**Clinical Study Protocol**

| | |
|---|---|
| Drug Substance | AZD3199 |
| Study Code | D0570C00003 |
| Edition Number | 1 |
| Date | [redacted] |

# A 4-week, phase-II, double-blind, placebo-controlled, randomized, parallel group, multi-centre study to assess the efficacy and tolerability/safety of inhaled AZD3199 once daily compared to 9 µg formoterol bid and placebo in patients with moderate to severe COPD

**Sponsor:**

[redacted]

**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 4-week, phase-II, double-blind, placebo-controlled, randomized, parallel group, multi-centre study to assess the efficacy and tolerability/safety of inhaled AZD3199 once daily compared to 9 µg formoterol bid and placebo in patients with moderate to severe COPD

**International Co-ordinating Investigator**

[redacted]

**Study centres and number of patients planned**

The present study will include approximately 300 randomized patients, recruited from approximately 55 centres in about 5 countries. In order to reach about 300 randomised patients it is estimated that approximately 500 patients need to be enrolled.

| **Study period** | **Phase of development** |
|---|---|
| Estimated date of first patient enrolled: [redacted] | II |
| Estimated date for end of study (last patient last visit) : [redacted] | |

**Objectives**

Primary objective is:

- To compare the clinical efficacy of AZD3199 inhaled once daily with 9 µg formoterol twice daily and placebo over a 4-week treatment period in adults with chronic obstructive pulmonary disease (COPD)

The secondary objectives of the study are:

- To investigate the safety of AZD3199 by assessment of the nature, incidence, and severity of adverse events (AE), safety laboratory variables, pulse, blood pressure, and ECG
- To investigate the effect of regular treatment with AZD3199 on the reversibility in $FEV_1$ after inhalation of salbutamol
- To determine the pharmacokinetics (PK) of AZD3199 in COPD patients

The explorative objectives are

- To explore morning and evening PEF and $FEV_{1(eDiary)}$ measurements using an electronic diary device with electronic peak flow device
- To collect pharmacogenetic samples for possible retrospective pooled analysis

**Study design**

This study is a 4-week, double-blind, placebo-controlled, randomized, parallel-group, multi-centre, phase II study to investigate the effects, drug exposure, tolerability and safety of inhaled AZD3199 in patients with moderate to severe COPD.

Eligible patients will be enrolled to a 2-week run-in period. After the run-in period, patients who fulfil the randomization criteria will start a 4-week treatment period with either AZD3199, formoterol or placebo. Patients will visit the clinic 3 times during the treatment period. A follow-up visit will take place 2-3 weeks after the completion of treatment.

**Target patient population**

Randomized patients will have moderate to severe COPD, with symptoms for more than 1 year. Post-bronchodilator $FEV_1$ value must be between 40 and 80% of predicted normal and $FEV_1/FVC<70\%$. Patients must be current or ex-smokers with a smoking history of at least 10 pack years.

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

AZD3199 100, 200 and 400 µg/inhalation will be provided as dry powder for 2 oral inhalations once daily, administered with Turbuhaler. 3 different doses of AZD3199 will be investigated; 200, 400, 800 µg delivered dose.

**Comparator, dosage and mode of administration**

Formoterol 4.5 µg/inhalation will be provided as dry powder for 2 oral inhalations twice daily, administered with Turbuhaler.

Placebo inhalers matching AZD3199 and formoterol will be provided.

**Duration of treatment**

The study will include a 2-week run-in period followed by a 4-week treatment period, and then a 2-3-week follow-up period.

**Outcome variable(s):**

**Primary outcome variable** is $FEV_1$, assessed both with regard to maximum bronchodilation and to trough effects 24 h after the morning administration

- **Efficacy variables** are
  - $FEV_1$
  - FVC
  - Patient reported outcomes (AZ COPD Symptom Scores, CCQ, SGRQ-C)
  - Use of reliever medication
- **Safety variables** are
  - Adverse Events (AE)
  - Safety laboratory assessments
  - Pulse and Blood pressure
  - ECG
- **Pharmacokinetic variables** are
  - $C_{max}$ and $AUC_{0-24h}$ post-dose (Visit 5)

**Statistical methods**

Efficacy parameters will be compared using ANOVA. Safety and pharmacokinetic data will be summarised using descriptive statistics and qualitative analysis.

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

| Abbreviation or special term | Explanation |
|---|---|
| AE | Adverse event (see definition in Section 7.3.1) |
| ANOVA | Analysis of Variance |
| ATS | American Thoracic Society |
| AUC | Area Under the plasma concentration-time Curve |
| BMI | Body Mass Index |
| CCQ | Clinical COPD Questionnaire |
| $C_{max}$ | Maximum plasma concentration |
| COC | Combined Oral Contraceptive |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CSA | Clinical Study Agreement |
| CSP | Clinical Study Protocol |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Event |
| DAE | Discontinuation due to Adverse Event |
| Delivered dose | The amount of drug delivered by (leaving) the device. The fraction of the delivered dose via Turbuhaler reaching the lungs is estimated at 40% for AZD3199 |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ePEF | evening PEF |
| ERS | European Respiratory Society |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| $FEV_{1(eDiary)}$ | Forced Expiratory Volume in 1 second, collected with an electronic device by the patient at home |

| Abbreviation or special term | Explanation |
|---|---|
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| GCS | Glucocorticosteriod |
| GMP | Good Manufacturing Practice |
| GOLD | Global initiative for chronic Obstructive Lung Disease |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC/IRB | Independent Ethics Committee/Institutional Review Board |
| 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. |
| Investigational Product | This term includes test product, comparator product and placebo |
| Investigator(s) | The investigator(s) in this study protocol means the principal investigator and sub-investigators. When specification is necessary, either principal investigator or sub-investigator is specified |
| IPS | Investigational Products |
| ISF | Investigators Study File |
| IUD/IUS | Intra-Uterine Device/System |
| JRS | Japan Respiratory Society |
| LABA | Long-acting $\beta_2$-agonist |
| LLOQ | Lower Limit of Quantification |
| MAD | Multiple Ascending Dose study |
| mPEF | morning PEF |
| OAE | Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment; see definition in Section 12.2.3) |
| PEF | Peak Expiratory Flow |
| PGx | Pharmacogenetics |

| Abbreviation or special term | Explanation |
|---|---|
| PK | Pharmacokinetics |
| PRO | Patient Reported Outcome |
| QT | ECG interval measured from the beginning of th Q wave (or the R wave if Q is missing) to the end of the T wave; the time interval of ventricular activiation and recovery. |
| QTcF | QT interval corrected for heart rate using Fredericia formula |
| SABA | Short-acting $\beta_2$-agonist |
| SAD | Single Ascending Dose study |
| SAE | Serious adverse event (see definition in Section 7.3.2) |
| SDV | Source Data Verification |
| SGRQ-C | St George's Respiratory Questionnaire for COPD |
| Study drugs | This term covers investigational product and additional drug e.g reliever medication |
| VC | Vital Capacity |
| WBDC | Web Based Data Capture |
| WOCBP | Women Of Child Bearing Potential |

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

## 1.1 Medical emergencies and AstraZeneca contacts

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an serious adverse event (SAE) and is to be reported as such, see Section 7.3.4**

When the appropriate management of the patient necessitates knowledge of the treatment randomization , the treatment code can be broken, see Section 6.3.2. If the code is broken, the date, time and reason should be recorded.

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

The investigator can also contact the Local Study Delivery Team (LSDT) Leader or Monitor. If the LSDT leader/monitor is not available, the LSDT physician or the LSDT safety physician/representative at the marketing company (MC) can be contacted.

| Name | Role in the Study | Address & telephone number |
|---|---|---|
| [redacted] | Study Delivery Team Leader responsible for the protocol at central R&D site | [redacted] |
| [redacted] | Study Delivery Team Physician responsible for the protocol at central R&D site | [redacted] |

Local contact persons:

The local AstraZeneca representatives could be found in the Supplement A: Study Delivery Team Contacts in the Event of Emergency

At Visit 2, all randomized patients will receive a Study Participation Card in the local language. See Table 1 for a sample of the English master.

**Table 1 Study Participation Card**

| | |
|---|---|
| IMPORTANT MEDICAL INFORMATION<br>This patient participates in a clinical study and is being treated with either the non-registered compound AZD3199, formoterol or placebo.<br>Name: .....<br>Enrolment code: .....<br>Study code: D0570C00003 | IMPORTANT MEDICAL INFORMATION<br>If you have any queries please contact:<br>Dr.: .....<br>Nurse: .....<br>Hospital: .....<br>Phone: ..... |

## 1.2 Overdose

For AZD3199, intake of more than a total daily dose of 3360 µg is defined as an overdose, and must be reported as described below.

For formoterol, intake of more than a total daily dose of 90 µg is defined as an overdose and must be reported as described below.

- An overdose with associated Adverse Events (AE) is recorded as the AE diagnosis/symptoms on the relevant AE modules in the electronic Case Report Form (eCRF) and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If any overdose occurs in the course of the study, the investigator(s) or other site personnel must inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 7.3.4. For other overdoses, reporting should be done within 30 days.

**AZD3199**

Serious intolerability resulting from drug administration cannot be excluded. No experience from patients who have overdosed AZD3199 is currently available. In the case of known or suspected intolerability or overdose, symptomatic treatment as well as monitoring of vital functions should be performed, based on the judgment of the investigator.

***AZD3199 intoxication: Symptoms***

Since there have been no reports on AZD3199 intoxication this paragraph is, by necessity, speculative and based on the experiences with other $\beta_2$-agonists. An overdose would likely lead to effects that are typical of $\beta_2$-agonists such as headache, tremor, muscle cramps, nausea, vomiting, restlessness and somnolence. The most significant side effects are related to the effects of $\beta_2$-agonists on the heart and they include tachycardia, palpitations, cardiac arrhythmia and hyper- or hypotension. Metabolic effects include acidosis, hyperglycemia, hypokalemia, and in serious cases possibly rhabdomyolysis and renal failure.

***AZD3199 intoxication: Treatment***

Usually no treatment is required. If it can be suspected that significant amounts have been swallowed, the following measures should be considered: gastric lavage, activated charcoal. Determine acid-base balance, blood glucose and electrolytes. Monitor ECG (heart rate and rhythm) and blood pressure.

Use of cardioselective β-blockers may be considered, but only subject to extreme caution since the use of β-adrenerigic blocker medication may provoke bronchospasm. If the $\beta_2$-mediated reduction in perpheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given. Correct any hypokalemia or metabolic acidosis. Provide symptomatic therapy.

Symptomatic tachycardia and ventricular arrhythmias in non-asthmatic patients can be treated with metoprolol or propranolol.

In cases of unrest, give diazepam 5-10 mg by i.v . Correct any hypokalemia or metabolic acidosis. Provide symptomatic therapy.

## 1.3 Pregnancy

All outcomes of pregnancy must be reported to AstraZeneca.

### 1.3.1 Maternal exposure

Women of childbearing potential (WOCBP) must use reliable contraception, see Section 5.1. In addition, pregnancy tests will be performed on all women at screening, before the first dose and after the last dose.

Should a pregnancy occur, the patient must be discontinued from the study and the pregnancy must be documented and reported as described below.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of

a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, the investigator(s) or other site personnel must inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he/she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the appropriate AstraZeneca Patient Safety data entry site within 30 calendar days.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

### 1.3.2 Paternal exposure

Male patients must refrain from fathering a child during the study and **3** months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, have not yet been thoroughly investigated

Pregnancy of the patients partners is not considered to be an adverse event. If the investigator receives information that a pregnancy has occurred during the study despite these restrictions, the investigator should ask the subject whether this information can be forwarded to AstraZeneca. If this permission is granted, the investigator should inform the AstraZeneca representative. The investigator will follow up and document the outcome of the pregnancy (spontaneous miscarriage, elective termination, normal birth or congenital abnormality), as described in Section 1.3.1.

# 2. INTRODUCTION

## 2.1 Background

There is a high unmet medical need for effective treatment in chronic obstructive pulmonary disease (COPD), a major cause of morbidity and mortality throughout the world. COPD is usually characterised by a progressive development of airflow limitation that is not fully reversible. COPD encompasses chronic obstructive bronchitis affecting the small airways and emphysema characterised by destruction of lung parenchyma, loss of lung elasticity and enlargement of air spaces. There is a chronic inflammatory process in COPD that differs markedly from that seen in asthma in terms of cellular influx, inflammatory mediators and response to treatment, therefore different treatment approaches are needed. Symptomatic treatment with bronchodilators is recommended as the first step in the drug treatment of

COPD and since symptoms have to be treated continuously, long-acting bronchodilators are more convenient for the patient than short-acting alternatives (GOLD 2008).

The AZD3199 project objective is to develop a well-tolerated inhaled once daily, long-acting $\beta_2$-agonist (LABA) with fast onset of bronchodilation. The systemic side effect profile should be similar to, or better than, that of inhaled formoterol at comparable peak bronchodilating effects. Effect duration is aimed to be in parity with that of for example Indacaterol, ie, at least 24 hour duration of action (Beeh et al 2007). AZD3199 has been selected for development by AstraZeneca based on its selectivity and high potency as a $\beta_2$-agonist in vitro. Treatment with AZD3199 could then significantly improve the pharmacological treatment of obstructive pulmonary diseases such as asthma and COPD.

Previous studies have shown that AZD3199 is a potent long-acting $\beta_2$-receptor agonist with a bronchodilatory effect that persists over 24 hours. Thus, a once daily dosing is possible which will be more convenient and possibly also more effective than long-acting β-agonists available on the market.

AZD3199 has been administered to 54 healthy volunteers and 51 asthma patients in the previous studies. Results of the clinical studies as well as relevant pre-clinical studies, ie, pharmacology, toxicology, safety pharmacology and pharmacokinetic studies, are summarised in the Investigator's Brochure (IB).

AstraZeneca intends to perform genetic research in the AZD3199 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD3199.

Future research may suggest other genes or gene categories as candidates for influencing response to AZD3199. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to drug action.

## 2.2 Research hypothesis

A once daily regimen of inhaled AZD3199 can be at least as efficacious as the twice daily alternative of formoterol 9 μg in patients with moderate to severe COPD, and at matching doses have a similar or better safety profile.

## 2.3 Rationale for conducting this study

The primary objective is to study the efficacy of inhaled once-daily-regimens of AZD3199 in moderate to severe COPD patients, and specifically to determine a dose of AZD3199 with an adequately maintained bronchodilation for 24 hours. The study is placebo controlled and inhaled formoterol 9 ug twice daily will constitute the established reference treatment. Salbutamol is provided/prescribed as reliever medication.

The aim is to define an appropriate dose (dose range) to be used in subsequent studies. The dose range to be investigated is chosen on the basis of the outcome of a single dose crossover study in asthmatic patients.

## 2.4 Benefit/risk and ethical assessment

It is uncertain whether or not recruited COPD patients will have any individual benefit from the study. Potential risks have been identified through preclinical animal studies, in the previous clinical studies with AZD3199, and by reviewing literature.

There are several inhaled LABAs in clinical use and under development for the treatment of asthma and COPD. The most cited adverse effects are palpitation, headache and tremor. At higher doses tachycardia, hyperglycemia, hypokalemia and an increased QTc interval may be seen. These effects are dose-related class effects of $\beta_2$-agonists.

Doses in the study have been chosen to evaluate if AZD3199 given once daily can match a currently used bronchodilator (formoterol) given twice daily with regard to efficacy and to compare them regarding safety. 3 doses will be used to study dose-dependent effects of AZD3199; 200, 400 and 800 μg.

The adverse effects observed in the non-clinical studies with AZD3199 with potential relevance for humans are: signs of irritation in the nose and larynx in the rat, mouse and dog, and heart rate increase, QTc prolongation and decrease in plasma potassium in the dog. Throat irritation was occasionally reported after administration of the highest dose (1920 μg) in the single dose study in asthmatic patients, and once in the MAD study (720 μg). Minor well-known dose related class effects of $\beta_2$-agonists such as effects on potassium, heart rate and QTc were seen in man after administration of AZD3199 compared to placebo.

Overall, AZD3199 was safe an well tolerated and no adverse events (AEs) of any safety concern were identified in the clinical studies. The most common AEs after administration of AZD3199 were headache in healthy volunteers, and headache and nasopharyngitis in patients with asthma. No patterns of any clinically significant abnormalities in ECG parameters, blood pressure, pulse, lung function, body temperature, clinical chemistry, haematology or urinalysis after administration of AZD3199 have been observed.

Some of the patients randomized in this study will be exposed to formoterol, a LABA marketed in many countries and frequently used in asthma and COPD patients. The extensive clinical experience with formoterol indicates that the safety profile is similar to that of other inhaled $\beta_2$-agonists. Typically reported adverse effects of formoterol are class effects of $\beta_2$-agonists which tend to be mild and decrease with regular therapy. The administration of formoterol does thus not call upon additional safety precautions.

Treatment with placebo is not considered to be an important risk to patient safety in a controlled setting of a 4-week clinical trial where patients continue their previous glucocorticosteroids (GCS) treatment if applicable, and are provided with/prescribed reliever medication.

The restrictions in the concomitant medications (see Section 6.5) are not considered to involve any increased risk of a COPD exacerbation in patients randomized in this study, as the withdrawal is of short duration. Patients will be thoroughly monitored throughout the study, e.g. by frequent visits to the clinic including lung function assessments and through daily diary recordings of symptoms, use of reliever medication and lung function. Patients on inhaled GCS will continue with those during the study. In addition, reliever medication will be available to the patients at all times.

For an overall risk benefit assessment see the IB.

# 3. STUDY OBJECTIVES

## 3.1 Primary objective

Primary objective is to compare the clinical efficacy of AZD3199 inhaled once daily with 9 µg formoterol twice daily and placebo over a 4-week treatment period in adults with COPD.

The primary outcome variable is forced expiratory volume in 1 s ($FEV_1$) assessed both with regard to maximum bronchodilation and to trough effects 24 h after the morning administration.

The following secondary outcome variables will be assessed: Forced Vital Capacity (FVC), Patient Reported Outcomes (AZ COPD Symptom Scores, Clinical COPD Questionnaire (CCQ) and St George's Respiratory Questionnaire (SGRQ-C)), and use of reliever medication.

## 3.2 Secondary objectives

The secondary objectives of the study are:

- To investigate the safety of AZD3199 by assessment of the nature, incidence and severity of AEs, safety laboratory variables, pulse, blood pressure, and ECG
- To investigate the effect of regular treatment with AZD3199 on the reversibility in $FEV_1$ after inhalation of salbutamol
- To determine the pharmacokinetics (PK) of AZD3199 in COPD patients

## 3.3 Explorative objective

- To explore morning and evening PEF and $FEV_{1(eDiary)}$ measurements using an electronic diary device with electronic peak flow device
- To collect pharmacogenetic samples for possible retrospective pooled analysis, by evaluation of genes or gene categories involved in the response to AZD3199.

# 4. STUDY PLAN AND PROCEDURES

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

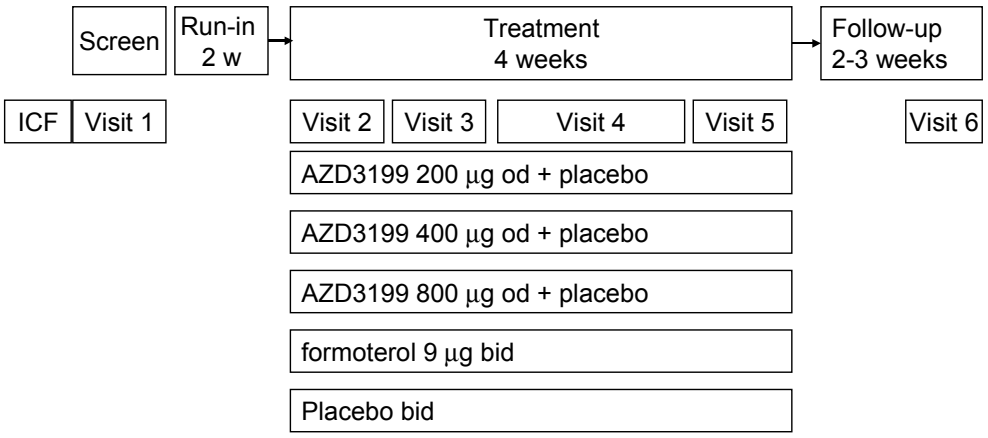
## 4.1 Overall study design and flow chart

The study design will be double-blind, placebo-controlled, randomized, parallel-group, multi-centre, in adults (≥40 years) with moderate to severe COPD.

All potentially suitable patients will attend a formal screening assessment (Visit 1) where the study will be explained to them and written informed consent will be obtained. Patients that fulfil the inclusion criteria and none of the exclusion criteria will enter a 2-week run-in period with salbutamol as needed (and GCS if applicable) as the only allowed COPD medication. After the run-in period, at Visit 2, patients who fulfil the randomization criteria will be randomized into the 4-week double-blind treatment period to receive either one of the 3 different doses of AZD3199 (200, 400 or 800 µg), to be inhaled once daily in the morning, or formoterol 9 µg bid, or placebo. In addition, salbutamol will be provided/prescribed as reliever medication to all patients. Patients will start with the inhalations in the evening on the day of Visit 2. Visits 3, 4, and 5 will take place after 1, 2, and 4 weeks (±1 day) respectively. Patients will be asked to fill in a diary during the complete study period (Visits 1- 5). Patients will come back to the clinic for a follow-up visit, 2-3 weeks after the last dose (Visit 6).

The pre-dose lung function measurements at Visits 3-5 should be performed ±1 hour in relation to the time at Visit 2 (baseline) and between 8 and 11 am.

**Figure 1 Study Design**




### Visit 1

All potentially suitable patients will attend a formal screening assessment (Visit 1) where the study will be explained to them and informed consent (ICF) will be obtained. Assessments at Visit 1 can be done at two occasions if needed for practical reasons, e.g. withdrawal of concomitant medications, see Section 6.5. Patients that fulfil the inclusion criteria and do not meet any of the exclusion criteria will enter a 2-week run-in period.

### Visits 2 to 5

After the 2-week run-in period, patients who fulfil the randomization criteria will be randomized into the 4-week double blind treatment period to receive either one of the 3 different doses of AZD3199, 200 µg, 400 µg, 800 µg, or formoterol 9 µg bid, or placebo. Inhalations will start at home, in the evening on the day of Visit 2. Visits 3, 4, and 5 will take place after 1, 2, and 4 weeks (±1 day) respectively.

At Visit 5, serial measurements of lung function ($FEV_1$ and FVC) will be done up to 26 hours post dose, and blood for PK analysis will be drawn. The patients will be resident at the clinic from the morning, until 4 hours after dosing and then either stay overnight or go home and come back again the following morning for the 24 and 26 hour measurements. Before attending the clinic for Visit 5, breakfast must be finished at least 1 hour prior to dosing, and no food will be allowed until after the 1 hour post dose assessments. The treatment compliance during Visit 5 is of outmost importance as the evaluation of the primary objective includes the 24 and 26 hour measurements. For patients who are not resident at the clinic during the entire assessment period, personnel at the site will stress the importance of taking

the evening dose on time, i.e 12 h ±1 after the morning dose. In addition, an alarm is set in the eDiary to remind the patient.

Informed consent for participation in the genetic part of the study, can be obtained at any visit after randomization . For those patients who have signed the genetic ICF, blood samples will be collected at any visit after randomization .

**Visit 6**

Patients will return to the clinic for a safety follow-up 2-3 weeks after the last dose of study drug (Visit 6).

**Table 2 Study plan**

| Visit | 1 Screen | 2 Rand Visit | 3 | 4 | 5[a] | 6 Follow-up |
|---|---|---|---|---|---|---|
| Time (weeks) | -2[b] | 0 | 1 ±1 day | 2 ±1 day | 4 ±1 day | 6-7 |
| Signed Informed consent main study | x[b] | | | | | |
| Allocation of enrolment code | x[b] | | | | | |
| Demogra-phy | x | | | | | |
| Medi-cal/Surgical history | x | | | | | |
| COPD history | x | | | | | |
| Smoking history | x | | | | | |
| Height, weight | x | | | | | |
| Contracep-tive history (WOCBP only) | x | x | x | x | x | x |

**(Continued)**

Table 2 Study plan

| Visit | 1 Screen | 2 Rand Visit | 3 | 4 | 5[a] | 6 Follow-up |
|---|---|---|---|---|---|---|
| Inclusion/exclusion criteria checked | x | x | | | | |
| Laboratory assessment | x | x | x(pre) | x(pre) | x | x |
| Pregnancy test (women only) | x | x | | | | x |
| Physical examination | x | x[c] | x(pre)[c] | x(pre)[c] | x[c] | x |
| 12-lead ECG | x | x | x(pre) | x(pre) | x | x |
| Pulse and blood pressure | x | x | x(pre) | x(pre) | x | x |
| Spirometry, $FEV_1$, FVC | x (post bronchodilator at rev test) | x (pre bronchodilator at rev test) | x (predose and post dose +60 min) | x (predose and post dose +60 min) | x | |
| Reversibility test | x | x | | | x | |
| CCQ | x (training) | x | x | x | x | |
| SGRQ-C | x (training) | x | | | x | |
| eDiary incl AZ COPD symptom scores, use of reliever medication, PEF and $FEV_1$ | td | r | r | r | r | |
| Allocation of randomization code | | x | | | | |

**(Continued)**

Table 2 Study plan

| Visit | 1 Screen | 2 Rand Visit | 3 | 4 | 5[a] | 6 Follow-up |
|---|---|---|---|---|---|---|
| Dispensing/prescription of reliever medication | x | | | | | |
| Dispensing/return of investigational product[f] | | d | | r/d | r | |
| Inhalation of drug and/or placebo | | x (morning and evening every day)[d] | | | | |
| Blood sampling for AZD3199 PK | | | | | x | |
| Signed ICF and Blood sampling for PGx | | | x[e] | | | |
| Adverse Events | x | x | x | x | x | x |
| Recording of concomitant medication | x | x | x | x | x | |

a Two-day visit. For timings see Table 3

b Provision of informed consent and allocation of enrolment code can be performed prior to Visit 1 or at Visit 1 (according to local regulations) but before any study related procedures has been performed, i.e. more than 2 weeks before randomization

c Brief; auscultation of heart and lung

d Starting at home in the evening of Visit 2

e For patients that signed the separate ICF genetics, PGx sample can be collected at any visit after randomization .

f t=train d= deliver, r=review/return

**Table 3 Study Time Schedule Visit 5**

| Assess-ment/Time point | Pre-dose | 0 | 5 min | 15 min | 60 min | 2 h | 4 h | 12 h | 24 h | 26 h |
|---|---|---|---|---|---|---|---|---|---|---|
| CCQ, SGRQ-C | x | | | | | | | | | |
| 12-lead ECG | x | | | | | | | | | |
| Pulse and blood pressure | x | | | | | | | | | |
| Physical examination | x[a] | | | | | | | | | |
| Laboratory assessment | x | | | | x[b] | | | | | |
| Blood sampling for AZD3199 PK | x | | | x | x | | x | | x | |
| Spirometry, $FEV_1$, FVC | x | | x | x | x | x | x | | x | x(pre bron-cho-dila-tor at rev test) |
| Reversibility test | | | | | | | | | | x |
| Fasting | x[c] | | | | | | | | | |
| Administration of drug or placebo | | x | | | | | | x[d] | | |
| Adverse Events | x | | | | | | | | | |
| eDiary [e] | r | | | | | | | | r | |

a Brief; auscultation of heart and lung

b Potassium only

c From 1 h before dosing to 1 h post-dose

d Remind patient to take evening dose if patient is at home. This is the last intake of investigational product.

e r= review

**Order of assessments**

When there is more than one assessment at the same time point, the following order of assessments apply:

- CCQ, SGRQ-C
- ECG
- Pulse and blood pressure
- Physical examination (auscultation heart and lungs)
- Laboratory sample collection (safety, PK, and if applicable PGx)
- Spirometry ($FEV_1$, FVC)

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

**Study rationale**

At similar peak effect, AZD3199 indicates to maintain bronchodilation longer than formoterol, thus it may be suitable for a once-daily regimen. The overall aim of the present study is to explore the prospect of using a once-daily regimen of inhaled AZD3199 that could match an established twice-daily regimen of formoterol regarding bronchodilation in COPD patients, but having a beneficial side effect profile.

**Reference treatment and central design elements**

Formoterol Turbuhaler 9 µg twice daily typically constitute a standard regular bronchodilating treatment of COPD patients and will be the active reference to AZD3199 once daily in the present study. Treatment effects will be assessed and compared with placebo based on the evaluation of spirometric measurements. The primary variable for assessment of bronchodilation will be $FEV_1$, and the outcome variables of efficacy will be average bronchodilation over first 4 hours and remaining bronchodilation 24-26 hours after dose. To improve the assessment of efficacy, especially duration of action, the main assessment will be performed on the basis of serial measurements at Visit 5, starting with a pre-dose assessment, followed by the morning administration of investigational product, and 4 hours of repeated measurements to establish the initial effect. The patient may then return home, takes his/her evening medication 12 h after the morning administration as prompted via the alarm in the eDiary, and finally returns to the clinic in the morning for the 24 and 26 h measurements in relation to the previous morning dose to assess duration of action. Anticholinergics, both short- and long-acting alternatives, will be disallowed during the study. This is to optimize the conditions for studying the effects of AZD3199 and possibly to achieve a larger effect on lung function, thereby enabling a lesser number

of patients needing to be exposed in the study in order to fulfill the objectives. Regular use of long-acting bronchodilators has been associated with the potential risk of desensitizing the patient to short-acting alternatives used as needed. To investigate whether AZD3199 possesses any such effect, a reversibility test with salbutamol has been included at baseline before the first dose of study drug and after 4 weeks of treatment.

**Dosing rationale**

The bronchodilating potential of AZD3199 120, 480, and 1920 µg was compared with that of formoterol 9 and 36 µg (delivered doses via Turbuhaler) and placebo in a single dose study of asthmatic patients. AZD3199 and formoterol were shown dose-dependently to increase peak $FEV_1$ within the studied dose ranges. 450 µg of AZD3199 was estimated to be equipotent regarding peak effect to formoterol 9 µg but with a prolonged duration of action. Moreover, AZD3199 was safe and well tolerated in the MAD study in healthy men at once daily delivered doses of 240, 720, and 1680 µg via Turbuhaler. COPD patients will now be recruited for the first time; the maximum dose should have an approximate two-fold safety margin to the maximum dose in MAD. Furthermore, considering the report of occasional throat irritation on the highest dose (1920 µg) in the single dose study in asthmatic patients and histological signs in preclinical toxicology studies, it is prudent to apply a safety margin in this 4-week trial in patients with COPD. As shown in the single dose study in asthmatic patients, more than 120 µg of AZD3199 is necessary to achieve a 24-hour duration of effect. Thus, to spread the doses evenly in the interval the following doses has been chosen; a high dose of 800 µg (2x400 µg), a medium dose of 400 µg (2x200 µg), and low dose of 200 µg (2x100 µg) (delivered doses).

# 5. PATIENT SELECTION CRITERIA

Investigator(s) must keep a record of patients who entered pre-studyl screening but were never enrolled eg, patient screening log. Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

## 5.1 Inclusion criteria

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

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

2. Men or women, aged ≥40 years. Women must be of non-childbearing potential or must have used a highly effective contraceptive method for the last 3 months prior to Visit 1 (the start date of the run-in period), see below for details

3. Clinical diagnosis of COPD, with symptoms for more than 1 year

4. Current or ex-smokers with a smoking history of at least 10 pack years (1 pack year = 20 cigarettes smoked per day for one year)

5. 40% ≤ $FEV_1$ <80% of the predicted normal value (post-bronchodilator) and post-bronchodilator $FEV_1$/FVC < 70%

Randomization criteria at Visit 2:

6. Total AZ COPD symptom scores ≥2 per day for at least half the number of days of the run-in period (by totalling the breathlessness, cough, chest tightness and night time awakening scores from the diary)

7. $FEV_1$ pre-bronchodilator must be reproducible within a maximum of 8 attempts, see Section 7.4.1

For voluntary participation in the genetic part of the study:

8. Provision of informed consent for genetic part of the study

**Women of non-childbearing potential**

Women are considered to be of non-childbearing potential if they meet one of the following criteria:

- aged >50 years and have been amenorrheic for 12 months or more and have not used exogenous hormonal treatment
- aged >50 years and have been amenorrheic for 12 months or more, following cessation of all exogenous hormonal treatments
- aged >57 years regardless of whether they are on Hormonal Replacement Therapy (HRT)
- Permanent sterilisation by hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy

**Highly effective contraceptive methods**

Women of childbearing potential must use one of the following highly effective contraceptive methods:

- True sexual abstinence (i.e. not just stopping intercourse for the duration of the study)

- Vasectomised sexual partner (with appropriate post-vasectomy documentation of the absence of sperm in ejaculate)
- Etonogestrel slow-release subcutaneous implant (e.g Implanon)
- Female sterilisation by tubal occlusion
- IUD/IUS provided coils are copper-banded (Steel or copper wire devices are not acceptable)
- IUS containing levonorgestrel, eg. Mirena®
- Medroxyprogesterone injections, eg. Depo Provera®
- Normal or low dose combined oral contraceptive (COC) with fixed doses of estrogen and progestin only if used in a TriCycle regime -TriCycle regime means instead of taking a single 3- week course of COC pills followed by 1 week off COC, the patient takes 3 or 4 courses together (ie, 9-12 weeks of daily COC) with, between each 9-12 week cycle, a shortened 4-day pill free interval (PFI) rather than the usual 7-day PFI. Note: Triphasic pills, which have different strength pills in the same pack, are not considered highly effective and are therefore excluded from this instruction
- Norelgestromin/ethinyl estradiol transdermal system, eg. Evra Patch - only if used in above Tricycle regime with 4-day patch-free intervals after each long cycle
- Intravaginal device containing ethinyloestradiol and etonogestrel (3-ketodesogestrel), eg. Nuvaring - only if used in above Tricycle regime with 4-day ring-free intervals after each long cycle
- Cerazette™ (desogestrel-releasing progestogen-only pill with established failure rate of <1 per 100 women in first year)

**Unacceptable contraceptive methods**

Unacceptable contraception includes:

- Triphasic COCs
- All progesterone only pills except Cerazette™
- All barrier methods
- Non Tricycle Combined hormonal pills/patches/rings plus barrier methods

- Non copper containing IUDs
- Fertility awareness methods
- Coitus interruptus

## 5.2 Exclusion criteria

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

1. Current or a history of asthma
2. A history of atopic disease, such as allergic rhinitis, before 40 years of age
3. Any current respiratory tract disorder other than COPD, including respiratory diseases described in GOLD 2008 or JRS Guidelines 2004 as needed to be differentiated from COPD, which is considered by the investigator to be clinically significant
4. Significant disease or disorder (e.g. cardiovascular, pulmonary other than COPD, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which, in the opinion of the investigator, may either put the patient at risk because of participation in the study, or influence the results of the study, or the patient's ability to participate in the study
5. Any clinically relevant abnormal findings in clinical chemistry, haematology, urinalysis, physical examination, pulse, blood pressure or ECG at Visit 1, which, in the opinion of the investigator, may put the patient at risk because of his/her participation in the study
6. Body mass index (BMI) <18 kg/$m^2$ or a body weight <30 kg
7. A marked baseline prolongation of QT and/or QTcF (QTcF interval > 450 ms or QT > 500 ms for both males and females)
8. A history of additional risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, family history of Long QT syndrome)
9. Requirement for regular oxygen therapy
10. An exacerbation of COPD (defined as use of systemic antibiotics and/or systemic glucocorticosteroids and/or hospitalisation related to COPD) within 30 days of Visit 1 (the start date of the run-in period)

11. Known or suspected hypersensitivity to study therapy or excipients of the investigational product

12. Pregnancy or lactation

13. Past or present alcohol or drug abuse

14. Participation in another study involving blood donation (>500 ml) within 3 months of Visit 1 (the start date of the run-in period)

15. A suspected/manifested infection according to IATA categories A and B, see Appendix C

16. Participation in any clinical study with an investigational drug or new formulation of a marketed drug in the 3 months prior to Visit 1(the start date of the run-in period)

17. Planned in-patient surgery or hospitalisation during the study.

18. Previous enrolment into the present study (unless the discontinuation is due to practical reasons, see Section 6.2)

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

For voluntary participation in the genetic part of the study:

20. Previous bone marrow transplant

21. Whole blood transfusion within 120 days of the date of genetic sample collection

## 5.3 Procedures for handling incorrectly included patients

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

Where patients that do not meet the study criteria are randomized 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 AZ Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped.

## 5.4 Withdrawal of patients

### 5.4.1 Criteria for discontinuation from the study

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

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Risk to patients as judged by the investigator and /or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrectly enrolled patients
- Patient lost to follow-up
- Withdrawal of informed consent to the use of biological samples collected as an integral part of the study (i.e. safety and PK samples), see Section 8.5
- An exacerbation of COPD (defined as use of systemic antibiotics and/or systemic glucocorticosteroids and/or hospitalisation related to COPD)
- Pregnancy detected during the course of the study
- Any significant and clinically relevant changes in the safety parameters (e.g. ECG, blood pressure, pulse, laboratory assessments and AEs) making the continuation of dosing unjustified

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

A patient that discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. The investigator(s) will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. Adverse events will be followed up (See Section 7.3.3 and Section 7.3.4); Diary and study drugs should be returned by the patient.

If a patient prematurely discontinues participation in the study after randomization, the patient should complete Visit 6 (2-3 weeks after last dose, if possible). This is also applicable to patients withdrawn due to incorrect inclusion and to patients for whom the treatment code has been prematurely broken by the investigator.

If the patient discontinues participation in the study due to a COPD exacerbation, the reason for discontinuation should always be recorded as study specific discontinuation criteria on the TERM module. In addition, the investigator has to assess whether the COPD exacerbation fulfils any AE criterion as defined under 'Symptoms of the disease under study' in Section 7.3.3 and also should be recorded on the AELOG module.

## 5.5 Precautions to minimise risk of pregnancy

Women of child bearing potential must have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial.

Two negative urine pregnancy tests are required prior to the first dose and will be performed at Visits 1 and 2. At Visit 6, a follow-up pregnancy test will be performed, to check that the patient did not become pregnant during the study.

Vomiting within 3 hours of taking oral contraception does pose a risk equivalent to a missed pill. Patients will be instructed to contact the investigator on how to follow the guidelines for a missed pill (WHO 2004) whenever they suspect unprotected intercourse.

In the event of suspected pregnancy during the study, the test should be repeated and if pregnant the patient should be discontinued.

Contraceptive history should be re-checked throughout the study and patients should be made aware of the availability of emergency "post-coital" contraception if there is an indication for it (e.g missing IUD threads or a late injection).

# 6. STUDY CONDUCT

## 6.1 Restrictions during the study

Patients will be required to:

- Abstain from smoking for at least 30 minutes prior to and after dose administration, within at least 30 minutes prior to spirometry measurements, or whenever study procedures demand it
- Abstain from taking any medication other than those allowed according to study protocol, see Section 6.5
- Abstain from donating blood or plasma during the study other than for study purposes
- Avoid sperm donation or having procreative sex during the study

Patients will be recommended to:

- Abstain from donating blood or plasma up to 3 months after the last dose
- Avoid sperm donation or having procreative sex up to 3 months after last dose

Before attending the clinic for Visit 5, breakfast must be finished at least 1 hour prior to dosing, and no food will be allowed until after the 1 hour post dose measurements.

## 6.2 Patient enrolment and randomization

The principal investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed
2. Assign potential patient a unique enrolment number, beginning with "E#", at Visit 1. The enrolment number (E-code) will consist of E + 4 digit centre number + 3 digit serial number.
3. Determine patient eligibility. See Section 5.1 and Section 5.2
4. Assign eligible patient unique randomization code (patient number), beginning with "#", at Visit 2

At Visit 1 all patients who sign the ICF will receive an E-code. Patients who fulfil all inclusion criteria and do not meet any of the exclusion criteria, will enter the run-in period.

If a patient discontinues from the study before randomization, the E-code will not be reused, and the patient will not be allowed to re-enter the study, unless the discontinuation is due to practical reasons and not the ability to fulfil the eligibility criteria. The patient will then be assigned a new E-code.

If the patient is eligible and fulfils the criteria at Visit 2, the patient will be allocated a randomization code. Patients will receive randomization codes strictly sequentially per site as patients are eligible for randomization. If a patient discontinues from the study, the randomization code will not be reused, and the patient will not be allowed to re-enter the study.

### 6.2.1 Procedures for randomization

The randomization code will be assigned from a randomization list prepared by a computerised system at AstraZeneca, and the randomization will be done in blocks. The investigator will be provided with the blinded randomization code for each patient.

## 6.3 Blinding and procedures for unblinding the study

### 6.3.1 Methods for ensuring blinding

Packaging and labelling will be performed in a way that ensures blinding. Turbuhaler for AZD3199, formoterol, and placebo will be of identical appearance.

The following personnel will have access to the randomization list

- the personnel carrying out packaging and labelling of investigational product
- the personnel sorting and analysing the PK samples

The information in the randomization lists must be kept in a secure location until the end of the study.

### 6.3.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available as sealed code envelopes, to the investigators or pharmacists at the study centres, to the local AstraZeneca Marketing Companies, and in Japan, the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca KK.

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

AstraZeneca retains the right to break the code for Serious Adverse Events (SAEs) that are unexpected and are suspected to be causally related to the 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.

## 6.4 Treatments

### 6.4.1 Identity of investigational product(s)

| Investigational product | Active ingredient | Dosage form and strength[a] | Excipient | Manufacturer[b] |
|---|---|---|---|---|
| AZD3199 Turbuhaler® | AZD3199 dihydrobromide | Dry powder for inhalation, 100, 200, 400 µg/dose, 60 doses | Lactose monohydrate | AstraZeneca |

| Investigational product | Active ingredient | Dosage form and strength[a] | Excipient | Manufacturer[b] |
|---|---|---|---|---|
| Placebo Turbuhaler® | none | Dry powder for inhalation, 60 doses | Lactose monohydrate | AstraZeneca |
| Formoterol 4.5 Turbuhaler® | formoterol fumarate dihydrate | Dry powder for inhalation, 4.5 µg/dose, 60 doses | Lactose monohydrate | AstraZeneca |

a Strength per dose refers to delivered dose from Turbuhaler.

b Formulation numbers and batch numbers will be recorded in the Study Master File and identified in the Clinical Study Report.

AZD3199 Turbuhaler contains a powder mixture of AZD3199 dihydrobromide and lactose monohydrate. 1 g of AZD3199 is equivalent to 1.28 g of AZD3199 dihydrobromide.

### 6.4.2 Additional study drug

Salbutamol pMDI HFA, 100 µg per actuation, will be used as reliever medication during the study, and also for reversibility tests.

| Additional study drug | Active ingredient | Dosage form and strength | Excipient | Manufacturer |
|---|---|---|---|---|
| In Japan: Sultanol® Inhaler In Bulgaria, Poland, Russia: Ventolin Evohaler® In Canada: Ventolin® Inhaler | salbutamol sulphate | Aerosol in pMDI, 100 µg/actuation, Ca 200 actuations | HFA 134a | GlaxoSmithKline |

### 6.4.3 Doses and treatment regimens

AZD3199 and formoterol will be provided as dry powder for oral inhalation that will be administered with Turbuhaler. A matching placebo will also be provided.

The study will start with a 2-week run-in period, followed by a 4-week treatment period. At Visit 2 patients will be randomized to one of 5 treatment arms. Patients will receive one of the following 5 treatments (given as Turbuhaler delivered doses):

- AZD3199 200 µg (morning) + placebo (evening)
- AZD3199 400 µg (morning) + placebo (evening)
- AZD3199 800 µg (morning) + placebo (evening)
- Formoterol 9 µg twice daily
- Placebo twice daily

Patients will take 2 inhalations from the Turbuhaler inhaler in the morning and 2 inhalations from a different Turbuhaler inhaler in the evening.

**Demonstration**

At Visit 1 and 2, the patient will be instructed on how to use a Turbuhaler inhaler in the correct manner. A written instruction will also be provided.

**Run-in period**

All patients will be provided with/prescribed salbutamol pMDI at Visit 1, to be used as reliever medication during the run-in period and throughout the study. Patients will be instructed to use the salbutamol pMDI whenever needed to relieve COPD symptoms but not for prophylactic reasons. During the run-in period, patients will continue to use the same inhaled GCS at the same dose as previous treatment, if applicable. In case the patient is treated with a combination drug before entering the study, this should be switched to the same dose (or the nearest available on the market) of the steroid as single drug. This switch should be done after the ICF has been signed and no later than 48 hours prior to the reversibility test at Visit 1.

**Treatment period**

During the treatment period, patients will continue with their prescribed GCS (same steroid (not combination product) as in the run-in period), if applicable. At Visit 2, eligible patients will receive investigational product. The first dose of investigational product will be taken at home, in the evening on the day of Visit 2. The patients will be instructed to take 2 inhalations every morning upon rising, and 2 inhalations every evening, ie, 12 hours ±1 hour after the morning dose. The dose should be taken after PEF and $FEV_1$ measurements. The maintenance medication (eg GCS) will be taken at the same time as the investigational products, if applicable. On the days of Visits 3, 4 and 5, the morning doses of investigational product will be taken at the clinic. Patients will be instructed to use the salbutamol inhaler whenever needed to relieve COPD symptoms but not for prophylactic reasons.

At Visit 5, repeated PK samples are collected and clinic staff must take precautions to avoid contamination of the samples. Inhalation of study drug is preferably done in a room separate from the blood sampling area. Both patients and clinic staff involved in the study drug administration should wear protective gloves and clothing, during the inhalation.

**Follow-up period**

After Visit 5, the patients will return to their ordinary COPD treatment, and after 2-3 weeks the patient will return for a follow-up visit.

### 6.4.4 Labelling

The packaging and labelling will be performed by Investigational Products (IPS), AstraZeneca R&D Mölndal, Sweden. All supplies and labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil local guidelines and GMP Annex 13 requirements for labelling.

The study drug will be sent to the local AstraZeneca Distribution site, who will forward the medication to the centre/hospital pharmacy. The name of the principal investigator will be filled in on each patient box, and also on each Turbuhaler (except for Japan). This will be done at AstraZeneca Distribution site or centre/hospital pharmacy.

The study medication for randomized patients will be individually labelled and packed in patient boxes containing 2 Turbuhaler inhalers; 1 for the morning doses and 1 for the evening doses. Each box will have a label with a detachable part, which will be inserted into a separate Study Drug Accountability Form and filed in the Investigator Study File (ISF). The Turbuhaler inhalers for the evening doses will be provided with yellow labels.

### 6.4.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. For all countries except Japan, the investigational product label on the Turbuhaler cover and the patient box specifies the appropriate storage. In Japan, a description of the appropriate storage conditions is specified in the document ‘Procedure of storage conditions for investigational product’.

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

The Informed Consent Form must be signed before conducting any study-related procedure, eg, discontinuation of pre-study treatment.

Medications **not allowed during the study** , from Visit 1 to end of Visit 5 and time limits prior to lung function measurements at Visit 1:

**Table 4 Non allowed medication**

| Treatments to be withdrawn before/at Visit 1 to end of Visit 5 | Time limits prior to Visit 1 |
|---|---|
| Depot parenteral GCSs | 12 weeks |
| Oral, parenteral, or rectal GCSs | 30 days |
| Inhaled disodium cromoglycate or inhaled nedocromil sodium | 72 hours |
| Parenteral $\beta_2$-agonists | 48 hours |
| Inhaled LABAs | 48 hours |
| Inhaled SABAs[a] | 6 hours |
| Oral $\beta_2$-agonists short-acting | 8 hours |
| Oral $\beta_2$-agonists depot | 24 hours |
| Oral $\beta_2$-agonists long-acting | 48 hours |
| Transdermal $\beta_2$-agonists | 24 hours |
| Xanthines once daily | 48 hours |
| Xanthines twice daily | 24 hours |
| Inhaled anticholinergics short-acting | 8 hours |
| Inhaled anticholinergics long-acting | 72 hours |
| Ephedrine containing drugs | 48 hours |
| $PDE_4$ inhibitors | 48 hours |
| Leucotriene antagonists and 5-LO inhibitors | 48 hours |
| Non-selective β-blockers, including eye-drops | |
| Medication that prolong the QT/QTc interval (other than inhaled $\beta_2$-agonists), e.g. certain anti-arrhythmics and anti-psycotics | |

a Salbutamol pMDI HFA 100 µg provided/prescribed as reliever medication and for reversibility tests is allowed during the study, but it is strongly recommended not to take salbutamol 6 hours prior to clinic visits or immediately before PEF/$FEV_{1(eDiary)}$ measurements

**Table 5 Allowed medication**

| Treatments allowed during the study |
|---|
| Inhaled salbutamol pMDI HFA 100 µg/actuation. [a] |

**(Continued)**

Table 5 Allowed medication

| **Treatments allowed during the study** |
|---|
| Cardioselective β-blockers on constant dose |
| Nasal and dermal glucocorticosteroids |
| Inhaled glucocorticosteroids (not combination product) on constant dose |
| Mucolytics (e.g. N-acetylcystein) |

a Strongly recommended not to be used 6 hours prior to a clinic visit, or immediately before recording of $PEF/FEV_1$ measurements

In case the patient is treated with a combination drug (glucocorticosteroid + non alllowed medication) before entering the study, this should be switched to the same dose (or the nearest available on the market) of the glucocorticosteroid as a single drug. Patients must have been treated with GCS (combination product or single drug) for at least 30 days preceeding Visit 1 (start of run-in period).

After the 26-hour measurements Visit 5, patients will return to their ordinary treatment according to the investigator´s judgement.

Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator. The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF.

## 6.6 Treatment compliance

The administration of all medication (investigational products, reliever and concomitant medication) must be recorded in the appropriate sections of the eCRFs.

The patient will record intake of investigational product and reliever medication in the eDiary on a daily basis, and adherence to prescribed treatment will be checked by the Investigator or delegate continuously.

### 6.6.1 Accountability

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

The study personnel at each site will account for, and record in the ISF, all drugs dispensed and returned.

The AstraZeneca monitors will ensure that all drug handling procedures at the sites are appropriate.

In all countries except for Japan the following paragraph is applicable:

Any unused products are accounted for and returned to a designated facility or to AstraZeneca for destruction, or may be destroyed locally as per local regulatory requirements. Certificates of delivery, destruction and return must be signed.

In Japan the following paragraph is applicable:

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the return of all unused and remaining study drug to AstraZeneca. AstraZeneca will provide the study documents "Procedures for drug accountability" and "Procedure of storage conditions for investigational product" which describes the specific requirements. Certification of delivery and return must be signed. The investigator(s) is responsible for ensuring that the patient has returned all unused study drug. The patient must be asked to return used and unused study drug, empty cartons and packaging. Any study drug materials returned by the patient must be promptly passed to the Investigational Product Storage Manager to complete drug accountability.

# 7. COLLECTION OF STUDY VARIABLES

## 7.1 Recording of data

The principal investigator will provide AstraZeneca with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, and timeliness of the data reported to AstraZeneca in the eCRF and in all required reports.

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data specified in the protocol into the WBDC system and according to the eCRF Instructions. When data have been entered, reviewed, and edited by study personnel and Source Data Verification (SDV) has been performed by AZ representative, the data will be frozen to prevent further editing. The principal investigator will be notified to sign the eCRF electronically as per the eCRF instructions. A copy of the eCRF data will be archived at the study site.

The investigator(s) will record data on the observations, tests and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The eCRF will be accompanied with 'Instructions for the Investigator', which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change

data incorrectly recorded. These instructions are an important part of quality control and standardisation across the study. Quality control procedures will be applied to each stage of the data handling to ensure that all data are reliable and have been processed correctly.

## 7.2 Screening and demography procedures

Assessments at Visit 1 can be done at two occasions if needed for practical reasons, e.g. withdrawal of concomitant medications.

After the patient has signed the informed consent form, the following data will be collected for each patient and recorded in the eCRF.

- Date of birth, sex and race
- COPD history and current prescribed COPD medication
- Medical and surgical history relevant for the purpose of the study and prescribed medication
- Spirometry, $FEV_1$, FVC and reversibility test
- Smoking history incl pack years (1 pack year = 20 cigarettes smoked per day, for one year)
- Physical examination
- Pulse and blood pressure
- Height and weight; height will be measured in cm (no shoes) and weight in kg (light clothing and no shoes)
- ECG
- Laboratory safety assessment
- Pregnancy test (women only)
- Concomitant medication (including contraceptive method for WOCBP)

In addition, patients will receive training on how to handle the eDiary (recording of symptoms, PEF and $FEV_1$, use of reliever medication, and filling in the CCQ and SGRQ-C).

Patients eligible for randomization will be scheduled to Visit 2.

### 7.2.1 Follow-up procedures

A post study follow-up visit (Visit 6) will be performed 2-3 weeks after administration of last dose of study drug. This will consist of:

- Physical examination
- Laboratory safety assessment
- Pregnancy test (women only)
- Pulse and blood pressure
- ECG
- Concomitant medication
- Adverse events

## 7.3 Safety

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

### 7.3.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). 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.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

### 7.3.2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to adverse events), except hospitalisation that has been planned before enrolment
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

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

### 7.3.3 Recording of adverse events

AEs will be collected from the enrolment visit (the date of singed informed consent) and throughout the run-in, treatment and follow-up periods.

**Variables**

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

The patient will be asked to assess the intensity of the reported AEs according to the following scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

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

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

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

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

**Adverse Events based on signs and symptoms**

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *“Have you had any health problems since the previous visit?” or "Have you had any health problems since the last time you were asked?"*, 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 they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment at Visit 1, 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).

**Symptoms of the disease under the study**

Deterioration in COPD and signs or symptoms thereof are not to be recorded as AEs in the eCRF unless:

- the sign or symptom is serious according to definitions, see Section 7.3.2 or
- the patient discontinues the study due to the sign or symptom or
- the sign or symptom is new to the patient or not consistent with the patient's pre-existing COPD history as judged by the investigator.

The following (or terms judged synonymous with these) will be considered symptoms of COPD:

- cough
- chest tightness
- dyspnoea
- breathlessness
- wheeze
- sputum increased

**Follow-up of unresolved adverse events**

Any AEs not resolved at the time the patient completes or discontinues participation in the study must be followed up by the investigator(s) up to 14 days after the completion or discontinuation and recorded on the eCRF, thereafter ongoing AEs should be followed-up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### 7.3.4 Reporting of serious adverse events

**Procedures for reporting of SAEs in all countries except Japan**

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

The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, informing Ethics Committees and Regulatory Authorities will be performed by AstraZeneca.

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

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

SAE information will be entered and submitted into the WBDC system on the relevant eCRF modules. The WBDC system will generate an automated email alert to the designated AstraZeneca representative.

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

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

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

The reference document for definition of expectness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SPC) for the active comparator product, formoterol

**Procedures for reporting of SAEs in Japan**

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.

Investigator and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The principal investigator should provide detailed information to AstraZeneca in writing within 4 calendar days of the initial report. The principal investigator should notify the serious adverse events in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s); study code, site number, Enrolment code, adverse event, seriousness, start date.

The following detailed information should be sent to AstraZeneca as soon as it becomes available; severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of adverse event, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

In addition AstraZeneca will provide details of any unexpected serious adverse drug reactions or expected fatal or life-threatening serious adverse drug reactions reported with regard to the test product and the control drug if not unblinded in this study or other compound available overseas in which the active ingredient is known to be equivalent to the test product, to the Head of the study site, principal investigator and the regulatory agency. The Head of the study site should submit a written report to the IRB providing the details of all adverse event case(s) reported by AstraZeneca.

The investigator(s) and other site personnel will access the WBDC system and report SAE information by entering it into the relevant eCRF module. Upon entry of the SAE information, an automated email alert will be sent to the designated AstraZeneca representative. If the system is unavailable, the investigator(s) should take other appropriate

measures to provide SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The investigator(s) is responsible for completing the eCRF as soon as the system becomes available again.

If initial or the subsequent reports are made by means other than WBDC, necessary information on any SAEs should finally be entered into eCRF via WBDC system by the investigator(s).

### 7.3.5 Laboratory safety assessment

A laboratory screening, which includes haematology, clinical chemistry and urinalysis will be done at Visits 1-6.

Central laboratories or their designees will be used to supply materials for blood sampling for the laboratory assessments, provide sample transportation, and to perform the analyses.

Laboratory reports for haematology and clinical chemistry must be signed and dated by the investigator and stored in the ISF.

Urinalysis including pregnancy tests, will be analysed at the clinic. The results from the urinalysis will be entered into the eCRF.

Separate instructions on sampling, labelling and shipment will be given in the Manual of Procedures.

The following laboratory variables will be measured:

| **Clinical Chemistry (serum or plasma)** | **Haematology (whole blood)** |
|---|---|
| S/P-Creatinine | B-Haemoglobin |
| S/P-Bilirubin | B-Platelet count |
| S/P-Alkaline phosphatase | B-Leucocyte count |
| S/P-Aspartate aminotransferase | B-Leucocyte differential count (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) |
| S/P-Alanine aminotranferase | |
| S/P-Albumin | |
| S/P-Potassium | **Urinanalysis** |
| S/P Calcium (total) | U-Protein/Albumin |
| S/P Sodium | U-Hb/Erytrocytes/Blood |
| S/P-Glucose | U-Glucose |

| | |
|---|---|
| S/P-Thyroxine free | U-HCG (pregnancy test, women only, Visits 1, 2 and 6) |
| S/P-Thyroid-stimulating hormone | |
| S/P-C-Reactive Protein | |

For blood volumes see Section 8.1

### 7.3.6 Physical examination

A full physical examination, according to normal clinical routines, will be performed on all patients at Visit 1 (baseline) and Visit 6 including examination of general appearance, skin, lymphnodes, thyroid, muscoskeletal/extremities, neurological, mouth, teeth, throat, cardiovascular, lungs and abdomen. The outcome of the examination is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified.

In addition, at Visits 2-5, a brief physical examination including an auscultation of heart and lungs only, will be performed.

### 7.3.7 ECG

#### 7.3.7.1 Resting 12-lead ECG

12-lead ECG recordings will be obtained after 10 minutes' rest in the supine position, at Visits 1-6. The outcome of the overall evaluation is to be recorded as normal/abnormal in the eCRF, with any abnormalities specified. The printout of the ECG is to be signed, dated and filed in the ISF along with a signed and dated copy (if the printouts are not on archive-quality paper).

### 7.3.8 Vital signs

#### 7.3.8.1 Pulse and blood pressure

Supine pulse (beats/min) and blood pressure (mmHg) will be measured at Visits 1-6. Measurements will be performed according to local procedures, subsequent to a 10-minute rest. Systolic and diastolic blood pressure will be measured using the same cuff size, appropriate for arm circumference, throughout the study.

## 7.4 Efficacy

### 7.4.1 Lung function measurements

At Visit 1, lung function measurements will be performed to ensure inclusion criteria are met by measuring $FEV_1$ and FVC. The post bronchodilator $FEV_1$ and FVC values in the

reversibility test are used for the inclusion criteria. A reversibility test is performed to characterize the patient.

At Visit 2 to 5, lung function measurements are performed to assess effect of AZD3199, by measuring $FEV_1$ and FVC and by performing reversibility tests. For timings see Table 2 and Table 3.

**Equipment**

The spirometer must meet or exceed the ATS/ERS 2005 recommendations. The spirometer should be serviced once a year at an authorised facility or according to the manufacture's instruction. Calibration is to be in accordance with each trademark specification. If not other specified, the site staff should calibrate the spirometer every day the patient will use it. All calibration reports should be signed (by the staff doing the calibration), dated and filed in the ISF along with a signed and dated copy (if the calibration reports are not on archive-quality paper). If a calibration report can not be printed, the results should be documented in writing in the ISF.

**Measurements/Conditions**

Before lung function measurements the patients are strongly recommended to avoid taking any salbutamol the preceeding 6 hours, see Section 6.5 and to abstain from smoking the preceeding 30 minutes.

Lung function measurements will be performed according to Quanjer et al 1993.

The pre-dose lung function measurements at Visits 3-5 should be performed ±1 hour in relation to the time at Visit 2 (pre bronchodilator) and between 8 and 11 am.

The spirometry will be performed in a sitting upright position. The patient will wear a noseclip, and the thorax should be able to move freely, hence tight clothing should be loosened.

The print-outs from the lung function measurements must be signed, dated, and marked with study code, E-code/randomization code, date and time of measurement and visit number, and must be filed in the ISF.

**$FEV_1$ and FVC**

$FEV_1$ and FVC will be measured at Visits 1 to 5, as defined in Table 2 and Table 3.

$FEV_1$ values will be recorded with 2 decimals throughout the study.

Lung function tests will consist of 3 expiratory manoeuvres, during which the patient should exhale from full inspiration as hard and fast and long as possible. The manoeuvres should be technically satisfactory and reproducible, ie, the difference between the largest and the second largest $FEV_1$ should not be more than 5% or 100 ml, whichever is the greater.

If reproducibility is not fulfilled, additional trials should be attempted to meet the above criteria but not more than 8 manoeuvres depending on the patient's condition. If the criteria are still not fulfilled after the maximum of performed manoeuvres, the highest value should be reported in the eCRF with a comment.

However, for the $FEV_1$ assessments at Visit 1 (post bronchodilator) and Visit 2 (pre-bronchodilator), patients cannot be randomized if reproducibility has not been reached within 8 manoeuvres. Patients may be rescheduled once to show reproducibility.

$FEV_1$ and FVC will be measured repeatedly at Visit 5, according to time points detailed in Table 3. To avoid obstruction due to repeated spirometry manoeuvres, a maximum of 3 attempts at the 5, and 15 minutes' measurements at Visit 5, are recommended even if reproducibility is not met.

The highest values of $FEV_1$ and FVC should be recorded in the eCRF. The highest $FEV_1$ and FVC can come from different curves.

**Reversibility test**

A reversibility in $FEV_1$ in response to salbutamol will be assessed at Visits 1, 2 and 5. After baseline $FEV_1$ is recorded, the patient will inhale 400 µg salbutamol (4x100 µg), and the post bronchodilator $FEV_1$ will be recorded 15-30 minutes later. The reversibility at Visit 1 is calculated according to the formula below:

$$Reversibility = \frac{FEV_{1(after)} - FEV_{1(before)}}{FEV_{1(before)}} X100 \quad (1)$$

**Predicted normal calculations**

The Predicted Normal (PN) $FEV_1$ value will be calculated according to ERS (Quanjer et al 1993)

**Table 6 $FEV_1$ predicted normal**

| **$FEV_1$ Predicted Normal** | | |
|---|---|---|
| Women | $FEV_1$ PN = | (3.95 x H) - (0.025 x A) - 2.60 |
| Men | $FEV_1$ PN = | (4.30 x H) - (0.029 x A) - 2.49 |

H: standing height in meters
A: age (year)

### 7.4.2 Electronic Patient reported outcomes (ePRO)

The PRO questionnaires used in this study are the CCQ and SGRQ-C.

The patients need to be able to read and understand the local language to be able to answer the questions.

#### 7.4.2.1 Clinical COPD Questionnaire (CCQ)

The Clinical COPD Questionnaire (CCQ, Van der Molen et al 2003) is a short health status measure for patients with COPD. It is a multidimensional questionnaire and includes 10 questions in 3 domains:

- Symptoms (4 questions)
- Functional State (4 questions)
- Mental State (2 questions)

The CCQ has been developed according to generally accepted rules and has been shown to have strong evaluative and discriminative properties. The CCQ is available in two versions, as weekly (visit) and daily (diary) versions and the weekly version will be used in this study. Translations of the CCQ into local languages have been performed according to a linguistic validation process. The paper version is included in Appendix D.

**Methods of assessment**

The CCQ will be self-administered electronically through the eDiary device during Visit 1 (for training purposes only), and Visits 2 to 5. To answer the 10 questions takes approximately 2-3 minutes.

**Administration of CCQ**

It is important to administer the CCQ according to the guidelines for standardized administration. A brief introduction on how to complete the questionnaire will be given at

Visit 1 prior to the training assessment. At Visits 2-5, the patients will answer the questions in the CCQ before any other study related procedures take place.

The questionnaire 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 patients 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 questions the patient may have. After completion of the questionnaire, the study personnel will review the document for completeness only.

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

The SGRQ-C is a modified version of the St. George's Respiratory Questionnaire (SGRQ), which has been developed to measure the impact of respiratory disease on health status (Jones 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 et al 1992). For COPD patients, SGRQ-C has been shown to have even more favourable measurement properties than the original SGRQ (Meguro et al 2007) and it has the further advantage of being directly applicable in an electronic format. Translations of the SGRQ-C into local languages have been performed according to a linguistic validation process. The paper version is included in Appendix D.

**Methods of assessment**

The SGRQ-C will be self-administered electronically through the eDiary device during Visit 1 (for training purposes only), and Visits 2 and 5. It takes approximately 10 minutes to answer the questionnaire.

**Administration of SGRQ-C**

It is important to administer the SGRQ-C questionnaire according to the guidelines for standardized administration. A brief introduction on how to complete the questionnaire will be given at Visit 1 prior to the training assessment. At Visits 2-5, the patients will answer the questions in the SGRQ-C after CCQ, but before any other study related procedures take place.

The questionnaire 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.

#### 7.4.2.3 Electronic diary

Patients will be supplied with an electronic diary device and an electronic peak flow device for the run-in period and the treatment period. The eDiary will be completed in the morning and in the evening each day. Patients should be strongly recommended not to take salbutamol immediately before PEF/$FEV_{1(eDiary)}$ measurements.

At Visit 2 (end of run-in period and beginning of treatment period) and at Visits 3 to 5 (treatment period), the investigator, or his/her delegate, should carefully review the eDiary together with the patient for compliance and for information recorded (e.g., entries or comments) potentially judged by the investigator to be an AE.

The eDiary will include the following daily recordings:

- COPD symptoms (breathlessness, cough, chest tightness, and night-time awakenings)
- Number of inhalations of reliever medication
- PEF
- $FEV_{1(eDiary)}$
- Intake of investigational product (not included in the diary for the run-in period)

**COPD Symptoms**

The AstraZeneca COPD Symptom scores will be used to capture symptoms of breathlessness, cough, chest tightness, and night-time awakenings due to COPD symptoms. The question about night-time awakening will be asked in the morning before the morning dose, and the other 3 COPD symptom questions (breathlessness, cough, chest tightness,) will be asked in the evening, after the evening dose, at bedtime, throughout the study from Visit 1 to 5 (+24 h). All 4 COPD symptom questions will be assessed on a 5-point Likert-type scale, ranging from 0 to 4.

Patients must have complete diaries for at least half the number of days in the run-in period, i.e. minimum 7 days, see Section 5.1.

The COPD symptom questions and response alternatives will be translated into local languages. The paper version of the questions and responses is included in Appendix D.

**Use of reliever medication**

The number of inhalations of reliever medication taken during day- and night-time will be recorded by the patient in the eDiary every morning and evening from Visit 1 to 5 (+24 h). 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.

**Peak Expiratory Flow (PEF) and $FEV_{1(eDiary)}$ measurements**

An electronic peak flow meter will be dispensed at Visit 1 together with the eDiary. The patient will be carefully instructed in the use of the peak flow meter and how to transfer the value to the eDiary electronically. The principal investigator is responsible to ensure that this training is performed at Visit 1.

Measurements of PEF and $FEV_{1(eDiary)}$, expressed in L/min and L respectively, will be performed during the entire study including the run-in period. The patients will be requested to perform 3 full FVC manoeuvres twice daily (morning and evening), where the highest reading will be transferred to the eDiary. It is important that the patient performs full FVC manoeuvres, to ensure that the exhalation lasts long enough to collect a correct $FEV_{1(eDiary)}$. The measurements should be done upon rising in the morning and in the evening, before intake of any drugs. The measurements should be made while standing. The patient should use the same peak flow meter during the entire study.

**Intake of study medication**

Intake of study medication 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 study medication but will be used as a measure of compliance. In the morning, patients will be asked to take their study medication after the other eDiary assessments have been performed. In the evening, patients are reminded to take their evening dose 12 hours ±1 after the morning dose, i.e. after the evening PEF and $FEV_{1(eDiary)}$, but prior to the other eDiary assessments, which are performed at bedtime. An alarm can be set in the eDiary, to remind the patients to take the evening dose.

At Visit 5, it is of outmost importance that patients take their evening dose on time, i.e. 12 h ±1 after the morning dose, before the 24 and 26 hour measurements. An alarm will be set

in the eDiary to remind the patient. In addition, the patient will be asked to enter the time of the evening dose in the eDiary.

## 7.5 Pharmacokinetics

### 7.5.1 Collection of biological samples

Blood samples for determination of AZD3199 in plasma will be taken at Visit 5 at the time points presented in Table 3. Blood samples will be collected, labelled and shipped as detailed in the Manual of Procedure. The date and time of collection will be recorded in the eCRF.

Plasma samples should be stored at -20°C or below and analysed within the time frame after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported.

For blood volume see Section 8.1.

### 7.5.2 Determination of drug concentration in biological samples

Plasma samples for determination of drug concentration will be analysed by a laboratory contracted by Clinical Pharmacology and DMPK, AstraZeneca R&D Charnwood, using HPLC/MS/MS after solid phase extraction. The lower limit of quantification (LLOQ) plasma is 10 pmol/L. Details of the methods used will be referred to in the clinical study report.

For formoterol and placebo treatments, no plasma samples will be analysed.

## 7.6 Pharmacogenetics

### 7.6.1 Collection of samples

The blood sample for genetic research is optional and will be obtained from patients who have signed the separate genetic informed consent, after randomization. Genotype is a stable parameter, therefore the blood sample may be taken at any visit until the last study visit. Samples will be collected, labelled stored and shipped as detailed in the Manual of Procedure.

## 7.7 Health economics (Not applicable)

# 8. BIOLOGICAL SAMPLING PROCEDURES

## 8.1 Volume of blood

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

**Table 7 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Safety | Clinical chemistry | 8.5 | 6 | 51 |
| | Haematology | 4 | 6 | 24 |
| | Potassium | 2.5 | 1 | 2.5 |
| Pharmacokinetic (AZD3199) | | 3 | 5 | 15 |
| Pharmacogenetics[a] | | 10 | 1 | 10 |
| **Total** | | | | **102.5** |

a Blood sample for PGx will be obtained from patients that have signed the separate ICF for PGx

## 8.2 Handling, storage and destruction of biological samples

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

### 8.2.1 Safety samples

All laboratory safety samples will be collected, handled and analysed according to the central laboratory instructions in the Manual of procedure.

If not completely used in the analysis process, samples will be disposed of after the clinical study report has been finalised.

### 8.2.2 Pharmacokinetic samples

Samples for AZD3199 concentration analysis will be collected, labelled, stored, and shipped as detailed in the Manual of Procedures. Samples will be frozen (-20°C or below) and must remain frozen at all time.

If not completely used in the analysis process, samples will be disposed of after the clinical study report has been finalised.

### 8.2.3 Pharmacogenetic samples

The blood sample for genetic research is optional and will be obtained from patients who have signed the separate genetic informed consent. Samples for DNA extraction will be collected, labelled, stored, and shipped as detailed in the Manual of Procedures.

The samples collected from the patients will be used only for analysis related to this study.

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

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

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

DNA will be extracted for possible future research and will be retained at R&D Alderley Park, on behalf of AstraZeneca for a maximum of 15 years following the finalisation of the Clinical Study Report. The results from future analysis will not be reported in the Clinical Study Report but separately in a Clinical Study Report Amendment/Scientific Report or Scientific Publication.

## 8.3 Labelling and shipment of biohazard samples

The principal investigator ensures that samples are labelled and shipped in accordance with the IATA 6.2 Regulations Guidance described in Appendix C.

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

## 8.4 Chain of custody of biological samples

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

The principal investigator at each centre is accountable for keeping traceability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

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

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

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

## 8.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed/destroyed, if not already analysed and documented. If collection of the biological samples is an integral part of the study then the patient is withdrawn from further study participation (safety and PK samples). If collection of the biological samples is a voluntary part of the study then the patient may continue in the study (PGx samples). The principal investigator:

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

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

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

# 9. ETHICAL AND REGULATORY REQUIREMENTS

## 9.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable

regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The applicable regulatory requirements in Japan are 'Good Clinical Practice for Trials on Drugs (MHLW Ordinance No. 28, 27 March 1997)', partially revised by MHLW Ordinance and their related notifications.

## 9.2 Patient data protection

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

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

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separated.

## 9.3 Ethics and regulatory review

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

The opinion of the Ethics Committee must be given in writing. In all countries except Japan, the investigator must submit a copy of the written approval to AstraZeneca before enrolment of any patient into the study. Whereas in Japan, the head of the study site must submit a notification of direction/determination as well as a copy of the Ethics Committee written approval to AstraZeneca before enrolment of any patient into the study.

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

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

In Japan, and also in other countries if required by local regulations, the protocol must be re-approved by the Ethics Committee annually. The principal investigator must submit

progress reports to the Ethics Committee via the head of the study site at the time of the protocol re-approval.

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

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

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

Also a valid contract between the study site and AstraZeneca must be signed before the investigator can enrol any subjects into the study.

## 9.4 Informed consent

The principal investigator(s) at each centre will:

- Ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure that the patient is notified that he/she is free to discontinue from the study at any time
- Ensure that the patient is given the opportunity to ask questions and allowed time to consider the information provided
- Obtain and document the patient's signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form is stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient

If any new information on the study medication becomes available which may influence the decision of the subject to continue the study, the investigator(s) must inform the subject of such information immediately, record this in a written form, and confirm with the subject if he/she wishes to continue the participation in the study. In addition, if the investigator(s) deem it necessary to revise the Informed Consent Form, they must revise it immediately (see Section 9.5). The investigator(s) must re-inform the subjects using updated Informed Consent

Form even if the subjects have already been informed of the new information verbally. Written informed consent to continue participation in the study must be provided separately.

## 9.5 Changes to the protocol and informed consent form

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

If it is necessary for the study protocol to be amended,

- in all countries except Japan, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to or approved by each Ethics Committee according to local regulations.
- in Japan, the amendment must be submitted to the head of the study site and must be approved by its Ethics Committee.

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to Ethics Committee see Section 9.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

## 9.6 Audits and inspections

All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

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

regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.



# 10. STUDY MANAGEMENT BY ASTRAZENECA

## 10.1 Pre-study activities

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

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

## 10.2 Training of study site personnel

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

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

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

## 10.3 Monitoring of the study

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

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, 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) incl. verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).

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

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

### 10.3.1 Source data

Refer to Clinical Study Agreement for location of source data.

## 10.4 Study agreements

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

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

In Japan the following paragraphs are applicable.

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the principal investigator and AstraZeneca or the Ethics Committee approval based on its deliberations.

The investigator(s) will record all deviations from the protocol appropriately on the source documents such as medical records. The principal investigator should submit a report to AstraZeneca and the head of the study site (and the Ethics Committee via the head of the study site), to notify any change which may give a significant impact on the conduct of the study or increase a risk to the patient.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the principal investigator and AstraZeneca or the Ethics Committee approval, only in the event of a medical emergency, eg. it is only way to avoid an emergency risk to the patient. In such case, the principal investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to AstraZeneca and the head of the study site (and Ethics Committee via the head of the study site) as soon as

possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as AstraZeneca should be obtained via the head of the study site.

## 10.5 Study timetable and end of study

The end of the entire study is defined as ”Last patient out (the last visit of the last patient undergoing the study)”.

Planned duration of the study:

- First patient in: [redacted]
- Last patient in: [redacted]
- Last patient out: [redacted]

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 AZD3199.

For Japan the following two paragraphs apply.

**Discontinuation or suspension of the whole study programme**

If AstraZeneca decides to prematurely terminate or suspend the study, the principal investigator, sub investigator, the head of the institution, and regulatory authorities should receive written notification of the reasons for the premature termination or suspension. The investigator(s) will immediately notify the decision to the subjects, give appropriate medical treatment; take necessary measures, and record treatment or measures provided on the source documents.

**Completion of the study**

Upon terminating the study, the investigator(s) will report in writing the completion of the study as well as the summary of the results to the head of the study site in accordance with the institution’s rules. The head of the study site, who is informed of the termination by the investigator, will provide a written notification of the results to the IRB and AstraZeneca.

# 11. DATA MANAGEMENT BY COGNIZANT TECHNOLOGY SOLUTIONS

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the principal investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

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

Genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system, separate from the database used for the main study.

# 12. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

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

### 12.1.1 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.

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.

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

### 12.2.1 Spirometry

The primary outcome variable for evaluation of the effect of AZD3199 is $FEV_1$ from clinic visits. Four different measures will be computed: the average value at Visit 5 from before to 4 h after morning dose, $E_{0\text{-}4}$; the average value at Visit 5 between 24 and 26 h following the morning dose, $E_{24\text{-}26}$; the mean pre-dose $FEV_1$ from Visits 3-5; and the mean 1 h post-dose $FEV_1$ from Visits 3-5. $E_{0\text{-}4}$ will be the primary outcome for bronchodilator potency and $E_{24\text{-}26}$ will be the primary outcome for duration of effect. The pre-bronchodilator $FEV_1$ at Visit 2 will constitute baseline. If appropriate, $FEV_1$ at 5 minutes post-dose at Visit 5 could be used to assess the onset of bronchodilatory effect.

Reversibility tests with salbutamol 400 µg will be performed at Visit 2 (baseline) and 26 h following morning dose administration at Visit 5. Outcome variables will be the percentage change in $FEV_1$ from before to after salbutamol administration and the absolute $FEV_1$ after the test.

FVC will be recorded at the same time-points as $FEV_1$, primarily as a check on the validity of the $FEV_1$ recordings. For analysis purposes, the same parameters as for $FEV_1$ will be calculated. The pre-bronchodilator FVC at Visit 2 will constitute baseline.

### 12.2.2 eDiary variables

eDiary variables will include COPD symptom scores of breathlessness, chest tightness, cough and night-time awakenings, and morning and evening use of reliever medication. For each variable a baseline mean will be computed over at least 7 days of the run-in period and a treatment period mean will be computed using all data collected in the 4-week treatment period except recordings from the randomization day. In addition, outcome variables such as total daily symptom score and total daily reliever use will be computed by adding the period means for the ingoing components.

In addition, morning and evening PEF and $FEV_{1(eDiary)}$ are exploratory variables and will not be included in the clinical study report.

### 12.2.3 Questionnaires

Two questionaires will be used in the study, the weekly CCQ and the SGRQ-C. For each questionnaire and assessment occasion, the domain scores and the total score will be calculated. For CCQ the means over Visits 3-5 and for SGRQ-C the Visit 5 value will be used as outcome variables. The values from Visit 2 will be used as baseline.

## 12.3 Calculation or derivation of pharmacokinetic variables

Pharmacokinetic parameters will include the maximum plasma concentration (Cmax), time to Cmax (tmax), and area under the plasma concentration-time curve from zero to 24 h (AUC[0-24h]). Parameters will be determined using standard non-compartmental methods based on plasma concentrations collected at Visit 5 (steady state).

## 12.4 Calculation or derivation of pharmacodynamic variable(s) (Not Applicable)

## 12.5 Calculation or derivation of pharmacogenetic variables

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to 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.

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

# 13. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

## 13.1 Description of analysis sets

Patients who were enrolled in the study but not randomized will not be included in any analysis. Erroneously treated patients (e.g., those randomized to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

### 13.1.1 Analysis of safety population

All randomized patients who received at least one dose of investigational product and for whom post-dose safety data are available will be included in the safety population.

### 13.1.2 Analysis of efficacy population

The efficacy analyses will be based on the 'full analysis set', as defined in the ICH E9 guideline. The full analysis set will consist of all randomized patients who have taken at least one dose of investigational product and for whom post-dose efficacy data are available. Stability analyses using other definitions of the efficacy population may be performed as appropriate.

## 13.2 Methods of statistical analyses

The efficacy variables, as defined in Section 12.2, will be compared between treatments using analysis of variance (ANOVA) models with treatment and country as fixed factors and, if appropriate, baseline as a covariate. For spirometry, multiplicative models may be considered, otherwise models will be additive. Pairwise treatment contrasts will be calculated including estimated mean differences with 95% confidence intervals and p-values.

AZD3199 will be compared to placebo using a closed test procedure as follows: first the highest dose of AZD3199 will be compared to placebo, if this is statistically significant the next-highest dose of AZD3199 will be compared to placebo, and finally if this is statistically significant the lowest dose of AZD3199 will be compared to placebo. Secondarily formoterol will be compared to placebo and then AZD3199 will be compared to formoterol. If dose-dependent effects of AZD3199 is found, comparisons between AZD3199 and formoterol may be done on the dose-scale.

Patients withdrawn and patients experiencing a COPD exacerbation during the study will be summarised by treatment group.

Pharmacokinetic parameters will be summarised using descriptive statistics for each dose level.

The changes in laboratory safety, clinical vital signs and ECG data from baseline to last value on treatment will be compared between treatment regimens. Data will further be comprehensively described in terms of figures, descriptive statistics and listings, and values fulfilling criteria of a treatment emerging laboratory change (TELC) will be identified..

Adverse events will be analysed using descriptive statistics and qualitative analysis.

All tests will be two-sided at a 5% significance level.

Special summaries will be prepared for the Japanese cohort in order to compare the efficacy and safety in this cohort with the full study population.

A statistical analysis plan will be prepared where appropriate.

## 13.3 Determination of sample size

The sample size computation is based on the repeated $FEV_1$assessments from Visit 5. There is limited previous experience from serial spirometries in COPD, but it has been estimated that a coefficient of variation of 10% could be expected for the 0-4 hours AUC. With 60 patients per group and a two-sided test at a 5% significance level, this will give an 80% chance to detect a true difference of 5% between any two treatments. The baseline $FEV_1$ in this study population is assumed to be around 1.5 L. Thus, on the mL scale, this corresponds to a standard deviation of 150 mL and a detectable limit of 75 mL. The variability in $FEV_1$ from 24-26 hours is expected to be somewhat larger with a detectable limit around 100 mL. These detectable limits have been considered reasonable to judge both the potency and the duration of effect of AZD3199 compared to placebo.

The study will include a cohort of Japanese COPD patients. Based on guidelines, these will constitute 25% of the total study population or 15 patients per treatment group.

## 13.4 Interim analyses (Not applicable)

## 13.5 Data monitoring committee (Not applicable)

# 14. LIST OF REFERENCES

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