Clinical Study Protocol

Drug Substance	AZD5069
Study Code	D3550C00014
Edition Number	2
Date	

A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28-Day Oral Administration of AZD5069 Twice Daily in Patients with Bronchiectasis

Sponsor: AstraZeneca AB,

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28-Day Oral Administration of AZD5069 Twice Daily in Patients with Bronchiectasis

International Co-ordinating Investigator

Professor
Queen Elizabeth Hospital

Telephone:

Study centre(s) and number of subjects planned

It is planned to randomise at least 60 patients to have 50 patients complete the study. This study will be conducted in approximately 14 sites, in 2 to 3 countries. Each site is expected to aim to recruit 8 patients to have around 5 randomised patients per site.

Study period	Phase of development
Estimated date of first subject enrolled	Phase IIa
Estimated date of last subject completed	Phase IIa

Objectives

Primary objective:

The primary objective is to investigate the effect of AZD5069 on absolute neutrophil cell count in the sputum of bronchiectasis patients.

Secondary objectives:

- To investigate the effect of AZD5069 on percentage neutrophil cell count in the sputum of bronchiectasis patients.
- To investigate the effect of AZD5069 on signs and symptoms of bronchiectasis (including effects on quality of life).
- To investigate the safety and tolerability of 28 days' dosing with AZD5069 in bronchiectasis patients.

- To investigate the effect of AZD5069 on other inflammatory markers in sputum.
- To investigate the effect of AZD5069 on inflammatory markers in blood.
- To investigate the plasma pharmacokinetics (PK) of AZD5069 in bronchiectasis patients.

Exploratory objectives

- To investigate the relationship between plasma drug concentrations, exposure and/or dose with adverse events (AEs), pharmacodynamic (PD) parameters and/or clinical endpoints using a PK/ PD approach.
- To investigate the effect of AZD5069 on markers of mucus hyper-secretion.
- To investigate the effect of AZD5069 on the bacterial content of patients' sputum by analysing at least one pre-treatment sample and at least one post-treatment sample from each patient. Analysis will include but not be limited to: pseudomonas aeruginosa, streptococcus pneumonia, haemophilus influenza and moraxella catarrhalis.
- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5069.

If undertaken, the results from these exploratory analyses will be reported separately outside the clinical study report (CSR). The results of PK/PD analysis will be reported separately as a PK/PD report by AstraZeneca.

Study design

This is a randomised, double-blind placebo-controlled, parallel group study in patients with bronchiectasis. This study is planned to be performed in approximately 14 centres across 2 to 3 countries to randomise at least 60 patients to have 50 patients complete the study.

After patients have provided informed consent, they will be enrolled into the study. Patients who complete the study will be required to participate in 11 visits, some of which may be undertaken in their own home.

At Visit 2, eligible patients will be randomised to receive either AZD5069 or placebo in a 1:1 ratio. At Visit2, patients will be given sufficient capsules to allow self-dosing (80 mg, bd or corresponding placebo, bd), until Visit 4 (28 days ±2 days).

Target subject population

Patients (18 to 80 years, inclusive) with a clinical diagnosis of idiopathic or post infective bronchiectasis as diagnosed with a historical high resolution computerised tomography (HRCT) or bronchogram.

Investigational product, dosage and mode of administration

AZD5069 80 mg (4 x 20 mg capsules) administered twice daily (bd) orally.

Comparator, dosage and mode of administration

Matching placebo capsules administered bd orally.

Duration of treatment

Four weeks.

Outcome variable(s):

- **Primary efficacy variable:** Absolute neutrophil cell count in sputum
- **Secondary variables:**
  - Percentage neutrophil cell count in sputum
  - Bronkotest© diary card
  - 24-hour sputum collection weight
  - St George's Respiratory Questionnaire
  - Lung function tests
  - Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI)
  - Safety and tolerability of AZD5069
  - Inflammatory markers in sputum
  - Inflammatory markers in blood
  - Pharmacokinetics: PK parameters which may include: C_{max}, t_{max}, λ_z, $t_{½}$, AUC_{τ}, AUC CL/F, V_z/F and mean residence time (MRT).

Statistical methods

The primary outcome variable absolute neutrophils in sputum will be compared between AZD5069 and placebo using an analysis of variance model with fixed factors treatment and country (or centre) and using baseline as a covariate. A 2-sided 90% confidence interval (CI) will be constructed for the treatment difference and p values given. If the assumptions of ANOVA are violated, data transformation (eg, log-transformed) may be utilized or an appropriate non-parametric technique (eg, Wilcoxon rank sum) will be used instead.

The secondary outcome variables from the Bronkotest© diary card (continuous variables only), St George's Respiratory Questionnaire, lung function, 24-hour sputum weight, sputum

and blood collections will be compared between AZD5069 and placebo using an analysis of variance (ANOVA) model with fixed factors treatment and country (or centre) and using baseline as a covariate. Two-sided 90% CIs will be constructed for the treatment difference and p values given. If the assumptions of ANOVA are violated, data transformation (eg, log-transformed) may be utilized or an appropriate non-parametric technique (eg, Wilcoxon rank sum) will be used instead. In addition, a statistical analysis and summary will be produced for data derived from BDI/TDI.

All other data will be summarised and listed.

There will not be an interim analysis for this study.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
AMOS	AstraZeneca database
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification of Drug
AUC	Area under the plasma concentration time curve from time zero to infinity
$AUC_{(0-t)}$	AUC from 0 to last measured plasma concentration
$AUC_{(0-t)ss}$	AUC from 0 to last measured plasma concentration at steady-state
$AUC_{\tau, ss}$	AUC during the dosing period at steady-state
AUC_{τ}	AUC during the dosing period
AZ	AstraZeneca
BAL	Bronchoalveolar lavage
bd	Twice daily dosing (Latin)
BDI/TDI	Baseline Dyspnea Index/Transition Dyspnea Index
CL/F	Apparent plasma clearance following oral drug administration
$CL/F_{,ss}$	CL/F at steady-state
C_{max}	Observed peak or maximum plasma concentration following drug administration
$C_{max,ss}$	C_{max} at steady-state
CRF	Case Report Form (electronic/paper)
COPD	Chronic Obstructive Pulmonary Disease
CPD	Clinical Pharmacology, Drug Metabolism and Pharmacokinetics
CPK	Creatinine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical study report
CSA	Clinical Study Agreement

Abbreviation or special term	Explanation
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Event
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
Ecode	Enrolment code
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine tetra-acetic acid
EU	European union
FEF_{25-75}	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
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GMP	Good Medical Practice
GRand	Global randomisation system
GRO-α	Growth-related oncogene-α
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

Abbreviation or special term	Explanation
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LABA	Long-acting β agonists
LAMA	Long-acting muscarinic antagonist
LFT	Liver function test(s)
LIMS	Laboratory information management system
LLN	Lower limit of normal
LLOQ	Lower Limit of Quantification
MAD	Multiple ascending dose
MCP-1	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MID	Minimal clinically important difference
MRT	Mean residence time
MUC5AC	Mucin 5AC
NOAEL	No observed adverse 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 11.2.2
PD	Pharmacodynamic(s)
PEF	Peak Expiratory flow
PGx	Pharmacogenetic(s)
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
QTc	Corrected QT
R&D	Research and development
RANTES	Regulated on activation, normal T cell expressed and secreted
SABA	Short-acting β agonists
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.4.2)

Abbreviation or special term	Explanation
SAMA	Short-acting muscarinic antagonist
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SGRQ-C	St Georges Respiratory Questionnaire for COPD patients
SOP	Standard operating procedure
SVC	Slow Vital Capacity
$t_{½}$	Half-life
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
UK	United Kingdom
ULN	Upper limit of normal
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

1. INTRODUCTION

1.1 Background

AZD5069 is a potent, reversible, small molecule, CXCR2 (CXC chemokine receptor 2) antagonist that is proposed to have potential as a novel oral treatment of inflammatory diseases, including chronic obstructive pulmonary disease (COPD).

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

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

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 (Angrill 2001; Barker 2002). As in COPD the airway inflammation in bronchiectasis is characterised by neutrophilic inflammation and increased concentrations of chemokines such as TNF-α, interleukin-6 (IL-6) and IL-8 (Fuschillo 2008). Although there is evidence of a correlation between neutrophil numbers and the presence of pathogenic organisms and toxic neutrophil products contribute to the chronic airway inflammation, neutrophils are present in large numbers even in patients with sterile bronchi (Angrill 2001). In some respects, bronchiectasis may be regarded as an exaggerated model of COPD (see Section 1.3) as neutrophil numbers in the sputum are consistently higher in this condition than in stable COPD.

A CXCR2 antagonist previously studied by AstraZeneca, AZD8309, has been shown to inhibit GRO-α induced CD11b expression on human neutrophils and to reduce numbers of

peripheral blood neutrophils when given orally to healthy subjects. Oral dosing of AZD8309 also reduced neutrophil counts in induced sputum following lipopolysaccharide (LPS) challenge to healthy subjects.

There are a number of CXCR2 receptor antagonists currently in development by other companies. As far as is known the most advanced of these is SCH527123, currently in Phase II clinical trials. Single and multiple ascending dose studies in healthy subjects have shown this compound to have an acceptable safety profile (Khalilieh et al 2007a; Khalilieh et al 2007b). A dose-related decline in circulating neutrophils was seen, which could be reversed by administration of G-CSF (Khalilieh et al 2007a). No evidence of a cumulative effect was seen with multiple doses (Khalilieh et al 2007b). SCH527123 inhibited ozone-induced airway neutrophilia in a double-blind controlled study (Holz et al 2010). The compound had no effect on acquired immunity to hepatitis A vaccine (Khalilieh et al 2007c).

Additional relevant information of note is detailed below:

- AZD5069 is a potent reversible antagonist at human CXCR2 and a potent inhibitor of CXCR2-mediated calcium mobilisation, adhesion molecule expression and chemotaxis in human neutrophils in vitro.
- A probe CXCR2 antagonist, AZ10397767, reduced LPS induced neutrophil influx in rat and rabbit lung. In the rabbit, this effect was associated with inhibition of histological indicators of the pulmonary inflammatory response. Since AZ10397767 is a selective CXCR2 antagonist in the rabbit (CXCR2:CXCR1 selectivity 400-fold), its efficacy in this species indicates that, despite the theoretical potential for redundancy of CXCR pathways, CXCR2 antagonism alone is sufficient to substantially reduce a pulmonary inflammatory response.
- Investigation of the position and frequency of polymorphisms in African-American, Caucasian (Western European) and Japanese populations has provided no evidence of common (frequency >5%) polymorphisms in human CXCR2 that would be anticipated to modify interaction of AZD5069 with the receptor.
- Immunocytochemical assessment of lung tissue from human lung resections from normal donors and from patients with COPD ranging from moderate to severe has shown an increase in CXCR2 expression in COPD.
- AZD5069 demonstrated a high degree (>100-fold) of selectivity and specificity for the human CXCR2 receptor compared with other chemokine receptor subtypes and all other receptor or enzyme targets investigated.
- In safety pharmacology studies, the only observations of particular note were impaired gastric emptying and decreased gastrointestinal motility after single doses of 350 mg/kg in the rat.

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

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

- No gastrointestinal adverse events (AEs) of concern were observed in either SAD or MAD studies.

- In the SAD and MAD studies, there were no severe or serious adverse events (SAEs) relating to AZD5069 and no clinically significant laboratory abnormalities, apart from reductions in circulating neutrophils and total white cell count, which were expected with a CXCR2 antagonist.

PK Summary

- AZD5069 pharmacokinetics have been investigated in 3 studies to date in healthy subjects, (SAD, MAD studies and an ongoing Fed/Fasted/Elderly study), following single oral doses up to 200 mg and twice a day dosing up to 100 mg AZD5069.

- AZD5069 generally displayed dose proportional pharmacokinetics, following both single dose and at steady-state over the dose range tested.

- Steady-state kinetics appears to be attained following 2-3 days of dosing. This is consistent with the mean terminal elimination half-lives of approximately 11 hours seen over the 17.99 to 200 mg dose range, which started at approximately 24 hours post-dose.

- AZD5069 is absorbed relatively quickly; median t_{max} ranges from 1-2 hours post-dose, independent of dose.

- Following peak plasma AZD5069 concentrations (C_{max}), plasma AZD5069 concentrations appear to decline in a multi-exponential manner. Over the 8- to 24-hour post-dose period, drug concentrations declined with an elimination half-life of approximately 4 hours, which may potentially be the pharmacologically relevant half-life.

- Over the dose range investigated, less than 5% of the oral dose was excreted as parent drug in urine following single doses and at steady-state.

- Preliminary draft data suggests that dosing AZD5069 with a high-fat meal reduced the rate of drug absorption (C_{max} decreased by approximately 50%, t_{max} was later [4 hours versus 1.5 hours] compared to the fasted state), but did not influence the extent of drug absorption (AUC).

PK/PD summary

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

Details of pre-clinical and clinical pharmacology, toxicity and safety and tolerability of AZD5069 are given in the Investigator's Brochure (IB) Edition 2.

Further studies detailing the PK, safety and tolerability of AZD5069 in healthy elderly and healthy young Japanese subjects are on-going.

This study will be performed in parallel with a 28-day Phase IIa safety study in COPD patients.

1.2 Research hypothesis

The research hypothesis is that the CXCR2 chemokine receptor antagonist, AZD5069, shows an effect on the numbers of neutrophils in sputum in patients with bronchiectasis and is safe and well tolerated when given orally at a dose of 80 mg bd for 28 days.

1.3 Rationale for conducting this study

The current study is a proof-of-principle (PoP) study in patients with bronchiectasis to investigate if it is possible to demonstrate that AZD5069 inhibits neutrophil migration in the lung and examine some of the downstream effects that may follow this.

AZD5069 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 CXCR2 chemokine receptor antagonist 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 neutrophils 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 a therapy designed to inhibit the migration of neutrophils into the lung. Hence, this condition is considered a suitable exaggerated model of the neutrophilic inflammation seen in 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 CXCR2 chemokine receptor antagonism 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 sputum neutrophil numbers, a 4-week study offers an increased likelihood of observing changes in clinical outcomes and provide more information on the safety and tolerability of multiple doses of AZD5069.

AstraZeneca may perform genetic research in the AZD5069 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD5069. Collection of DNA samples from populations with well described clinical characteristics may 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.

1.4 Benefit/risk and ethical assessment

Patients with COPD are the main target population for the CXCR2 chemokine receptor antagonist, AZD5069. The main purpose of this study is to establish the proof-of-principle that the CXCR2 chemokine receptor antagonist AZD5069 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.

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

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

animals dosed at 0.5 mg/kg bd. Following the cessation of dosing, both parameters returned to baseline levels during the recovery period. A dose level of 0.1 mg/kg bd was determined to be NOAEL for changes in neutrophils and CRP.

In contrast, the major effect seen to date in the SAD (D3550C00001) and MAD (D3550C00007) studies has been a reduction in circulating neutrophils. This appears to be dose-related in the SAD and MAD studies, with more subjects having reductions and for longer periods at higher doses. In the MAD study reductions in circulating neutrophils have been observed. One subject, who was treated with AZD5069 100 mg bd for 6 days, was withdrawn from the MAD study because of a reduction in circulating neutrophils lasting for longer than 48 hours. A reduction in neutrophils is an expected effect of a CXCR2 antagonist and was also seen with AZD8309 (see AZD8309 IB) and with SCH527123 (Khalilieh et al 2007a; Khalilieh et al 2007b, Khalilieh et al 2007c).

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

Based on data from the SAD and MAD studies in healthy subjects, 80 mg bd is predicted to be the highest dose which can be given while minimising the likelihood of patients' circulating neutrophils falling below a concentration of $1.0x10^9$/L for more than 24 hours. Preliminary data from healthy subjects suggest dosing in the presence of food reduces the rate of drug absorption (a later t_{max} and a lower C_{max}), while the total quantity of drug absorbed was unaltered (ie, AUC). Thus, in order to reduce the potential variability in plasma concentrations due to different dosing conditions, the drug will be dosed in the fed state in this study.

In this study bronchiectasis is chosen as an exaggerated model of COPD with regard to neutrophilic inflammation in the lung, so that proof that a CXCR2 chemokine receptor antagonist 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 CXCR2 chemokine receptor antagonist could be useful in bronchiectasis *per se.*

For a more detailed risk benefit assessment of developing a CXCR2 chemokine receptor antagonist in COPD, see the IB (Edition 2).

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective is to investigate the effect of AZD5069 on absolute neutrophil cell count in the sputum of bronchiectasis patients.

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

Table 1 Primary outcome variable

Outcome Variables	Description
Absolute neutrophil cell count in sputum	Sputum cytospin slides will be produced for assessment of absolute neutrophil cell count

2.2 Secondary objectives

The secondary objectives are:

- To investigate the effect of AZD5069 on percentage neutrophil cell count in the sputum of bronchiectasis patients.
- To investigate the effect of AZD5069 on signs and symptoms of bronchiectasis (including effects on quality of life).
- To investigate the safety and tolerability of 28 days' dosing with AZD5069 in bronchiectasis patients.
- To investigate the effect of AZD5069 on other inflammatory markers in sputum.
- To investigate the effect of AZD5069 on inflammatory markers in blood.
- To investigate the plasma pharmacokinetics of AZD5069 in this patient population.

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
Percentage neutrophil cell count in sputum	Sputum cytospin slides will be produced for assessment of percentage neutrophil 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), FEV_1(forced expiratory volume in 1 second), FVC (forced vital capacity), forced expiratory flow between 25 and 75% of forced vital capacity (FEF_{25-75})
Baseline Dyspnea Index (BDI)/ Transition Dyspnea Index (TDI)	These indices will be assessed at clinical visit 2 (BDI) and Visit 4 (TDI)
Safety and tolerability of AZD5069	Vital signs, physical examination, body temperature, 12-lead ECG, haematology, clinical chemistry, urinalysis, sputum quantitative microbiological analysis, adverse events
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): TNF-α, IL-8, IL-6, IL-1β, RANTES, MCP-1, GRO-α
Inflammatory markers in blood	Blood samples will be collected for assessment of the following markers (including, but not limited to): Neutrophil concentration, TNF-α, IL-8, high sensitivity CRP, Amyloid-A, IL-6, IL-1β, GRO-α
Pharmacokinetic parameters	Concentration of AZD5069 in plasma and derived PK parameters which may include: C_{max}, t_{max}, λ_z, $t_{½}$, AUC_τ, AUC CL/F, V_z/F and mean residence time (MRT)

2.3 Exploratory objectives

The exploratory objectives are:

- To investigate the relationship between plasma drug concentrations, exposure and/or dose with AEs, pharmacodynamic (PD) parameters and/or clinical endpoints using a PK/PD approach.
- To investigate the effect of AZD5069 on markers of mucus hyper-secretion.
- To investigate the effect of AZD5069 on the bacterial content of patients' sputum by analysing at least one pre-treatment sample and at least one post-treatment sample from each patient. Analysis will include but not be limited to: pseudomonas aeruginosa, streptococcus pneumonia, haemophilus influenza and moraxella catarrhalis.
- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD5069.

If undertaken, the results from these exploratory analyses will be reported separately outside the clinical study report (CSR). The results of PK/PD analysis will be reported separately as a PK/PD report by AstraZeneca.

3. STUDY PLAN AND PROCEDURES

This CSP has been subject to a peer review according to AstraZeneca standard procedures.

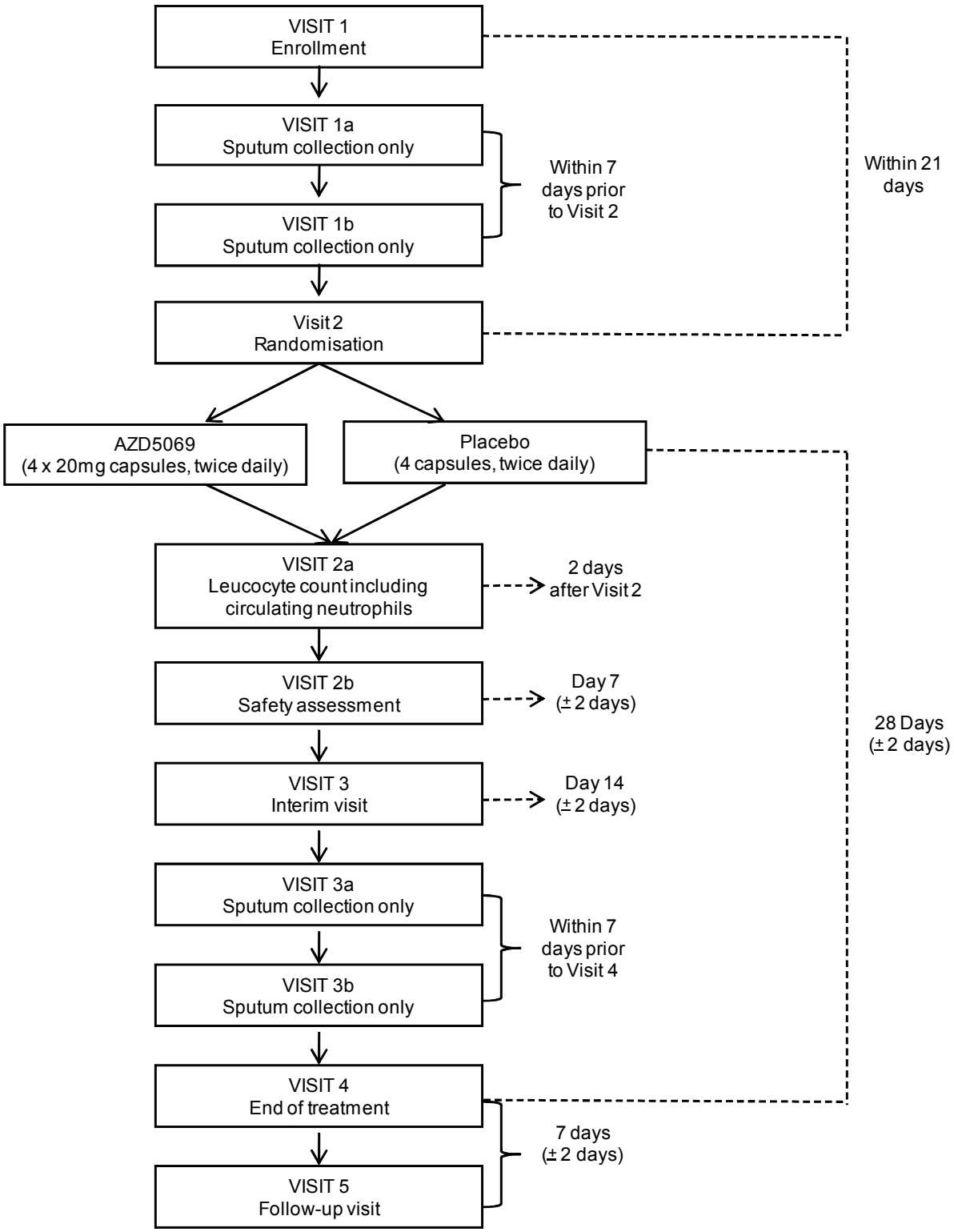
3.1 Overall study design and flow chart

This is a randomised, double-blind placebo-controlled, parallel group study in patients with bronchiectasis. This study is planned to be performed in approximately 14 centres across 2 to 3 countries to randomise at least 60 patients to have 50 patients complete the study.

After patients have provided informed consent, they will be enrolled into the study. Patients who complete the study will be required to participate in 11 visits, some of which may be undertaken in their own home. The overall study design is outlined in Figure 1.

At Visit 2, eligible patients will be randomised to receive either AZD5069 or placebo in a 1:1 ratio. At Visit 2, patients will be given sufficient capsules to allow self-dosing (80 mg, bd or corresponding placebo, bd), until Visit 4 (28 days ±2 days).

Figure 1 Study flow chart



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

PK will be performed at Visit 2, Visit 3 and Visit 4. Patients will come to the clinic in the morning for Visit 2, Visit 3 and Visit 4.

Patients must also withhold their morning dose of medication on Visits 3 and 4 as the dose will be taken at clinic following the pre-dose assessments (as outlined in Table 3). At Visit 3a and Visit 3b, patients must 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**	**2b**	**3**	**3a**	**3b**	**4**	**5** [a]
Timing	Day -21 to Day -8	Within 7 days of Visit 2 [b]	Within 7 days of Visit 2 [b]	Day 1	2 days after Visit 2	Day 7 (±2 days)	Day 14 (±2 days)	Within 7 days of Visit 4 [b-]	Within 7 days of Visit 4 [b-]	Day 28 (±2 days)	7 days (±2 days) after Visit 4
Detail	**Enrolment**	**Sputum**	**Sputum**	**Start of treatment**		**Interim visit**	**Interim visit**	**Sputum**	**Sputum**	**End of treatment**	**Follow-up visit**
Written informed consent [c]	✓										
Demographics	✓										
Height	✓										
Weight	✓										
Physical examination	✓										✓
Medical/surgical/ respiratory history	✓										
Dispense study drugs				✓							
Safety blood sampling	✓d			✓e		✓	✓			✓e	✓
Urine pregnancy test [f-]	✓										✓
Leucocyte count including circulating neutrophils [g]	✓			✓	✓	✓	✓			✓	✓
Urinalysis	✓			✓e		✓	✓			✓e	✓
Inclusion/exclusion criteria	✓			✓ e							
Lung function tests	✓			✓e						✓e	✓
BDI/TDI				BDI e						TDI e	
Vital signs	✓			✓e			✓			✓e	✓
Body temperature	✓			✓		✓	✓			✓	✓
12-lead ECG	✓						✓				✓
Drug accountability							✓			✓	

Table 3 Table of study assessments

Study Visit	1	1a	1b	2	2a	2b	3	3a	3b	4	5 [a]
Timing	Day -21 to Day -8	Within 7 days of Visit 2 [b]	Within 7 days of Visit 2 [b]	Day 1	2 days after Visit 2	Day 7 (±2 days)	Day 14 (±2 days)	Within 7 days of Visit 4 [b-]	Within 7 days of Visit 4 [b-]	Day 28 (±2 days)	7 days (±2 days) after Visit 4
Detail	**Enrolment**	**Sputum**	**Sputum**	**Start of treatment**		**Interim visit**	**Interim visit**	**Sputum**	**Sputum**	**End of treatment**	**Follow-up visit**
Bronkotest© diary card [h]	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓
Concomitant medications recorded	✓			✓		✓	✓			✓	✓
Adverse event questioning	✓			✓		✓	✓			✓	✓
Pharmacogenetics blood sampling[i]				✓							
Return 24 hr sputum collection (for weight)[j]		✓j	✓j							✓j	
Randomisation (AZD5069/placebo)				✓							
Waking to 2 hours sputum sample [k, l, m]		✓e	✓e	✓e				✓e	✓ e	✓e	
Quantitative microbiological analysis		✓n	✓n	✓n				✓n	✓n	✓n	
AZD5069 PK sample (blood)				✓o			✓o			✓o	
Blood sampling for pharmacodynamic markers				✓e, p						✓e, p	
St George's Respiratory Questionnaire				✓						✓	

[a] If the patient discontinues after randomisation, the patient should be asked to attend for Visit 5.
[b] Visit 1a/3a should occur at least 24 hours before Visit 1b/3b; these visits are for sputum collections to be returned to the clinic either by the patient or by courier.
[c] The informed consent should be signed before any study-related procedures, restrictions or screening assessments are performed.
[d] To include measurement of FSH and LH (menopausal status) for female patients at Visit 1; serology for HIV+HBV+HCV at Visit 1.

[e] Prior to first dose of the day. Lung function assessments should be performed prior to administration of any bronchodilators; Slow Vital Capacity (SVC) should be measured first.

[f] All women.

[g] Circulating leucocytes counts (including neutrophils) will be analysed at a laboratory within 2 hours (maximum 4 hours) of sample draw as circulating neutrophils deteriorate rapidly after blood has been taken. The leucocyte results from Visit 2-4 (inclusive) will be blinded from the site staff; refer to Section 5.4.1.

[h] Bronkotest diary card© issued at Visit 1 and patient should be instructed to bring the diary card to each clinic visit, for review by site staff. The diary card should be completed daily until termination from the study.

[i] Sample should be taken at any point after randomisation.

[j] Patients should be instructed to start 24-hour collection on rising the day before their scheduled visit. They should collect all sputum for the 24-hour period leading to either Visit 1a **or** Visit 1b and Visit 4.

[k] On waking, patients should collect all sputum produced for 2 hours into the sample pot provided. Immediately after finishing collection of the sputum sample, it should be taken directly to the clinic or dispatched directly to the local sputum processing laboratory (dependent on the clinic appointment time and/or patient's preference).

[l] Details of all analytes measured in these spontaneous sputum samples can be found in Table 4.

[m] If the sputum sample is limited, analysis should take place in the following order: highest priority = cytospin production; next priority = PD biomarkers; lowest priority = quantitative microbiological analysis.

[n] The aliquot for the quantitative microbiological analysis will be taken from the 2-hour waking sample at Visit 2 and Visit 4.

[o] Two samples at minimum 90 minutes apart.

[p] Two separate blood samples: 1 x 8.5 mL for serum and 1 x 2 mL for plasma.

Table 4 Frequency of waking to 2-hour samples

Timing of sample	Visit 1	Visit 1a	Visit 1b	Visit 2 (pre dose)	Visit 2a	Visit 2b	Visit 3	Visit 3a	Visit 3b	Visit 4 (pre-dose)	Visit 5
Analysis											
Cytospin production		✓	✓	✓				✓	✓	✓	
Aliquots for pharmacodynamic marker (including inflammatory and mucus hyper-secretion markers)		✓	✓	✓				✓	✓	✓	
Quantitative microbiological analysis		✓	✓	✓				✓	✓	✓	

3.2 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 1.3.

3.2.1 Study design

The study will be a randomised, placebo-controlled and double-blind study to ensure a robust design and minimise bias, which could compromise the conduct of the study, the recording of data and/or interpretation of the results. As the leucocyte count (including neutrophil data) will potentially be unblinding to site and study personnel, the laboratory results data will be blinded from Visit 2 onwards. The study includes placebo in parallel with active investigational product, to allow better interpretation of the data and provide indications of whether effects are more likely to be due to the treatment received than to the study procedures. A parallel group design is considered more appropriate than a crossover design, as the possible duration of effect is uncertain and therefore a carry-over cannot be completely eliminated.

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

3.2.2 Selection of primary outcome variable

The absolute neutrophil cell count in the sputum will give an indication of whether AZD5069 at 80 mg twice daily (bd) in bronchiectasis patients inhibits neutrophil migration.

3.2.3 Dose consideration and treatment duration

AZD5069 80 mg bd will be administered to bronchiectasis patients for 4 weeks.

Based on a preliminary PK/PD assessment of systemic neutrophil effects from the SAD study, the present dose of 80 mg bd, in the presence of food, is predicted to be a dose near the top of the pharmacological dose range, where the majority of patients are predicted to be able to complete the study without having low neutrophil counts for prolonged periods and having to be withdrawn as a result, while producing maximum effects on sputum neutrophil counts.

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

4. SUBJECT SELECTION CRITERIA

The patient population should be selected without bias.

Investigators must keep a record, the patient screening log, of patients who entered pre-study screening.

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.

4.1 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; ie, women who are permanently or surgically sterilised or post-menopausal.

   Women will be considered post-menopausal if they are:

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

   or

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

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

3. Aged 18 to 80 years inclusive at screening (Visit 1)

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

5. 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 sputum on a daily basis and should be able to provide at least 2 of the 3 required baseline sputum samples with an average of 3 mL or more.

6. Be on a stable treatment regimen, as judged by the investigator.

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

4.2 Exclusion criteria

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

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

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

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

4. Patients with other latent or chronic infections (eg, recurrent sinusitis, urinary tract infection) or at risk of infection (surgery, trauma, significant infection within 90 days before Visit 2, history of skin abscesses or soft tissue infection within 90 days before Visit 2 or in the opinion of the investigator patients in regular contact with active pulmonary tuberculosis)

5. 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 within 30 days prior to Visit 2

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

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

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

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

10. Any clinically relevant abnormal findings in physical examination, clinical chemistry, haematology, urinalysis, vital signs or 12-lead ECG at baseline (Visit 1), which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or may influence the results of the study, or the patient's ability to participate in the study

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

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

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

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

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

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

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

18. Previous exposure to AZD5069

19. Scheduled inpatient surgery or hospitalisation during the study

20. Pregnancy or breast-feeding during the study

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

22. Previous randomization to treatment in the present study

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

24. Use of prohibited medications as detailed in Section 5.6

25. Patients who are receiving immunosuppressive medication such as oral or systemic corticosteroids.

26. Patients with active malignancy or who have had such a condition in the past 12 months.

27. Peripheral blood neutrophils below the laboratory normal reference range at Visit 1.

28. Patients with serum creatinine above the upper limit of the reference range at screening (Visit 1).

29. Patients with active or latent tuberculosis (TB), as judged by the investigator.

Exclusion criteria relating specifically to the optional pharmacogenetic research can be found in Appendix D.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

Refer to Section 5.6.2 for a detailed discussion of restricted concomitant medications during the study.

5.1 Restrictions during the study

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

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

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

2. Patients should observe the following restrictions prior to the clinic lung function tests (Visit 1, 2, 4 and 5):

   - No strenuous exercise within 2 hours
   - No smoking within 1 hour
   - No large meals within 2 hours

3. Use of disallowed concomitant medication (refer to Section 5.6.3)

4. Patients should not receive a vaccination during the study

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

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

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

5.2 Subject enrolment and randomisation and initiation of investigational product

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 4.1 and 4.2.

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

If judged appropriate by the Investigator, a patient who initially fails screening may have a repeat enrolment (ie, criteria relating to time windows for treatments / procedures). If a patient is re-enrolled, the patient will be assigned a new E code.

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

5.2.1 Procedures for randomisation

A dynamic randomisation approach will be applied. Randomisation codes will be generated by the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) provider using minimisation with biased coin assignment method which assigns patients to treatments in a clinical trial with stratifying factors on which it is desired to achieve balance.

Patients will be assigned to treatment groups using IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. Randomisation codes will be assigned to patients who are eligible for randomisation.

Randomisation will be stratified for 1) use of inhaled corticosteroids and 2) pseudomonas aeruginosa infection (past or current). Patients will be randomly allocated to AZD5069 80 mg bd or placebo in a 1:1 ratio. Patients who are withdrawn after randomisation will not be replaced.

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

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

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

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

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

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

AZD5069 will be provided as a capsule for oral administration and with a matching placebo. Capsules of AZD5069 will be provided in the strength of 20 mg.

As the leucocyte count (including neutrophil data) will potentially be unblinding to site and study personnel, the data will be transferred from the local laboratory performing the analysis to the central laboratory. The results for Visits 1 and 5 will be communicated to the sites, but for all other visits (Visits 2 to 4) the central laboratory will review the data and notify the site if a patient needs to be recalled for repeat sampling or needs to be withdrawn from the study. Furthermore, to ensure that the investigator is not unblinded by only patients on active treatment being recalled, a number of patients with a normal leucocyte count will be randomly selected for repeat leucocyte assessments. Full details of the above process are detailed in the laboratory specifications.

5.4.2 Methods for unblinding the study

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

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

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca or AstraZeneca's representative,

and study medical monitor without revealing the treatment given to the patient to the AstraZeneca staff.

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

5.5 Treatments

5.5.1 Identity of investigational product(s)

The investigational product (IP) will consist of 20 mg capsules of AZD5069.

AstraZeneca will supply the IP to the investigators via an IVRS/IWRS. The IP will be supplied as capsules for oral use according to the description in Table 5.

Placebo will be supplied as capsules matching AZD5069 to ensure the blinding of the study treatment.

Table 5 Identity of investigational products

Investigational product	Dosage form and strength	Manufacturer
AZD5069	Capsule 20 mg	AstraZeneca R&D,
Placebo for AZD5069	Capsule	AstraZeneca R&D,

Note: The batch number will be detailed in the Clinical Study Report (CSR).

5.5.2 Doses and treatment regimens

Patients will be advised to have food (meal) just before attending Visit 2 (Day 1) where they will be randomised in a 1:1 ratio to receive either AZD5069 capsules 80 mg or placebo capsules orally bd for 28 days (±2 days). The first dose should be administered within 30 minutes of having food (meal) and with 100 mL water, in the clinic in the morning of Day 1.

At Visit 2, patients will receive 1 study drug kit (one box) including 4 blister cards. Each blister card will have 16 blister pockets with 4 capsules of 20 mg AZD5069 or corresponding placebo in each pocket. One kit (1 box) will be issued to the randomised patients, sufficient to allow self-dosing until Visit 4.

At Visit 3 (Day 14 ±2 days) patients will be advised to have food (meal) just before attending the clinic in the morning, having withheld taking their dose of study medication, which will be taken in the clinic and administered with 100 mL of water. One kit will be issued to the randomised patients, sufficient to allow self-dosing until Visit 4.

At Visit 4 (Day 28 ±2 days) patients will be advised to have food (meal) just before attending the clinic in the morning, having withheld taking their dose of study medication. Patients should take their last dose(s) of study medication in the clinic with 100mL water. There should only be 1 dose administered on this final day.

All other doses (ie, those not administered in the clinic) should be taken with approximately 100 mL water, within 30 minutes of food (meal) intake.

5.5.3 Additional study drug

No additional study drug will be provided for this study.

5.5.4 Labelling

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. Label text will be translated into local language.

The packaging and labelling will be performed by Investigational Products (IPS) AstraZeneca R&D Mölndal, Sweden. All supplies and labels will be prepared in accordance with GMP and local regulatory guidelines.

Each study drug kit (box), which contains 4 blister cards, will be labelled with a single-panel label without a tear-off part. Each blister card will be labelled with a small single-panel label.

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate conditions. The IP labels specify the appropriate storage.

5.6 Concomitant and post-study treatment(s)

5.6.1 Medication allowed during the study

Patients are allowed to continue long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), LABA/ inhaled corticosteroids (ICS) combinations unchanged throughout the study if they are already on these, but if possible should withhold these before lung function testing (see Section 5.6.2).

5.6.2 Restricted medication

As far as possible patients should 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 lung function tests. After they have had the test they may take their normal dose of the medication.

5.6.3 Disallowed medication

In addition, the following treatments are not allowed:

- Use of oral corticosteroids in the 30 days prior to Visit 2 and throughout the study (NB: 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 (NB: prophylactic use is allowed)
- Treatment with immunomodulatory agents within 8 weeks prior to Visit 2 and throughout the study
- Herbal medications, including but not limited to St John's Wort and Echinacea within 3 weeks prior to Visit 2 and throughout the study.

Although it is not expected from both non-clinical and in vitro data that AZD5069 at the dose to be used in this study will have any significant drug interactions, the following medications will not be allowed throughout the dosing period (ie, Visits 2 to 4):

- CYP2B6 substrates, in the 4 weeks prior to Visit 2, such as but not limited to: bupropion, cyclophosphamide, efavirenz, ifosfamide, selegiline, alfentanil, nevirapine, propofol, tamoxifen, valproic acid, artemisinin, pethidine, modafinil, sertraline, thiotepa
- PgP substrates, in the 4 weeks prior to Visit 2, including but not limited to: quinidine, tacrolimus, ivermectin, colchicines, etoposide, doxorubicin, vinblastine, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, cyclosporin, digoxin
- Warfarin in the 4 weeks prior to Visit 2 and until completion of the study follow-up visit (Visit 5).

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 electronic case report form (eCRF).

Please refer to Section 5.1 for other restrictions during the study.

5.7 Treatment compliance

The administration of all medication (including investigational product) must be recorded in the appropriate sections of the eCRF.

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

Information on patients who have missed and/or forgotten more than 3 consecutive doses should be discussed with the AstraZeneca Study Physician or AstraZeneca's representative and the study medical monitor for assessment as to whether the interruption in the investigational product (IP) constitutes discontinuation.

5.7.1 Accountability

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

The study personnel will account for all 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.

5.8 Discontinuation of investigational product

Patients may be discontinued from IP in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance to study protocol.
- Safety reasons (risk to patients as judged by the investigator and/or AstraZeneca).
- Eligibility criteria not fulfilled.
- Patient lost to follow-up.
- Other reasons:
  - Pregnancy (refer to Section 13.3)
  - Treatment code prematurely broken by the investigator.
- Death.

- Development of study-specific withdrawal criteria (in which case the patient must be withdrawn):

  – Clinically significant lower respiratory tract infection as judged by the investigator

  – Severe gastrointestinal event as judged by the investigator

  – Patient has haematological changes that have not recovered within 48 hours (or on repeat of 48 hour sample) defined as one or more of:

    - confirmed neutrophil count $<1.0 \times 10^9$/L
    - confirmed leucocyte count $<2.0 \times 10^9$/L

    Where low counts are detected, efforts should be made to obtain both morning and afternoon samples to ensure that results are not being influenced by diurnal variation. If haematological changes defined as above have not recovered, a repeat measurement should be taken between 14:00 and 20:00. If the values are still below those detailed above then the subject should discontinue study drug

  – Patient has hepatic toxicity defined as one or more of:

    - confirmed ALT or AST concentration >3 x ULN
    - confirmed isolated total bilirubin concentration >2 x ULN
    - confirmed ALT or AST concentration >2 x ULN concurrent with total bilirubin concentration >1.5 x ULN
    - any pattern of liver function test (LFT) abnormalities giving cause for concern in the opinion of the Investigator

    These events must be followed up as appropriate for the patient.

  – Confirmed serum creatinine >1.5 x ULN

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

Patients who have missed and/or forgotten more than 3 consecutive doses should be referred to the AstraZeneca Study Physician or AstraZeneca's representative for assessment as to whether the interruption in the IP constitutes discontinuation.

5.8.1 Procedures for discontinuation of a subject from investigational product

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an investigator(s). AEs will be followed up (See Sections 6.4.3 and 6.4.4); diary cards and study drug should be returned by the patient.

If a patient discontinues after randomisation they should be asked to return for the end of treatment visit (Visit 4) and the follow-up visit (Visit 5). The reason for discontinuation will be recorded in the eCRF.

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

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. AEs will be followed up (See Sections 6.4.3 and 6.4.4); diary cards, questionnaires (eg, for patient reported outcomes) and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

6. COLLECTION OF STUDY VARIABLES

6.1 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 eCRF 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 its completion where necessary.

6.2 Data collection and enrolment

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

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 eCRF:

- Demography (Date of birth, sex, race)
- Vital signs (Blood pressure and pulse)
- Body temperature
- Leucocyte count (analysed at local laboratory)
- Height and weight
- Surgical, medical and respiratory history (including nicotine and alcohol use)
- Physical examination
- Concomitant medications
- Safety blood samples
  - Haematology and clinical Chemistry
  - HBV, HCV, and HIV serology evaluations
- Mid-stream urine sample for urinalysis
- FSH and LH measurements will be included in the Visit 1 safety analysis for female patients
- Pregnancy test for all female patients
- A 12-lead ECG
- Lung function tests (SVC, FEV_1, FVC, FEF_{25-75})
- AEs.

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

6.2.1 Follow-up procedures

Investigators should refer to the study plan in Table 3 for a detailed list of study procedures and assessments to be performed at the follow up visit (Visit 5). The following assessments will be performed and recorded in the eCRF at this visit:

- Physical examination
- Safety blood samples (Haematology and Clinical Chemistry)
- Mid-stream urine sample for urinalysis

- Lung function tests (SVC, FEV_1, FVC, FEF_{25-75})
- Vital signs (Blood pressure and pulse)
- Body temperature
- Leucocyte count (analysed at local laboratory)
- A 12-lead ECG
- Concomitant medications
- Adverse event questioning
- Pregnancy test for all female patients.

In addition, the patients will return their completed Bronkotest© diary card and their spontaneous sputum collection for quantitative microbiological analysis as detailed in Section 6.4.9.1.

6.3 Efficacy

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

6.3.1 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 for 2 hours. Immediately after finishing collection of the sputum sample, it should be taken directly to the clinic or dispatched directly to the local sputum processing laboratory (dependent on the clinic appointment time and/or patient's preference).

Patients will be issued a patient aid on how to collect sputum samples. Details of the aliquots of sputum supernatant are covered under pharmacodynamic variables (Section 6.7.1) and the sputum cytospins will be used to determine the differential cell count. 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 laboratory, 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 regarding sampling times.

6.3.2 24-hour sputum weight

Patients will be provided with appropriately labelled collection pots at Visits 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 waking in 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 eCRF. Note that waking to 2-hour sputum sample should also be collected separately on Visit 1a, Visit 1b and Visit 4, in addition to the 24-hour sample (see Section 6.3.1).

6.3.3 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 (FEF_{25-75}).

The assessments should be performed prior to the administration of any bronchodilators (refer to Section 5.6) 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.

Calculation of PN FEV_1 value will be performed according to the European Steel and Coal Community (Quanjer et al 1993):

- Women: PN FEV1 = 3.95 x (H - 0.025) x (A - 2.60)
- Men: PN FEV1 = 4.30 x (H - 0.029) x (A - 2.49)

A record of the measurements must be made in the patient's notes and results recorded in the eCRF. 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 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.

6.3.4 Baseline Dyspnea Index/Transition Dyspnea Index

Dyspnoea will be assessed at start of treatment (Visit 2) according to the Baseline Dyspnoea Index as modified by Stoller et al (Stoller et al 1986) and at the final visit on treatment (Day 28, Visit 4) according to the Transition Dyspnoea Index (Mahler et al 1984).

6.4 Safety

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

6.4.1 Definition of adverse events

An AE 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 [ECG]). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.4.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of an SAE, see Appendix B to the CSP.

6.4.3 Recording of adverse events

Time period for collection of adverse events

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

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 eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE;

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

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

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

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

- date AE met criteria for SAE
- the date Investigator became aware of SAE
- the date when the SAE stopped
- AE is serious due to
- date of hospitalisation
- date of discharge
- primary/secondary cause of death
- date of death
- autopsy performed
- causality assessment in relation to study procedure(s)
- causality assessment in relation to other medication
- Description of AE.

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

Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the CSP.

Adverse Events based on signs and symptoms

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

Adverse Events based on examinations and tests

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

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

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

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

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

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

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

- Fulfils any of the SAE criteria. These should be reported as a SAE.
- Reason for discontinuation of treatment with the IP. These should be reported as a Discontinuation AE (DAE).

- Investigator decides additional diagnostics and/or treatment is required because he/she considers deterioration of any of the signs/symptoms/findings is clinically relevant. This should be reported as an AE (note, a repeat test showing the first abnormal result was not valid should not be reported as an AE).

Symptoms of disease under study

Any symptoms of bronchiectasis not present at baseline will be recorded as AEs.

Disease progression

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

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

AEs with recommended follow-up activities

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

6.4.4 Reporting of serious adverse events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within one calendar day of initial receipt for fatal and life threatening events and within five calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day; ie, immediately but no later than the end of the next business day of when he or she becomes aware of it. AE's and lab abnormalities should be followed to

resolution. AE(s) of infection should be followed up and risk factors, signs and symptoms and diagnostic investigations recorded in the appropriate module(s) provided in the eCRF. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. Details for how SAE reporting will be carried out will be described in the specific Safety Handling Plan for the study.

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

6.4.5 Laboratory safety assessment

Blood and urine samples will be analysed at a central laboratory with the exception of leucocyte counts and urinalysis (dipstick). The following will be assessed as part of the urinalysis dipstick: glucose, protein, and blood. In addition, samples will be sent to the central laboratory for urine microscopy and quantitative measurements of total protein, albumin and creatinine if the local dipstick test for protein and/or blood is positive or if the urine sample appears abnormal on macroscopic examination, eg, if it is cloudy.

Due to rapid degradation of neutrophils, leucocyte counts will be performed promptly in local laboratories within 2 hours (maximum 4 hours) of sample collection.

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

The laboratory variables to be measured are outlined in Table 6.

Table 6 Laboratory parameters

Haematology	Clinical chemistry	Urinalysis (urine)
B-Erythrocytes	Creatinine	U-Blood (dipstick)
B-Haemoglobin	Bilirubin (total)	U-Total protein (dipstick)
B-Leucocyte count	Alkaline phosphatase	
(absolute and differential count including neutrophils, basophils, lymphocytes, monocytes, eosinophils)	Aspartate aminotransferase (AST)	U-Glucose (dipstick)
B-Platelet count	Alanine aminotransferase (ALT)	
	Albumin	Urine microscopy (if required, refer to Section 6.4.5)
	Protein (total)	U-Albumin (if required, refer to Section 6.4.5)
	Potassium	U-Total protein (if required, refer to Section 6.4.5)
	Calcium (total)	U-Creatinine (if required, refer to Section 6.4.5)
	Sodium	
	Glucose (not fasted)	
	High-sensitivity C Reactive Protein (hs CRP)	
	Urate	
	Urea	
	HIV, HBV, HCV[a]	
	FSH, LH[a]	

[a] HIV, HBV, HCV, and FSH, LH at screening only.

For blood volume see Section 7.1.

6.4.5.1 Serology testing

Serology testing for HIV antibody, Hepatitis B (HBV), and Hepatitis C (HCV) will be performed on all patients at screening only. If the test result for HIV antibody is positive, the patient will not be allowed to proceed in the study.

Note: Although the results of the HIV and hepatitis screens must be documented in the patient's file, these results will not be collected on the eCRF and will therefore not be recorded in the study database.

6.4.6 Physical examination

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

The following should be assessed: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, musculo-skeletal (including spine and extremities), cardiovascular, lungs and abdomen.

Height (enrolment only) will be measured in centimetres and weight (enrolment only) in kilograms. Measurements should be taken without shoes and using calibrated scales for all measurements. BMI will be calculated from the height and weight.

6.4.7 Resting 12-lead ECG

At Visits 1, 3 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. Heart rate, QRS duration, PR, RR QT intervals will be recorded, and QTcF (Fridericia-corrected) will be derived subsequently Overall evaluation of the ECG (normal, abnormal or borderline) should be recorded along with a note of any abnormalities and whether or not they were clinically significant. The original ECG traces must be stored in the patient's record as source data.

6.4.8 Vital signs

6.4.8.1 Pulse and BP

Vital signs (pulse and BP) will be measured at Visits 1, 2, 3, 4 and 5 as detailed in Table 3. Supine BP and pulse rate will be measured using non invasive equipment after a 10-minute rest on a bed.

6.4.8.2 Body temperature

Body temperature (oral) will be measured in degrees Celsius using an automated thermometer at Visits 1, 2, 2b, 3, 4 and 5 as detailed in Table 3.

6.4.9 Other safety assessments

6.4.9.1 Sputum quantitative microbiological analysis

A sample of sputum will be frozen for transport to a central laboratory for quantitative microbiological analysis using PCR (Visits 1a, 1b, 2, 3a, 3b and 4). Details will be included in the laboratory manual (There will not be any local bacterial culture).

6.5 Patient reported outcomes (PRO)

The methods for collecting PRO data are outlined below.

6.5.1 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 AEs and medications are subsequently reflected in the eCRF. 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 is provided in Table 7.

Table 7 Bronkotest© Diary Card variables

Question	Answer	Databased?
Describe your breathing	1 – Better than usual 2 – Normal/Usual 3 – Worse than usual 4 – Much worse than usual	Yes
What colour is your sputum?	Choose a number from 0 to 8 from sputum colour chart attached to Bronkotest© diary card	Yes
The amount of sputum you produced	0 – None 1 – Some (up to a teaspoonful) 2 – A little (tablespoonful) 3 – Moderate (egg-cupful or more) 4 – A lot (cupful or more)	Yes
Type of sputum?	1 – Watery 2 – Sticky Liquid 3 – Semi-Solid 4 – Solid	Yes
How do you feel?	1 – Better than usual 2 – Normal/Usual 3 – Worse than usual 4 – Much worse than usual	Yes

Table 7 Bronkotest© Diary Card variables

Question	Answer	Databased?
How often do you cough?	0 – Rarely 1 – Occasionally 2 – Frequently 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 1 – Woke once because of chest symptoms 2 – Woke twice because of chest symptoms 3 – Woke more than twice because of chest symptoms 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
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 will not be databased directly but will be transferred into the relevant eCRF 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.

6.5.2 St George's Respiratory Questionnaire

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 adapted 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).

The SGRQ-C will be administered according to the guidelines for standardised administration. To avoid biasing responses, patients will answer the questionnaire at the clinic visits before any other study-related procedures take place.

The questions should be completed in a quiet place without influence from study personnel or accompanying family/friends. The subject should be informed about the importance of their participation and given adequate time to complete all items. No stated or implied time limit for completing the questionnaire will be given. If the subject should request help or clarification of any question in the questionnaire, study personnel are to instruct the subject to reread the instructions and to give the best answer possible to each question. Study personnel will not provide the subject with an answer to any question. After the subject has completed the questionnaire, the investigator or designee will review the questionnaire for completeness only. If the questionnaire (or any portion of it) is inappropriately incomplete, the subject will be given the opportunity to complete any missing items.

6.6 Pharmacokinetics

6.6.1 Collection of samples

Blood samples (4 mL KEDTA) for determination of AZD5069 in plasma will be taken at the times presented in the study plan 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.

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of AZD5069 in plasma will be analysed by the appointed bioanalytical laboratory on behalf of Clinical Pharmacology & DMPK, AstraZeneca, using a validated method of liquid chromatography and mass-spectrometry (LC-MS/MS) after protein precipitation. The lower limit of quantification (LLOQ) of AZD5069 in plasma is 1.00 nmol/L.

Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analyte of interest (ie, AZD5069) at time of receipt by the bioanalytical laboratory will be analysed. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Any results from such analyses will be reported separately from the CSR.

6.7 Pharmacodynamics

6.7.1 Sputum inflammatory markers

The 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 laboratory within 2 hours of collection for processing. Resulting aliquots of supernatant will then be sent to the appropriate analysis laboratory. 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, but not limited to, TNF-α, IL-8, IL-6, IL-1β, RANTES, MCP-1, GRO-α. Sputum cytospins will be used to determine the total and differential cell count.

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.

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

6.7.2 Blood inflammatory markers

Blood samples will be taken for assessment of inflammatory markers in serum. Subject to validated assays being available the markers in serum will be Amyloid-A and high-sensitivity

CRP (hsCRP) and those in plasma will include, but not limited to, TNF-α, IL-8, IL-6, IL-1β and GRO-α.

The neutrophil cell count will be taken from the haematology safety sample taken at the corresponding visit.

6.7.2.1 Collection of biological samples

A serum 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.

6.7.3 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.

6.7.3.1 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 the laboratory manual.

6.8 Pharmacogenetics

6.8.1 Collection of pharmacogenetic 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 7.1.

6.9 Health economics (not applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 8 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	2.5	1	2.5
	Clinical chemistry	5.0	6	30.0
	Haematology	3.0	6	18.0
Pharmacokinetic sample		4.0	6	24.0
Serum inflammatory marker sample		8.5	2	17.0
Plasma Inflammatory markers		2.0	2	4.0
PGx (optional) Visit 2		10.0	1	10.0
Total		35.0	24	105.5[a]

[a] If additional Pharmacogenetics consent has been obtained, an additional 10 mL sample will be drawn (see Appendix D).

7.2 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 Section 7.2.1). Disposal will be initiated 3 months after the finalisation of the relevant final analytical report. Exploratory Biomarker samples will be held for up to 15 years after last patient's last visit. After this time all samples will be destroyed.

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

7.2.2 Pharmacogenetic samples

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

7.3 Labelling and shipment of biohazard samples

The principal investigator ensures that samples are labelled and shipped in accordance with the laboratory manual and the Biological Substance Category B 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.

7.4 Chain of custody of biological samples

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

The principal investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment 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 or representative 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.

7.5 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.

- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/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.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Subject 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.

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

8.4 Informed consent

The principal investigator(s) at each centre will:

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

8.5 Changes to the protocol and informed consent form

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where appropriate a new version of the study protocol will be produced (Revised 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 8.3.

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.

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA OR REPRESENTATIVE

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the CSP 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).

9.3 Monitoring of the study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, 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.

9.3.1 Source data

Refer to the Clinical Study Agreement (CSA) for location of source data.

9.4 Study agreements

The PI at each centre must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail.

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

9.4.1 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

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

The study is expected to start in Q4, 2010 and to be completed by Q2, 2011.

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

10. DATA MANAGEMENT BY ASTRAZENECA OR REPRESENTATIVE

Data Management (DM) will be performed by the contract research organization (CRO). Data will be entered into the WBDC system at the study site. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the WBDC system. All sites will need internet access to access the eCRFs and will only have access to data for patients at their own sites. Data Management and other coordinator teams will have access to data at all sites.

All eCRFs are to be completed by an authorised member of the investigational staff and reviewed and signed by the investigator. All entries, corrections and alterations are to be made by the responsible investigator or an authorised member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any subject leaving the study should be completed at the time the study medication is terminated for whatever reason.

Electronic case report forms must accurately reflect data contained in patients' records (eg, source documents).

Dataflow

After data is entered into the eCRF by site, autoqueries that are generated by the WBDC system should be addressed by site. At the monitoring visit, the Study Monitor must perform the source data verification (SDV) of the required fields on completed forms and if there are no open queries, freeze the form. Data Management will run manual consistency checks outside of the WBDC system and will raise manual queries for sites to address; if the form is frozen, Data Management will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the WBDC system (eg, for SAE reconciliation). Once all data is entered, SDV complete on required fields, manual queries and electronic data reconciliation complete, and all queries closed, then the casebook can be signed. Once the casebook is signed, Data Management will then lock the casebook so that no amendments can be made.

Database lock

Once all patient eCRFs are locked, the final data transfer can be sent to statistics. A database lock checklist will also be completed by Data Management and the programmer to confirm all applicable quality control checks were confirmed.

Coding

All AEs and Medical Histories recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and all medications coded using AstraZeneca's Drug Dictionary. The coding will occur outside of the WBDC system and will be merged with the clinical datasets sent to statistics.

Investigator site file

At the beginning of the study, an investigator's study file will be established at the study centre. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

SAE reconciliation

The CRO will perform SAE reconciliation between the CRO and clinical study database and the AstraZeneca Clinical Patient Safety database.

Biological samples

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

Genetic data

Refer to Appendix D.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Differential cell count (absolute and percentage neutrophils) in sputum

The geometric 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 (geometric mean of the values at Visits 3a, 3b and 4) will be used as outcome variable(s). The other differential counts will be reported for completeness.

11.1.2 Weight of 24-hour sputum collection

The value from Visit 1a or Visit 1b will be used as baseline. The change from baseline to end of treatment (Visit 4) will be used as the outcome variable.

11.1.3 Clinic lung function tests

The value 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 end of treatment (Visit 4) will be used as the outcome variable.

11.1.4 Baseline Dyspnea Index/Transition Dyspnea Index

Dyspnoea will be assessed at the start of treatment (Visit 2) according to the Baseline Dyspnoea Index as modified by Stoller et al (Stoller et al 1986) and at the final visit on treatment (Day 28, Visit 4) according to the Transition Dyspnoea Index (Mahler et al 1984).

11.2 Calculation or derivation of safety variable(s)

11.2.1 Safety variables

The following safety data will be collected: vital signs, physical examination, body temperature, 12-lead ECG, haematology, clinical chemistry, urinalysis, sputum quantitative microbiological analysis and reported AEs. Change from baseline (Visit 2) to each post-treatment timepoint where scheduled assessments were made will be calculated for relevant measurements. AEs will be summarised by means of descriptive statistics and qualitative summaries.

11.2.2 Other significant adverse events (OAE)

During the evaluation of the blinded AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR.

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

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 Bronkotest© diary card data

Bronkotest© data that are numeric will be summarised as the mean of each period: Baseline period (last 7 days prior to start of treatment), Day 1 to Day 7, Day 8 to Day 14, Day 15 to Day 21, Day 22 to Day 28, end of treatment period (last 7 days on treatment) and follow-up (first 5 days after end of treatment). The change from baseline to treatment will be used as the outcome variable.

For Bronkotest© data that has a yes/no response, the frequency of yes responses by each period will be displayed.

Note: Morning and evening PEF recordings will be calculated separately.

11.3.2 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 (Meguro et al 2007). The outcome variable for SGRQ-C will be the change in total score from baseline (Visit 2) to Visit 4 (using the last available value). The domain scores will be handled in the same way.

11.4 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at (or under the guidance of) AstraZeneca R&D. The actual sampling times will be used in the PK calculations. Details of the population kinetic analysis and the resulting outputs, which may include C_{max}, t_{max}, λ_z, $t_{½}$, AUC_{τ}, AUC CL/F, V_z/F and MRT will be documented in a Pharmacokinetic Analysis Plan prior to database lock

11.5 Calculation or derivation of pharmacodynamic variable(s)

The sputum sample: waking to 2-hour sample will be derived and analysed separately.

PD variables will be derived from blood and sputum samples separately.

Blood sample for PD markers will be collected at Visits 2 and 4. The corresponding measurements will be taken as the values of baseline and end of treatment. For each marker variable, the change from baseline will be used as the endpoint.

The sputum samples will be collected at timings specified in Table 3. The inflammatory markers will be derived from the sputum samples. For each of inflammatory markers, the geometric mean of the values prior to treatment (Visit 1a, Visit 1b and Visit 2) will be used as baseline, and the change from baseline to end of treatment (geometric mean of the values at Visit 3a, Visit 3b and Visit 4) will be used as the endpoint.

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

The relationship between plasma AZD5069 concentrations, exposure and/or dose with AEs, pharmacodynamic (PD) parameters and/or clinical endpoints will be investigated using a PK/PD approach. The PK/PD analyses will be performed at (or under the guidance of) AstraZeneca R&D. The actual sampling times will be used in the PK calculations. Details of the population kinetic analysis and the resulting outputs will be documented in a Pharmacokinetic Analysis Plan prior to database lock.

11.6 Calculation or derivation of pharmacogenetic variables

Details can be found in Appendix D.

11.7 Calculation or derivation of health economic variables (not applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR REPRESENTATIVE

A comprehensive statistical analysis plan (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 Quintiles UK, using SAS® version 8.2 and, where appropriate, additional validated software. These analyses will be performed in accordance with the SAP, which will detail analyses to be performed, define analysis sets, and summaries to be produced for the CSR.

Pharmacokinetic and pharmacodynamic analyses will be carried out by AstraZeneca.

12.1 Description of analysis sets

12.1.1 All subjects analysis set

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

12.1.2 Efficacy analysis set

All patients who have received at least one dose of Investigational Product and have post-dose data available will be included in the efficacy analysis set. Unless there is evidence to the contrary, it will be assumed that errors where patients receive treatment other than the one they were randomised to, were genuine and patients will be summarised according to the treatment they actually received. It is probable that this dataset will be the same as the safety analysis set. All efficacy (excluding PK and PD) analyses and summaries will be based on this analysis set.

12.1.3 Safety analysis set

All patients who have received at least one dose of IP and have post-dose data available will be included in the safety analysis set. Patients will be summarised according to the treatment they actually received irrespective of what treatment they were randomised to. All safety summaries will be based on this analysis set.

12.1.4 PK analysis set

All patients receiving AZD5069 and for whom PK blood samples assumed not to be affected by factors such as protocol violations (eg, disallowed medication) are available from, will be included in the PK analysis set. All PK summaries will be based on this analysis set.

12.1.5 PD analysis set

All patients receiving at least 1 dose of IP and for whom PD samples are available (assumed not to be affected by factors such as protocol violations) will be included in the PD analysis set. All PD summaries will be based on this analysis set.

12.1.6 Per protocol analysis set

The blinded data will be investigated during the blind review of the data and if appropriate, a per protocol analysis set may be defined. This will be a subset of the efficacy analysis set, excluding patients who have had a major protocol deviation which could influence the data. Analyses to be performed using this dataset will be defined in the SAP.

12.2 Methods of statistical analyses

A SAP will be produced including details of the assumptions being made about the data, the analyses to be performed on the data and the analysis sets upon which these will be based, and how issues such as missing data and multiplicity will be dealt with.

Demography and baseline characteristics will be summarised for each treatment group based on the treatment they actually received and overall, but will not be statistically tested since the study is randomised and it is therefore assumed that any differences between the treatment groups would be random.

12.2.1 Primary outcome variable

The primary outcome variable is:

- Change from baseline (geometric mean of the values at Visit 1a, 1b and 2) to treatment (geometric mean of the values at Visit 3a, 3b and 4) in sputum absolute neutrophils.

The primary outcome variable will be compared between AZD5069 and placebo using an analysis of variance (ANOVA) model with fixed factors treatment and country (or centre) and using baseline as a covariate. Two-sided 90% confidence intervals (CIs) will be constructed for the treatment difference and p values given. If the assumptions of ANOVA are violated, data transformation (eg, log-transformed) may be utilized or an appropriate non-parametric technique (eg, Wilcoxon rank sum) will be used instead.

The primary outcome variable analysis will be carried out on the PD analysis set.

12.2.2 Secondary outcome variables

The secondary outcome variables are:

- Change from baseline (geometric mean of the values at Visits 1a, 1b and 2) to treatment (geometric mean of the values at Visit 3a, 3b and 4) in percentage neutrophils.

- Change from baseline (Visit 1a or Visit 1b) to end of treatment (Visit 4) in 24-hour sputum collection weight.
- Change from baseline (Visit 2) to treatment (Visit 4) in FEV_1.
- Change from baseline (Visit 2) to treatment (Visit 4) in SVC.
- Change from baseline (Visit 2) to treatment (Visit 4) in FEF_{25-75}.
- Change from baseline (Visit 2) to treatment (Visit 4) in FVC.
- Change from baseline period (mean of last 7 days prior to start of treatment) to treatment period (mean of the last 7 days on treatment) in symptom score diary card (Bronkotest©).
- Change from baseline (Visit 2) to treatment (Visit 4) in mean total score and domain scores from St George's Respiratory Questionnaire.
- Change from baseline to treatment in sputum inflammatory markers including, but not limited to (and subject to the availability of validated assays): TNF-α, IL-8, IL-6, IL-1β, RANTES, MCP-1, GRO-α.
- Change from baseline to treatment in blood inflammatory markers including, but not limited to (and subject to the availability of validated assays): neutrophil concentration, TNF-α, IL-8, high sensitivity CRP, Amyloid-A, IL-6, IL-1β, GRO-α.
- Pharmacokinetic parameters (AZD5069 concentration measured in plasma).

The secondary outcome variables from the Bronkotest© diary card (continuous variables only), St George's Respiratory Questionnaire, lung function, 24-hour sputum weight, sputum and blood collections will be compared between AZD5069 and placebo using an analysis of variance model with fixed factors treatment and country (or centre) and using baseline as a covariate. Two-sided 90% CIs 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. In addition, the statistical analysis and summary will be produced for data derived from BDI/TDI. The further details will be provided in the SAP.

Whilst statistical testing is being performed, with the exception of the primary variable, such testing is deemed to be exploratory and as such no multiplicity corrections will be made.

No formal statistical analysis will be carried out on the other secondary outcome variables.

AEs will be summarised by means of descriptive statistics and qualitative summaries. AEs will be listed for each patient and summarised by System Organ class and Preferred Term assigned to the event by using MedDRA. Laboratory safety variables will be summarised

using standard summary statistics and plots as appropriate. Other safety variables will be summarised as appropriate. Further details will be provided in the SAP.

Laboratory data for haematology and clinical chemistry will be summarized. The frequency of changes with respect to normal ranges between baseline and each post-treatment timepoint will be tabulated. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will also be given. Shifts from normal to abnormal between baseline and each post-treatment timepoint will be evaluated for urinalysis.

Changes in vital signs, body temperature and ECGs will be examined at each visit and at endpoint. Frequencies of clinically noteworthy values (defined in the SAP) occurring during the clinical study will be presented. Shifts from normal to abnormal between baseline and follow-up will be evaluated for the physical examination.

12.2.3 Other data

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.

Exploratory data will be presented separately from the CSR.

12.2.4 Interim analyses

No interim analysis is planned.

12.3 Determination of sample size

The sample size for this study was selected in accordance with the research hypothesis as described in Section 1.2.

Data from a previous study in bronchiectasis patients showed that the standard deviation of the differences in absolute sputum neutrophils between the active and placebo groups was approximately 1. Assuming that the standard deviation (SD) would be similar in this study, 25 patients in each treatment group would be required to detect a 50% decrease in neutrophils, using a 1-sided test with a 5% significance level (SL) and 80% power. In order to ensure that we have data on this number as a minimum, it is intended to randomise 30 patients into each treatment group; ie, a total of 60 patients.

12.4 Data monitoring committee (not applicable)

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 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 6.4.4.**

In the case of a medical emergency the investigator should contact the following personnel:

Name	Role in the study	Address & telephone number
Dr	Medical Monitor (study delivery team physician)	Quintiles, Inc
Dr	SDT Physician responsible for the protocol at central R&D site	AstraZeneca
Dr	Medical Science Director	AstraZeneca

13.2 Overdose

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

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

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

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

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

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

Male patients must refrain from fathering a child during the study and 3 months following the last dose (refer to Section 13.3.1).

Pregnancy of a patient's partner is not considered to be an adverse event. However, the outcome of any pregnancy occurring from the date of the first dose until 3 months after the last dose must be followed up and reported within 5 days to the Data Entry Site.

14. LIST OF REFERENCES

Angrill 2001
Angrill J, Agusti C, De Celis R, Filella X, Rano A, Elena M, et al. Bronchial inflammation and colonisation in patients with clinically stable bronchiectasis. Am J Respir Crit Care Med 2001;164:1628-1632.

Barker 2002
Barker AF. Bronchiectasis. N Engl J Med 2002;346:1383–1393.

Fuschillo 2008
Fuschillo S, De Felice A,Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. Eur Respir J 2008;31:396-406.

Hageman et al 2003
Hageman GJ, Larik I, Pennings HJ, Haenen GR, Wouters EF, Bast A. Systemic poly(ADP-ribose) polymerase-1 activation, chronic inflammation, and oxidative stress in COPD patients. Free Radic Biol Med 2003;35(2):140-8.

Holz et al 2010
Holz O, Khalilieh S, Ludwig-Sengpiel A, Watz H, Stryzsak P, Soni P, et al. SCH527123, a novel CXCR2 antagonist, inhibits ozone induced neutrophilia in healthy subjects. Eur Respir J 2010 35(3):564-570.

Khalilieh et al 2007a
Khalilieh S, Tsai M, de Vries D, Kraan M. Rising single-dose safety and pharmacokinetics of oral SCH527123, a novel antagonist of CXCR2, in healthy volunteers. Eur Respir J [17th Annu Congr Eur Respir Soc (ERS) (Sept 15-19, Stockholm) 2007] 2007, 30(Suppl. S1): Abst P3599.

Khalilieh et al 2007b
Khalilieh S, Tsai M, van Marle S, Kraan M. Rising multiple dose safety and pharmacokinetics of oral SCH527123, a novel antagonist of CXCR2, in healthy smokers. Eur Respir J [17th Annu Congr Eur Respir Soc (ERS) (Sept 15-19, Stockholm) 2007] 2007, 30(Suppl. S1): Abst P3597.

Khalilieh et al 2007c
Khalilieh S, Kassera C, Tsai M, Seiberling M, Kraan M. Effects of oral SCH527123, a CXCR2 antagonist, on acquired immunity in healthy adults. Eur Respir J [17th Annu Congr Eur Respir Soc (ERS) (Sept 15-19, Stockholm) 2007] 2007, 30(Suppl. S1): Abst P3600.

Mahler et al 1984
Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984:85;751-758.

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.

Miller et al 2005
Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-338.

Perng et al 2004
Perng DW, Huang HY, Chen HM, Lee YC, Perng RP. Characteristics of airway inflammation and bronchodilator reversibility in COPD: a potential guide to treatment. Chest 2004;126(2):375-81.

Quanjer et al 1993
Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party: standardization of lung function tests. European community for steel and coal. official statement of the European respiratory society. Eur Respir J 1993;6Suppl:5-40.

Rutgers et al 2000
Rutgers SR, Timens W, Kaufmann HF, van der Mark TW, Koeter GH, Postma DS. Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD. Eur Respir J 2000;15(1):109-15.

Stoller et al 1986
Stoller JK, Ferranti R, Feinstein AR. Further specification and evaluation of a new clinical index for dyspnea. Am Rev Resp Dis 1986:134;1129-1134.

Traves et al 2002
Traves SL, Culpitt SV, Russell RE, Barnes PJ, Donnelly LE. Increased levels of the chemokines GROalpha and MCP-1 in sputum samples from patients with COPD. Thorax 2002;57(7):590-5.