed in the sections below and include some patient reported outcomes (PRO).

### 7.4.1 Efficacy Variables

#### 7.4.1.1 Differential cell count in sputum

Patients will be provided with appropriately labelled pots and instructions to collect spontaneous sputum samples at Visits 1a, 1b, 2, 3a, 3b and 4. On each of these visit days, patients will collect a sputum sample on waking, in one pot. Another sample (of at least 1-2g sputum) should be collected in another pot, over a maximum of 2 hrs. Immediately after finishing collection of the 2 hr sample, all sputum samples should be taken directly to the clinic or dispatched directly to the local sputum processing lab (dependent on the clinic appointment time and/or patient's preference). In addition, patients will be asked to produce a spontaneous sputum sample post-dose (1 to 2 hours) at Visit 4 in the clinic.

The sputum will be processed locally according to the process detailed in the laboratory manual and will result in the production of cytospin slides and aliquots of sputum supernatant. Details of the aliquots of sputum supernatant are covered under pharmacodynamic variables

(Section 7.6.1) and the sputum cytospins will be used to determine the cell count and differential. N.B. Absolute and percentage neutrophil cell count will be determined and the other differential counts will be reported for completeness.

These cytospins will be produced locally before being shipped to the analysis lab, to have a differential cell count performed. Details of analysis laboratory, shipping and sample handling can be found in the laboratory manual.

Please refer to Table 3 for further detail around sampling times.

#### 7.4.1.2 24 hour sputum weight

Patients will be provided with appropriately labelled collection pots at Visit 1 and 3, to enable them to collect all sputum produced during a 24 hour period at Visit 1a or 1b and Visit 4.

Patients should be instructed to collect the sputum from the morning prior to the scheduled visit for a full 24 hour period. This complete collection will be sent, or brought to site (as agreed, in advance, with staff and patient), weighed by the site staff and the weight recorded in the pCRF.

#### 7.4.1.3 Lung function tests

Lung function tests will be performed at the clinic at Visits 1, 2, 4 and 5. Where these occur on dosing visits ie, Visits 2 and 4, they should be performed pre-dose.

The tests being performed are Slow Vital Capacity (SVC), Forced Expiratory Volume in 1 second ($FEV_1$), Forced Vital Capacity (FVC) and forced expiratory flow between 25 and 75% of forced vital capacity (FEF25-75).

The assessments should be performed prior to the administration of any bronchodilators (refer to Section 6.5) and should be performed with the patient in an upright, seated position, having rested for 15 minutes. At each visit SVC should be measured first.

A record of the measurements must be made in the patient's notes and results recorded in the pCRF. All printouts should be marked with date and enrolment or patient number. Measurements should be performed according to Miller et al 2005. In general:

- An electronic spirometer or a whole body plethysmograph 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

- 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 the 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

### 7.4.2 Patient reported outcomes (PRO)

The methods for collecting patient reported outcomes (PRO) data are outlined below.

#### 7.4.2.1 Bronkotest© diary card

The Bronkotest © diary card is a paper based diary card which will be given to the patients on entry into the study at Visit 1. Study site staff should provide a clear overview and guidance for the satisfactory completion of the diary card. The diary card will be completed on a daily basis by the patients at home and they should be instructed to bring it into each clinic visit. As a minimum, at Visits 2, 3, 4 and 5, the site staff should photocopy the pages that have been completed since last visit, review the diary and feedback any issues with unsatisfactory or ambiguous completion. The Investigator should review the content of the diary card and ensure that any information regarding adverse events and medications are subsequently reflected in the pCRF. Missing values should not be completed by study site staff at the visit.

**Diary Card**

The Bronkotest© diary card is used to collect the patients assessment of their condition. On a daily basis the patients will be asked to record their Peak Expiratory Flow (PEF) (morning and evening) and answer the following questions:

**Table 7 Bronkotest © Diary Card variables**

| Question | Answer | Databased? |
|---|---|---|
| Describe your breathing | 1 – Better than usual<br>2 – Normal/Usual<br>3 – Worse than usual<br>4 – Much worse than usual | Yes |
| What colour is your sputum ? | Choose a number from 0-8 from sputum colour chart attached to Bronkotest © diary card | Yes |

**Table 7 Bronkotest © Diary Card variables**

| Question | Answer | Databased? |
|---|---|---|
| The amount of sputum you produced | 0 – None<br>1 – Some (up to a teaspoonful)<br>2 – A little (tablespoonful)<br>3 – Moderate (egg-cupful or more)<br>4 – A lot (cupful or more) | Yes |
| Type of sputum? | 1 – Watery<br>2 – Sticky Liquid<br>3 – Semi-Solid<br>4 – Solid | Yes |
| How do you feel? | 1 – Better than usual<br>2 – Normal/Usual<br>3 – Worse than usual<br>4 – Much worse than usual | Yes |
| How often do you cough? | 0 – Rarely<br>1 – Occasionally<br>2 – Frequently<br>3 – Persistently | Yes |
| Do you have chest pain? | Tick for yes | Yes |
| Do you have cold or flu? | Tick for yes | Yes |
| How much of your reliever medication have you taken today? (Enter number of puffs of inhalers, number of times of nebuliser use or number of tablets) | Free text field for a number to be inserted | Yes |
| Have you taken antibiotics/ steroid tablets today? | Tick for yes | Yes |
| Score the symptoms you have felt last night | 0 – Slept well<br>1 – Woke once because of chest symptoms<br>2 – Woke twice because of chest symptoms<br>3 – Woke more than twice because of chest symptoms<br>4 – Unable to sleep because of symptoms | Yes |
| Peak Flow (morning) | Record value from peak flow meter | Yes |
| Peak Flow (evening) | Record value from peak flow meter | Yes |
| Regular treatment | Drug name and strength; Dose | No |

**Table 7 Bronkotest © Diary Card variables**

| Question | Answer | Databased? |
|---|---|---|
| New medication | Date; Drug name and strength; Dose; Reason | No |
| New antibiotics | Date; Drug name and strength; Dose; Reason | No |
| Symptoms of cold/flu | Tick if symptom is present; Date symptom started; Date symptom resolved | No |
| Additional comments | Free text field | No |

The majority of the data will be databased, however, medication, cold and flu symptoms and any additional comments (see Table 7) will not be databased directly but will transferred into the relevant pCRF modules by the Investigator.

**Administration of PRO questionnaires**

The Bronkotest © diary card is paper based and answers should be completed daily, by hand, by the patient at home.

#### 7.4.2.2 St George's Respiratory Questionnaire (SGRQ-C)

The St George's Respiratory Questionnaire (SGRQ-C) will be completed by patients at Visits 2 and 4 (as outlined in Table 3). The questionnaire takes approximately 10 minutes to answer the questions.

**Questionnaire**

The St George's Respiratory Questionnaire (SGRQ) has been developed to measure the impact of respiratory disease on health status. The SGRQ-C is a shorter version of the SGRQ specially adapated for COPD (Meguro et al 2007). The SGRQ-C contains 3 domains: Symptoms (distress due to respiratory symptoms), Activity (disturbance of physical activity) and Impacts (overall impact on daily life and well being). The UK English version is attached in Appendix E, and is the version translated into other local languages as required.

**Administration of PRO questionnaires**

The SGRQ-C is paper based and answers should be completed, by hand, by the patient at the relevant clinic visits (refer to Table 3).

## 7.5 Pharmacokinetics

### 7.5.1 Collection of biological samples

Blood samples (3 mL K2EDTA) for determination of AZD9668 in plasma will be taken at the times presented in the study plan Table 3

Sputum supernatant aliquots for determination of AZD9668 in sputum will be taken at the times presented in Table 3.

Samples will be collected, handled, labelled, stored and shipped as detailed in the laboratory manual. The date and time of collection will be recorded.

Samples should be stored at -18°C or below and analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported. The methods used will be referred to in the clinical study report.

Samples will be disposed of within one month after the clinical study report has been finalised.

Full details can be found in the laboratory manual. For blood volume see Section 8.1.

### 7.5.2 Determination of drug concentration in biological samples

Samples for determination of AZD9668 in plasma will be analysed by [redacted] on behalf of [redacted], AstraZeneca, using a validated method of liquid chromatography and mass-spectrometry (LC-MS/MS) after protein precipitation. The lower limit of quantification (LLOQ) of AZD9668 in plasma will be 1.00 nM.

Measurement of AZD9668 concentrations in sputum will be analysed by [redacted], AstraZeneca R&D [redacted]. An investigation of the AZD9668 concentrations in sputum will be conducted using a method of liquid chromatography and mass spectometry (LC-MS/MS) based on that validated for human plasma. The AZD9668 sputum analysis method will not be formally validated, but will be supported by investigations into the stability of AZD9668 in this matrix and each batch of samples will include quality control samples to demonstrate the performance of the method.

## 7.6 Pharmacodynamics

For blood volume see Section 8.1.

### 7.6.1 Sputum inflammatory markers

The spontaneous sample produced by the patient will be processed locally and full details of the processing method can be found in the laboratory manual. The supernatant aliquots produced will be used for the measurement of several pharmacodynamic markers in the sputum. Subject to validated assays being available the markers will include NE activity, TNF-α, IL-6, IL-1β, RANTES, MCP-1, IL-8, LTB-4.

A priority list will be provided to the analysis laboratories to clarify what to do in the event of there being insufficient sputum aliquots to perform all detailed analyses. Details of this priority list can be found in the laboratory manual.

#### 7.6.1.1 Collection of biological samples

A spontaneous sputum sample produced by the patient at the timings reflected in Table 3, will be processed locally. Samples will be sent to the local sputum processing lab within 2 hours of collection for processing. Resulting aliquots of supernatant will then be sent to the appropriate analysis laboratory.

Full details of sample handling and shipping can be found in the laboratory manual.

### 7.6.2 Blood inflammatory markers

A serum and plasma sample will be taken for assessment of inflammatory markers in blood. Subject to validated assays being available the markers in serum will be, Serum Amyloid-A and high-sensitivity CRP (hsCRP) and those in plasma will be, TNF-α, IL-8, IL-6, and IL-1β.

The absolute and percentage differential cell count will be taken from the haematology safety sample taken at the corresponding visit.

#### 7.6.2.1 Collection of biological samples

A serum and plasma sample will be taken at the timepoints illustrated in Table 3. They will be processed as outlined in the laboratory manual and sent to the appropriate laboratory for analysis. Full details of sample handling and shipping can be found in the laboratory manual.

### 7.6.3 Markers of tissue degradation

Subject to validated assays being available, markers of tissue degradation will be measured in plasma, urine and sputum. The marker in plasma and urine is desmosine and in sputum it is hydroxyproline.

#### 7.6.3.1 Collection of biological samples

An aliquot of the plasma sample taken (as detailed in Section 7.6.2) at the timepoints shown in Table 3 will be sent for desmosine analysis.

Patients will be instructed to collect all urine over a 24 hour period, as detailed in Table 3. The urine weight will be noted at clinic when the patient returns their collection and the sample will be sent for desmosine analysis (as detailed in laboratory manual).

An aliquot of sputum supernatant produced from the spontaneous sputum collection, will be used to measure hydroxyproline.

Full details of analysis laboratories, sample handling and shipment can be found in the laboratory manual.

### 7.6.4 Marker of mucus hyper-secretion

Subject to a validated method being available, the mucus hyper-secretion marker, MUC5AC will be measured in sputum supernatant at the timepoints shown in Table 4.

#### 7.6.4.1 Collection of biological samples

An aliquot of sputum supernatant produced from the spontaneous sputum collection, will be used to measure MUC5AC.

Samples will be collected, labelled, stored and shipped as detailed in laboratory manual.

## 7.7 Pharmacogenetics

### 7.7.1 Collection of samples

The blood sample for genetic research will be obtained from the patients after randomization. Samples will be collected, labelled, stored and shipped as detailed in laboratory manual. Full details of the pharmacogenetic component can be found in Appendix D.

For blood volume see Section 8.1.

## 7.8 Health economics (Not Applicable)

This is not applicable. There is no health economics component to this study.

# 8. BIOLOGICAL SAMPLING PROCEDURES

## 8.1 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 | 2.5 | 1 | 2.5 |
| | Clinical chemistry | 5.0 | 6 | 30.0 |
| | Haematology | 3.0 | 6 | 18.0 |
| Pharmacokinetic sample | | 3.0 | 4 | 12.0 |
| Plasma inflammatory marker sample | | 10.0 | 2 | 20.0 |
| Plasma inflammatory marker sample | | 3.0 | 2 | 6.0 |
| Serum inflammatory marker sample | | 3.0 | 2 | 6.0 |
| **Total** | | 29.5 | 23 | 94.5[a] |

[a] If additional Pharmacogenetics consent has been obtained, an additional 9mL sample will be drawn (See Appendix D)

## 8.2 Handling, storage and destruction of biological samples

The samples (sputum, urine, plasma and serum) will be used up or disposed after analyses (except PK samples as described in 8.2.1). Disposal will be initiated 3 months after the finalisation of the relevant final analytical report.

### 8.2.1 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 validation in incurred samples can be retained at [redacted] on behalf of [redacted], AstraZeneca for a maximum of one year following the finalisation of the Clinical Study Report. The results from the validation will not be reported in the Clinical Study Report but separately in the bioanalytical method validation report.

### 8.2.2 Pharmacogenetic samples

Full details of pharmacogenetic sample handling, coding and storage can be found in Appendix D.

## 8.3 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 Criteria (materials containing or suspected to contain infectious substances that do not meet Category A). See IATA 6.2 Regulations Guidance in Appendix C.

Any samples identified as Infectious Category A materials are not shipped and further samples taken from the patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

## 8.4 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 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.

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 AstraZeneca bio bank system during the entire life cycle.

## 8.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

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

If collection of the biological samples is a voluntary part of the study then the patient may continue in the study.

The principal investigator:

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

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

In the event that analysis/research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

# 9. ETHICAL AND REGULATORY REQUIREMENTS

## 9.1 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.

## 9.2 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.

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.

## 9.3 Ethics and regulatory review

An Ethics Committee must approve the final study protocol, including the final version of the Informed Consent Form and any other written information 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 must be given in writing. The investigator must submit the written approval to AstraZeneca before enrolment of any patient into the study.

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

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

If required by local regulations, the protocol must 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.

The distribution of any of these documents to the national regulatory authorities will be handled by AstraZeneca.

AstraZeneca will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

## 9.4 Informed consent

The principal investigator(s) at each centre will:

- Ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

- Ensure that the patients are notified that they are free to discontinue from the study at any time.

- Ensure that the patient are given the opportunity to ask questions and allowed time to consider the information provided.

- Obtain and document the patient's signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File.

- Ensure a copy of the signed Informed Consent Form is given to the patient.

- Ensure that the patient signs the optional pharmacogenetics ICF if they provide consent for the optional pharmacogenetics component of the study

## 9.5 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 appropriate a new version of the study protocol will be produced (Amended Protocol).

The amendment must be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements must be followed for amended 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 9.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee must 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.

## 9.6 Audits and inspections

Authorized 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.

# 10. STUDY MANAGEMENT BY ASTRAZENECA

## 10.1 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
- 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
- Discuss where the identification of data will be recorded eg, pCRF, medical records and other associated documents. This will be documented in a Clinical Study Agreement
- Discuss the specific requirements of the genetic research with the investigator(s) (and other personnel involved with the study).

## 10.2 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 system(s) 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).

## 10.3 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 CRFs, and that investigational product accountability checks are being performed.

- Perform source data verification (a comparison of the data in the CRFs 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/destructed 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.

### 10.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

## 10.4 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

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

## 10.5 Study timetable and end of study

The end of the entire study is defined as "the last visit of the last patient undergoing the trial".

The study is expected to start in quarter 2, 2008 and to be completed by quarter 4, 2008

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 AZD9668.

# 11. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

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

Case Report Forms will be provided for the recording of data. The forms will be 3 level NCR (no carbon required) paper. Data are to be recorded legibly onto the case report forms in black or blue ballpoint ink. Corrections should be made legibly and initialled and dated by approved personnel; the reasons for significant changes must be provided. Correction fluid or covering labels must not be used. The top original, 1st and 2nd copy of each completed form will be collected. The top original and the 1st copy will be sent to data management personnel, the 2nd copy will be retained by the monitor. The 3rd copy will be retained at the investigator site.

The method of distribution of data queries will be documented in the study Data Management Plan (DMP). The original signed data query will be returned to data management personnel. The monitor will retain one copy and the other retained at the investigator site. On receipt of the data query by data management the database will be edited appropriately. It is not planned to raise any queries on patient completed data (including Bronkotest© diary card), however, full details of how this data should be entered into AMOS will be provided in the study Data Entry Instructions.

The CRF data will be verified against any source data before the pCRFs are collected from the study site by an AstraZeneca monitor, or AstraZeneca nominated monitor. The monitor will collect the original edited pCRF pages on an ongoing basis throughout the study, and return them to the relevant Local AstraZeneca Marketing Company (MC)/Clinical Research Region (CRR) or other agreed third party.

AstraZeneca R&D [redacted] will define the set-up of the AMOS database (modules, variables and dataset structures). The Local AstraZeneca MC/CRR or agreed third party will continuously enter data during the study into the AstraZeneca Monitoring System (AMOS) database held at AstraZeneca R&D [redacted]. No transfer of data will be required, as remote AMOS (RAMOS) will be used.

Electronic data checks will be used to validate the data entered into AMOS. Any missing, impossible, inconsistent or illegible entries in the pCRF will be referred back to the investigator via the monitor using Data Query Forms (DQFs) and responses returned to the Local AstraZeneca MC/CRR or third party responsible for data processing. If needed, the database will be updated accordingly.

Relevant study data will be coded using the most current version of the MedDRA and WHO Drug dictionaries, as outlined in the DMP, by the UK Coding Group (or agreed third party). If available, the global tool, GARNET, will be used to perform SAE reconciliation on an ongoing basis throughout the study, as outlined in the DMP, otherwise an alternative process will be defined within the DMP. Laboratory data will be electronically loaded into the database on an ongoing basis.

Prior to breaking the treatment codes, all decisions on the evaluability of the data from each individual patient must have been made and documented. The Study Delivery Team at AstraZeneca R&D [redacted] will document the date of clean file and database lock.

The Data Management Plan will describe the methods used to collect, check, process and quality control clinical data in greater detail. It will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

In the case of genotypic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the pCRF and database. The genotypic data will not be merged with the clinical dataset collected from the patient population for statistical analysis.

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used 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. The results from this genetic research will be reported separately from the clinical study report for the main study

# 12. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

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

### 12.1.1 Safety variables

The following safety data will be collected: vital signs, ECG, haematology, clinical chemistry, urinalysis, sputum culture, reported adverse events. Change from baseline (Visit 2) to end of treatment will be calculated for relevant measurements.

### 12.1.2 Other significant adverse events (OAE)

During the evaluation of the 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 Drug Safety Physician, be considered OAEs and reported as such in the Clinical Study Report.

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.

## 12.2 Calculation or derivation of efficacy variable(s)

### 12.2.1 Differential cell count (absolute and percentage neutrophils)

The Sputum samples: waking sample, the 2 hour collection and the 1 to 2 hour post-dose samples will be derived and analysed separately.

The mean of the values from Visit 1a, 1b and 2 will be used as baseline for differential cell count. The change from baseline to treatment (mean of the values at Visits 3a, 3b and 4, or Visit 4 only, where appropriate) will be used as outcome variable(s). The other differential counts will be reported for completeness.

### 12.2.2 Weight of 24 hour sputum collection

The value from Visit 2 will be used as baseline. The change from baseline to end of treatment (Visit 4) will be the primary analysis.

### 12.2.3 Lung function tests

The values from Visit 2 will be used as baseline for lung function parameters. If the Visit 2 value is missing, the Visit 1 value will be used as baseline instead. The change from baseline to treatment will be used as outcome variable(s).

Change from baseline to Visit 4 will be the primary analysis.

### 12.2.4 Calculation and derivation of patient reported outcome variables

#### 12.2.4.1 Bronkotest © diary card data

Bronkotest © data will be summarised as the mean of each period: Baseline period – the mean of the last 7 days prior to start of treatment, and Treatment period - the mean of the last 7 days. The change from baseline to treatment will be used as the outcome variable.

N.B. Morning and evening PEF recordings will be calculated separately.

#### 12.2.4.2 St George's Respiratory Questionnaire (SGRQ-C)

The SGRQ-C will be summarized as 3 different domain scores (symptom, activity and impacts) and a total score given for each patient and visit. Each questionnaire response will be scored using weights according to the SGRQ-C manual. Questions not applicable for some patients will be given the weight zero. The domain scores will be calculated by dividing the summed weights by the maximum possible score for that component and expressing it as a percentage. The minimal clinically important difference (MID) has been defined as a change in score of ≥4 units in the total score and impact score. The primary outcome variable for SGRQ-C will be the change in mean total score from baseline (Visit 2) to Visit 4 (using the last available value). The domain scores will be handled in the same way.

## 12.3 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at (or under the guidance of) AstraZeneca R&D [redacted]. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined: Concentration of AZD9668 in plasma and sputum.

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

The Sputum samples: waking sample, the 2 hour collection and the 1 to 2 hour post dose samples will be derived and analysed separately.

The mean of the values, pre treatment (Visit 1a and/or Visit 1b and/or Visit 2, as applicable) will be used as baseline for inflammatory markers (blood, sputum and urine). The values recorded at the end of the treatment (Visits 3a and/or Visit 3b and/or Visit 4 as applicable) will be investigated for variability and if acceptable the change from baseline to the mean of these values will be used as the endpoint.

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

Relationship between AZD9668 sputum concentration and the effect on NE activity will be presented graphically (subject to a validated assay being available). If appropriate concentration-effect relationships will be explored.

## 12.5 Calculation or derivation of pharmacogenetic variables

Details can be found in Appendix D.

## 12.6 Calculation or derivation of health economics variables (Not Applicable)

# 13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

A comprehensive SAP will be prepared before database lock and unblinding of the data in order to avoid any potential bias due to knowledge of the treatment received.

Statistical analyses will be performed by the [redacted] AstraZeneca, using SAS® version 8.1 and, where appropriate, additional validated software. These analyses will be performed in accordance with this Statistical Analysis Plan (SAP), which will detail analyses to be performed and summaries to be produced for the Clinical Study Report (CSR).

Pharmacokinetic, pharmacodynamic and pharmacogenetic analyses will be carried out by AstraZeneca.

## 13.1 Description of analysis sets

There will be one Efficacy Analysis Set which will be used for all analysis; this set will comprise all patients randomised into the study, who have received at least one dose of study medication and have at least one piece of evaluable data. This dataset should be the same as the safety analysis set, this will be confirmed at the Blind Review.

The blinded data will be investigated further at the Blind Review and if appropriate a Per Protocol analysis set may be defined. The Per Protocol analysis set would consist of all patients in the Efficacy Analysis Set, except for those who had a major protocol deviation (as defined at the Blind Review).

### 13.1.1 Analysis of Safety population

All patients who received at least 1 dose of Investigational Product (IP) and for whom post-dose data are available will be included in the safety population. Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

## 13.2 Methods of statistical analyses

The outcome variables from the Bronkotest© diary card, lung function, sputum and blood collections will be compared between AZD9668 and placebo using an analysis of variance model with fixed factors treatment and country (or centre) and using baseline as a covariate. As the study is exploratory in nature, a p-value of <0.1 will be considered significant. A 2-sided 90% confidence interval will be constructed for the treatment difference and p-values given. For variables with a skewed distribution, data may be log-transformed prior to analysis or a non-parametric test (Wilcoxon rank sum) used instead.

The sputum samples: waking sample, the 2 hour collection and the 1 to 2 hour post dose samples will be analysed separately, with the 2 hour sample being the primary sample for data analysis.

All data will be listed, and will be summarised and plotted as appropriate, further details of the output to be produced will be contained in the SAP.

Withdrawal rates will be compared graphically between AZD9668 and placebo and may be investigated further.

Adverse events will be analysed by means of descriptive statistics and qualitative analysis. AEs will be listed for each patient and summarised by System Organ Class and preferred term assigned to event by using MedDRA.

Concomitant medications will be classified according to the WHO Drug Dictionary, the ATC system and the CPMP route of administration dictionary. All concomitant medications reported at entry and recorded during the study will be listed.

## 13.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 2.2.

This study is exploratory and as such the sample size in this study has not been based on obtaining power to detect specific effects. There is not adequate data to do such a powering. However, assuming that the variability is such (SD=1 on logged data) that we would not miss

(80% power) a 50% decrease in neutrophil numbers in the sputum, a sample size of 40 patients (20 per group) would be sufficient.

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

## 13.4 Interim analyses

No interim analysis is planned.

## 13.5 Data monitoring committee (Not Applicable)

Not applicable to this study. There will be no data monitoring committees involved.

# 14. LIST OF REFERENCES

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**Miller et al 2005**
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**Meguro et al 2007**
Meguro M, Barley EA, Spencer S, Jones PW. Development and Validation of an Improved COPD-Specific Version of the St. George Respiratory Questionnaire. Chest 2007;132:456-463