Clinical Study Protocol

Drug Substance	AZD9668
Study Code	D0520C00014
Edition Number	1
Date	

A 12-week, Phase-II, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multi-Centre Study to Assess the Effect of 60 mg AZD9668 Administered Orally Twice Daily on Structural Changes in the Airways by Multi-Slice Computed Tomography (MSCT) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Sponsor:

AstraZeneca AB, .

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

Amendment Number	Date of Amendment	Local Amendment Number	Date of Local Amendment

Administrative change Number	Date of Administrative Change	Local Administrative change Number	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A 12-week, Phase-II, Double-Blind, Placebo-Controlled, Randomised, Parallel-Group, Multi-Centre Study to Assess the Effect of 60 mg AZD9668 Administered Orally Twice Daily on Structural Changes in the Airways by Multi-Slice Computed Tomography (MSCT) in Patients with Chronic Obstructive Pulmonary Disease (COPD)

International Co-ordinating Investigator

Professor, MD,

Study centre(s) and number of patients planned

The plan is to randomise approximately 50 patients in Canada and Europe. Approximately 15 centres are planned to participate with 3 to 10 patients per centre.

Study period	**Phase of development**
Estimated date of first patient enrolled Q1,	IIb
Estimated date of last patient completed Q4,	

Objectives

The primary objective of the study is to evaluate structural changes effected by AZD9668 in the airways of adults with Chronic Obstructive Pulmonary Disease (COPD) by Multi-Slice Computed Tomography (MSCT).

The secondary objectives of the study are:

- to relate structural changes in the airways to pulmonary function variables and symptoms of COPD.
- to evaluate safety of AZD9668 in COPD patients.

The exploratory objectives of the study are:

- to investigate the effects of AZD9668 on urine desmosine in COPD patients
- to collect samples for possible retrospective pharmacogenetics analysis to investigate influence of genotypic variation on response.

Study design

This is a 12-week randomised, double-blind, placebo-controlled, parallel-group, multi-centre phase IIb study to assess the effect of orally administered 60 mg AZD9668 twice daily on structural changes in the airways by MSCT in COPD patients.

Target patient population

Included patients, men and women, must be 50 to 80 years of age inclusive and have a clinical diagnosis of COPD. The patients' postbronchodilator FEV_1 must be 40 to 70% of the predicted normal value and FEV_1/FVC must be <70%, post-bronchodilator. Patients must also be ex-smokers and have a smoking history of 10 or more pack years.

Investigational product, dosage and mode of administration

AZD9668, 60 mg (2 x 30 mg tablets) administered orally twice daily.

Comparator, dosage and mode of administration

Placebo (matching the investigational product).

Additional drug, dosage and mode of administration

Tiotropium bromide (Spiriva®) 18 µg/dose, 1 oral inhalation once daily as maintenance medication.

Short-acting β_2-agonists (SABA), as needed to relieve COPD symptoms.

Duration of treatment

An enrolment period of 1 - 21 days depending on pre-study medication, followed by a 2-week run-in period, a 12-week treatment period and a 2-week follow-up period. The total duration of the study is 16 to 19 weeks.

Outcome variable(s):

- **Efficacy**

  The primary efficacy variable for the study is airway wall thickness, as defined by AWT-Pi10 (airway wall thickness of a theoretical airway with an internal perimeter of 10 mm), measured in segmental and subsegmental airways.

  The secondary efficacy variables are:

  - 5^{th} generation wall area %
  - air trapping index (ATI) on expiratory scans
  - pre-bronchodilator Inspiratory Capacity (IC), Total Lung Capacity (TLC), Functional Residual Capacity (FRC), Residual Volume (RV) and Specific Airway Conductance (SGaw)
  - pre-bronchodilator DL_{CO}
  - pre- and post-bronchodilator Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) and Slow Vital Capacity (SVC)
  - Peak Expiratory Flow (PEF) and FEV_1 morning and evening (daily recordings)
  - use of reliever medication
  - exacerbations.

- **Patient reported outcomes (PROs)**

  - Breathlessness, Cough and Sputum Scale (BCSS)
  - EXAcerbations of Chronic pulmonary disease Tool (EXACT)
  - St George's Respiratory Questionnaire for COPD patients (SGRQ-C).

- **Safety**

  - adverse events (nature, incidence and severity)
  - clinical laboratory variables including clinical chemistry, haematology and urinalysis

- vital signs
- 12-lead ECG
- physical examination.

• **Exploratory**

- MSCT variables:
  - volume adjusted 15th percentile density (PD15)
  - mean wall area % for airways of 4th to 6th generation
  - emphysema index (or relative area)
- Pharmacodynamics:
  - urine biomarkers, including, but not limited to desmosine (creatinine normalised)
- Pharmacogenetics:
  - please refer to Appendix D.

Statistical methods

The analysis set for efficacy will be based on the Full Analysis Set in line with the ICH E9 guidelines.

The outcome variables from the MSCT will be compared between AZD9668 and placebo using an Analysis of Variance (ANOVA) model with fixed factors treatment and country and using baseline as a covariate. A 90% confidence interval will be constructed for the treatment difference and p values given. Plots of MSCT variables vs clinic lung function variables will be produced.

Analysis of lung function data, diary data and PROs will be analysed using an ANOVA model in a similar manner to the MSCT variables.

The incidence of adverse events will be calculated and results from laboratory safety measurements, vital signs and ECG will be analysed primarily by means of descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ANOVA	Analysis of Variance
ATI	Air Trapping Index
ATS	American Thoracic Society
AWT-Pi10	Airway wall thickness of a theoretical airway with an internal perimeter of 10 mm
BCSS	Breathlessness, Cough & Sputum Scale
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CT	Computer Tomography
DAE	Discontinuation due to Adverse Event
DL_{CO}	Diffusion Capacity of Carbon Monoxide
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ERS	European Respiratory Society
EXACT-PRO	EXAcerbations of Chronic pulmonary disease Tool – Patient Reported Outcome
FEV_1	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Glucocorticosteroids
HU	Hounsfield Unit
IC	Inspiratory Capacity

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
iGCS	Inhaled Glucocorticosteriod
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.
IPS	Investigational Products AstraZeneca R&D
ISF	Investigator's Study File
LABA	Long-acting β_2-agonist
MC	Marketing Company
MSCT	Multi-Slice Computer Tomography
mSv	milliSievert
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 11.2.1)
PD15	15th Percentile Density
PEF	Peak Expiratory Flow
PGx	Pharmacogenetics
PRO	Patient Reported Outcome
QTcB	QT corrected according to Bazett's formula
RV	Residual Volume
SABA	Short-acting β_2-agonist
SAE	Serious adverse event (see definition in Section 6.4.2)
SGaw	Specific Airway Conductance
SGRQ-C	St George's Respiratory Questionnaire for COPD patients
SRC	Safety Review Committee
SVC	Slow Vital Capacity
TLC	Total Lung Capacity
ULN	Upper Limit of Normal

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

COPD is the fourth leading cause of mortality in the United States of America (USA), (US Department of Health and Human Services 2007), and worldwide is projected to rank fifth in burden of disease in 2020 (Lopez AD and Murray CJL 1998). It is characterized by airflow limitation that is not fully reversible, and this is associated with an abnormal chronic inflammatory response in the respiratory system to noxious particles or gases (GOLD 2008). Currently, the mainstay treatment of airflow limitation is bronchodilators. Despite a prominent inflammatory response in the airways in COPD, in contrast to asthma, anti-inflammatory therapy with corticosteroids have limited efficacy. Therefore, there is a need to explore the possibilities of developing other therapies for COPD.

Neutrophils are recognized as major cellular mediators of inflammation and play a central role in many of the features of COPD. Neutrophil elastase (NE), a serine protease found in high levels in neutrophils, is able to degrade extracellular matrix and proteins leading to the destruction of the lung parenchyma. Inhibition of NE therefore has the potential to inhibit this proteolytic lung destruction raising the possibility of halting the progressive decline in lung function that is characteristic of COPD. If, as predicted from *in vivo* animal studies, NE inhibition can affect not only lung destruction but also epithelial metaplasia, goblet cell hyperplasia and the loss of cilia caused by exposure to cigarette smoke, as well as infiltration of inflammatory cells, shorter-term symptomatic benefits are also possible with this approach.

AZD9668 is a potent, orally active, selective, reversible inhibitor of human NE that is being developed as a possible therapeutic agent, both for symptomatic treatment as well as disease modification in COPD.

In pre-clinical toxicology studies of AZD9668, minor effects on haematological parameters (indicative of increased turnover of erythrocytes) and renal function (small increases in plasma creatinine) were observed. Effects on liver function and cardiovascular parameters have also been observed. In mice, an increased incidence of minimal to slight focal necrosis in the liver was noted. Overall this effect is regarded as a non-specific response in mice, and the relevance for humans is likely to be limited. A small effect on QT interval was observed at high doses in dogs that occurred at plasma exposures well above the maximum exposure expected in humans.

The safety, tolerability and pharmacokinetics of AZD9668 have been investigated in 2 healthy volunteer studies and 1 study in COPD. The first of these was a single and multiple ascending dose study in healthy volunteers. AZD9668 was administered at single doses of 2 mg, 10 mg, 30 mg, 60 mg, 120 mg and 150 mg to 36 subjects, and at multiple doses of 30 mg, 70 mg and 120 mg once daily for 8 days to 18 subjects. In the second healthy volunteer study, 32 subjects were randomised in 2 cohorts, each comprising 8 Japanese and 8

Caucasian subjects. Six subjects in each cohort received 2 single ascending doses (Cohort 1, 30 and 60 mg; Cohort 2, 90 and 120 mg) and 1 multiple dose (Cohort 1, 30 mg bid; Cohort 2, 70 mg bid for 6.5 days) of AZD9668. In the third study, 12 subjects with COPD received AZD9668 60 mg twice daily for 14 days. All these studies were double-blind and placebo-controlled. In all 3 studies, the drug was well tolerated. There was no evidence of clinically relevant changes related to AZD9668 in clinical chemistry, haematology or ECG parameters. In the COPD study, where lung function was measured, there was no adverse effect on lung function.

There have been 2 further proof of principle studies of the efficacy of AZD9668 60mg twice daily in patients with bronchiectasis and cystic fibrosis. The bronchiectasis study has been completed and is in the process of being reported. In this study, 1 patient treated with AZD9668 had raised transaminases during treatment with AZD9668 however there were no associated changes in bilirubin or other liver function tests. A relationship of these changes to study drug cannot be excluded for this patient. This or a similar pattern of liver function changes, has not been seen in any other patients or healthy volunteers treated with AZD9668. The cystic fibrosis study is ongoing, and to date there have been no safety issues of concern.

A parallel phase IIb proof of concept study (D0520C00012) is currently in the recruitment phase, with tiotropium as the background maintenance therapy for COPD.

Further details of the preclinical toxicology, clinical pharmacology and safety of AZD9668 can be found in the Investigator Brochure (IB). Details of the optional pharmacogenetic component of this study are given in Appendix D.

1.2 Research hypothesis

AZD9668 is a novel agent, which by its inhibitory action on NE could prevent structural degradation of lung parenchyma and remodelling of airways. Inhibition of the effects of NE on inflammation and mucus glands could also lead to a reduction of inflammation within the airway wall and a reduction in wall thickness, with a corresponding improvement in airway physiology. It is postulated that these airway wall changes will be detectable by computed tomography (CT) within 12 weeks. Additionally, these may translate to an improvement in lung function and an improvement in the signs and symptoms of COPD.

1.3 Rationale for conducting this study

Alterations in the structure of the airways, collectively termed airway remodelling, and destruction of the lung parenchyma (or emphysema) are the two key pathological processes that contribute to air flow limitation in COPD. Airway remodelling is defined as changes in the composition, content and organization of the cellular and molecular constituents of the airway wall. These changes can lead to thickening of the airway wall and narrowing of

the lumen of the airways, which in turn can exaggerate the effects of airflow obstruction caused by airway smooth muscle contraction.

Recent technical advances in CT allows accurate, reproducible measurements of the structural changes of the airways and lung parenchyma, non-invasively, in patients with COPD. With multi-slice CT scanners (MSCT) in particular, it is now possible to acquire thin-slice images of the whole chest, often known as volumetric imaging, with 0.5 to 1 mm thick slices during a single breath-hold, with acceptable radiation exposures.

Use of CT in COPD to assess lung parenchyma and the airways has been validated by population based longitudinal and cross-sectional studies (Coxson HO 2008, Kim WJ et al 2009, Naunheim KS et al 2006). Changes of airway dimensions due to wall thickening in the airways of 3rd to 6th generation (transition between large and small airways) correlated well with airflow limitation (Hasegawa M et al 2009). CT measurements of airways with a Pi of 0.75 mm or more can be used to estimate the dimensions of the small conducting airways, which is the major site of airway obstruction in COPD (Nakano Y et al 2005).

The current study aims to establish structural endpoints assessed by MSCT related to airway wall thickness as an efficacy endpoint. A standardized measure for airway wall thickness can be derived by plotting the square root of the airway wall area against the internal perimeter of each measured airway that is cut in cross section on the chest CT, and using the resulting regression line to calculate the wall area for a "theoretical airway" with an internal perimeter of 10 mm (AWT-Pi10). Airway changes measured in this manner have been shown to respond to anti-inflammatory treatments (steroids) and bronchodilators within 12 weeks, and provide accurate structural information related to the changes in both proximal and distal airways (Capraz F et al 2007, Niimi A et al 2004). As NE has proinflammatory effects and effects on mucus glands and goblet cells, a NE inhibitor such as AZD9668 can be envisaged to have effects on airway remodelling that could manifest as a reduction in the airway wall thickness similar to that seen with steroid in asthma. A treatment period of 12 weeks is deemed sufficient to show such an effect of AZD9668 on the airways.

Another approach for studying airways that are too small to visualize on CT is to perform expiratory scans, and assess the extent and degree of air trapping. Small airways disease causes early airway closure during expiration and air trapping in the alveoli supplied by the closed airway. The extent of air trapping therefore is an indirect index of the extent of small airways disease. Air trapping is manifested physiologically as an increase in residual volume (RV) or by an increase of the ratio of RV to total lung capacity (TLC). It is a significant determinant of the exercise capacity and has been used in clinical trials to measure treatment efficacy in COPD patients (Stav D and Raz M 2009). CT provides accurate estimates of the total volume and weight of the two lungs combined, as well as regional volume changes related to inspiration and expiration (Coxson HO et al 1995), and can provide an index

of air trapping. The normal specific volume of the lung at TLC is shown to be 6.0 mL/g, corresponding to a CT density of -856 Hounsfield Units (HU). Hence at functional residual capacity (FRC) percentage of pixels below a threshold of –856 HU on expiratory CT scan (Air Trapping Index) has shown good correlation with measures of airtrapping such as RV and RV/TLC ratio (Jain N et al 2005).

A timeframe of 12 weeks is considered too short to clearly detect any changes to the CT measurements for the extent of emphysema (PD15 and Emphysema Index). These parameters are included in this study as exploratory variables to explore potential trends. However, urine desmosine is included as a biomarker of lung matrix degradation, which could potentially show a change within 12 weeks of treatment aimed at preventing tissue degradation.

The study will also provide knowledge and learning about the conduct, feasibility, endpoint variability and sensitivity in patients with COPD treated with AZD9668. It is expected that a 3-month timeframe will be sufficient to observe changes in airway wall thickness that could be attributed to anti-inflammatory effects of treatment and that could be associated with functional changes. Information from the study, taken together with information from the two large clinical endpoint Phase IIb trials being conducted in parallel, will be used to design a longer, larger imaging study or studies with AZD9668 during the Phase III programme.

It is also intended in this study to obtain further safety and tolerability data on AZD9668 in COPD subjects to establish if AZD9668 has an acceptable benefit-risk profile.

1.4 Benefit/risk and ethical assessment

A detailed assessment of the overall risk/benefit of developing a NE inhibitor in COPD is given in the Investigator's Brochure (IB).

COPD is an area of high unmet medical need, and given the possible multiple biological effects of NE and it's possible roles in COPD, orally active NE inhibitors have represented a compelling target for drug development for quite some time. However, development efforts to directly test this concept have so far been hampered by the failure to find a drug with adequate PK, exposure and tolerability.

AZD9668 inhibits NE and is therefore expected to be of clinical benefit in patients with COPD. It binds non-covalently and reversibly to NE and the pharmacokinetics support twice daily oral dosing. This may give AZD9668 a better tolerability/safety profile, and hence a chance to succeed in chronic therapy of COPD, both for symptom control (by its anti-inflammatory and anti-secretory effects) and disease modification (by its effects on preventing lung destruction).

Two Phase I studies, a Phase IIa safety and tolerability study in patients with COPD (12 patients treated with AZD9668) and a Phase IIa study in patients with bronchiectasis (22

patients treated with AZD9668) have been completed, and a Phase IIa study in patients with cystic fibrosis is ongoing. AZD9668 was generally well tolerated in these studies. One patient in the bronchiectasis study had raised transaminases during treatment with AZD9668 however there were no associated changes in bilirubin or other liver function tests. A relationship to study drug for this patient could not be excluded. This or a similar pattern of liver function changes, has not been seen in any other patients or healthy volunteers treated with AZD9668. To minimise any possible risk of liver effects to patients, patients with an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level ≥ 1.5 x upper limit of normal (ULN) will be excluded from the study. Study drug will be discontinued if patients have an ALT/AST level ≥ 3 x upper limit of normal, or if patients develop any pattern of liver function test abnormality that the Investigator or AstraZeneca considers as indicating an unacceptable level of risk to the patient. A guidance document has been created for the follow up of both liver function parameters that reach the discontinuation criteria, and also those that have not reached the discontinuation criteria but are of concern, see Section 5.8.

To mitigate the other risks that may be associated with the pre-clinical signals summarised in Section 1.1, in addition to standard inclusion/exclusion criteria, subjects with an estimated creatinine clearance of <50 mL/min will be excluded from the study (see Section 4.3). Haematological and biochemical parameters including evidence for haemolysis will be monitored during the study. Although no significant QT abnormalities were observed in clinical studies to date, patients with a prolonged QTc value will not be enrolled. A 12 lead ECG will be recorded at screening, prior to the first dose of AZD9668 at the randomisation visit and around 4 hours post-dose at this visit and at regular intervals during the study thereafter. Patients will be withdrawn if they develop QTc > 500 msec or a prolongation of QTc > 60 msec compared to baseline.

Additionally, an Independent Safety Review Committee (SRC) will review the safety data on an ongoing basis, throughout the study (see Section 12.4 for further details).

To minimise the variability of the response to AZD9668 that could occur as a result of patients being on different background medications for COPD, all patients will be standardised to maintenance therapy with tiotropium. This will entail patients on inhaled GCS (including combination therapy with LABA) being withdrawn from that treatment, and switched to tiotropium only. However, this would only be done with the patient's express consent and if the investigator assesses that it is safe to do so. To mitigate the risks associated with inhaled GCS withdrawal, only patients with an FEV_1 of ≥40 % of predicted normal value will be recruited to this study. Also, as all patients will receive tiotropium, the risk of inhaled GCS withdrawal in a short-term study is considered to be small. Additionally, patients will be closely monitored during the run-in period and throughout the study with daily FEV_1 and PEF measurements and symptom diaries.

The use of MSCT involves ionizing radiation that increases the risk of radiogenic tumors in patients. The data related to biological effects of CT radiation and recommendations from different committees has been considered in the design of the study (Mayo JR 2008). The risk is known to be age and gender dependant and higher in children, young adults, women, and pregnancy (high radiosensitive group). The risk from radiation exposure is known to be cumulative, and may involve other factors like use of contrast agents. MSCT has been applied in several clinical studies for COPD and asthma and the risk-benefit evaluation has been done, and literature is available. AstraZeneca has considerable experience in appplicaton of CT imaging for COPD and has been involved in population studies and cross sectional studies (Brown RH et al 2005, Coxson HO et al 2008b, Capraz F et al 2007, Lee YM et al 2004). The understanding of the risk – benefit aspects helps in optimising the CT radiation dose to the endpoint. Since the participation in the present study may not offer direct benefit to the patient, a dose constraint will be applied based on ALARA (As Low As Reasonably Achievable) principle. Detailed information on the potential risks of radiation, the aims, methods, benefits and potential hazards of the study will be given to patient during the informed consent process.

The total radiation dose for the study is expected to be around 10 – 12 mSv. This dose is close to accepted radiation dose for biological research (1 to 10 mSev). In the present study the radiosensitive group has been therefore excluded to a major extent.The older demographic of patients fall into a low risk profile for risk of radiation, and the laboratory safety results from Visit 1b must be reviewed and considered eligible prior to baseline scan to avoid any unnecessary radiation exposure. The selection of patients includes male and female patients aged 50 - 80 years. Each patient will receive 4 scans, 2 scans (a paired inspiratory and expiratory scan) at each visit, 3 months apart. The imaging protocol and study design is based on the EU guidance (See Guidance document). The potential benefits of the study are expected to be Category IIB (aimed directly at the diagnosis, cure or prevention of disease). Since this is a study to establish the feasibility of a clinical trial in COPD evaluated by MSCT the study has not been adequately powered to demonstrate efficacy but only to detect a trend.

The study design chosen for this study is considered to optimal to detect a clinically meaningful effect of AZD9668 while the safety risks are minimised. The benefit/risk balance of using AZD9668 in the present study in patients with COPD can therefore be considered acceptable.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to evaluate structural changes effected by AZD9668 in the airways of adults with COPD by MSCT.

Primary outcome variable aligned to the primary objective:

- AWT-Pi10 (airway wall thickness of a theoretical airway with an internal perimeter of 10 mm) (See Section 3.2.3)

Secondary outcome variables aligned to the primary objective:

- 5^{th} generation wall area % (See Section 3.2.3)
- Air Trapping Index (ATI) on expiratory scans (See Section 3.2.3)

Exploratory outcome variables aligned to the primary objective:

- Volume adjusted 15^{th} percentile density (See Section 3.2.3)
- Mean wall area % for airways of 4^{th} to 6^{th} generation (See Section 3.2.3)
- Emphysema index (or relative area) (See Section 3.2.3)

2.2 Secondary objective(s)

The secondary objectives of the study are:

- To relate structural changes in the airways to pulmonary function variables and symptoms of COPD
- To evaluate safety of AZD9668 in COPD patients

Outcome variables aligned to these objectives are:
Lung function parameters

- pre-bronchodilator IC, TLC, FRC, RV and SGaw
- pre-bronchodilator DL_{CO}
- pre- and post-bronchodilator FEV_1, FVC and SVC
- PEF morning and evening (daily recordings)
- FEV_1 morning and evening (daily recordings)

Symptoms

- Breathlessness, Couch and Sputum Scale (BCSS)

- EXAcerbations of Chronic Pulmonary disease Tool (EXACT)
- St George's Respiratory Questionnaire for COPD patients (SGRQ-C)
- Use of reliever medication
- Exacerbations

Safety

- AEs
- Heamatology
- Clinical chemistry
- Urinalysis
- Vital signs
- 12-lead ECG
- Physical examination

2.3 Exploratory objectives

The exploratory objectives are:

- To investigate the effects of AZD9668 on urine desmosine in COPD patients.
- To collect samples for possible retrospective pharmacogenetics analysis to investigate influence of genotypic variation on response.

Exploratory outcome variables aligned to these objectives are:

- Urine biomarkers, including but not limited to desmosine (creatinine normalised).
- Pharmacogenetics, please refer to Appendix D for further details.

None of the exploratory objectives will form part of the Clinical Study Report.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This is a 12-week randomised, double-blind, placebo-controlled, parallel-group, multi-centre phase IIb study to assess the effect of AZD9668 on structural changes in the airways in COPD patients. The primary variable is AWT-Pi10 assessed by MSCT.

The plan is to enrol approximately 70 patients, men and women aged 50 to 80 years inclusive, to obtain approximately 50 randomised patients. Approximately 15 centres in Canada and Europe are planned to participate in the study with 3 to 10 patients per centre.

There will be 8 visits to the clinic: Visit 1a (enrolment), Visit 1b (screening), Visit 2 (randomisation), Visits 3, 4, 5 and 6 (after 1, 4, 8 and 12 weeks of treatment) and Visit 7 (follow-up).

All inclusion/exclusion criteria that can be assessed at each visit should be checked carefully, including patients suitability to use electronic devices/perform home spirometry, before therapy is changed and before randomisation.

At Visit 1a all patients will be informed about the study and, if willing to take part in the study, sign the informed consent form and have demographic data collected. Signing the informed consent form must be done before any study-related procedures, restrictions or screening assessments are performed. The timing of this visit in relation to Visit 1b will be dependent on the medication being taken by the patient on entry to the study as described in Section 5.5.3.2.

At Visit 1b, all patients must be on tiotropium alone as maintenance therapy. In addition to tiotropium maintenance therapy, patients will be allowed to use short-acting β_2-agonists (SABA) as reliever medication throughout the study. See Section 5.5.3.2 regarding provision of tiotropium and SABA.

At Visit 1b, patients will be screened and evaluated for eligibility to enter the 14-17 day run-in period. Included patients must have a documented COPD history with symptoms for at least 1 year according to GOLD 2008, and they must be ex-smokers with a smoking history of at least 10 pack years. Their FEV_1 must be 40 - 70% of the predicted normal value and FEV_1/FVC <70%, both values post-bronchodilator.

Included patients will be asked to fill in an electronic diary and to measure FEV_1 and PEF morning and evening from Visits 1b to 6.

To be randomised to the 12-week treatment period a visually acceptable MSCT scan with no clinically relevant abnormal CT findings must have been performed 2 to 7 days before Visit 2. Before the patient has the baseline MSCT scan the laboratory safety results from Visit 1b must be reviewed and considered eligible (refer to exclusion criterion 8). The patient must also show complete morning recordings of daily FEV_1 data at least 10 of the last 14 days before Visit 2.

At Visit 2 eligible patients will be randomised to either

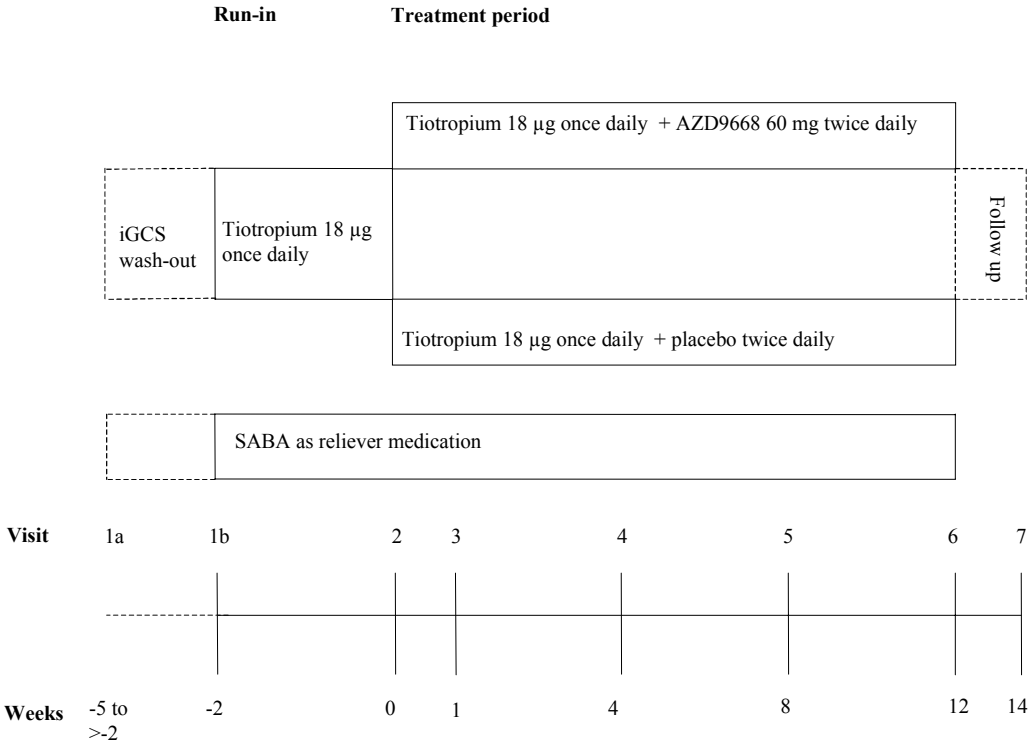
- AZD9668, 60 mg twice daily
- placebo to match AZD9668

Two weeks after stopping study medication there will be a follow up visit.

An independent safety review committee will review available safety data, see Section 12.4.

The pharmacogenetic part of the study is described in Appendix D.

Figure 1 Study Flow Chart



Refer to Table 1, Visit Schedule, and Table 2, Study Plan, for further details of visits and assessments.

Table 1 Visit schedule

Visit No.	Type of Visit	No. of weeks ± no of days between visits
1a	Enrolment Visit	Patients not taking inhaled glucocorticosteroids (iGCS): before Visit 1b depending on previous medication Patients on iGCS: >3 weeks before Visit 1b
1b	Screening Visit	14-17 days before Visit 2
2	Randomisation Visit	Day 1
3	Treatment visit	1 week ±1 day after Visit 2
4	Treatment visit	4 weeks ±3 days after Visit 2

(Continued)

Table 1 Visit schedule

Visit No.	Type of Visit	No. of weeks ± no of days between visits
5	Treatment visit	8 weeks ±3 days after Visit 2
6	End of treatment visit	12 weeks -3 days after Visit 2
7	Follow-up Visit	14 weeks ±3 days after Visit 2

Table 2 Study Plan

Study Visit	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Written informed consent	x							
Demography (date of birth, sex and race)	x							
Physical examination		x	x	x	x	x	x	x
Height/Weight		x					x (weight only)	
Medical/surgical history		x						
COPD history		x						
Smoking history		x						
Smoking habits			x				x	
MSCT (pre-visit, see Section 6.3.1)			2 to 7 days before Visit 2				0 to 3 days before Visit 6	
Clinical chemistry, haematology and urinalysis[b]		x	x	x	x	x	x	x
Pregnancy test[a]		x	x					x
Inclusion/exclusion criteria	x	x	x					
Randomisation			x					
Vital signs, 12-lead ECG[b]		x	x[c]	x	x	x	x	x
Spirometry (FEV_1, FVC, SVC)[b]		x	x	x	x	x	x	
Body Plethysmography (IC, TLC, FRC, RV, SGaw)[b]			x				x	
DL_{CO}[b]			x				x	
Dispense maintenance and reliever drugs	(x)	x	(x)	(x)	(x)	(x)		

(Continued)

Table 2 Study Plan

Study Visit	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Administer AZD9668 morning dose at clinic after spirometry			x	x	x	x	x	
AZD9668/placebo Dispense/ Check/ Return (d/c/r)			d		d / c / r	d / c / r	c / r	
e-PRO / Home spirometry device[d] training/ dispense/ check/ return (t / d / c / r)	(t)	t / d	c	c	c	c	c / r	
BCSS, EXACT, FEV_1, PEF and intake of study drugs - assessed at the patient's home		x ---------- x						
SGRQ-C[b]		(x)[e]	x				x	
Desmosine urine sampling			x		x		x	
Concomitant medications recorded	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x
Exacerbation recording		x	x	x	x	x	x	x
Pharmacogenetics blood sampling (optional)[f]			x					

a Pregnancy tests at Visit 1b and 7 to be taken in blood and pregnancy test at Visit 2 to be taken in urine.

b Assessments to be done pre-dose of AZD9668 at Visits 2-6.

c A second ECG and vital signs measurement should be done 3-4 hours post-dose of AZD9668 at Visit 2.

d ePRO including BCSS and EXACT questionnaires, Questions on intake of study drugs and Spirometry measurements of PEF and FEV_1,

e Training session, data not to be collected in study database.

f Only 1 pharmacogenetic sample is required. This should be taken at Visit 2 or any subsequent visit once separate written informed consent has been obtained.

3.2 Rationale for study design, doses and control groups

The rationale for conducting this study in patients with COPD is given in Section 1.3. The rationale for the optional pharmacogenetics component of the study is included in Appendix D.

3.2.1 Rationale for patient population and control groups

The patients with a FEV_1 range of 40 – 70% predicted are selected for this study with the expectation that at these levels of FEV_1 they will have sufficient airways disease detectable by CT and that be able to show a response to treatment, while avoiding patients with too severe disease who may deteriorate on withdrawal of ICS/LABA. To reduce the radiation risk only patients aged 50 years or above will be enrolled as older patients have a reduced risk of cancer from ionising radiation.

To minimise the variability that could occur as a result of patients being on different medications for COPD, all patients will be standardised to maintenance therapy with tiotropium.

To provide a comparator for the treatment effects of AZD9668 a placebo group is chosen as a standard design for estimating efficacy.

3.2.2 Rationale for study design

The study will be randomised, placebo-controlled and double-blind to ensure a robust design and minimise bias, which could compromise the conduct of the study and/or interpretation of the results.

3.2.3 Rationale for the selection of outcome variables

The end-points chosen as primary and secondary variables are those that could be expected to improve with an anti-inflammatory drug in airways disease.

MSCT variables

The airway wall thickness on inspiratory scan (AWT-Pi10), which represents the wall changes over the entire airway tree, is selected as the primary variable as similar measurements (such as Wall Area Percentage, WA%) have been shown to respond to anti-inflammatory treatment in obstructive lung disease like asthma in 12 weeks.

Wall changes in 5^{th} generation airways have been shown to correlate well with lung function changes (Matsuoka S et al 2008, Coxson HO et al 2008a). Air Trapping on expiratory CT is known to correlate well with symptom scores and physiological air trapping (Lee YK et al 2008). Airway wall thickness and wall area % of airways from 4^{th} (sub-segmental) to 6^{th} generation airway tree will be evaluated to see any specific

changes related to small airways (Hasegawa M et al 2005, Hogg JC 2006). Lung density will be measured using a cut-off of -856HU, -910 HU and -950 HU on inspiratory scan to measure the extent of emphysema (Density mask method). The extent of emphysema will be represented as a percentage of lung that is emphysematous (relative area). Lung density will be measured using the histogram method to identify the extent of emphysema in the inspiratory scan over whole lung field. To accommodate for any small volume differences the PD15 values will be corrected for lung volume (Adjusted density = observed density x observed volume / predicted TLC) as described in Dirksen A 2008.

3.2.4 Rationale for dose consideration and treatment duration

A dose of 60 mg twice daily has been chosen for this study since this is the highest dose expected to be well tolerated, whilst achieving steady state concentrations and is shown to produce 90% inhibition of zymosan stimulated NE activity in whole blood (based on previous study data), which is assumed to be directly related to the clinical effects.

A 3 month treatment duration is considered sufficient to show an effect on the primary and secondary variables (Capraz F et al 2007, Niimi A et al 2004), but will not apply to emphysema scores given the short study time frame.

4. PATIENT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Male or female aged 50-80 years inclusive at Visit 1b.
   Female patients may be of non-childbearing potential (ie, post menopausal or surgically sterile) or of child bearing potential:

   - Women will be considered post menopausal if they are
     i) over 50 years old and have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments or
     ii) over 57 years old

- Surgically sterile is defined as having undergone hysterectomy and/or bilateral oophrectomy and/or bilateral salpingectomy; tubal ligation on its own is not adequate

- Women will be considered of child bearing potential if they are between menarche and menopause, and have not been permanently or surgically sterilised. Women of child bearing potential must have a pregnancy test at Visit 1b and at Visit 2 prior to randomisation, and at the follow up visit, and must be using suitable methods of birth control. Further details of methods of birth control that are considered suitable for use are given in Section 5.1.

3. Documented clinical diagnosis of COPD, according to GOLD guidelines (GOLD 2008) with symptoms for ≥1 year before Visit 1b.

4. Ex-smokers for at least 12 months prior to Visit 1b.

5. A smoking history of at least 10 pack years (1 pack year = tobacco consumption corresponding to 20 cigarettes smoked per day for 1 year).

6. FEV_1 40-70% (inclusive) of the predicted normal value (post-bronchodilator) at Visit 1b.

7. FEV_1/FVC <70% (post-bronchodilator) at Visit 1b.

8. Able to use the handheld electronic devices (assessed at Visit 1a).

4.2 Randomisation inclusion criteria (at Visit 2)

For randomisation into the study at Visit 2 the patients must also fulfil the following criteria:

1. MSCT performed during the last 2 to 7 days before randomisation with acceptable quality and the whole lung is visible on the images, as judged by the radiologist visual read.

2. No clinically relevant abnormal findings in baseline CT besides CT changes related to COPD, (eg, congestive heart failure, lung cancer, tuberculosis, lung fibrosis, sarcoidosis, cystic fibrosis) which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to participate in the study.

3. Complete morning recordings of daily FEV_1 data at least 10 days out of the last 14 days before Visit 2.

4.3 Exclusion criteria

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

1. Any clinically relevant disease or disorder (eg, infectious/viral disease (including hepatitis B or C) cardiovascular, pulmonary other than COPD, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment), past or present, 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.

2. Significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension, or any other relevant cardiovascular disorder as judged by the Investigator.

3. Current diagnosis of asthma according to GINA guidelines (GINA 2008).

4. Malignancy or neoplastic disease within the past 5 years other than treated basal/squamous cell skin carcinoma or treated cervical cancer in situ.

5. Patients who require long term oxygen therapy (LTOT).

6. Worsening of COPD within 4 weeks prior to Visit 1b and during the run-in period (defined as an increase in respiratory symptoms requiring hospitalisation and/or a course of oral glucocorticosteroids and/or increased usage/dose of inhaled steroids and/or antibiotic treatment).

7. Acute infections requiring treatment in the 4 weeks prior to Visit 1b and during the run-in period.

8. Any clinically relevant abnormal findings in physical examination, vital signs, haematology, clinical chemistry, or urinalysis at Visit 1b, which in the opinion of the Investigator, may put the patient at risk because of his/her participation in the study, or may influence the results of the study, or the patient's ability to participate in the study.

9. A QTcB interval of >450 msec for males and >470 msec for females at Visit 1b.

10. Any ECG abnormality (including arrhythmia), which in the opinion of the investigator may put the patient at risk or interfere with study assessments at Visit 1b.

11. A past history of or current clinical or laboratory evidence of renal failure, or an estimated creatinine clearance of <50 mL/min (as calculated by the Cockcroft-Gault formula) at Visit 1b.

12. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) level ≥1.5 x upper limit of normal (ULN) at Visit 1b.

13. Pregnancy, breast-feeding or planned pregnancy during the study.

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

15. Previous randomisation to treatment in the present study.

16. Previous participation in a study with AZD9668.

17. Participation (defined as administration of at least 1 dose of investigational product) in another clinical study, the last follow-up visit of which is within 12 weeks of Visit 1b in this study.

18. Excessive alcohol consumption or known drug abuse, as judged by the investigator.

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

20. Patients scheduled for an intensive COPD rehabilitation programme. (Patients who are in the maintenance phase of a rehabilitation programme are eligible to take part.)

21. Known or suspected hypersensitivity to the investigational product or excipients or additional non-investigational study drugs provided for the study (tiotropium and reliever medication).

22. Patients with conditions that may worsen if treated with tiotropium, according to the prescribing information for tiotropium in each participating country.

23. Patient with an unremovable metallic object in the chest area (including piercing, pacemakers, stents).

24. Patient with a history of lung/cardiothoracic surgery in the past (lung volume reduction surgery, lung transplant, bypass etc.).

25. MSCT performed during the last 9 months before Visit 1b.

26. Presence of 1 or more non-calcified lung nodules with diameter ≥5 mm, identified from baseline MSCT scan.

Exclusion criteria for the pharmacogenetic part of the study are specified in Appendix D.

Procedures for withdrawal of incorrectly enrolled patients are described in Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

The following restrictions apply:

- Use of disallowed concomitant medication (refer to Section 5.6.3)
- All female patients must have a serum pregnancy test at Visit 1b and Visit 7. Women of child bearing potential must undergo an additional urine pregnancy test at Visit 2 prior to randomisation. Women of child bearing potential must be using highly effective methods of birth control:
  - Total sexual abstinence. Abstinence must be for the total duration of the study.
  - Vasectomised sexual partner (with participant assurance that the partner received post-vasectomy confirmation of azoospermia).
  - Tubal occlusion
  - Intra-uterine device (coils must be copper banded)
  - Intra-utrine system (IUS) (Levonorgestrel IUS eg, Mirena)
  - Medroxyprogesterone injections (Depo-provera)
- Prior to the clinic lung function tests:
  - No alcohol within 4 hours
  - No vigorous exercise within 2 hours
  - No large meals within 2 hours
  - No prohibited medication as listed in Section 5.6.3.1
- The patient should not start smoking during the study.

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

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

5.2 Patient enrolment and randomisation

The Principal Investigator will:

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

2. Assign the 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, 4.2 and 4.3.

4. Assign eligible patient unique randomisation code (patient number) at Visit 2.

Re-enrolment is allowed only if enrolment has failed due to technical problems, eg, with the eDiary. Patients failing to meet an inclusion or meeting an exclusion criterion must not re-enter the study. If a patient discontinue the study after randomisation he/she can not re-enter the study.

If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused. Patients who discontinue the study after randomisation will not be replaced.

5.2.1 Procedures for randomisation

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation. An eligible patient will be randomised to the lowest available randomisation code at the centre.

Randomisation codes will be computer generated by AstraZeneca R&D using the AstraZeneca Global Randomisation System (GRand). There will be no formal stratification.

5.3 Procedures for handling patients incorrectly enrolled or randomised

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 randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Delivery Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment.

The AstraZeneca Study Delivery Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

AZD9668 30mg will be provided as tablets for oral administration and with matching placebo tablets of the same appearance. Patients in both treatment arms will take the same dosage of investigational product ie, 2 tablets twice daily.

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 at the study centre. All code break envelopes must be kept in a safe but accessible place.

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

A patient whose randomisation code has been broken will be discontinued from the study (see Section 5.8).

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.

On completion of the study, the monitor will ensure and document the return of the code envelopes and also document the reason for any opened envelope, dated and signed by the principal investigator.

5.5 Treatment(s)

5.5.1 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer
AZD9668	Coated tablet 30 mg (corresponding to 39.5 mg AZD9668 tosylate)	AstraZeneca
Placebo to AZD9668	Coated tablet placebo	AstraZeneca

The formulation number and batch number will be recorded in the Study Master File and identified in the Clinical Study Report.

Tablets will be supplied at Visits 2, 4 and 5 in a box containing 2 bottles with 72 tablets each. This is sufficient for 28 days+/-3 days dosing twice daily plus overage.

5.5.2 Identity of additional study drugs

	Salbutamol sulphate, used as reliever medication during run-in and treatment period	Tiotropium bromide, used for maintenance treatment during run-in and treatment period
Trade Name:	See Section 5.5.3.2	Spiriva® given via HandiHaler®
Active ingredients:	salbutamol sulphate	tiotropium bromide
Excipients:	dependent on product provided	lactose monohydrate
Dosage form:	pMDI	inhalation powder, hard capsules
No. of doses:	200 actuations	30 capsules/package
Strength:	100 µg/dose	18 µg/dose
Manufacturer:	dependent on product provided	Boehringer Ingelheim

5.5.3 Doses and treatment regimens

5.5.3.1 Randomised treatment during treatment period

At Visit 2 patients will receive either AZD9668 tablets 30 mg or placebo tablets for oral use. Patients will take 2 tablets twice daily for 12 weeks, with doses approximately 12 hours apart. The patients will be issued with sufficient tablets to allow self-dosing until Visit 4.

At Visit 4 the patients will be issued with sufficient tablets to allow self-dosing until Visit 5.

At Visit 5 the patients will be issued with sufficient tablets to allow self-dosing until Visit 6.

The first dose of investigational product will be the morning dose taken in the clinic at Visit 2 after completing post-bronchodilator spirometry measurements. The last dose of investigational product will be the morning dose taken in the clinic at Visit 6. In the morning of Visit 3 to 6 the investigational product must not be taken at home. Instead it will be taken at the clinic after completing post-bronchodilator spirometry and other pre-dose clinical assessments. All other doses will be taken by the patient at home.

It is not necessary for the patients to restrict food around administration of their doses. All doses will be taken with water.

5.5.3.2 Open treatment during enrolment, run-in and treatment periods

Patients who use inhaled glucocorticosteroids (GCS) (including combination therapy with long-acting β_2-agonists (LABA) before the study should, based on the investigator's judgement that it is safe for the patient and after signing informed consent, stop inhaled GCS (including combination products) at Visit 1a, >3 weeks before attending the screening visit (Visit 1b), i.e., these patients will be on tiotropium for at least 5 weeks before randomisation. These patients will receive tiotropium at the same occasion (Visit 1a).

Patients not taking inhaled GCS prior to the study will begin treatment with tiotropium at Visit 1b. For these patients, Visit 1a can be performed closer to Visit 1b. The informed consent must be signed prior to any medications being withheld and timeframes for withholding medications taken into account (see Section 5.6.3). At Visit 1b, all patients must be on tiotropium alone as maintenance therapy.

Eligible patients will be enrolled to a 2 week run-in period, during which all patients will be treated with tiotropium 18 µg once daily.

The patients will be provided with maintenance and reliever medication throughout the run-in period and treatment period. Spiriva® (tiotropium bromide, 18 µg/dose, 30 capsules/package) will be provided by AstraZeneca R&D or be supplied locally by the AstraZeneca Marketing Company (MC). The reliever medication, Ventolin™ Evohaler™ (salbutamol sulphate 100 µg/dose, 200 actuations), will be supplied locally by the AstraZeneca MC or prescribed by the investigator. Products provided must contain the same active ingredient and use the same dosage form and be an equivalent strength as the medications specified in Section 5.5.2. When tiotropium and salbutamol are locally sourced local regulatory guidelines will be adhered to.

If the patient prefers to use their existing reliever medication (SABA only, dry powder inhalers are allowed) they may do so. If so, the same SABA should be used throughout the study.

When receiving the reliever and maintenance medications, the patient will be carefully instructed and trained on how to inhale from the inhalers to ensure good inhalation technique during the study. Written information will be provided to each patient in his/her local language.

Maintenance and reliever medication will be first dispensed at either Visit 1a or Visit 1b, depending on which COPD treatment patients use prior to the study. Maintenance and reliever medication will then be dispensed when needed at Visits 2 to 5. After Visit 6, the patients will return to their ordinary COPD treatment, at the discretion of the investigator.

Maintenance medication: Tiotropium 18 µg/dose will be given via HandiHaler® inhaler in an open manner, 1 oral inhalation every morning throughout the study. For patients on inhaled GCS (including combination therapy with LABA), Visit 1a should be > 3 weeks before Visit 1b to allow 3 weeks withdrawal of inhaled GCS and treatment with tiotropium before the run-in period. At Visit 1b all patients must be on tiotropium alone as maintenance therapy.

On visit days the maintenance medication will be taken at the clinic after completing spirometry (post bronchodilator) and other pre-dose clinical assessments.

Reliever medication: Salbutamol sulphate 100 µg/dose will be provided as reliever medication. The reliever medication provided by AstraZeneca should be used by the patient during the study period from Visit 1a/1b to Visit 6. If the patient chooses to use his/hers existing SABA as reliever medication during the study, the salbutamol inhaler provided by AstraZeneca should be used for all post-bronchodilator measurements at the clinic. Patients will be asked to refrain, if possible, from taking the reliever medication at least 6 hours prior to the clinic visits.

5.5.4 Labelling

The packaging and labelling of centrally provided study drugs will be performed by Investigational Products (IPS) AstraZeneca R&D or their designee. All supplies and labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The labels will include the following information:

- Name and address of sponsor
- Study drug dosage form, route of administration and quantity of dosage units
- Storage conditions

- Packaging Lot ID
- Study code
- Enrolment code and/or randomisation code
- Directions for use
- Expiry date
- Visit number (if applicable)
- The following standard statements
    - "for clinical trial use only" or similar wording
    - "keep out of the reach of children".

The bottles will be labelled with a single panel label. The boxes, containing 2 bottles, will be labelled with a 2-panel label. One part of the label will be permanently affixed to the box and the other part will be a tear-off part to attach to the drug accountability form in the Investigator's Study File (ISF) at the time of administration.

5.5.5 Storage

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

5.6 Concomitant and post-study treatment(s)

5.6.1 Medications allowed during the study

Medication allowed from Visit 1b:

- tiotropium alone as maintenance therapy. Patients should not take the morning dose at home on visit days.
- salbutamol (albuterol) sulphate or patient's own SABA as reliever medication. Patients will be asked to refrain from taking reliever medication at least 6 hours prior to clinic visits.
- other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator.

All medication, including study drugs, should be recorded in the appropriate sections of the electronic Case Report Form (eCRF).

5.6.2 Medications allowed for the treatment of exacerbations

Medication allowed from Visit 2 and throughout the study:

- Oral steroids, ie, prednisolone/prednisone
- Antibiotics when signs of infection are present
- Parenteral steroids (single injections but not depot formulations)
- All disallowed medications listed in Section 5.6.3 are allowed during emergency room treatment/hospitalization due to an exacerbation (except depot parenteral corticosteroids and non-cardioselective β-blockers).

5.6.3 Disallowed medications

5.6.3.1 Treatments to be withdrawn before/at Visit 1b until Visit 6

	Time limits prior to Visit 1b
Inhaled SABA (allowed throughout the study but withheld 6 hours prior to Visit 1b and Visits 2-6 if possible)	6 hours
Inhaled LABA	48 hours
Combinations of inhaled GCS/LABA	at Visit 1a, >3 weeks prior to Visit 1b
Oral β_2-agonists as follows: - short acting formulations - depot formulations - long acting formulations	8 hours 24 hours 48 hours
Transdermal β_2-agonists	24 hours
Parenteral β_2-agonists	48 hours
Inhaled short-acting anticholinergics	8 hours
Inhaled long-acting anticholinergics (except for tiotropium study drug which is allowed throughout the study but withheld 24 hours prior to clinic visits if possible)	24 hours
Xanthine-containing derivatives once daily	48 hours
Xanthine-containing derivatives twice daily	24 hours
Any medication containing ephedrine	24 hours

	Time limits prior to Visit 1b
Inhaled GCS	3 weeks
Oral, parenteral and rectal GCS	4 weeks
Depot parenteral GCS	12 weeks
Disodium cromoglycates, antihistamines and mucolytics (eg, N-acetylcystein)	At Visit 1b
Leukotriene antagonists and 5-Lipoxygenase (5-LO) inhibitors	48 hours

In addition, treatment with non-cardioselective β-blockers (including eye-drops) is prohibited from Visit 1b and throughout the study.

5.6.3.2 Treatments to be withdrawn before/at Visit 2 until Visit 6

	Time limits prior to Visit 2
Immunomodulatory agents	8 weeks
The following CYP2C9 substrates: - Phenytoin - Warfarin, coumarins - Fluvastatin - High dose, continuous Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (documented prn use of NSAIDs is allowed)	At Visit 2 At Visit 2 At Visit 2 At Visit 2

The last dose of study drug (tiotropium and investigational product) will be given at Visit 6. Patients will then return to their ordinary COPD treatment at the discretion of the investigator.

5.7 Treatment compliance

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF and the drug accountability/dispensing record. Investigational product accountability will be performed at Visits 4, 5 and 6. Intake of investigational product will be recorded in the eDiary morning and evening as “yes” or “no”. Intake of maintenance medication will be recorded in the morning eDiary as “yes” or “no”. This does not mean that the patient has an option not to take the study medications but will be used as a measures of compliance.

5.7.1 Accountability

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

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

The AstraZeneca monitor will ensure that all drug handling procedures are followed correctly. The destruction of used and unused study drug should preferably be done by the study site. If destruction at the study site is not possible, the monitor should return the study drug to the organisation responsible for distribution (for example the distribution site) and will account for all received study drugs and return all unused study drugs. All destruction of study drug must be done by an appropriately qualified organisation.

AstraZeneca personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

5.8 Discontinuation of a patient from the study

Patients may be discontinued from the study in the following situations:

1. Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

2. Severe non-compliance to study protocol as judged by the investigator and/or AstraZeneca

3. Risk to patients as judged by the investigator and/or AstraZeneca

4. Incorrectly enrolled patients

5. Patient lost to follow-up

6. Pregnancy

7. Treatment code prematurely broken by the investigator

Development of any of the specific discontinuation criteria listed below:

8. Change in QTcB >60 msec from baseline value (pre-dose Visit 2) or QTcB >500 msec, (to be confirmed by repeat ECG performed within 30-60 minutes of the initial assessment), or any other clinically significant ECG abnormality.

9. An ALT / AST level ≥ 3x upper limit of normal (ULN) (confirmed on repeat sample) or any pattern of liver function test (LFT) abnormalities that the investigator or AstraZeneca consider indicates an unacceptable level of risk to the patient. These events should be followed up as appropriate for the patient. A

guidance document for the follow-up of liver function parameters of concern is provided separately.

10. Evidence of haemolysis as evidenced by the following:

- Reticulocyte count of over 5%, **AND** at least 2 of the following:
  - a drop in haemoglobin below 10.5 g/dL
  - decrease of 25% in haptoglobin. (The value post-dose to be compared with the average of 2 pre-dose values. The value should also be 15% below lower limit of normal (LLN)
  - increase of 25% in unconjugated bilirubin or lactate dehydrogenase (LDH). (The value post-dose to be compared with the average of 2 pre-dose values. The value should also be 15% above upper limit of normal (ULN).

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

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

Withdrawal of consent for donated biological samples is included in Section 7.5.

5.8.1 Procedures for discontinuation of a patient from the study

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

For patients discontinuing during the enrolment period or run-in period, only assessment for AEs will be performed. The reason for discontinuation should be recorded in the eCRF.

If a patient discontinues participation in the study due to study specific discontinuation criteria no 8 to 11, this should always be recorded as “study specific discontinuation criteria met” on the termination form. In addition, the investigator has to assess whether the discontinuation should also be reported as a discontinuation due to adverse event (DAE) on the AE form.

If a patient discontinues after randomisation he/she should be asked to attend the end of treatment visit, Visit 6, and the follow-up visit, Visit 7. All assessments should be carried out at these visits unless the patient is unwilling to do so, with the exception of MSCT for patients who have had less than 2 months of randomised treatment. The reason for discontinuation will be recorded in the eCRF.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. Trained site personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified (SDV), reviewed/queried and updated as needed. The data will be validated as defined in the Data Management Plan. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

At clinic visits patients will enter data on paper questionnaires (SGRQ-C) and these data will be entered into the eCRF by the site personnel.

Patients will enter diary data and perform peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) measurements twice daily in a electronic diary/home spirometry device at home between visits. At Visit 1b all patients will be carefully instructed and trained in how to fill in the eDiary, how to blow PEF and FEV_1 and how to handle the device. Written instructions will be provided to the patient in their local language.

6.2 Data collection and enrolment

In order to include eligible patients the investigator will be asked to screen patients based on:

- Age
- COPD history and current prescribed COPD medication
- Smoking history

- Concomitant medications and medical history.

At Visit 1a (enrolment visit), patients will sign the informed consent form prior to any study procedure or restriction being applied and will be assigned a unique enrolment code (see Section 5.2). The following data will be recorded in the eCRF:

- Date of birth, sex and race

At Visit 1b patients will be evaluated for eligibility to enter the study. The procedures to be followed are listed in the Study Plan, (Table 2) and the following data will be captured in the eCRF:

- COPD history including exacerbation history, date of diagnosis according to GOLD 2008 and current prescribed COPD medication (including 4 weeks preceding Visit 1b)
- Medical and surgical history relevant for the purpose of the study and current prescribed medication (including 4 weeks preceding Visit 1b)
- Smoking history
- Weight and height
- Physical examination
- Vital signs (pulse and blood pressure)
- 12-lead ECG
- Spirometry, pre- and post- bronchodilator FEV_1 , forced vital capacity (FVC) and slow vital capacity (SVC)
- Urinalysis
- Exacerbation recording
- Adverse events
- Dispensing of maintenance and reliever medication
- Check of inclusion/Exclusion criteria.

Height will be measured in cm (without shoes) and weight in kg (light clothes and without shoes).

The evaluation of pack years is described in the eCRF.

After evaluation of the laboratory safety variables and 2 to 7 days before Visit 2 eligible patients should be assessed by MSCT scanning.

6.2.1 Follow-up procedures

The procedures to be followed at the follow-up visit, Visit 7, are listed in the Study Plan, (Table 2).

6.3 Efficacy

The efficacy variables collected in the study are detailed in the sections below.

6.3.1 MSCT variables

A baseline MSCT assessment (paired inspiratory and expiratory scan) will be performed 2 to 7 days prior to randomisation (Visit 2) to assess airway wall thickness, lung density and expiratory air trapping. The scan will be done after evaluation of the laboratory safety results from Visit 1b and it will be visually evaluated by a radiologist within 48 hours and prior to randomisation. The scan must be visually acceptable with no artefacts related to motion or streak or metal. If any defects are noted they will be recorded in the CRF and may result in loss of scan and patient. A second assessment will be performed at 0 to 3 days prior to Visit 6. The second MSCT assessment may be done after the clinic visit on the day of Visit 6.

The performance of each site and scanner will be assessed before the first patient is enrolled.

All sites will be provided with a separate manual containing all necessary instructions for MSCT assessments.

Images will be transferred to a core lab at a CRO for analysis. Images will be analysed by VIDA software and the baseline scans will be double-read for quality check.

Equipment

Scanners that meet or exceed the study protocol with volumetric scan capabilities and at least 16 detectors will be used for MSCT scanning. The CRO and monitor are responsible to ensure appropriate equipment is available for scanning. During the course of the study sites are recommended not to change the scanners. No contrast agent will be used. If possible the same radiographer should perform all examinations.

Calibration

The scanners will be calibrated on a daily basis using air and water calibration. The calibration data will be evaluated by site and periodic reports may be requested by the

sponsor. To ensure cross-site standardization a specific phantom will be circulated to the sites in the set-up phase to obtain phantom scans. Detailed instructions (protocol settings, reconstruction parameters etc.) for the phantom will be included in a separate MSCT manual.

Measurements/Conditions

Detailed instructions on the imaging protocol are defined in the MSCT scan protocol. The MSCT scan will be done at full expiration and full inspiration. The patients will be trained on breath holding few times before the actual scan is taken. No respiratory or cardiac gating will be used. Following the procedure the patient can leave the scanning area and no medical check-up will be needed at the end of the scanning procedure. During the procedure the patient is asked not to move, as any significant movement can affect scan quality. The entire scan process is expected to take approximately 30 mins.

Inspiratory scan

The patient will be asked to take a full inspiration and breath hold before a scan is taken. The scan is expected to take a few seconds. The manouvere will be practiced 3-4 times before the actual scan to support good inspiratory scan.

Expiratory scan

Similar to the inspiratory scan the patient will be asked to exhale and hold the breath. The expiratory scan uses a low radiation dose protocol and is expected to take few seconds.

6.3.2 Lung function measurements by body plethysmography

Lung volumes, IC (L), TLC (L), FRC (L), RV (L) and SGaw (sec^{-1} x kPa^{-1}) will be measured at Visits 2 and 6 using body plethysmography. Measurements should be performed before pre-bronchodilator spirometry measurements.

Body plethysmography measurements should be performed according to ERS guidelines (Wanger J et al 2005).

All results will be recorded in the eCRF and the detailed instructions are given in a separate manual of procedures.

Equipment

Body plethysmography parameters will be measured using the body plethysmograph available at the study site.

Calibration

Calibration of the body plethysmograph should be done continuously during the study according to ERS guidelines (Wanger J et al 2005).

Measurements/Conditions

After the patient enters the body plethysmograph, the measurements will start when the box pressure becomes stable. The patient will wear a nose clip while breathing through the mouthpiece. At the end of a normal expiration, the airways will be closed by the shutter for 2-3 seconds. During this time the rate of airflow and the mouth- and plethysmograph pressures will be recorded during gentle panting against the shutter. FRC will be estimated. Immediately after releasing the shutter, the patient will be instructed to perform a maximal expiration to RV followed by a maximal slow inspiration to obtain IC and TLC. This manoeuvre will be then repeated twice. Means of the 2 highest measurements will be recorded. SGaw will be obtained at flow rate of 0.5 L/sec of inspiratory and expiratory flows at a respiratory rate of 0.5 Hz. Means of three measurements will be recorded.

6.3.3 Diffusion capacity of the lung for carbon monoxide (DL_{CO})

Diffusion capacity (mmol/min/kPa) will be measured before pre-bronchodilator spirometry measurements at Visits 2 and 6.

Diffusion capacity will be measured based on the single breath diffusion capacity manoeuvre according to ERS guidelines (Macintyre N et al 2005).

Measurements/conditions

The patient will rest for at least 10 minutes. The measurement will be conducted in sitting position. The mean of at least 2 measurements will be recorded.

The patient inhales a known volume of test gas (10% helium, 0.3% carbon monoxide, 21% oxygen, and the remainder nitrogen), and holds his or her breath for 10 seconds. The patient exhales to wash out a conservative overestimate of mechanical and anatomic dead space. Hemoglobin concentration is important for assessing DL_{CO}, and the DL_{CO} assessment has to be corrected for the patient's hemoglobin level according to normal routine at the site.

6.3.4 Lung function measurements by spirometry

Pulmonary function, FEV_1 (L), FVC (L) and SVC (L), will be measured by spirometry (pre- and post-bronchdilator) and collected in the eCRF at Visits 1b to 6 as defined in Table 2. Measurements at Visits 2 to 6 should be performed pre-dose of AZD9668.

Equipment

Spirometers used in this study should meet the American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations (Miller MR et al 2005) and the same spirometer should be used for each patient throughout the study. The monitor is responsible for checking that the spirometer in use meets these recommendations.

The spirometer should be serviced once a year or according to the manufacturer's instruction at an authorised facility. All service measures and repairs must be documented.

A nose-clip should be used for the manoeuvre. Mouthpieces of the same dimension and shape should be used throughout the study.

Spirometry data should be given at BTPS (body temperature, barometric pressure and saturated with water vapour), using a calibrated spirometer.

Calibration

Calibration should be in accordance with the specification for the trademark.

If nothing else is specified, calibration should be performed every day when a patient visits the clinic. Instead of using a 3 L syringe, a 1 L syringe can be used 3 times. The accuracy of the calibration must be within ± 3% of the reading or ± 0.05 L, whichever is greater. All calibration reports should be signed, dated and filed in the ISF along with a signed and dated copy (if the calibration reports are not on archive proof paper). If a calibration report can not be printed, the results should be documented in writing in the ISF.

Measurements/Conditions

Spirometry should be performed according to the ATS/ERS considerations for lung function testing guideline (Miller MR et al 2005, Miller MR et al 2005). It is of great importance that all spirometry measurements take place ±1 hour relative to the time of the Visit 2 measurement (baseline) and between 7am and 11am.

Before spirometry testing the following restrictions apply:

- Patients taking tiotropium from Visit 1a should not take their morning dose at home before Visit 1b
- Patients should not take tiotropium at home in the morning of Visit 2
- Patients should not take investigational product (AZD9668 or placebo) or tiotropium at home in the morning of Visits 3 to 6
- Patients should refrain from taking their reliever medication, if possible, within 6 hours prior to the measurements at the clinic
- No alcohol within 4 hours
- No vigorous exercise within 2 hours

- No large meals within 2 hours
- No prohibited medication as listed in Section 5.6.3.1.

The medications will be taken in clinic after completing spirometry (post bronchodilator) and other pre-dose clinical assessments.

Rescheduling the patient should be considered if less than 6 hours have passed since intake of reliever medication.

Each patient should preferably use the same spirometer during the entire study period. Preferably, the same study personnel should test the patient's lung function throughout the study to reach optimal performance and to enhance reproducibility. The patient should rest at least 15 minutes prior to the test. At repeated measurements, eg, to assess best of 3, a short pause (1 min.) between measurements is recommended.

The measurements are to be made with the patient seated in an upright position (preferably) or, if not comfortable, in standing position. The same position should be used during the entire study. The head must not be tilted during measurements. During the breathing manoeuvres, the thorax should be able to move freely; hence tight clothing should be loosened.

The spirometry measurements should always start with slow manoeuvres (SVC) and will be followed by forced manoeuvres (FVC, FEV_1). Between manoeuvres, the patient will be allowed to take a rest by breathing freely for about 1-2 minutes.

Pre-bronchodilator SVC

Slow manoeuvre

If the patient is not familiar with the assessment it is recommended to arrange a practise session, preferably done at the enrolment visit (1a) outside the ordinary lung function assessment schedule.

Before the actual measurement starts for obtaining SVC, the patient should have taken 3-5 normal breaths with the spirometer mouthpiece in place. The patient will then be prompted that after the next normal breath out, breath in until the lungs are full and then try to give an extra effort to fill up even more. They will be asked to do this fairly quickly so as not to interrupt breathing for very long. The manoeuvre will end with a normal (slow and even), unforced exhalation.

The SVC manoeuvre may be considered either as an inspiratory vital capacity (VC), where the patient inhales completely from a position of full expiration, or as an expiratory VC, where the patient exhales completely from a position of full inspiration.

The patient should be encouraged throughout the manoeuvres. For a technically satisfactory manoeuvre, it must be checked that none of the following occurs; coughing, leak or obstruction of mouthpiece (by eg, tongue or teeth).

For SVC the largest value from the acceptable manoeuvres should be reported.

A minimum of 3 technically satisfactory manoeuvres should be obtained with a maximum of 4 attempts, and with a difference in SVC between the highest and second highest of <150 mL. If less than 3 are achieved, the highest of the acceptable attempts will be used, and noted on the print-out.

Pre-bronchodilator FVC and FEV_1

Forced manoeuvre

The forced expiratory manoeuvre, both to make maximal inspiration and complete expiration as hard and fast as possible, is started immediately after a maximum inspiration. The expiration should last for at least 6 seconds. It is important to encourage the patient throughout the manoeuvre, which should be as hard and fast as possible. Check that none of the following has occurred; coughing during the first second, glottis closure, leak or obstruction of mouthpiece (by the tongue).

At least 3 technically satisfactory FVC manoeuvres should be performed. The difference between highest and second highest FVC should not vary by more than 5% or 0.15 L (whichever is greater) or 100 mL if FVC is ≤1.0L. A maximum of 8 manoeuvres should be performed in attempting to meet reproducibility criteria. If the reproducibility criteria cannot be met within 8 manoeuvres, the highest FVC value should be recorded, and a comment should be entered on the print-out.

FEV_1 values will be taken from the FVC curves. After examining the data from all acceptable curves the highest FVC value and the highest FEV_1 value should be recorded in the eCRF, even if the 2 values do not come from the same curve. FEV_1 and FVC values will be recorded with 2 decimals throughout the study.

Signed and dated copies of the 3 best printouts for the slow and forced manoeuvres respectively must be kept in the ISF for source data verification. It is acceptable to store (in the ISF) only 1 spirometry printout if the spirometer in use automatically selects and prints the best out of 3 FVC and FEV_1 curves. The printouts must be signed and marked with study code, enrolment code, date and time of measurement, visit number and patient

initials and filed in the ISF along with a signed and dated copy (if the printouts are not on archive proof paper).

Post-bronchodilator assessments

After the slow and forced pre-bronchodilator manoeuvres the patient should take 4 inhalations of salbutamol pMDI 100 µg/actuation via spacer, wait for 15 - 30 minutes and repeat the slow and forced spirometry manoeuvres as described above for pre-bronchodilator SVC, FVC and FEV_1.

FEV_1 predicted normal value

At Visit 1b the post-bronchodilatory FEV_1 value will be used for calculation of percentage of FEV_1 predicted normal (PN) value to be used for eligibility. FEV_1 % of PN value will be based on the reference values from European Respiratory Society guidelines for adult patients (Quanjer PH et al 1993). PN values by gender and age are calculated using the formulas below (Table 3). A reference list with pre-calculated PN values will be provided to the study staff at the clinic by AstraZeneca.

Table 3 FEV_1 predicted normal value

FEV_1 predicted normal value		
Women	FEV_1 PN	= $(3.95 \times H)^a - (0.025 \times A)^b - 2.60$
Men	FEV_1 PN	= $(4.30 \times H) - (0.029 \times A) - 2.49$

a H: standing height in metres

b A: age (year)

FEV_1 expressed as percent of PN value will be calculated according to Equation 1 below.

$$FEV_1\% \text{ of PN} = \frac{FEV_1}{FEV_{1PN}} \times 100 \quad (1)$$

N.B. When determining if a patient is eligible for enrolment according to inclusion criterion # 6 (see Section 4.1), the value for FEV_1 % of PN should always be taken from the reference list provided by AstraZeneca, not from the spirometer.

Post-bronchodilator FEV_1/FVC ratio at Visit 1b

This ratio is obtained by dividing highest FEV_1 measurement (L) by the highest FVC measurement (L) taken from the post-bronchodilator measurements at Visit 1b, and is used for Inclusion criterion #7 (see Section 4.1).

6.3.5 Daily lung function measurements by patients

An electronic diary/handheld spirometer will be dispensed at Visit 1b. The patient will be carefully instructed on how to use the diary/spirometer and written information will be supplied to each patient. The patient must understand and be willing to use the device and be instructed of how and where to request help if problems occur. The principal investigator is responsible to ensure that this training is performed at Visit 1b.

PEF

Measurements of PEF in the morning and in the evening, expressed in L/min, will be performed from the evening of Visit 1b to the morning of Visit 6. The patient will be requested to perform 3 manoeuvres twice daily (morning and evening). The measurements should be done upon rising in the morning before intake of morning dose of tiotropium and investigational product but after clearing out mucus. Patients should also refrain from taking their reliever medication prior to the morning measurements if possible. Evening measurements to be performed before bedtime. The measurements should be made while standing. The patient should use the same handheld spirometer during the entire study. Data from the PEF recordings are transferred to a database at the clinic visits.

FEV_1

FEV_1 readings will be made from the PEF measurements. It is important that the patients follow the instructions on how to perform the measurements, to ensure that the exhalation lasts long enough to collect a correct FEV_1 value.

6.3.6 Patient reported outcomes (PRO)

The Patient Reported Outcomes used in the study are the BCSS, EXACT and SGRQ-C. The BCSS and EXACT are, together with questions about use of reliever medication and intake of investigational product and maintenance medication, included in the eDiary and will be completed by the patient at home. The SGRQ-C will be administered as paper questionnaires to be completed by the patient at clinic visits. The PRO data collected in the eDiary are presented in Section 6.3.8.

St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

The SGRQ-C is a modified version of the St. George's Respiratory Questionnaire, which has been developed to measure the impact of respiratory disease on health status (Jones W et al 1991). The SGRQ-C includes 40 questions in 3 domains:

- Symptoms (distress due to respiratory symptoms, 7 questions)
- Activity (disturbance of physical activity, 13 questions)

- Impacts (overall impact on daily life and well-being, 20 questions).

The original SGRQ has undergone rigorous validation and has shown to have strong evaluative and discriminative measurement properties (Jones PW et al 1992). For COPD patients, SGRQ-C has been shown to have even more favourable measurement properties than the original SGRQ (Meguro M et al 2007). Translations of the SGRQ-C into local languages have been performed according to a linguistic validation process. The English version is included in Appendix E.

Methods of assessment

The SGRQ-C will be self-administered on paper during clinic Visit 1b (for training purposes only), and Visits 2 and 6. It takes approximately 10 minutes to answer the questionnaire.

6.3.7 Administration of PRO questionnaires

It is important to administer the questionnaires according to the guidelines for standardized administration and, for SGRQ-C, prior to other examinations at the clinic. A brief introduction on how to complete each questionnaire will be given at Visit 1b prior to the assessment. The SGRQ-C will be filled in on paper at the clinic visits and before any other study related procedures take place. The training session at Visit 1b will take place after the lung function test has been performed. BCSS and EXACT will be integrated in the eDiary and filled in by the patient at home (see Section 6.3.8).

The questionnaires should be completed in a quiet place without influence from study personnel or accompanied family or friend. The patient should be informed about the importance of their participation and be given adequate time to complete all items, ie, no time limits for completing the questions should be given. The study personnel are not to help the patient to choose an answer, and must be neutral in their response to any questions from the patient. The study personnel must neither interpret nor rephrase the questions the patient may have. After completion of the questionnaire, the study personnel will review the questionnaire for completeness only.

6.3.8 Measurements recorded in electronic diary (eDiary)

Patients will be supplied with an electronic diary/handheld spirometer to be maintained for the run-in period and the treatment period. At Visit 1b all patients will be carefully instructed and trained in how to fill in the diary and how to handle the device. Written information will be supplied to each patient. The patients must understand and be willing to use the eDiary and be instructed of how and where to request help if problems occur.

The patients should also be informed that the recordings made electronically can not be retrospectively or prospectively entered.

The diary will be completed each day from the evening of Visit 1b to the morning of Visit 6. Reliever medication should be avoided prior to the morning assessments. The diary will include the following daily recordings:

- Use of reliever medication (morning and evening)
- Intake of investigational product (morning and evening, not included during the run-in period)
- Intake of maintenance medication (morning)
- BCSS (evening)
- EXACT (evening).

Use of reliever medication

The number of inhalations of reliever medication taken during daytime and night-time will be recorded by the patient in the eDiary from Visit 1b to 6. The number of reliever inhalations taken during the day (from rising from bed until going to bed) will be recorded in the evening, and the number of reliever inhalations taken during the night (from going to bed until rising from bed) will be recorded in the morning.

Intake of investigational product

Intake of investigational product will be recorded in the eDiary morning and evening as "yes" or "no". This does not mean that the patients have an option not to take the investigational product but will be used as a measure of compliance.

Intake of maintenance medication

Intake of maintenance medication will be recorded in the morning eDiary as "yes" or "no". This does not mean that the patients have an option not to take the maintenance medication but will be used as a measure of compliance.

Breathlessness, Cough and Sputum Scale (BCSS)

The BCSS has been developed to assess the severity of 3 cardinal symptoms of COPD, and it includes 1 question for each of the symptoms of breathlessness, cough, and sputum. In evaluations of the measurement properties of the BCSS it has been shown to be a reliable, valid, and responsive measure of symptoms in clinical trial settings (Leidy NK et al 2003). Linguistically validated translations of the BCSS will be used. The English version is included in Appendix F.

Methods of assessment

The BCSS questions will be used as a daily diary and will be included in the eDiary. The BCSS questions will be completed in the evening from Visit 1b to Visit 6. All 3 symptoms are responded to on a 5-point Likert-type scale ranging from 0 to 4, with a higher score indicating a more severe manifestation of the given symptom. The minimally important difference has been defined as a change in total score of >0.3 units. For calculation or derivation of outcome variable, see Section 11.3.

EXAcerbations of Chronic pulmonary disaease Tool (EXACT)

The EXACT is a PRO measure designed to measure the frequency, severity, and duration of an acute exacerbation in patients with COPD. The EXACT evaluates the cardinal respiratory symptoms of COPD together with other respiratory and systemic manifestations of exacerbation identified by patients and confirmed by clinical experts. The EXACT is composed of 14 items and response options are tailored to each specific item, but all are evaluated on a 5 or 6 point scale (eg, not at all, slightly, moderately, severely, extremely).

Values for the total score range from 0 to 100, with higher values indicating a more severe exacerbation. The EXACT is designed to be completed daily just prior to bedtime with the patient reflecting on how he or she felt that day. The English version is included in Appendix G.

6.3.9 COPD exacerbations

In this study a COPD exacerbation is defined as worsening in COPD requiring a course of antibiotics and/or systemic steroids (oral or parenteral) and/or Emergency Room (ER) treatment and/or hospitalisation.

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

One day without any criteria for fulfilment of an exacerbation is required to start to count a new exacerbation. The investigator should tick all the criteria fulfilled by a patient having an exacerbation in the appropriate section of the eCRF. Please also refer to Section 6.4.3, Symptoms of disease under study.

6.4 Safety

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

6.4.1 Definition of adverse events

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

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

6.4.2 Definition of serious adverse events

A Serious Adverse Event (SAE) is an AE occurring during any study phase (ie, enrolment, run-in, treatment, follow-up), that fulfils 1 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 1 of the outcomes listed above.

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

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent and throughout the treatment period and the follow-up period (until Visit 7, last contact). The first AE questioning will be done at Visit 1b.

SAEs will be recorded from the time of signed informed consent.

Follow-up of unresolved non-serious 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. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion. When refining data before clean file all unresolved AEs must be checked and discussed with Study Delivery Team Physician to decide if further follow-up is necessary.

Follow-up of unresolved serious adverse events

All SAEs must be followed until resolution or until considered stable and unlikely to resolve further by the Investigator - even where this is post the last study visit. If the SAE resolves prior to the finalisation of the clinical study report (CSR) then this information will be included in the report. If the SAE resolves after the CSR is delivered the information will be recorded in the Patient Safety database only.

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

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- the date 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

- AE caused patient's withdrawal from study (yes or no)
- 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 serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- 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 the causal relationship between Investigational Product and each Adverse Event, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

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

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

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the 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

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

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

- Results in discontinuation of investigational product. This should be reported as a Discontinuation Adverse Event (DAE)

- Meets the SAE reporting criteria. This should be reported as a SAE.

If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated

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

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

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

AEs with recommended follow-up activities

If an investigator reports pneumonia (including bronchopneumonia) as an adverse event, this will need to be followed up with a chest x-ray, measurement of C-reactive protein and total and differential leucocyte count.

Patients with abnormal liver function tests that meet the discontinuation criteria (see Section 5.8) should have the elevation(s) reported as DAE(s) and be followed up. Abnormal liver function tests that are of concern (even if these do not meet discontinuation criteria) should be confirmed with a repeat test (via the central laboratory) as soon as possible, preferably within 48 hours. Should the abnormalities and concern persist and if in the investigator's judgment they meet the criteria of an AE, the abnormal liver findings should be reported as AE(s) and followed up. To assist with the determination of the aetiology or causality of abnormal liver function tests, a guidance document is provided by AstraZeneca which contains suggested additional investigations to consider, as clinically indicated.

If non-calcified lung nodules are discovered in an MSCT scan the following is recommended, unless local guidelines are followed:

- Non-calcified lung nodules with diameter below 5 mm to be checked with repeat scan after 12 months
- Nodules between 5-10 mm to be checked with repeat scan after 3 months
- Nodules larger than 10 mm to be referred for diagnostic work-up.

If a nodule of greater than 5 mm is found at the baseline scan the patient will be excluded from the study, see Section 4.3, and will continue with the regular clinical care protocol at site

Symptoms of disease under study

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

- the sign or symptom is serious according to definitions, see Section 6.4.2 and/or

- the patient discontinues the study due to the signs or symptoms and/or
- the sign or symptom is new to the patient or not consistent with the patient's pre-existing COPD history (defined as within 1 year of Visit 1b).

COPD exacerbations (see Section 6.3.9) that meet the SAE criteria as defined in Section 6.4.2 should be reported as SAEs.

Post study events

After study completion (eg, after the scheduled follow-up period has ended) there is no obligation to actively report information on new AEs occurring in former study patients. Any SAEs that are reported by the investigator after the patient has completed a clinical study may still qualify for expedited reporting and must be handled as such. Post-study SAEs are usually not included in the statistical analysis of the study, and normally not entered into the clinical study database but may be entered onto the Patient Safety database for regulatory reporting.

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). All SAEs will be recorded in the eCRF.

The Investigator and/or sponsor is responsible for informing the Ethics Committee and/or Regulatory Authority of the SAE as per local requirements.

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within 1 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 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

Reporting procedure of SAEs using WBDC system

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

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

The reference document for definition of expectedness/listedness is the IB for AZD9668 and the local Summary of Product Characteristics (SPC) for additional study drugs as defined in Section 5.5.2.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the visits indicated in the Study Plan (see Table 2) and before intake of the morning dose of investigational product. Blood samples will be analysed at a central laboratory. Urinalysis will be performed locally at the study site using dipsticks provided by the central laboratory.

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 central laboratory will also provide up to date reference ranges throughout the study for the management of patient safety.

Clinically relevant deviations from the reference range in the lab values will be handled as outlined in Section 6.4.3, adverse events based on examinations and tests.

The following laboratory variables will be measured:

Haematology		
Haemoglobin	Mean Cell Volume (MCV)	Platelet count
Erythrocyte count	Mean Cell Haemoglobin (MCH)	Reticulocyte count
Haematocrit	Mean Cell Haemoglobin Concentration (MCHC)	Leucocyte count (absolute and percentage including neutrophil, lymphocyte, monocyte, eosinophil and basophil counts)

Clinical Chemistry		
Creatinine	Potassium	Creatinine kinase (CK)[a]
C-Reactive Protein (CRP)	Calcium, total	Lactate dehydrogenase (LDH)
Total bilirubin[b]	Sodium	Glucose
Alkaline phosphatase	Cholesterol	Free thyroxine (T4) (Visit 1b only)
Aspartate aminotransferase (AST)	Triglycerides	Thyroid stimulating hormone (TSH) (Visit 1b only)
Alanine aminotransferase (ALT)	Urea	Haptoglobin
Albumin	Gamma Glutamyltransferase (GGT)	hCG[c]

a CKMB fraction to be measured if CK is elevated >2 x ULN (as detailed in the laboratory manual)

b Unconjugated and conjugated bilirubin will be measured if the total bilirubin is elevated

c Visit 1b and Visit 7, only for female patients

For blood volumes see Section 7.1.

Urinalysis		
Protein	Glucose	Haemoglobin

Please refer to Section 5.8 for the discontinuation criteria relating to laboratory safety variables.

6.4.6 Physical examination

A complete physical examination will be performed at Visits 1b to 7, as indicated in the Study Plan, Table 2. The following should be assessed as part of the full physical examination: general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculo-skeletal (including spine and extremities), cardiovascular, respiratory and neurological systems.

Clinically relevant deterioration from baseline will be handled as outlined in Section 6.4.3, adverse events based on examinations and tests.

6.4.7 ECG

A resting 12-lead ECG will be performed at Visits 1b to 7, as indicated in the Study Plan, Table 2. The ECG will be recorded pre-dose at Visits 2 to 6 and at Visit 2 an additional ECG will be taken at 3-4 hours post-dose.

ECGs will be recorded in the supine position or with no more than 30 degrees of hip angulation after the patient has rested for 10 minutes. Heart rate, QRS duration and PR, RR, QT and QTc intervals will be recorded. Overall evaluation of the ECG (normal, abnormal or borderline) should be recorded in the eCRF along with a note of any abnormalities and whether or not they were clinically significant. The printout of the ECG is to be signed, dated and marked with study code, E-code, date and time of measurement and patient initials and filed in the ISF along with a signed and dated copy (if the printouts are not on archive-proof paper).

Clinically relevant deterioration from baseline will be handled as outlined in Section 6.4.3, adverse events based on examinations and tests.

Please refer to Section 5.8 for the discontinuation criterion relating to QTcB.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Vital signs (pulse and blood pressure) will be measured at Visits 1b to 7 as indicated in the Study plan, Table 2. Pulse and blood pressure will be recorded pre-dose at Visits 2 to 6 and at Visit 2 an additional measurement will be taken at 3 to 4 hours post-dose. Pulse (beats/min) will be measured before blood pressure and over 30 seconds according to local procedures, subsequent to a 5-minute rest. Systolic and diastolic blood pressure (mmHg) will be measured using the same cuff size, appropriate for arm circumference, throughout the study. The results will be recorded in the eCRF.

Clinically relevant deterioration from baseline will be handled as outlined in Section 6.4.3, adverse events based on examinations and tests.

6.4.9 Pregnancy testing

A pregnancy test (blood sample) will be collected from all women at Visits 1b and 7.

In addition a urine pregnancy test will be performed on women of child bearing potential at Visit 2. The study personnel at the centre will analyse urine from a mid-stream urine sample using dipsticks provided by the central laboratory. The result will be recorded in the eCRF. See Section 13.3 for reporting procedures if pregnancy should occur during the course of the study.

6.5 Patient reported outcomes

PROs are described in Sections 6.3.6 and 6.3.8.

6.6 Pharmacokinetics (not applicable)

6.7 Pharmacodynamics

6.7.1 Collection of pharmacodynamic markers

Urine samples will be collected pre-dose at Visits 2, 4 and 6. Samples will be collected, labelled stored and shipped as detailed in Laboratory Manual. Analysis will be conducted by a suitably qualified laboratory.

Urine will be collected from a first morning void to generate samples for biomarker analysis to include (but not limited to) desmosine. Creatinine concentration will also be determined for the purpose of normalisation.

This data will not form part of the Clinical Study Report.

6.8 Pharmacogenetics

Collection of pharmacogenetic sample is described in Appendix D. This data will not form part of the Clinical Study Report.

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 4 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry (including Haptoglobin, TSH and Free T4[a])	5	7	35
	Haematology	3	7	21
Pharmacogenetics		10	1	10
Total				66

a TSH and Free T4 at Visit 1b only.

The maximum total volume of blood drawn from a patient will not exceed 100 mL. Additional samples may be required to follow safety findings.

7.2 Handling, storage and destruction of biological samples

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

7.2.1 Safety samples

The clinical chemistry, haematology and urinalysis samples will be used up during analysis or disposed of after analysis.

7.2.2 Pharmacodynamic samples

Samples will be disposed of after the Clinical Study Report (CSR) has been finalised, unless retained for future analyses, see below.

Urine biomarker samples for future research can be retained under the care of AstraZeneca R&D for a maximum of 2 years following the finalisation of the CSR. The results from future analysis will not be reported in the CSR but separately in a CSR Amendment/Errata, Scientific Report or Scientific Publication.

7.2.3 Pharmacogenetic samples

Please refer to Appendix D.

7.3 Labelling and shipment of biohazard samples

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

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

7.4 Chain of custody of biological samples

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

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

Collection of biological samples for safety assessment is an integral part of the study. If the patient withdraws consent to the use of these samples then the patient is withdrawn from further study participation.

Collection of biological samples for pharmacodynamic and pharmacogenetic assessments are an optional part of the study. If the patient withdraws consent to the use of these samples then the patient may continue in the study.

The Principal Investigator:

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

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

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

Please refer to Appendix D for a description of patient data protection for the pharmacogenetic part of the study.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

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

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

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

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

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements. For studies in

countries implementing the EU Clinical Trials Directive, informing Ethics Committees and Regulatory Authorities will be performed by AstraZeneca.

In the US and Canada, and may also be applicable to other countries, each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the ISF.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the Informed Consent Form that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator, and the Principal Investigator and AstraZeneca.

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

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

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

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

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

8.6 Audits and inspections

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

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

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

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

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the MSCT, the WBDC and ePRO 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, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.3.1 Source data

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

9.4 Study agreements

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

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

9.4.1 Archiving of study documentation

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.5 Study timetable and end of study

The study is expected to start in Q1 2010 and to end by Q4 2010.

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

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD9668.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre staff or other party.

Data will be entered in the WBDC system as described in Section 6.1.

MSCT data and ePRO (diary and handheld spirometer) data will be collected electronically and data will be transferred to AstraZeneca via the respective service providers.

Analytical results from the central laboratory will be saved to a central database. Data verification will be performed to ensure data quality.

The data collected through third party sources will be obtained and reconciled against study data.

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

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The principal investigator will then sign the eCRF electronically.

When all data have been coded, validated, signed and locked, clean file will be declared. The data will be frozen and then locked to prevent further editing. Any treatment revealing data may thereafter be added and the final database will be locked.

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

See Appendix D regarding data management activities relevant for the pharmacogenetic part of the study.

10.1 Serious Adverse Event (SAE) Reconciliation

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

10.2 Management of external data

AstraZeneca Data Management Centre (AZDMC) staff determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). AZDMC staff will ensure that the data collection tool will be tested/validated as needed. External data reconciliation will be done with the clinical database as applicable. The data reconciliation will be performed as defined in the Data Management Plan.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

11.1 Calculation or derivation of efficacy variables

MSCT variables (AWT-Pi10, 5th generation wall area %, ATI, PD15, mean wall area % for airways of 4th to 6th generation, and emphysema index) will be provided by the chosen MSCT CRO. The outcome variable will be the Visit 6 values; Visit 2 will be the baseline.

Lung function measurements at home (PEF and FEV_1) and use of reliever medication will be reduced to period means before statistical analysis. As baseline the average of the last 10 days recorded prior to randomisation will be used. As outcome variable the average of the last 6 weeks on treatment will be used. The outcome variable for clinic assessments (spirometry, body plethysmography and DL_{CO}) will be Visit 6; Visit 2 will be the baseline. The exacerbation endpoint will be the time to first clinic identified COPD exacerbation.

11.1.1 Calculation of MSCT variables

Primary variable: Airway wall thickness on Inspiratory Scan (AWT-Pi10)

The square root of the wall area at Internal Perimeter (Pi) of 10 mm allows for the comparison of overall airway wall thickness between patients while accounting for the different airway sizes measured in each patient. All assessable airways up to 6th generation will be included in measurement of AWT-Pi10.

Wall area and wall area percent are directly related to the size of the airway. Wall area is greater in larger airways, while the wall area percent decreases as airway size increases. By plotting the Internal Perimeter of each airway against the square root of wall area for each individual patient, a linear regression equation can be derived (Bosken CH et al 1990). Using this equation, the square root of the wall area at a standard Pi (usually 10 mm) can be calculated for each patient.

Secondary variable: Air trapping

Air trapping index provides an estimate of the air trapping in the entire lung based on CT (CT ATI). CT ATI has been shown to correlate well with physiologic ATI (VC - FVC) (Lee YK et al 2008). Air trapping will be measured by applying a threshold of –856 HU on expiratory scan.

Exploratory variable: Volume adjusted 15th Percentile Density (PD15)

The actual density of lung will be estimated by using the formula 1000 + PD15 and is represented in g/L. For volume adjustment the following formula is used: Adjusted PD15 = observed PD15 x observed volume / predicted TLC.

11.2 Calculation or derivation of safety variable(s)

The following safety data will be collected: AEs, haematology, clinical chemistry, urinalysis, vital signs, 12-lead ECG, physical examination. Change from baseline (Visit 2) to end of treatment will be calculated for relevant measurements.

All AEs will be analysed in terms of descriptive statistics and qualitative analysis. AEs will be listed for each patient and summarised by System Organ Class and preferred term by using MedDRA. Laboratory safety assessments and vital sign data outside the AstraZeneca extended reference ranges will be highlighted.

11.2.1 Other significant adverse events (OAE)

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

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

11.3 Calculation or derivation of patient reported outcome variables

Outcome variables for other diary card variables (EXACT, BCSS) will be computed in a similar manner to efficacy diary card variables (PEF, FEV_1 and use of reliever medication). In addition to this a total score for BCSS and EXACT, separately, will be computed and will serve as the main outcome variable for such data. The entire EXACT tool will be used to assess COPD exacerbations in addition to the per protocol analysis. However, a select number of items from the EXACT tool will be used to assess symptoms of COPD.

For SGRQ-C measured at the clinic, an overall score will be computed on each of the 3 different domains (symptoms, activity and impact) and a total score will be computed according to the rules defined by the questionnaire.

11.4 Calculation or derivation of pharmacokinetic variables (not applicable)

11.5 Calculation or derivation of pharmacodynamic variable(s)

Markers of tissue degradation (urine desmosine) levels from Visits 2 to 6 will be evaluated. Urine desmosine will be normalised for creatinine.

11.6 Calculation or derivation of pharmacogenetic variables

Please refer to Appendix D.

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

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

There will be 1 efficacy analysis set based on the 'full analysis set', as defined in the international conference of harmonization E9 guideline. This means that all patients who receive at least 1 dose of investigational product (AZD9668 or placebo) and for whom post-dose efficacy data are available will be included in the efficacy analysis set.

12.1.2 Safety analysis set

All patients who received at least 1 dose of randomised investigational product (AZD9668 or placebo) and for whom any post-dose data are available will be included in the safety analysis set.

12.2 Methods of statistical analyses

AWT-Pi10 will be the primary variable. The outcome variables from the MSCT will be compared between AZD9668 and placebo using an Analysis of Variance (ANOVA) model with fixed factors treatment and country and using baseline as a covariate. A 90% confidence interval will be constructed for the treatment difference and p values given. If appropriate, data will be log-transformed before analysis.

Plots of MSCT variables vs clinic lung function variables will be produced. In addition, the correlation of MSCT variables with the clinic lung function variables may be assessed.

Analysis of clinic lung function data (spirometry, body plethysmography and DL_{CO}), diary data and PROs will be analysed using an ANOVA model in a similar manner to the MSCT variables.

Mean value plots of effect versus time will be produced for most variables. These mean values are to be computed using the principle of last value carried forward, so that the number of patients are the same on each assessment time. For variables obtained at the clinic, the time scale will be visit number, for diary data it will be days since randomisation.

Analysis of exacerbations may be done, if there are a sufficient number to make such an analysis meaningful. If so, the time to first clinic identified COPD exacerbation will be analysed using a Cox proportional hazards model. Further analyses may be performed. The movement of the EXACT will be explored in relation to the clinic defined exacerbations. The movement of some of the items on the EXACT will be explored to assess the symptoms of COPD.

Adverse events will be analysed by means of descriptive statistics and qualitative analysis. Adverse Events will be listed for each patient and summarised by System Organ Class and preferred term assigned to event by using Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be classified according to the AstraZeneca Drug Dictionary, the Anatomical Therapeutic Chemical Classification (ATC) system and the Committee for Proprietary Medicinal Products (CPMP) route of administration dictionary. All concomitant medications reported at entry and recorded during the study will be listed.

12.3 Determination of sample size

This study is a feasibility study and as such the sample size in this study has not been based on obtaining power to detect specific effects. There is not adequate data to do such a powering. The sample size is 25 patients in each arm. This number has been considered sufficient to detect clinically relevant effects on AWT-Pi10. Assuming the effect size is at least 0.5 (ie, the standard deviation is not more than twice that of the treatment difference observed), we will have at least 80% power to demonstrate an effect at the 5% significance level with a 1-sided test. The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2. The sample size is based on similar studies in asthmatics where anti-inflammatory treatments have shown a treatment effect in 12 weeks (Capraz F et al 2007, Niimi A et al 2004) and has been kept low to ensure minimal radiation exposure for a feasibility study

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

12.4 Safety Review Committee

An independent SRC has been constituted to review accumulated blinded safety data on an ongoing basis throughout the duration of the study. Where necessary, SRC members may have access to unblinded data however no members of the Study team will have access to unblinded data until after database lock is declared. The SRC are governed by a specific SRC charter.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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

The study code may be prematurely broken in a medical emergency when appropriate management of the patient necessitates knowledge of the treatment randomisation, see Section 5.4.2.

In the case of a medical emergency the investigator may contact the appropriate local AstraZeneca representatives. If not available contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at AstraZeneca Research and Development.

Name	Role in the Study	Address & telephone number
	Study Delivery Team Leader responsible for the protocol at central R&D site	
	SDT Physician responsible for the protocol at central R&D site	
Local contact persons to be provided by AstraZeneca MC		

13.1.1 Study Participation Card

At Visit 2, all randomised patients will receive a Study Participation Card in local language, see Table 5.

Table 5 Study participation card

IMPORTANT MEDICAL INFORMATION Name: ..... Enrolment code: ..... Study code: D0520C00014 This patient participates in a clinical study and is being treated with AZD9668 twice daily on top of tiotropium as maintenance medication and a short-acting β_2-agonist as reliever medication.	IMPORTANT MEDICAL INFORMATION Study code: D0520C00014 If you have any queries please contact: Dr.: ..... Nurse: ..... Hospital: ..... Phone: .....

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 specific antidote to AZD9668. In case of a known or suspected overdose, appropriate supportive measures should be undertaken.

- 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 1 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 must be reported to AstraZeneca.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, 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 1 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 PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

Pregnancy of a patient's partner is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented as specified in Section 13.3.1 above. The outcomes of any conception occurring from the date of the first dose until 3 months after the last dose must be followed up and documented.

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