A phase IIa, randomised, multi-centre, double-blind, placebo-controlled, 3 periods, crossover study to investigate the efficacy, pharmacokinetics, safety and tolerability of inhaled AZD8871 administered once daily for 2 weeks in patients with moderate to severe COPD

VERSION HISTORY

Version 3.0, 16 December 2016
Changes to the protocol are summarised below

1) Section 3.2 (Exclusion criteria) was updated to add 2 exclusion criteria to specify that patients who had 2 or more exacerbations of COPD within the last year prior to Screening and patients who were placed in an institution due to a regulatory or court order were not to be included in the study.
2) Section 3.9 (Discontinuation of investigational product) was updated to add study-specific withdrawal criteria (based on measurable parameters for vital signs, laboratory results, electrocardiograms, lung function, and worsening of COPD.
3) Appendix C (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law) was updated to align with the update to Section 3.9.

Version 2.0, 22 September 2016
Changes to the protocol are summarised below

1) Protocol synopsis, Section 1.2 (Rationale for study design, doses and control groups), Section 1.4 (Study design), Section 3.5 (Methods for assigning treatment groups), Section 7.1 (Identity of investigational product(s)), Section 7.2.2 (Treatment periods), and Section 8.2 (Sample size estimate), and Section 8.5.3 (Analysis of the primary efficacy variable): The high dose level was changed from 900 µg to 600 µg based on the exposure levels seen in the Phase I Study D6640C00003.
2) Protocol synopsis and Section 7.1 (Identity of investigational product(s)): Dosage form for 300 µg was removed as this is no longer required (due to the change in the high dose from 900 µg to 600 µg).
3) Protocol synopsis and Section 7.1(Identity of investigational product(s)): The requirement of 2 dry powder inhaler s (DPIs) per administration was changed to one DPI per administration (due to the change in the high dose from 900 µg to 600 µg).
4) Section 1.2 (Rationale for study design, doses and control groups) and Section 1.3 (Benefit/risk and ethical assessment): Newly available data from a previously reported study (D6640C00003) were added. Typo-error in the study number (D6640C00003) was corrected.
5) Section 6.3.6 (Adverse events based on examinations and tests) and Section 6.4 (Reporting of serious adverse events): The serious adverse event reporting process was updated in

alignment with the update on Sponsor's processes.

6) Section 4.2.3 (Visit 5, 8 and 11 (Treatment Day 14) and Section 5.3 (Other assessments): Additional text was added for the instruction on timing of taste assessment, for clarity.

7) Protocol synopsis: Typo-error regarding the number of treatments in the study was corrected from 4 to 3.

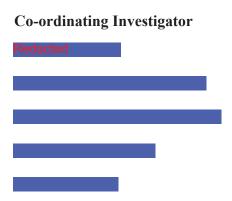**Version 1.0, 09 August 2016**

Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A phase IIa, randomised, multi-centre, double-blind, placebo-controlled, 3 periods, crossover study to investigate the efficacy, pharmacokinetics, safety and tolerability of inhaled AZD8871 administered once daily for 2 weeks in patients with moderate to severe COPD

Co-ordinating Investigator

Redacted

Study site(s) and number of patients planned

It is planned that approximately 42 patients with moderate to severe chronic obstructive pulmonary disease (COPD) will be randomised into the study.

The study will be conducted at 2 sites in Germany and the United Kingdom (UK). Estimated study duration is 6 months.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2016	IIa
Estimated date of last patient completed	Q2 2017	

Study design

This is a proof-of-concept, randomised, double-blind, 3-way complete crossover William's design, multiple dose study of 2 dose levels of AZD8871 and placebo administered by a dry powder inhaler (DPI) device. Approximately 42 male and non-childbearing female patients with moderate to severe COPD as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2016) guidelines will be randomised into the study. A subset of 20 patients,

who will have specifically consented for pharmacokinetics (PK), will undergo PK assessments. The aim is to ensure at least 30 patients complete the study.

The study will consist of a Screening period, 3 treatment periods (each separated by a wash-out period), and a Follow-up Visit.

Screening period: This will last up to 28 days and consists of a Screening Visit (Visit 1), Visit 2, and a run-in period.

Patients will be withdrawn from their usual COPD therapy after signing the informed consent form (ICF) at Visit 1 and maintained on their usual inhaled corticosteroid (ICS) therapy, if any. Those patients that were taking any long-acting muscarinic antagonist (LAMA), they will be maintained with ipratropium (following the approved dosage and regimen) between Visit 1 and Visit 2. In addition, salbutamol will be administered as rescue medication during the study as needed (salbutamol will be discontinued 6 hours previous any pulmonary function test).

Visit 1 and Visit 2 could be performed on the same day if no wash-out of prior medication is required and the patient visits the site in fasting condition. In case any wash-out of prior medication is required, then Visit 2 will be performed after the wash-out is complete. All the screening assessments can be performed at Visit 1 or Visit 2, based on the site's preference, except for the following:

- ICF: This must be completed at Visit 1 before any study-specific assessments are performed

- Reversibility test with salbutamol and spirometry (confirm inclusion criteria #6 and #7): These must be performed at Visit 2.

If reversibility criteria and forced expiratory volume in 1 second (FEV_1) predicted values are fulfilled according to inclusion criteria, the patient will be started on run-in period to assess clinical stability. If reversibility criteria or FEV_1 predicted values are not met, pulmonary function tests could be rescheduled at the latest, up to Day -14.

Run-in period: The duration of run-in period will be between a minimum of 14 and a maximum of 28 days (from Visit 2 to Visit 3). During the run-in period, all patients will receive ipratropium following the approved dosage and regimen (must be discontinued 8 hours prior to previous any pulmonary function test).

After the run-in period patients who fulfil all inclusion and none of the exclusion criteria will be randomised at Visit 3 to receive each of the 3 treatments (AZD8871 or placebo).

Treatment periods: The duration of each treatment period will be 14 days. In each treatment period, patients will receive one of the following 3 treatments according to a William's design with 3 periods and 6 sequences, using a balanced randomisation ratio per treatment sequence:

- AZD8871 100 µg once daily (double-blind)

- AZD8871 600 µg once daily (double-blind)

- Placebo (double-blind)

Each of the 3 treatment periods will include 2 overnight stays at the study site and one ambulatory visit at the study site.

Visits 3, 6 and 9 (corresponding to Treatment Day 1 in each period) and Visits 5, 8 and 11 (corresponding to Treatment Day 14 in each period) will include an overnight stay in the unit. At these visits, safety and tolerability assessments and pulmonary function measurements will be taken pre-dose and up to 24 hours post-dose.

Visits 4, 7 and 10 corresponding to Treatment Day 8 will have duration of approximately 5 hours where safety and tolerability assessments as well as spirometry measurements will be performed pre-dose and up to 4 hours post-dose.

Drug administration during all the visits at the sites (Day 1, Day 2, Day 8, and Day 14 of each treatment period) will be supervised by study personnel.

At Visits 3 to 11, a subset of 20 patients will undergo PK assessments. Blood samples will be collected pre-dose and up to 24 hours post-dose.

From treatment period 2 onwards, on Day 1 of every new treatment period, a FEV_1 stability test will be performed pre-dose. FEV1 stability check will be based on the pre-best test review (BTR). At Visits 6 and 9 the mean of the pre-dose FEV_1 (mean of the 2 measured values) should be within (±)20% or (±)200 mL compared to the pre-dose FEV_1 (mean of the 2 measured values) of the first treatment period (Visit 3).

Drug administration compliance will be recorded in the e-Diary of the patient when the patient is not at the site.

Wash-out periods: Between each treatment period, there will be a wash-out period of 28 to 35 days. During this period, all patients will receive ipratropium following the approved dosage and regimen (must be discontinued 8 hours before any pulmonary function test).

Follow-up Visit: Patients will come to the site for a Follow-up Visit, 28 days (up to 35 days) after the last investigational product (IP) administration, for adverse events (AEs) assessment, safety laboratory, electrocardiogram (ECG), vital signs and physical examination.

Objectives

Primary Objective:	Outcome Measures:
To evaluate the efficacy of inhaled AZD8871 in patients with moderate to severe COPD	**Primary** • Change from baseline in Trough FEV_1 on Day 15 **Secondary** • Change from baseline in Trough FEV_1 on Day 2, and Day 8 • Change from baseline in Peak FEV_1 on Day 1, Day 8 and Day 14 • Change from baseline in Trough FEV_1 over treatment duration (Day 8 to Day 15) • Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14) • Change from baseline in Total Score of Breathlessness, Cough Sputum Scale (BCSS) questionnaire and cough, breathlessness and sputum individual domain scores from Day 1 to Day 8 after treatment, from Day 8 to Day 14 after treatment and during the whole treatment duration • Rescue medication use

Secondary Objective:	Outcome Measures:
To investigate the PK of AZD8871 and its metabolites after multiple dose administration of AZD8871 in patients with moderate to severe COPD	• On serial PK sampling days, the following PK parameters will be calculated for AZD8871 and its metabolites LAS191861 and LAS34850 when applicable: Day 1: Maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration (AUC_{last}), area under the plasma concentration-curve from time 0 to 24 hours post-dose $AUC_{(0-24)}$ Day 14: C_{max}, t_{max}, AUC_{last}, $AUC_{(0-24)}$, average plasma concentration during a dosing interval ($C_{avg,}$), fluctuation index during a dosing interval (%Fluctuation), accumulation ratio for C_{max} [$Rac(C_{max})$] and accumulation ratio for $AUC_{(0-24)}$ [$Rac(AUC_{(0-24)})$] Additional parameters may be determined where appropriate

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of inhaled AZD8871 in patients with moderate to severe COPD	• AEs/Serious Adverse Events (SAEs) • Vital signs • ECG • Clinical laboratory assessments

Exploratory Objective:	Outcome Measure:
To evaluate the taste of inhaled AZD8871 in patients with moderate to severe COPD	• Taste assessment

Target patient population

The study will be performed in adult male and non-childbearing female patients 40 to 80 years of age with moderate to severe COPD.

Duration of treatment

Each of the 3 treatment periods will last for 14 days and will be followed (except the last one) by a wash-out period of 28 days (up to 35 days). The entire study period is scheduled to take from a minimum of 4.5 months (140 days) to a maximum of 5.6 months (175 days) for each individual patient.

Investigational product, dosage and mode of administration

Investigational product

Investigational product	Dosage form and strength	Manufacturer
AZD8871	Powder for inhalation administered via single dose DPI 100 and 600 µg/inhalation	Industrias Farmacéuticas Almirall S.A. Redacted
Placebo	Powder for inhalation administered via single dose DPI	Industrias Farmacéuticas Almirall S.A. Redacted

DPI=Dry powder inhaler.

Product dosage and mode of administration

Study treatment	IP administration	Comments
AZD8871 100 µg	100 µg single dose DPI	1 inhalation QD
AZD8871 600 µg	600 µg single dose DPI	1 inhalation QD
Placebo	Placebo single dose DPI	1 inhalation QD

DPI=Dry powder inhaler; QD=Once a day.
All investigational products will be administered by oral inhalation. Patients will be provided with 1 single dose DPI per day during the treatment periods.

Statistical methods

Sample size

The study will be powered to demonstrate superiority of AZD8871 100 µg and 600 µg versus placebo for the primary efficacy endpoint. With a total of 30 patients, there is 80% power to detect a difference between actives and placebo for the change from baseline to trough FEV_1 at Day 15 equal to 100 mL, assuming a within-patient standard deviation (SD) of 135 mL, 2-sided 5% significance level and a normal distribution. Assuming an approximate 25% dropout, the total sample size will be approximately 42 (multiple of 6 sequences). From previous studies, the screening failure rate is estimated to be approximately 55%, therefore approximately 93 screened patients will be required to achieve the goal of approximately 42 randomised patients.

Due to the exploratory nature of the study, there will be no adjustment for multiple comparisons.

Statistical analyses

The analysis of all the efficacy variables will be performed on the Full Analysis Set population. In addition, the primary efficacy variable will be also analysed using the Per-Protocol population.

All demographic and baseline characteristics, safety outcomes and other variables will be analysed using the Safety population.

Pharmacokinetic parameters will be analysed in the PK population on the subset of 20 patients who will have specifically consented to participation in the PK assessments.

Analysis of the primary efficacy variable

The primary efficacy variable is the change from baseline in trough FEV_1 at Day 15 (ie, after 14 days of treatment).

Baseline for FEV_1 will be defined as the mean of the 2 measured values for the corresponding variable (2 measurements 45 min apart, at -1 hour and -15 min), prior to the morning IP administration on Day 1 of each treatment period. If both are missing, the Visit 2 pre-bronchodilator value will be used instead.

Trough is defined as the mean of the FEV_1 values obtained at 23 hours and 23 hours and 45 min after the morning IP administration on Day 1 and Day 14 (ie, obtained on Day 2 and Day 15). On Day 8, trough is defined as the mean of the FEV_1 pre-dose values (-1 hour and -15 min). If one of the values is missing, the available value will be used as trough.

This variable will be analysed by means of a mixed model; a random effects model with fixed effects for treatment, sequence, and period. The patient will be fitted as a random effect and the pre-dose FEV_1 of each period will be included as a covariate.

Analyses of secondary variables:

Efficacy analyses

All continuous variables defined as change from baseline or observed values will be analysed using mixed models.

Peak FEV_1 will be defined as the maximum value from 0 to 4 hours.

All baselines will be the pre-dose values of each treatment period except for the Total BCSS questionnaire score where the run-in period baseline will be used for all treatments in each sequence.

Categorical variables will be analysed descriptively.

Pharmacokinetic analyses

Plasma concentrations and PK parameters will be listed and summarised for AZD8871 and its metabolites per treatment and day using appropriate descriptive statistics.

Product accumulation will be evaluated by comparing $AUC_{(0-24)}$ (Day 14) with $AUC_{(0-24)}$ (Day 1) and C_{max} (Day 14) with C_{max} (Day 1). A linear mixed-effect model will be used with the logarithm of the PK parameters as the response variable and dose, day and dose by day interaction as fixed effects.

Safety analyses

Safety will be assessed by descriptive analysis of AEs, vital signs, ECGs and clinical laboratory assessments. Heart rate and QT data will be analysed using mixed models.

Exploratory analyses

Each question of the taste questionnaire will be analysed using descriptive statistics. In addition, the overall evaluation of taste will be compared among treatment groups using an analysis of variance (ANOVA) model for crossover designs.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
%Fluctuation	Fluctuation index during a dosing interval
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Code
ATS	American Thoracic Society
AUC	Area under the plasma concentration-curve
$AUC_{(0-24)}$	Area under the plasma concentration-curve from time 0 to 24 hours post-dose
AUC_{last}	Area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration
BCSS	Breathlessness, Cough, Sputum Scale
BDRM	Blind Data Review Meeting
BID	Twice a day (bis in die)
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beats per minute
BTR	Best Test Review
BUN	Blood urea nitrogen
C_{avg}	Average plasma concentration during a dosing interval
CI	Confidence interval
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CPMP	Committee for Proprietary Medicinal Products
CSA	Clinical Study Agreement
CSR	Clinical Study Report

Abbreviation or special term	Explanation
CV	Coefficient of variation
DBP	Diastolic blood pressure
DES	Data entry site
DGR	Dangerous goods regulations
DILI	Drug-induced liver injury
DMP	Data Management Plan
DPI	Dry powder inhaler
DVS	Data Validation Specification
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ERS	European Respiratory Society
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IP	Investigational Product
LABA	Long-acting β_2-agonist

Abbreviation or special term	Explanation
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
LS	Least square
MABA	Muscarinic receptor antagonist and β_2 adrenoceptor agonist
MCH	Mean cell haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
ND	Not determined
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetic(s)
PP	Per-protocol
PRO	Patient-reported outcome
QD	Once a day (quaque die)
QID	Four times a day (quarter in die)
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett formula
QTcF	QT interval corrected using Fridericia's formula
Rac	Accumulation ratio
Rac(AUC_{0-24})	Accumulation ratio for $AUC_{(0-24)}$
Rac(C_{max})	Accumulation ratio for C_{max}
SABA	Short-acting β_2-agonist
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

Abbreviation or special term	Explanation
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SOP	Standard Operating Procedure
TBL	Total bilirubin
TCS	Tata Consultancy Services
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum plasma concentration
UK	United Kingdom
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Background and rationale for conducting this study

AZD8871 is a new chemical entity with the combined properties of a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) in a single molecule. AZD8871 is being developed as an inhaled long-acting bronchodilator for the maintenance treatment of chronic obstructive pulmonary disease (COPD), formulated with alpha-lactose monohydrate and delivered by dry powder inhaler (DPI) that allows delivery of a single dose of the study drug.

COPD is a significant cause of morbidity and mortality worldwide (Global Initiative for Chronic Obstructive Lung Disease 2009 [GOLD 2016]). It is a common, preventable and treatable disease characterised by persistent airflow limitations. The disease is usually progressive and associated with and enhanced chronic inflammatory response in the airways and the lung to noxious particle or gases (GOLD 2016). It is primarily regarded as a heterogeneous lung disease, where the chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contribution of which vary from person to person. There are also significant extrapulmonary effects and associated comorbidities. The most common risk factor worldwide is smoking.

Chronic inflammation causes structural changes and narrowing of the small airways. Destruction of the lung parenchyma, also by inflammatory processes leads to the loss of alveolar attachments to the small airways and decreases elastic recoil; in turns these changes diminish the ability of the airway to remain open during expiration. The lung pathology typically results in an airflow limitation that is not fully reversible and is usually progressive, reflected in a decline in the forced expiratory volume in 1 second (FEV_1) that is more rapid than that normally seen with increasing age. The characteristic clinical symptoms of COPD are chronic and progressive dyspnoea, cough and sputum production. Exercise tolerance and health-related quality of life are increasingly affected as the disease progresses, particularly in association with exacerbations, ie, acute worsening.

Long-acting bronchodilators are an established therapeutic class to control symptoms in COPD; LABAs and LAMAs are preferred over short-acting formulations (GOLD 2016 categories B, C, D). The GOLD guidelines propose to combine LABA and LAMA treatments as possible initial treatment for patients of Group D (among first choices), B and C (among alternative choice). Combining bronchodilators with different mechanisms allows increasing the degree of bronchodilation for equivalent or lesser side effects than increasing the dose of a single component (Tashkin and Ferguson 2013).

By combining the activities of a LAMA and a LABA in to a single molecule, AZD8871 aims at providing a novel approach to the treatment of COPD with greater efficacy than single-mechanism bronchodilators, equivalent to LAMA and LABA administered as free- or fixed-dose combination therapies, with an equivalent or superior safety and tolerability

profile. A muscarinic receptor antagonist and β_2 adrenoceptor agonist (MABA) compound will represent an important treatment option for patients with COPD.

1.2 Rationale for study design, doses and control groups

The objective of the study is to assess the efficacy, safety and pharmacokinetics (PK) of AZD8871 after a 14-day treatment period at 2 different doses in patients with moderate to severe COPD. The target population includes male and female (non-childbearing potential) adult patients with clinical diagnosis of moderate to severe COPD as per the criteria of the GOLD guidelines.

A double-blinded, double-dummy design has been chosen to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical study arising from the influence which the knowledge of treatment may have on the recruitment and allocation of patients. It is considered the optimal approach according to International Conference on Harmonisation (ICH) E9 "Statistical principles in clinical studies."

The crossover design has been chosen to avoid inter-patient variability and optimize sample size. By randomly assigning treatment sequence, differences in baseline characteristics of the treatment groups will be minimised. The inclusion of a placebo arm is considered the most reliable method to minimise patient and Investigator bias according to ICH Topic E10 (Choice of control group in clinical trials) ICH/364/96 guideline adopted by the Committee for Proprietary Medicinal Products (CPMP), CPMP/EWP/562/98 and Food and Drug Administration (FDA).

The proposed dose levels of AZD8871 in this study are 100 and 600 µg of AZD8871 given by inhalation once daily during 14 days through a single dose DPI. Doses have been selected based on the safety, tolerability, PK and pharmacodynamics (PD) information generated in previous clinical trials with AZD8871. At the time of writing of this document, 2 clinical studies are ongoing with AZD8871, studies D6640C00001 and D6640C00003.

Study D6640C00001 is a 2-part placebo-controlled study in asthmatic and COPD patients. Part 1 of the D6640C00001 was the first time in human study with AZD8871. This part has been completed and is in the reporting phase. Part 1 was a single ascending dose safety, tolerability, PK and PD investigation in 16 male, mild asthmatic patients. Single doses ranging from 50 to 2100 µg of AZD8871 were administered and were found to be safe and well-tolerated. Pharmacokinetic data generated for AZD8871 showed dose proportionality increase for systemic exposure parameters (maximum plasma concentration [C_{max}] and area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration [AUC_{last}] and linear PK). Maximum exposure limits predefined in the protocol were not reached (Mean preliminary C_{max} and area under the plasma concentration-curve from time 0 to 24 hours post-dose [$AUC_{(0-24)}$] achieved for AZD8871 after 2100 µg represented 68% and 84%, respectively of the predefined human exposure limits. Mean terminal half-lives found in the study for AZD8871 (calculated over 36 hours) ranged from 16 to 23 hours. The active metabolite, LAS191861, was also measured and systemic exposure represented about 23% of the parent compound exposure. Significant and sustained PD (bronchodilation) dose-

response effect with peak and trough FEV_1 reaching a plateau of around 500-600 mL and 300-400 mL, respectively at doses of ≥ 400 µg) was observed.

Part 2 of study D6640C00001 is a randomised, single dose, placebo- and active comparator-controlled 5-way complete crossover investigation in 38 moderate to severe COPD patients. The last patient, last visit for this study has been completed; data analysis is currently ongoing and final results are expected to be reported in December 2016. Two dose levels of AZD8871 (400 and 1800 µg) are being compared against placebo and 2 active reference agents (indacaterol 150 µg and tiotropium 18 µg). These dose levels were selected based on safety and exposure obtained in the first part of the study. At the time of writing this document between 28 to 30 patients had received these 2 doses of AZD8871.

Study D6640C00003 is a Phase I, randomised, multiple ascending dose study to investigate safety, tolerability and PK of AZD8871 administered for 12 days to healthy male subjects. This study entitles 3 dose levels: 300 µg (cohort 1), 600 µg (cohort 2) and up to 1800 µg (cohort 3, exact dose is to be decided). Data from the first 2 cohorts of subjects dosed with 300 µg and 600 µg of AZD8871 have been generated and both the dose levels were found to be safe and well tolerated. Preliminary interim results generated at 300 µg and 600 µg dose levels demonstrated time independent kinetics of AZD8871 and steady-state achievement for AZD8871 after 5 days of once daily dosing. There was evidence of accumulation of AZD8871 in plasma based on $AUC_{(0-24)}$ with geometric mean accumulation ratios ranging from 1.5 to 1.7. No accumulation was observed for C_{max}. Based on a sampling scheme of up to 96 hour post-dose, mean preliminary estimates for the terminal elimination half-life of AZD8871 ranged from 64.4 to 78.8 hours, after 12 days of repeated administration. Mean AZD8871 steady-state C_{max} and $AUC_{(0-24)}$ achieved after 600 µg represented 55 and 78% of the predefined human exposure limits. Preliminary PK data have been also generated for the active metabolite LAS191861 after repeated administration of AZD8871. There was evidence of accumulation of LAS191861 in plasma with a geometric mean accumulation ratios for $AUC_{(0-24)}$ ranging from 2.4 to 3.5 and for C_{max} from 1.9 to 2.7. Mean metabolite $AUC_{(0-24)}$ after 12 days of daily treatment represented approximately 23% of the parent compound $AUC_{(0-24)}$, being the ratios significantly lower than those observed in preclinical species. Mean metabolite terminal half-lives observed after repeated administration ranged from 116 to 138 hours.

Based on the information of terminal elimination half-lives observed for AZD8871 and LAS191861 in MAD study (D6640C00003), the wash-out period proposed for this current study is a minimum of 28 days and up to 35 days in order to avoid any carry-over effect between periods.

In light of the safety, tolerability and PK data generated in studies D6640C00001 and D6640C00003, the proposed doses for study D6640C00004 are anticipated to be well tolerated. The broad dose range selected (6-fold range from 100 to 600 µg) has been chosen to span the likely therapeutic dose and facilitate the Phase 2b study dose selection.

Clinical Study Protocol
Drug Substance AZD8871
Study Code D6640C00004
Version 3.0
Date 16 December 2016

1.3   Benefit/risk and ethical assessment

A detailed assessment of the overall benefit/risk of AZD8871 is discussed in the Investigator's Brochure (IB).

Currently, no single molecule with dual β_2-agonist and muscarinic antagonist properties is licensed for medical use, though similar molecules are currently in development (Wielders et al, 2013; Bateman et al, 2013). However, there is extensive and increasing experience from clinical practice regarding products with effect on each of these receptors separately and in free and fixed combination. The most commonly cited adverse effects (AEs) of β_2-agonists are palpitations, headache and tremor. At higher doses, tachycardia, hyperglycaemia, hypokalaemia and an increased corrected QT interval (QTc) may be seen. These effects can be monitored in clinical studies using standard safety monitoring. Examples of systemically mediated AEs caused by muscarinic antagonists are: dryness of mouth, dilated pupils, glaucoma, increased heart rate, urinary retention and constipation. However, systemic availability after inhalation is limited and the most frequently reported side effect after inhalation of the LAMAs is dryness of mouth, with irritation in the upper airways and cough reported as potential local side effects.

Findings in non-clinical toxicology and safety pharmacology studies with AZD8871 reflect the dual antimuscarinic and β_2-adrenoreceptor agonist activities associated with the primary pharmacology of this compound and are summarised in the IB. PR-prolongation and atrio-ventricular blocks were recorded in the dog single dose cardiovascular safety study at 0.36 mg/kg, a dose above those causing tachycardia. This dose was associated with a systemic peak plasma concentration of 5.14 ng/mL (4 times higher than the values observed at the highest dose tested in Part 1 of the study D6640C00001 in asthma patients). These changes can be monitored and a higher dose was not associated with any unexpected cardiac toxicity with AZD8871 in Part 1 of study D6640C0001 and during the 12 consecutive days of treatment with the first dose in study D6640C00003.

Among the 16 patients included in Part 1 of Study D6640C0001, 14 patients reported 16 treatment emergent adverse events (TEAEs), all of them were mild to moderate in intensity. None of these TEAEs led to study discontinuation and all were resolved by the end of each period. Among the different TEAEs, 4 episodes of headache in the same patient and 1 episode of dizziness were assessed by the investigator as related to AZD8871. The most frequently reported TEAEs were headache and nasopharyngitis. Only 2 potential anticholinergic events were reported in the Part 1 of the Study D6640C00001: pre-syncope was observed in one patient (placebo group) and dizziness was reported in 2 patients (one each, in the 200 μg and placebo groups). No positive dose-response was observed with any specific TEAE during the exposure of AZD8871 in the part 1 of this study. No paradoxical bronchospasm or any TEAE with fatal outcome were reported in any of the doses level tested. No clinically relevant ECG abnormalities or laboratory abnormalities were observed in this first part of the trial.

For Study D6640C00003, data from the first 2 cohorts of subjects have been generated:

- First dose level (300 µg) of study D6640C00003 tested in 8 healthy volunteers during 12 days was well tolerated. There were 5 subjects that reported TEAEs (one moderate toothache, one moderate headache, and one mild headache in the 300 µg group; and in the placebo group, one subject experienced a mild bruise from venepuncture site on left arm and the other subject experienced mild dry cough, mild sore throat, and mild runny nose). None of these TEAEs led to study discontinuation and all were resolved by the end of each period. Among the TEAEs, no serious adverse events (SAEs) and no severe AEs were reported by this cohort. No relevant laboratory or ECG abnormalities were reported by this cohort.

- Second dose level (600 µg) of study D6640C00003 tested in 8 healthy volunteers during 12 days was well tolerated. Two subjects reported TEAEs. One subject in the 600 µg group had a moderate headache; one subject in the placebo group had a mild upper back pain. None of these TEAEs led to study discontinuation and both events were resolved by the end of each period. Among the TEAEs, no SAEs and no severe AEs were reported by this cohort. No relevant laboratory or ECG abnormalities were reported by this cohort.

To limit the risks for the patients enrolled in this study D6640C00004 and who will be required to stop their usual COPD therapy and to assess investigational product (IP) efficacy, patients will maintain their usual inhaled corticosteroid (ICS), if any. They will also be provided with salbutamol to be used as rescue medication. In addition, those patients that were taking any LAMA, they will be maintained with ipratropium between Visit 1 and Visit 2. All patients will receive ipratropium (following the approved dosage and regimen) during run-in and wash-out period to ensure stability of the patient.

Considering the expected efficacy in patients with COPD and the available data to date, it is anticipated the benefits will outweigh the risks and support the continued investigation of AZD8871 in clinical studies.

1.4   Study design

This is a proof-of-concept, randomised, double-blind, placebo-controlled, 3-way, complete crossover William's design, multiple dose study to investigate the efficacy, PK, safety, and tolerability of 2 dose levels of AZD8871 and placebo, administered using a DPI device once daily, for 2 weeks, in patients with moderate to severe COPD.

This multi-centre study will be conducted at 2 sites in Europe (Germany and United Kingdom [UK]). It is planned that approximately 42 men and women of non-childbearing potential aged 40 to 80 years (both inclusive) with moderate to severe COPD will be randomised to the study. A subset of 20 patients, who will have specifically consented, will also undergo PK assessments. The entire study period is scheduled to take from a minimum of 4.5 months (140 days) to a maximum of 5.6 months (175 days) for each individual patient. The study is anticipated to run for approximately 8 months and should not exceed 10 months.

Patients will be provided with salbutamol as rescue medication to be used as needed throughout the study and with ipratropium to be used according to the approved dosage and regimen during the run-in and wash-out periods.

The study will consist of a Screening period, 3 treatment periods (each separated by a wash-out period), and a Follow-up Visit.

Screening period: This will last up to 28 days and consists of a Screening Visit (Visit 1), Visit 2, and a run-in period.

Visit 1 and Visit 2 could be performed on the same day if no wash-out of prior medication is required and the patient visits the site in fasting condition. In case any wash-out of prior medication is required, then Visit 2 will be performed after the wash-out is complete. All the screening assessments can be performed at Visit 1 or Visit 2, based on the site's preference, except for the following:

- ICF: This must be completed at Visit 1 before any study-specific assessments are performed

- Reversibility test with salbutamol and spirometry (confirm inclusion criteria #6 and #7): These must be performed at Visit 2.

Only patients who fulfil the reversibility criterion (improvement of FEV_1 ≥12% and 200 mL after administration of salbutamol) and fulfil FEV_1 predicted values (FEV_1 ≥40% and <80% from predicted normal value and FEV_1/forced vital capacity (FVC) ratio <70%) post-salbutamol at Visit 2, will be started on the run-in period to assess clinical stability.

If the reversibility criteria or FEV_1 predicted values are not met, the tests may be repeated at the latest, up to Day-14. If any of these 2 criteria are not achieved at the repeat attempt, the patient will not be randomised.

The duration of run-in period will be between a minimum of 14 and a maximum of 28 days. During the run-in period, all patients will receive ipratropium following the approved dosage and regimen (must be discontinued 8 hours before any pulmonary function test).

During the randomised treatment period of the study, each patient will receive all 3 possible treatments, with every patient receiving placebo in one of the periods in addition to their ICS mono-component therapy, if any. Patient will receive one of the 3 following possible treatments in any given period, in a randomised manner:

- AZD8871 100 µg once daily

- AZD8871 600 µg once daily

- Placebo

Each of the 3 treatment periods will last for 14 days and will include 2 overnight stays at the study site and one ambulatory visit at the study site.

Each 14-day treatment period (except the last one) will be followed by a wash-out period of 28 up to 35 days, during which patients will receive ipratropium following the approved dosage and regimen (must be discontinued 8 hours before any pulmonary function test), in addition to their usual ICS therapy, if any.

From treatment period 2 onwards, on Day 1 of a new treatment period, a FEV_1 stability test will be performed pre-dose. FEV1 stability check will be based on the pre-best test review ([BTR]; details on BTR are presented in Section 5.1.1). At Visits 6 and 9, the mean of the pre-dose FEV_1 (mean of the 2 measured values) should be within ($\pm$)20% or ($\pm$)200 mL compared to the pre-dose FEV_1 (mean of the 2 measured values) of the first treatment period (Visit 3). If the FEV_1 stability criterion is not met, an additional measurement could be taken within 30 min of the second pre-dose measurement, and the mean of the last 2 measurements will be considered for the FEV_1 stability criterion. If the FEV_1 stability criterion is still not met, the test can be rescheduled as soon as possible, and if the FEV_1 stability criterion is not met after re-testing, the patient should be withdrawn.

There will be a Follow-up Visit scheduled to take place 28 up to 35 days after last administration of the IP.

Figure 1   Study flow chart

d=day; FU=follow-up; V=visit.

During periods 1 to 3 of the treatment period, each patient will randomly receive one of the 3 possible treatments (AZD8871 at the doses of 100 μg or 600 μg or placebo).

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measures:
To evaluate the efficacy of inhaled AZD8871 in patients with moderate to severe COPD	**Primary** • Change from baseline in Trough FEV_1 on Day 15 **Secondary** • Change from baseline in Trough FEV_1 on Day 2, and Day 8 • Change from baseline in Peak FEV_1 on Day 1, Day 8 and Day 14 • Change from baseline in Trough FEV_1 over treatment duration (Day 8 to Day 15) • Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14) • Change from baseline in Total Score of Breathlessness, Cough, Sputum Scale (BCSS) questionnaire and cough, breathlessness and sputum individual domain scores from Day 1 to Day 8 after treatment, from Day 8 to Day 14 after treatment and during the whole treatment duration • Rescue medication use

2.2 Secondary objectives

Secondary Objective:	Outcome Measures:
To investigate the PK of AZD8871 and its metabolites after multiple dose administration of AZD8871 in patients with moderate to severe COPD	• On serial PK sampling days, the following PK parameters will be calculated for AZD8871 and its metabolites LAS191861 and LAS34850 when applicable: Day 1: C_{max}, t_{max}, area under the plasma concentration-curve $(AUC)_{last}$, $AUC_{(0-24)}$ Day 14: C_{max}, t_{max}, AUC_{last}, $AUC_{(0-24)}$, average plasma concentration during a dosing interval (C_{avg}), fluctuation index during a dosing interval (%Fluctuation), accumulation ratio for C_{max} $[Rac(C_{max})]$ and accumulation ratio for $AUC_{(0-24)}$ $[Rac(AUC_{(0-24)})]$ Additional parameters may be determined where appropriate

2.3　　Safety objectives

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of inhaled AZD8871 in patients with moderate to severe COPD	• AEs/SAEs • Vital signs • Electrocardiogram (ECG) • Clinical laboratory assessments

2.4　　Exploratory objectives

Exploratory Objective:	Outcome Measures:
To evaluate the taste of inhaled AZD8871 in patients with moderate to severe COPD	• Taste assessment

3.　　PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1　　Inclusion criteria

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

1.　　Patient who provided of informed consent prior to any study-specific procedures

2.　　Male or female 40 to 80 years of age (both inclusive) at Screening (Visit 1). A female is eligible to enter and participate in the study if she is of non-childbearing potential.

Note: A female is considered to be of non-childbearing potential if she meets one of the following criteria:

• Permanently or surgically sterilised, including hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy

• Post-menopausal; aged <50 years and amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels in the post-menopausal range of the local laboratory

- Post-menopausal; aged ≥50 years and amenorrhoeic for 12 months or more, following cessation of all exogenous hormonal treatments

3.   Male patient should use a condom and spermicide to prevent pregnancy and drug exposure of a partner, regardless of the gender or childbearing potential of the partner from the day of the first administration of the IP until 3 months after the last administration of the IP.

4.   COPD Diagnosis: Patient with an established clinical history of COPD for more than 1 year at Screening, according to the GOLD 2016 COPD guidelines.

5.   Tobacco Use: Patient is a current or former smoker with a history of ≥10 pack-years of cigarette smoking [Number of pack-years=(number of cigarettes per day/20)xnumber of years smoked (eg, 1 pack-year=20 cigarettes smoked per day for 1 year)]. A former smoker is defined as one who has stopped smoking for at least 6 months prior to Screening.

     a.   Patient smoking other tobacco types will not be allowed, unless he/she meets the cigarette criterion as well.

6.   Patient with post-bronchodilator FEV_1/FVC ratio <70% based on the value reached after inhalation of salbutamol (400 μg) at Visit 2. If criterion is not met, the test can be repeated at the latest, up to Day -14.

7.   Patient with post-bronchodilator FEV_1 that must be ≥40% and <80% predicted normal value at Visit 2. If criterion is not met, the test can be repeated at the latest, up to Day -14.

8.   Patient who fulfils reversibility criteria to salbutamol at Visit 2. Reversibility is defined as ≥12% and ≥200 mL increase in FEV_1 after inhalation of 4 puffs of salbutamol (400 μg). If the criterion is not met, the test can be repeated at the latest, up to Day -14.

9.   Patient is willing and, in the opinion of the Investigator, able to change current COPD therapy as required by the protocol and willing to use ipratropium following the approved dosage and regimen (during run-in and wash-out periods) with or without ICS for maintenance therapy of COPD and rescue medication salbutamol (as needed) from Visit 1 up Visit 11.

10.   Patient is free from any clinically active disease other than COPD that may impact study outcome, as determined by medical history, physical examination, laboratory testing, and 12-lead ECG findings, at Screening.

11.   Patient is willing to remain at the study centre as required per protocol to complete all visit assessments.

12.   Patient with body mass index (BMI) <40 kg/m^2 at the time of Screening.

3.2   Exclusion criteria

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

1.   Patient previously enrolled in the present study.

2.   Patient has significant diseases other than COPD, ie, disease or condition or an abnormality in laboratory, ECG, medical history or physical examination which, in the opinion of the Investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the patient's ability to participate in the study.

3.   Childbearing potential female, pregnant or lactating.

4.   Patient who, in the opinion of the Investigator, has a current diagnosis of asthma.

5.   Patient has alpha-1 antitrypsin deficiency as the cause of COPD.

6.   Patient has other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnoea. Allergic rhinitis is not exclusionary.

7.   Lung surgery for volume reduction or lung transplantation: Patient has undergone lung volume reduction surgery, lobectomy, or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapour ablation, biological sealants, massive pulmonary embolism and airway implants) within 1 year of Screening (Visit 1).

8.   Patient is using nocturnal positive pressure (eg, continuous positive airway pressure or bi-level positive airway pressure). Patient is using any non-invasive positive pressure ventilation device.

       Note: A patient using continuous positive airway pressure or bi-level positive airway pressure for Sleep Apnoea Syndrome is allowed in the study.

9.   Patient who had 2 or more exacerbations of COPD (moderate or severe in intensity) within the last year prior to Screening (see Section 3.9 for definition of exacerbation of COPD).

10.   Patient has been hospitalised due to poorly controlled COPD within 3 months of Screening.

11.   Patient has acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6 week interval prior to Screening (Visit 1), or during the Screening Period (between Visits 1 and 3).

12.   Patient has had lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening.

13.   Patient cannot perform acceptable spirometry, ie, meet American Thoracic Society (ATS)/European Respiratory Society (ERS) acceptability criteria.

14.   Patient has changed their smoking status (ie, start or stop smoking) or initiation of a smoking cessation program within 6 weeks of Screening.

15.   Patient has participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Screening or who will enter the acute phase of a pulmonary rehabilitation program during the study. A patient in the maintenance phase of a pulmonary rehabilitation program is not to be excluded.

Cardiac disease:

16.   Patient with significant cardiovascular disease that may be vulnerable to cardiovascular instability.

Note: Some examples of clinically significant cardiovascular conditions are:

- Myocardial infarction within the 6 months prior to Screening Visit (Visit 1).

- Unstable angina or unstable arrhythmia meaning which has required changes in the pharmacological therapy or other intervention within 12 months prior to Screening Visit (Visit 1), or newly diagnosed arrhythmia within the previous 3 months prior to Screening Visit (Visit 1).

- Second degree atrio-ventricular block.

- Patient with clinically significant conduction or ECG abnormalities.

- Coronary artery disease.

- Use of pacemaker.

- Hospitalisation within 12 months prior to Screening Visit (Visit 1) for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV per the "New York Heart Association".

17.   Patient with QT interval corrected using Fridericia's formula (QTcF) value at Screening >450 ms for male and >470 ms for female or an ECG that is not suitable for QT measurements (eg, poorly defined termination of the T wave).

18.   Patient with heart rate <50 bpm.

19.   Patient has clinically significant uncontrolled hypertension as assessed by the Investigator.

Neurological:

20.   Patient with seizures or history of seizures requiring anticonvulsants within 12 months prior to Screening.

21.   Patient is taking selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors whose dose has not been stable for at least 4 weeks prior to Screening, or exceeds the maximum recommended dose.

Renal:

22.   Patient with symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.

23.   Patient with a serum potassium value <3.5 mmol/L at Screening and on repeat testing. Note: however potassium replacement and rescreening is allowed if serum potassium concentration was <3.5 mmol/L at Screening.

Others:

24.   Any laboratory abnormality or suspicion of any clinically relevant disease or disorder (on history or examination), including uncontrolled diabetes, which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results or the patient's ability to participate in the study, or any other safety concerns in the opinion of the Investigator.

25.   History of malignancy of any organ system, treated or untreated within the past 5 years, with the exception of localised basal cell carcinoma of the skin.

26.   Patient with known narrow-angle glaucoma.

27.   Patient has a history of hypersensitivity to β_2-agonists, muscarinic anticholinergics or lactose/milk protein. Lactose intolerance is not an exclusion criterion.

28.   The patient has a history of drug of abuse within the past 2 years or consuming more than 14 (female patients) or 21 (male patients) units of alcohol a week, or shows positive for drugs of abuse and alcohol tests at Screening and prior to randomisation.

Note: However, if a patient tests positive to any drugs of abuse tests, which cannot be explained by use of prescription medication, he/she will be excluded from the study. Unit=1 glass of wine (125 mL)=1 measure of spirits=½ pint of beer.

29.   Patient who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the study.

30.   Patient who received a live attenuated vaccination within 30 days prior to Screening.

Note: Inactivated influenza vaccination, pneumococcal vaccination, or any other inactivated vaccine is acceptable provided it is not administered within 7 days prior to Screening or randomisation Visit.

31.   Patient involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

32.   Patient treated with investigational drug or device in another clinical trial within the last 30 days or 5 half-lives (whichever is longer) prior to Screening.

Note: Patient participation in observational studies (ie, studies that do not require change to medication or an additional intervention) is not exclusionary.

33.   Patient who donated or lost >500 mL of blood and plasma within the previous 3 months prior to Screening.

34.   Patient is unlikely to co-operate with the requirements of the study, instructions of the Principal Investigator (PI), or have e-dairy completion rate of <70% during the run-in period.

35.   Patient with known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C infection.

36.   Patient who has been placed in an institution due to a regulatory or court order.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3   Patient enrolment and randomisation

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

At Visit 3, approximately 42 patients will be randomly assigned to one of the 3 possible treatment sequences, according to a William's design for crossover studies and using a balanced 1:1:1 randomisation ratio. Thus, 7 patients will be assigned to each treatment sequence. To ensure random allocation, each patient will be given the IP bearing the lowest available randomisation number at the site.

Prior to initiating the study, a computer generated randomisation schedule will be prepared to assign a treatment sequence to a randomisation number by PAREXEL through AZRand according to the relevant Standard Operating Procedure (SOP). The randomisation schedule will describe the link between the randomly assigned sequences of 3 treatments to each randomisation number. The block size will be determined in agreement with the Clinical Trial Manager and the Statistician, and will not be communicated to the Investigators.

The Investigator(s) will:

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

2. Assign a patient a unique patient identification number. This number will be composed of 2 parts: the first 4 digits (fixed) representing the site identifier. The next 3 digits (ascending) which will be assigned sequentially within each site, starting with 001. The patient identification number will be used to identify the patient throughout the study and will be recorded in the electronic Case Report Form (eCRF).

3. Determine patient eligibility. See Section 3.

4. For patients fulfilling the eligibility criteria at Visit 3, the Investigator will assign a unique randomisation number following chronological ascending order.

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

Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding of the allocated treatment of all study patients after locking the database upon termination of the study. When the study is completed and the data verified and locked and the populations defined, the randomisation codes will be made available for data analysis.

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation.

3.4 Procedures for handling incorrectly enrolled or randomised patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomised or initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomised in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study

Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

PAREXEL will be responsible for generating the randomisation scheme through AZRand.

The choice of treatment sequences was determined according to William's design and sequences are balanced. Patients will be allocated to the 3 treatment groups in a 1:1:1 ratio.

	Treatment Period 1	Treatment Period 2	Treatment Period 3
Sequence A (n=7)	AZD8871 100 µg	AZD8871 600 µg	Placebo
Sequence B (n=7)	AZD8871 100 µg	Placebo	AZD8871 600µg
Sequence C (n=7)	AZD8871 600 µg	AZD8871 100 µg	Placebo
Sequence D (n=7)	AZD8871 600 µg	Placebo	AZD8871 100µg
Sequence E (n=7)	Placebo	AZD8871 100 µg	AZD8871 600µg
Sequence F (n=7)	Placebo	AZD8871 600 µg	AZD8871 100µg

The randomisation numbers will be grouped in blocks. The block size will not be communicated to the Investigators.

The randomisation list will only be provided to Almirall personnel responsible for study medication preparation and to Covance Bioanalytical group responsible for PK analyses.

3.6 Methods for ensuring blinding

This study will be performed in a double-blind manner. All IPs will be supplied in identical packaging to enable double-blind conditions.

Placebo-containing DPI devices will be present with the same external appearance and the same composition as the AZD8871-containing devices, except for the active ingredient.

Supplies of salbutamol and ipratropium will be open-label.

3.7 Methods for unblinding

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the Investigator(s) or pharmacists at the study site.

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

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP 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.

3.8   Restrictions

Patients enrolled in the study should adhere to the following restrictions from the duration of the study. Any event likely to interfere with the objectives of the study will be communicated to the Investigator and reported without delay to the Sponsor.

1.   Patients should eat and drink only the standardised meals and drinks provided at the study centre during their entire stay at each treatment visit. No food intake will be allowed between meals.

2.   On Day 1, Day 8, and Day 14, patients will be required to undergo an 8-hour overnight fast before IP administration and will maintain a fasted condition for an additional 4 hours following dose administration on Days 1 and 14, but only up to 1 hour on Day 8. Meals should not include any xanthine-containing compounds (ie, caffeine) or grapefruit-containing foods or beverages. During the other treatment days, there are no fasting requirements prior to IP administration.

3.   Patient should fast for 4 hours before i-STAT (potassium and glucose measurements) and for 8 hours before routine safety laboratory testing. During patients' residency at the study centre, standardised meals will be served according to the study centre's standard practice.

4.   Exposure to dust or polluted air should be avoided for at least 1 hour before each visit until completion of all study procedures.

5.   Salbutamol should be withheld at least 6 hours before each visit where spirometry is performed up to the last spirometry procedure on that visit. However, patients are permitted to use salbutamol if its use is absolutely necessary during the visit, and with the approval of the Investigator.

6.   Ipratropium should be withheld at least 8 hours before Visits 3, 6 and 9 and during all treatment periods. This medication is to be used during the run-in and wash-out periods.

7.   Patients must abstain from any of the following:

- – Alcohol from 72 hours before each visit to the study centre and during residency at the study centre.

- – Smoking should be avoided for 1 hour prior to the pulmonary function tests.

- – Energy drinks containing taurine or glucuronolactone (eg, Red Bull) from 72 hours prior to administration of the IP at Visit 3 until the Follow-up Visit at the end of the study.

- – Caffeine-containing food and drinks for 24 hours prior to each visit to the study centre and during residency at the study centre. Decaffeinated drinks will be acceptable to be consumed during the study.

- – Poppy seeds (eg, found in bread) from time of consent until the final Follow-up Visit at the end of the study.

- – Grapefruit or grapefruit juice, Seville oranges (also called bitter orange, including marmalade) consumption from 48 hours prior to administration of the IP at Visit 3 and until the final Follow-up Visit at the end of the study.

- – Intake of water will not be allowed 1 hour prior to administration of the IP and 1 hour post-administration of the IP on Day 1, Day 8, and Day 14 of each treatment period.

- – Strenuous physical activity, which is not within the patient's normal daily routine, as from 72 hours before the Screening Visit until the Follow-up Visit at the end of the study.

- – Blood or plasma donation until 3 months after the Follow-up Visit at the end of the study.

- – Scheduled in-patient surgery or hospitalisation during the course of the study (patients are not required to abstain from emergency treatment).

- – Restrictions on medications (prescribed or over-the-counter products) are defined in Section 7.7.

3.9 Discontinuation of investigational product

Patients may be discontinued from IP at any time but once dosing has occurred every attempt should be made to continue assessments to ensure the safety of the patient. Specific reasons for withdrawing a patient will be:

- • Patient withdrawal: The patient is free to discontinue treatment at any time, without prejudice to further treatment. A patient who decides to discontinue the IP will always be asked about the reason(s) and the presence of any AEs. If possible, they will be

seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6.3) and all study drugs should be returned by the patient.

- AE: If a patient experiences an AE, their premature discontinuation will be considered at the discretion of either the Investigator or the patient regardless of the causal relationship to the IP. AE should be indicated as the reason for discontinuation.

- Protocol deviation: After randomisation, any protocol deviations detected should be corrected when possible and the patient should be allowed to continue. The following will lead to discontinuation of treatment: protocol deviations that could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor] might invalidate the trial by interfering with the IP); deviations due to patient non-compliance with the study protocol.

- Failure to meet randomisation criteria: Violations of inclusion and/or exclusion criteria detected after randomisation. See Section 3.4 for patients not fulfilling inclusion/exclusion criteria but detected after randomisation.

- Lost to follow-up: Non-attendance. In these cases, every effort should be made by the Investigator to ascertain the reason and to assure patient's attendance as soon as possible. Every effort (at least 3 documented attempts) should be made to contact the patient and documented in the medical records. If patient could not be reached after that, a registered mail letter will be sent to the patient and documented in the medical records.

- Pregnancy: In case of pregnancy the female patient will be immediately discontinued from the study.

- Clinical/FEV$_1$ stability criteria not fulfilled during the treatment periods.

- Development of study-specific withdrawal criteria: These criteria are listed below; in the event that any of these conditions are reported as an AE, then this AE should be reported as the primary reason for discontinuation in the eCRF.

(a) **Vital signs**

- Systolic blood pressure (SBP) increase of >40 mmHg from baseline (ie, before first dose of study drug) and SBP >180 mmHg at any time within the 12-hour interval after taking study drug.

(b)   Laboratory findings (any time after randomisation; test must be repeated to confirm that withdrawal criterion has been met)

- Haematologic toxicity defined as 1 or more of:

  – Confirmed leucocyte count $<2.0\times10^9$/L.

  – Confirmed neutrophil count $<1.0\times10^9$/L.

  – Confirmed platelet count $<75\times10^9$/L.

  – Confirmed lymphocyte count $<0.5\times10^9$/L.

- Hepatic toxicity defined as 1 or more of:

  – Confirmed alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase to $>3\times$the upper limit of normal (ULN).

  – Confirmed isolated total bilirubin (TBL) increase to $>2\times$ULN.

  – Confirmed ALT or AST increase to $>2\times$ULN concurrent with an increase in TBL to $>1.5\times$ULN.

- Serum potassium, checked within 4 hours post-dose on the days tested, <3.0 mmol/L, will be treated appropriately by the Investigator, and the patient will be withdrawn from the study.

(c)   ECG (within 4 hours of post-IP dosing):

- Symptomatic bradycardia defined as heart rate <45 beats per minute (bpm) or asymptomatic bradycardia defined as resting supine pulse <30 bpm while awake, persisting for at least 10 minutes.

- Heart rate of >120 bpm and an increase of >40 bpm during the first 4 hours post-dose, persisting for at least 10 minutes.

- QTcF interval prolongation exceeding >500 ms during the treatment period or >60 ms change from baseline (within 4 hours post-dose), persisting for at least 5 minutes.

(d)   Lung function

- FEV_1 decrease by$>20\%$ from baseline (ie, before first dose of study drug) on 2 consecutive spirometry assessments obtained at least 15 minutes apart with associated symptoms of dyspnoea at any time within the first 2-hour interval after taking study drug.

(e)   COPD worsening

- COPD exacerbation of moderate or severe intensity.

Note: A COPD exacerbation is defined as a change in the patient's baseline dyspnoea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasts ≥3 days, is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication. The severity of COPD exacerbations is classified as follows:

- Mild: Exacerbations that do not require systemic steroids or antibiotics and do not result in hospitalization or death.

- Moderate: Exacerbations that require treatment with systemic steroids and/or antibiotics, and do not result in hospitalization or death.

- Severe: Exacerbations that result in hospitalization or death.

- Other: Study cancellation or any other reason not described above.

- Patient withdrawal due to death.

Generally before discontinuation of a patient from the study, a discussion between Sponsor's Study Physician and Investigator is encouraged, as much as feasible.

3.9.1   Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (ie, IP and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue IP will always be asked about the reason(s) and the presence of any AE. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); e-Diary, paper diary and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

3.10   Criteria for withdrawal

3.10.1   Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen Failure' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study. The patient will return the e-Diary and paper diary.

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

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for withdrawal of consent must be documented.

3.11 Discontinuation of the study

The study will be stopped if:

- The PI/Co-ordinating Investigator and the Sponsor assessed that the type; number and/or severity of AEs justify discontinuation of the trial

- In the judgement of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

  – Are assessed as causally related to study drug

  – Are not considered to be consistent with continuation of the study

- New safety information emerges, which raise concern about the safety of the study drug and continuation would pose potential risk to the patient.
- The Sponsor decides to discontinue the study: For instance, if there is at least one case of fatal SAE considered related to AZD8871 or at least 2 cases of SAEs considered related to AZD8871.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The Study Plan detailing the procedures at Screening, during the treatment period and during follow-up is presented in Table 1.

Table 1   Study Plan detailing the procedures

Visit	Screening period 1[a]	Screening period 2[a]	Treatment periods (Period 1-Period 3) 3, 6, 9[b, d]	Treatment periods (Period 1-Period 3) 4, 7, 10[c]	Treatment periods (Period 1-Period 3) 5, 8, 11[b, d]	Follow-up/early termination Visit	For details see Protocol Section
Treatment Day	-28 to -14	-28 to -14	1 Overnight stay	8	14 Overnight stay	After 28 up to 35 days of Visit 11 (or last IP admin)	
Signed Informed Consent	X						10.4
Inclusion/exclusion criteria	X	X	X (Visit 3)				3.1 and 3.2
Demography	X						4.1.1
Smoking history	X						4.1.1
Medical/surgical history	X						4.1.1
Concomitant medications	X	X	X	X	X	X	7.7
Height/weight[e]	X					X	4.1.1
Physical examination[f]	X		X		X	X	5.2.2
Vital signs (BP)[g]	X		X	X	X	X	5.2.4
Inhaler training[h]			X				4.2.1
Safety laboratory tests[i]	X		X		X	X	5.2.1
Drugs of abuse and alcohol Screen[j]	X		X[k] (Visit 3)				
Urine pregnancy test in women	X						4.1.1

Table 1   Study Plan detailing the procedures

Visit	Screening period		Treatment periods (Period 1-Period 3)			Follow-up/early termination Visit	For details see Protocol Section
	1[a]	2[a]	3, 6, 9[b,d]	4, 7, 10[c]	5, 8, 11[b,d]		
Treatment Day	-28 to -14	-28 to -14	1 Overnight stay	8	14 Overnight stay	After 28 up to 35 days of Visit 11 (or last IP admin)	
i-STAT measurement[l]			X		X		5.2.1
Clinical stability check		X	X				5.1.3
FEV$_1$ stability check			X[m]				
Spirometry[n]		X	X	X	X		5.1.1
Reversibility testing[o]		X					5.1.2
12-lead ECG[p]	X		X	X	X	X	5.2.3
Ipratropium dispensation[q]	X	X	X		X		7.2
Salbutamol dispensation	X	X	X	X	X		4.1.1
Randomisation			X (Visit 3)				4.2.1
IP administration and IP kit dispensation[r]			X	X	X		7.2
AEs	X	X	X	X	X	X	6
BCSS questionnaire		X	X	X	X		5.1.4
Taste questionnaire					X		4.2.3
Dispense/Check		X	X	X	X		4

Clinical Study Protocol
Drug Substance AZD8871
Study Code D6640C00004
Version 3.0
Date 16 December 2016

Table 1   Study Plan detailing the procedures

Visit	Screening period		Treatment periods (Period 1-Period 3)			Follow-up/early termination Visit	For details see Protocol Section
	1[a]	2[a]	3, 6, 9[b, d]	4, 7, 10[c]	5, 8, 11[b, d]		
Treatment Day	-28 to -14	-28 to -14	1 Overnight stay	8	14 Overnight stay	After 28 up to 35 days of Visit 11 (or last IP admin)	
e-Diary/paper diary[s]							
PK blood collection[t]			X	X	X		5.4

AE=Adverse event; aPTT=Activated partial thromboplastin time; BCSS=Breathlessness, Cough, Sputum Scale; BP=Blood pressure; ECG=Electrocardiogram, FEV$_1$=Forced expiratory volume in 1 second; INR=International normalised ratio; IP=Investigational Product; PK=Pharmacokinetics; PTT=Partial thromboplastin time.

a.   All the screening assessments can be performed at Visit 1 or Visit 2, based on the site's preference, except for the following:

(i)   ICF: This must be completed at Visit 1 before any study-specific assessments are performed.
(ii)   Reversibility test with salbutamol and spirometry (confirm inclusion criteria #6 and #7): These must be performed at Visit 2 after wash-out is completed.
Visit 1 and Visit 2 could be performed on the same day if no wash-out of prior medication is required and the patient visits the site in fasting condition. In case any wash-out of prior medication is required, then Visit 2 will be performed after the wash-out is complete.

b.   Visits 3, 6 and 9 and Visits 5, 8 and 11 will be overnight stay visits; 6 overnight visits are required per patient.

c.   Visits 4, 7 and 10 will be outpatient visits with duration of approximately 5 hours.

d.   Interval between randomised treatment periods (wash-out period) will be 28 up to 35 days (from the last IP use).

e.   Height will be measured at Visit 1; weight will be measured at Visit 1 and at Follow-up Visit.

f.   Physical examination will be complete examination at Visit 1 and at Follow-up Visit. Brief physical examination will be performed at rest of visits during the study (Visits 3, 5, 6, 8, 9 and 11).

g.   Vital signs: Blood pressure will be assessed pre-dose and 1, 2, 4, and 24 hours at Visits 3, 5, 6, 8, 9 and 11. On Visits 4, 7 and 10 blood pressure will be measured at pre-dose, 1 and 4 hours post-dose. Body temperature will be measured at Screening and Follow-up Visits. Heart rate will be assessed by ECG.

h.   Inhaler training will be done before starting IP treatment on Day 1 at each treatment period.

i.   Safety laboratory tests will be done at Visit 1, pre-dose at Visits 3, 6, 9 and at 24 hours post-dose at Visits 5, 8, 11 and at Follow-up Visit. Safety laboratory tests will be done after 8 hours of fasting. Serology parameters will be measured at Visit 1 only, coagulation parameters (INR, PTT and aPTT) will be assessed at Visit 1 and at Follow-up Visit.

j.   Alcohol screen could be performed using a urine sample or a breath test.

k.   Drugs of abuse and alcohol screen will be performed at Visit 3 prior to randomisation.

l.   i-STAT for glucose and potassium measurements will be done pre-dose and then 1, 2, 4 and 24 hours post-dose on Visits 3, 5, 6, 8, 9 and 11. i-STAT will be done after 4 hours of fasting.

m.   FEV1 stability will be performed at Visits 6 and 9 based on the pre-BTR.

n.   Spirometry measurements will be done at -1 h and -15 min pre-dose and then 15 min, 30 min, 1, 2, 4, 8, 23, and 23:45 hours post-dose on Visits 3, 5, 6, 8, 9 and 11. At Visits 4, 7 and 10 spirometry measurements will be done at -1 h and -15 min pre-dose and at 15, 30 min, 1, 2, and 4 hours post-dose.

o.   Reversibility test includes a pre-salbutamol spirometry and then at 20-30 minutes post-salbutamol. If reversibility criterion is not fulfilled, a second spirometry can be performed up to 60 minutes post-salbutamol administration.

p.   12-Lead ECG measurements will be done pre-dose and 1, 2, 4, and 24 hours post-dose on Visits 3, 5, 6, 8, 9 and 11. At Visits 4, 7 and 10 measurements will be done at 1 and 4 hours post-dose. ECG should be performed before spirometry.

q.   All patients will receive ipratropium (following the approved dosage and regimen) during the run-in and wash-out periods. In addition, those patients that were taking any LAMA, they will be maintained with ipratropium between Visit 1 and Visit 2. Ipratropium should be held at least 8 hours before Visits 3, 6 and 9 (before any pulmonary function test) and during all treatment periods (until last pulmonary function test at Visits 5, 8 and 11).

r.   The first dose of IP is to be taken at the clinic at 9:00 AM±2 hours on Day 1 of each treatment period (Visits 3, 6 and 9) after the pre-dose specified procedures (and randomisation for Visit 3). On subsequent days of each treatment period, IP is to be taken within±1 hour of dosing time of Day 1 (and between 7 am and 11 am). IP administration will be at the site on Day 1, 2, 8 and 14 of each treatment period. This will be supervised at the clinic. Day 3 to Day 7 and Day 9 to Day 13 doses will be taken at home.

s.   E-Diary will be used to collect daily BCSS questionnaire and daily use of rescue medication (salbutamol) during the run-in and treatment periods. In addition, during treatment period daily IP intake will be recorded in the e-Diary. Paper diary will be used to collect AEs and concomitant medication during run-in and wash-out periods.

t.   PK blood samples will be collected from patients who will have specifically consented to the PK assessments at pre-dose and at 30 min, 1, 2, 4, 6, 8, 12, and 24 hours post-dose at Visits 3, 5, 6, 8, 9 and 11. At Visits 4, 7 and 10 measurements will be done pre-dose and 1 hour post-dose.

Note: For assessments occurring at the same time points, the recommended order of assessments is as follows: 1. ECG; 2. Vital signs; 3. i-STAT; 4. PK; and 5. Spirometry (on the actual time-points).

4.1 Enrolment/Screening period

This period will start with the signature of the ICF at the Screening Visit (Visit 1), and will end at pre-dose on Visit 3, Day 1 (randomisation). No study-specific procedures will be performed prior to signing ICF. **All the screening assessments can be performed at Visit 1 or Visit 2, based on the site's preference, except for the following:**

- ICF: This must be completed at Visit 1 before any study-specific assessments are performed.

- Reversibility test with salbutamol and spirometry (confirm inclusion criteria #6 and #7): These must be performed at Visit 2 after wash-out is completed.

Visit 1 and Visit 2 could be performed on the same day if no wash-out of prior medication is required and the patient visits the site in fasting condition. In case any wash-out of prior medication is required, then Visit 2 will be performed after the wash-out is complete.

4.1.1 Visit 1 – Screening

Screening procedures will be performed according to the Study Plan (Table 1). Any test can be repeated once within 28 days to re-confirm eligibility.

At Screening, to verify the eligibility of patients, the following evaluation will be performed:

1. Obtain informed consent.

2. Assess inclusion/exclusion criteria.

3. Review medical/surgical history, demographics (age, sex, race, and BMI), and smoking information (date of smoking initiation, former smoker, date of smoking cessation, and total pack-years).

4. Assess prior and current COPD medications and switch to ICS mono-component if applicable; if patient currently taking LAMA, provide them with ipratropium. Other current COPD therapy (other than usual ICS and use of ipratropium as specified in this protocol) should be stopped at this visit. Record all current medication usage and any medications taken during the previous 15 days.

5. Perform the 12-lead ECG. The ECG readings will be assessed by the Investigator.

6. Collect vital signs (including temperature) and perform complete physical examination, including body weight (in light indoor clothes, without shoes), and height.

7. Safety laboratory, urine pregnancy, and serology tests.

8. Test for drugs of abuse and alcohol screen

9. Dispense rescue medication (salbutamol) to all patients and ipratropium if applicable.

4.1.2 Visit 2 – Reversibility testing

1. Review inclusion/exclusion criteria

2. Assess the use of concomitant and rescue medications since previous visit. Confirm daily use of ICS mono-component, and ipratropium, if applicable

3. Assess AEs

4. Perform reversibility test and confirm clinical stability

5. Confirm inclusion criteria #6 and #7 with post-bronchodilator spirometry

6. Dispense the e-Diary and paper diary and instruct the patient how to use them.

7. Instruct the patient to record their use of rescue medication (salbutamol) and to complete the BCSS questionnaire on e-Diary every evening.

8. Instruct the patient to record AEs and concomitant medication during run-in and wash-out periods on the paper diary.

9. Dispense rescue medication (salbutamol) and ipratropium to all patients

If the reversibility criterion is not fulfilled or if inclusion criteria #6 and #7 are not confirmed, one repetition of pulmonary function tests, at the latest, up to Day -14 is allowed.

4.2 Treatment period

4.2.1 Visit 3 - Randomisation and Visits 6 and 9 (Treatment Day 1)

These visits will include an overnight stay at the study centre, and should last approximately 25 hours.

Visits 6 and 9 should occur after a wash-out period of 28 up to 35 days after last administration of IP.

Pre-dose assessments:

1. Test for drugs of abuse and alcohol screen prior to randomisation

2. Review inclusion/exclusion criteria (only at Visit 3, prior to randomisation)

3. Confirm clinical stability

4. At visit 3 only, randomise the patient if their eligibility is confirmed (assign the lowest available randomisation number)

5. Train the patient on the use of the DPI

6. Confirm the patient has not taken rescue medication (salbutamol) during the past 6 hours and ipratropium during the past 8 hours prior to pre-dose spirometry

7. Assess the use of concomitant medications since previous visit

8. Assess AEs since previous visit

9. Review completion of the e-Diary for BCSS questionnaire and rescue medication intake

10. Perform the 12-lead ECG

11. Collect vital signs (blood pressure) and perform brief physical examination

12. Collect blood for safety laboratory tests

13. Measure glucose and potassium (i-STAT)

14. Obtain pre-dose PK sample in the subset of 20 patients who specifically consented to this

15. Perform pre-dose spirometry at 60 min and 15 min prior to IP administration (reference value for subsequent visits for the stability criterion)

Administration of IP:

Patients will take the IP at the study site at 9:00 AM±2 hours.

Post-dose assessments:

The following assessments should be conducted:

1. Check vital signs (blood pressure) at 1, 2, 4, and 24 hours postdose

2. Perform brief physical examination at 24 hours post-dose

3. Perform the 12-lead ECG at 1, 2, 4, and 24 hours post-dose

4. Perform spirometry at 15 and 30 min, and at 1, 2, 4, 8, 23 and 23:45 hours post-dose

5. Measure glucose and potassium (i-STAT) at 1, 2, 4 and 24 hours post-dose

6. Obtain PK samples at 30 min and 1, 2, 4, 6, 8, 12, and 24 hours post-dose in the subset of 20 patients who specifically consented to this

51 (107)

7. Dispense the IP kit for Treatment Days 1 to 7 for the corresponding period (IP will be taken on site on Day 1 and Day 2)

8. Check and instruct the patient to record on e-Diary daily IP intake, rescue medication (salbutamol), and BCSS questionnaire every evening.

9. Dispense rescue medication (salbutamol) if needed

4.2.2 Visits 4, 7 and 10 (Treatment Day 8)

These visits will be ambulatory and should last approximately 5 hours. Patients should take the IP at the study site within±1 hour of dosing time of Day 1 and between 7 am and 11 am. The following assessments should be conducted:

1. Review completion of the e-Diary for IP compliance, BCSS questionnaire and rescue medication (salbutamol) intake

2. Assess AEs since previous visit

3. Assess the use of concomitant medications since previous visit

4. Perform the 12-lead ECG at 1 and 4 hours post-dose

5. Check vital signs (blood pressure) pre-dose and at 1 and 4 hours post-dose

6. Obtain PK samples pre-dose and 1 hours post-dose in the subset of 20 patients who specifically consented to this

7. Perform spirometry at -60 min and -15 min pre-dose and at 15 and 30 min, and at 1, 2, and 4 hours post-dose

8. Dispense the IP kit for Treatment Days 8 to 14 for the corresponding treatment period (IP will be taken on site on Day 8 and Day 14)

9. Dispense rescue medication (salbutamol) if needed

All attempts should be made to ensure that the patient visits the site on the scheduled date. In case of any unexpected change to the schedule, -1 day (minus one day) window may be allowed after consultation with the Sponsor for these visits.

4.2.3 Visit 5, 8 and 11 (Treatment Day 14)

These visits will include an overnight stay at the study centre, and should last approximately 25 hours. The following assessments should be conducted:

Pre-dose assessments:

1. Instruct the patient on how to complete the taste questionnaire and ask him/her to complete this at Visits 5, 8 and 11. All questions must be completed within 15 minutes after IP intake, except the question on the last page. The last page of the questionnaire must be completed by the patient within 2 hours after IP intake.

2. Review completion of the e-Diary for IP compliance, BCSS questionnaire and rescue medication (salbutamol) intake

3. Assess AEs since previous visit

4. Assess the use of concomitant medications since previous visit

5. Confirm the patient has not taken rescue medication during the past 6 hours to pre-dose spirometry

6. Perform the 12-lead ECG.

7. Collect vital signs (blood pressure) and perform brief physical examination

8. Measure glucose and potassium (i-STAT)

9. Obtain pre-dose PK sample in the subset of 20 patients who specifically consented to this

10. Perform pre-dose spirometry at 60 min and 15 min prior to IP administration

Administration of IP: Patients will take the IP at the study site at 9:00 AM ±2 hours.

Post-dose assessments

The following assessments should be conducted:

1. Check vital signs (blood pressure) at 1, 2, 4, and 24 hours post-dose

2. Perform brief physical examination at 24 hours post-dose

3. Perform safety laboratory tests at 24 hours post-dose

4. Perform the 12-lead ECG at 1, 2, 4, and 24 hours post-dose

5. Perform spirometry at 15 and 30 min, and at 1, 2, 4, 8, 23 and 23:45 hours post-dose

6. Measure glucose and potassium (i-STAT) at 1, 2, 4 and 24 hours post-dose

7. Obtain PK samples at 30 min and 1, 2, 4, 6, 8, 12, and 24 hours post-dose in the subset of 20 patients who specifically consented to this

8.   Check e-Diary for recording of IP intake, rescue medication, and BCSS questionnaire to be completed every evening

9.   Taste questionnaire must be completed by the patient within 15 minutes after IP intake (all questions except the question on the last page). The last page of the questionnaire must be completed by the patient within 2 hours after IP intake.

10.   Dispense rescue medication (salbutamol) and ipratropium (except at Visit 11).

All attempts should be made to ensure that the patient visits the site on the scheduled date for these visits. In case of any unexpected change to the schedule, -1 day (minus one day) window may be allowed after consultation with the Sponsor for Visits 5, 8 and 11.

4.3   Follow-up Visit (Visit 12)

The Follow-up Visit should occur 28 up to 35 days after the last visit of the treatment period. The following assessments should be conducted:

1.   Perform the safety laboratory tests

2.   Perform the 12-lead ECG

3.   Collect vital signs (including temperature) and perform complete physical examination, including body weight (in light indoor clothes, without shoes)

4.   Assess the use of concomitant medications since previous visit

5.   Assess AEs

4.4   Premature discontinuation visit

This visit should occur as soon as possible and no later than 35 days after the last administration of the IP. The following assessments should be conducted:

1.   Perform the safety laboratory tests

2.   Perform the 12-lead ECG

3.   Collect vital signs (including temperature) and perform complete physical examination, including body weight (in light indoor clothes, without shoes)

4.   Assess the use of concomitant and rescue medications since previous visit

5.   Assess AEs

5. STUDY ASSESSMENTS

An Electronic Data Capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

5.1 Efficacy assessments

Efficacy measurements will be made at the time indicated in the Study Plan (Table 1).

5.1.1 Pulmonary function test (spirometry)

A centralised spirometry company (ERT) will provide the spirometers and all necessary equipment (computer, calibration syringe, printer, paper, ink, etc.), a detailed study manual and training to the technicians and PI (as needed) in charge of conducting the spirometry for this clinical study. Spirometer will measure:

- FVC (maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration).

- FEV_1 (volume of air expressed in litres exhaled during the first second of performance of the FVC).

The circumstances of patient's tests should be similar on all occasions with respect to time of the day, temperature as well as the technician, as much as possible.

The ATS and ERS guidelines should be followed to provide accurate and comparable spirometric data. Spirometer will be configured to meet ATS/ERS recommendations for accuracy and precision (Miller et al, 2005). The computerised spirometer will check the consistency between tests and some of the requirements set out in the ATS/ERS spirometry guidelines, and will automatically alert the technician to the presence of some deviations from some ATS/ERS requirements. However, the technician must ensure that tests are performed with the correct technique, manually deselecting efforts which do not meet minimum standards. The technician must use their judgement to ensure that the optimum spirometry data is gained from the patient at each test session.

These data will be electronically transmitted by the Investigator to ERT typically at the end of each patient protocol visit. Throughout the study, a centralised reading of spirometric values will be performed by an independent spirometric expert at ERT, blinded to patient's IP allocation and patient's identity, in a 2-steps quality control:

- "Over-Read" process: The first review of the spirometry data (including review of tests rejected by the technician) qualifies spirometric curves according to ATS/ERS criteria. No changes are made to the data.

- "Best Test Review" process: During this procedure, the acceptability of tests is assessed first followed by repeatability. If quality problems are encountered on the spirometric curve pre-identified as the "best test", ERT will check if there is another curve that is acceptable. If a better "best test" is identified, site will be queried. If the site accepts the proposed new "best test" (as indicated by the Investigator signing a query form), this newly accepted measure will represent the "best test" in all analysis and reporting. No change on "best test" will be made without the approval of the Investigator.

Inclusion of patient in the study will be based on the post-BTR values from Visit 2. FEV_1 stability check will be based on the pre-BTR.

Prior to the first spirometry, the trained technician should demonstrate the procedure to the patient by using a detached mouthpiece then, allow some practice attempts. Demonstration should be repeated and the patient should practise the procedure as many times during the study course as deemed necessary.

Patients who are unable to produce acceptable spirometry tests must not be included in the study. The patient should be at rest for 10 minutes prior to the test and comfortable; tight clothing should be loosened to allow the thorax to move freely. Each manoeuvre comprises 1 "set of tests": 3 measurements (curves) technically adequate are needed according to the acceptability and repeatability criteria of the ATS/ERS spirometry guidelines. If both the acceptability and repeatability criteria are met, the manoeuvre session can conclude after 3 measurements. If 1 or both of these criteria are not met a maximum of 5 additional tests (up to a total of 8 tests) should be performed until either both criteria are met or patient is fatigued and could not provide any further useful data.

The operator performing the spirometry must print every spirometry test, sign and date them.

5.1.2   Reversibility testing

Airflow reversibility is not an outcome variable. Baseline reversibility testing will be performed at Visit 2.

Reversibility testing will include a pre-salbutamol spirometry, followed by administration of salbutamol by oral inhalation (100 µg×4 puffs). Spirometry will be performed 20 to 30 min post-salbutamol. If the reversibility criterion is not fulfilled, spirometry can be repeated up to 60 min post-salbutamol administration.

The reversibility test will be considered positive if patients show improvement of FEV_1 ≥12% and 200 mL after administration of salbutamol.

If the reversibility criteria are not fulfilled, the pulmonary function test can be repeated once, at the latest, up to Day -14.

5.1.3 FEV_1 and clinical stability check

FEV_1 stability check will be performed at Visits 6 and 9 (Day 1 of treatment periods 2 and 3). It is not an outcome measure. FEV_1 stability check will be based on the pre-BTR values. FEV_1 at these visits will be calculated as the mean of the 2 pre-dose values and compared with the mean of the pre-dose FEV_1 values measured at Visit 3. This should be within (±)20% or (±)200 mL compared to the pre-dose FEV_1 (mean of the 2 measured values) of the first treatment period (Visit 3). If the FEV_1 stability criterion is not met, an additional measurement could be taken within 30 min of the second pre-dose measurement, and the mean of the last 2 measurement will be considered for the FEV_1 stability criterion.

If the FEV_1 stability criterion is still not met, the test can be rescheduled as soon as possible, and if the FEV_1 stability criterion is not met after re-testing, the patient should be withdrawn.

Patient's clinical stability will be assessed at Visit 2 and before the start of each treatment period and defined as follows:

- No relevant respiratory signs/symptoms that modify the patient's baseline daily activities

- Not meeting criteria of COPD exacerbation (as per Investigator's clinical judgement)

- No SAEs

- No relevant AEs that potentially modify the absorption, distribution, metabolism, and excretion of IP

5.1.4 Breathlessness, cough, and sputum scale

The BCSS (Leidy et al, 2003) questionnaire is a 3-item, patient-reported outcome (PRO) measure. On a daily basis, patients are asked to evaluate each of their 3 symptoms (breathlessness, cough, and sputum) on a 5-point Likert scale ranging from 0 to 4, with higher scores indicating a higher severity of the symptom. The BCSS questionnaire is expressed as a daily total score, which is the sum of the 3 symptom scores, ranging from 0 to 12.

Patients will be provided with an e-Diary to collect their assessments of their 3 symptoms in the evening on a daily basis.

5.1.5 Rescue medication use

Patients will be provided with salbutamol, to be used as needed, as a rescue medication. Patients will be provided with an e-Diary to collect their daily use of rescue medication during the run-in and treatment periods.

Salbutamol should be held at least 6 hours before any pulmonary function tests.

5.2   Safety assessments

5.2.1   Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, haematology, and urinalysis will be taken at the times indicated in the Study Plan (see Section 4). The results of tests performed at Visit 1 will be regarded as baseline data.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 2   **Laboratory safety variables**

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haematocrit	S/P-Glucose (fasting)
B-Haemoglobin	S/P-Cholesterol, total
B-Erythrocytes (red blood cells)	S/P-Triglycerides
B-MCV	S/P-Creatinine
B-MCH	S/P-Bilirubin, total
B-MCHC	S/P-Protein, total
B-Leukocyte count (white blood cells)	S/P-Albumin
B- differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophil)	S/P-Uric acid and BUN
B-thrombocytes	S/P-Sodium
B-Platelet	S/P-Potassium
Coagulation parameters (INR, PTT and aPTT)[a]	S/P-Calcium, total
	S/P-Chloride
Urinalysis (dipstick)	S/P-Phosphorus, inorganic
U-pH	S/P-AST
U-Blood	S/P-ALT
U-leucocytes	S/P-ALP
U-Protein	S/P-GGT
U-Glucose	S/P-LDH
U-Bilirubin	S/P-Creatine kinase
U-Urobilinogen	
U-Ketones	
U-Nitrites	

ALP=Alkaline phosphatase; ALT=Alanine transaminase; aPTT=Activated partial thromboplastin time; AST=Aspartate transaminase; BUN=Blood urea nitrogen; GGT=Gamma glutamyl transferase; INR=International normalised ratio; LDH=Lactate dehydrogenase; MCH=Mean cell haemoglobin; MCHC=Mean corpuscular haemoglobin concentration; MCV=Mean corpuscular volume; PTT=Partial thromboplastin time.

a. Coagulation parameters will be assessed at Screening and Follow-up Visits only.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

NB. In case a patient shows an AST **or** ALT ≥3×ULN **or** TBL ≥2×ULN please refer to Appendix C, for further instructions.

As per AstraZeneca standards, during the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. Hy's Law guidance for the Investigator is included in Section 6.3.7 and Appendix C.

The following laboratory tests will be performed only at the Screening Visit to check the eligibility of the patient for participation in the study:

- Serology tests:

    – HIV I and II antibodies,

    – Hepatitis B surface antigen

    – Hepatitis B core (HBc) immunoglobulin antibodies (IgM)

    – Hepatitis C antibodies

- Urine pregnancy test in women

- Women aged less than 50 years (see inclusion criterion #2): Serum/plasma FSH and LH

Drugs of abuse and alcohol screen will be performed at Screening and Visit 3 (prior to randomisation) at the site. Alcohol screen could be performed using a urine sample or a breath test.

Table 3   Drugs of abuse and alcohol parameters

Drugs of Abuse (10 mL fresh urine sample) and Alcohol (breath or urine test)	
Amphetamine/Ecstasy	Benzodiazepines
Ethanol/Alcohol	Methadone
Cannabinoids/Tetrahydrocannabinol	Barbiturates
Cocaine	Urine Creatinine
Opiates	Phencyclidine
Tricyclic anti-depressants	Cotinine

a   If a patient tests positive for any drugs of abuse tests, which cannot be explained by use of prescription medication, he/she will be excluded from the study.

5.2.2 Physical examination

A complete physical examination will be performed at Screening (Visit 1) and at Follow-up Visit and will include an assessment of the following: general appearance, eye, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, neurological/psychiatric and throat.

Brief physical examination will be performed at other visits including an overnight stay and will include an assessment of the following: skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Body weight and height will be measured at Visit 1 (Screening) for calculation of BMI. Patients should be in light indoor clothes without shoes.

5.2.3 Electrocardiogram

Standard 12-lead ECG evaluations will be recorded after approximately 5 minutes resting in supine position before any blood sampling and spirometry test. 12-lead ECGs will be recorded preferably always by the same technician for each patient.

Electrocardiogram will be performed with the regular 12-lead ECG equipment at each site included in the study.

Electrode preparation to prevent interference in the ECG signal will be according to the recommendations of the supplier.

Electrocardiogram will be performed at the times presented in the Study Plan (Table 1).

Individual ECG analysis will be performed by the Investigator at each of the sites. Results will be collected and included in the eCRF.

The Investigator will review the reports to assess the clinical relevance of any abnormal findings and/or to decide if the patient is or remains eligible for the study.

The 12-lead ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined:

- Heart rate

- RR interval: Duration in milliseconds between 2 R peaks of 2 consecutive

- QRS complexes

- PR interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)

- QRS interval: Duration in milliseconds of the QRS complex

- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T wave

- QTc interval: QT interval corrected by heart rate:

  - QTcB interval: QT interval corrected using Bazett formula (QT[msec]/RR[sec]1/2)

  - QTcF interval: QT interval corrected using Fridericia's formula (QT[msec]/RR[sec]1/3)

At Visit 1, the 12-lead ECG should be recorded at a similar time to that to be obtained pre-dose during the course of the study. Investigators will assess patients' eligibility according to the manual reading report of Visit 1.

Any abnormal finding in the ECG tracing (rhythm, ectopy, conduction, morphology, myocardial infarction, ST segment, T wave and U wave observations) will be evaluated by the Investigator and will be specifically documented and registered on eCRF.

Throughout the study, clinically *relevant* new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded on the AE eCRF form. For information on how AEs based on ECG results should be recorded and reported, see Section 6.3.

In case of technical problems, the Investigator considers any result is clinically relevant or doubtful, additional 12-lead ECGs may be performed, using the same equipment, within a reasonable time.

5.2.4   Vital signs

For information on how AEs based on vital signs should be recorded and reported, see Section 6.3.

5.2.4.1   Heart rate and blood pressure

Heart rate will be assessed by ECG (Section 5.2.3). Systolic and diastolic blood pressure (SBP and DBP) (in mmHg) will be measured after at least 5 minutes resting, and also, before taking any blood sample and conducting any spirometry. Measurements will be carried out with patient in the supine position and preferably always on the same arm. Data will be recorded on the eCRF.

If there is any suspicion of unreliable measurement, blood pressure will be measured again. The value obtained on the second measurement will be considered as definitive and will be the one recorded on the eCRF.

Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the medical history/physical examination/blood pressure must be considered an AE and must be recorded on the AE form of the eCRF.

5.2.4.2   Body temperature

Patient's body temperature will be measured at Visit 1 (Screening) and Follow-up Visit (Visit 12).

5.2.5   Adverse events

Procedures for recording and assessing AEs are included in Section 6.3.

5.2.6   Unscheduled tests

As deemed necessary by the Investigator, additional safety test(s) can be performed at any time during the study in order to follow-up the progress of any clinically relevant abnormal finding, or to investigate any potential new AE. These additional tests out of the initial schedule of the study will be called "unscheduled tests" and will not be associated with any study visit.

5.2.7   Repeated tests

Any safety test may be repeated at the Investigator's discretion when there is any kind of problem with the first test (ie, technical problem with the ECG machine, blood sample haemolysed, presence of artefacts, etc.). The Investigator should repeat the individual test as soon as possible, prior to the next visit.

At Visits 3, 6 and 9 (Day 1), the pre-dose assessments can be rescheduled (and therefore repeated on another date) for technical reasons, if FEV_1 stability criterion is not met or if rescue medication is taken before the IP administration. Also, any laboratory test(s) meeting a withdrawal criterion should be repeated as soon as possible, prior to withdrawing the patient.

The repeated tests will be called "re-test" and will be identified with the same visit identifier as the first attempt.

5.3   Other assessments

Taste assessment after intake of IP: The patient will record responses to taste questionnaire (Appendix E) on a paper questionnaire within 15 minutes of IP intake (all questions, except the question on the last page). The last page of the questionnaire must be completed by the patient within 2 hours after IP intake. This questionnaire will be completed only on Day 14 of each treatment period (ie, Visits 5, 8 and 11) and will be transcribed in the eCRF.

5.4   Pharmacokinetics

5.4.1   Collection of samples

Blood samples for determination of AZD8871 and its primary metabolites LAS191861 and LAS34850 in plasma will be taken at the times presented in the Study Plan (Table 1). Blood

draw volume will be of 4 mL at all time points, for a total of 240 mL. A total of 20 patients will participate in the PK sampling.

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

5.4.2 Determination of drug concentration

Samples for determination of AZD8871 and its metabolites, LAS191861 and LAS34850 concentrations in plasma will be analysed by Covance on behalf of AstraZeneca, using 2 different, validated bioanalytical methods, one for AZD8871 and LAS191861, and another for LAS34850 quantification. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Results will be only reported for samples shipped within a timeframe for which the stability of AZD8871 and its metabolites, LAS191861 and LAS34850, in the samples has been validated and shown to be acceptable.

Placebo samples will not be analysed unless specified.

5.4.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

5.5 Pharmacodynamics

Pharmacodynamic samples will not be taken during the study.

5.6 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study.

5.7 Biomarker analysis

There will be no biomarker analysis in the study.

6.   SAFETY REPORTING AND MEDICAL MANAGEMENT

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

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the patients until the resolution of the AEs.

A valid case of adverse event will be the following:

•   A confirmed event

•   A reporter

•   A suspected study drug

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

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

6.2   Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, wash-out, follow-up), that fulfils one or more of the following criteria:

•   Results in death

•   Is immediately life-threatening

•   Requires in-patient hospitalisation or prolongation of existing hospitalisation

•   Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

•   Is a congenital abnormality or birth defect

•   Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events will be collected from the time of signature of informed consent throughout the treatment period and including the follow-up period (28-35 days after last dose of IP).

6.3.2 Follow-up of unresolved adverse events

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)

- The date and time when the AE started and stopped

- Intensity

- Whether the AE is serious or not

- Investigator causality rating against the IP (yes or no)

- Action taken with regard to IP

- AE caused patient's withdrawal from study (yes or no)

- Outcome

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

- Date AE met criteria for SAE

- Date Investigator became aware of SAE

- AE is serious due to

- Date of hospitalisation

- Date of discharge

- Probable cause of death

- Date of death

- Autopsy performed

- Causality assessment in relation to Study procedure(s)

- Causality assessment in relation to other medication

- Description of AE

For grading the intensity of an AE, the following intensity rating scale will be used:

1. Mild: awareness of sign or symptom, but easily tolerated (acceptable)

2. Moderate: discomfort sufficient to cause interference with normal activities (disturbing)

3. Severe: incapacitating, with inability to perform normal activities (unacceptable)

Adverse Events will be collected only once with its maximum intensity.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. 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 unless it meets the criteria shown in Section 6.2. 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 when it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

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

For SAEs causal relationship will also be assessed for 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 A to the Clinical Study Protocol.

6.3.5 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/you

were last 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.

6.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Medical disorders present at the time of signing the informed consent that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Relevant abnormalities detected before first IP administration in physical examination, laboratory value/vital sign, ECGs will not be considered AEs if already known as part of the medical history or in relation to prior medical conditions, and will be recorded in the eCRF history/physical examination form/page. However, relevant abnormalities detected in Screening/run-in/ baseline tests, thought to be due to a study procedure, will be considered AEs and recorded in eCRF.

During the study, abnormalities (newly occurring or worsening of previously known abnormalities) detected in laboratory values, vital signs, ECGs and physical examination which are considered clinically relevant by the Investigator or which require an intervention or a diagnosis test, or may result in the IP discontinuation, should be reported as AEs.

In addition, when an AE meets the criteria of seriousness (SAE), it must also be recorded in the eCRF and reported following the defined timelines (see Section 6.4).

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3xULN together with total bilirubin ≥2xULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied, (ie, COPD in this study). Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigator or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigator or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the EDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by fax or email.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. The reference document for definition of expectedness is the IB for the AstraZeneca drug.

6.5   Overdose

An overdose of AZD8871 is likely to lead to exaggerated pharmacological effects typical of β_2-adrenergic stimulants (ie, tachycardia, hypertension, hypotension, palpitations, ventricular arrhythmias, tremor, muscle cramps, headache, nausea, vomiting, nervousness, drowsiness, insomnia, fatigue, malaise, metabolic acidosis, hypokalaemia, hyperglycaemia, etc.) and anticholinergics (ie, dry mucous membranes, mydriasis, increased heart rate, increased intraocular pressure, hypertension, urinary retention, constipation, hypoactive bowel sounds, flushed skin, confusion, disorientation, agitation, ataxia, etc.).

Supportive and symptomatic treatment is indicated. In serious cases, patients should be hospitalised.

Reporting an overdose:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRF and on the Overdose form.

- An overdose without associated symptoms is only reported on the Overdose form.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** 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 DES.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca using the Pregnancy form.

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the IP should be discontinued immediately and the pregnancy reported to AstraZeneca.

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** 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 DES within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should use a condom and spermicide to prevent pregnancy and drug exposure of a partner regardless of the gender or childbearing potential of the partner and refrain from donating sperm or fathering a child from the first administration of the IP until 3 months after the last administration of the IP. In addition to a condom with spermicide, a second effective method of contraception should be used with female partners of childbearing potential.

In case of pregnancy of the patient's partners, the participant will not be necessarily discontinued from the study but the partner's pregnancy should be reported on the pregnancy form following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the patient's partners is not considered to be an AE. These pregnancies will be also followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be obtained and documented.

6.7 Management of IP related toxicities

There is no plan for dose reduction in this study.

6.8 Study governance and oversight

There will be no steering committee, data monitoring committee or scientific advisory committee.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product

These are the proposed dose strengths.

Investigational product	Dosage form and strength	Manufacturer
AZD8871	Powder for inhalation administered via single dose DPI 100 and 600 µg/inhalation	Industrias Farmacéuticas Almirall S.A. Redacted
Placebo	Powder for inhalation administered via single dose DPI	Industrias Farmacéuticas Almirall S.A. Redacted

DPI=Dry powder inhaler.

Product dosage and mode of administration

Study treatment	IP administration	Comments
AZD8871 100 µg	100 µg single dose DPI	1 inhalation QD
AZD8871 600 µg	600 µg single dose DPI	1 inhalation QD
Placebo	Placebo single dose DPI	1 inhalation QD

DPI=Dry powder inhaler: QD=Once a day.
All investigational products will be administered by oral inhalation.

The planned dose of AZD8871 or placebo will be administered via single dose DPI that is an adaptation of the commercially available Genuair® with a smaller internal volume to enable delivery of single doses. To maintain blinding, each patient will receive one inhaled dose from the AZD8871 or placebo DPI provided to him/her on each day of the treatment period.

Doses taken at Day 1, Day 2, Day 8 and Day 14 of each treatment period will be taken at the study site, while doses on other treatment days will be taken at patient's home.

The IP manufacturing, labelling, packaging and release will be conducted following Good Manufacturing Practice (GMP) by Almirall. Each DPI will be packed in an Aluminium Pouch including desiccant.

Patient kit for each treatment period will include IP to cover treatment from Day 1 to Day 7 or from Day 8 to Day 14 (2 kits for each treatment period). Further information will be provided in the Investigator drug manual.

The Almirall Qualified Person will provide a certificate of analysis as well as appropriate certificate of release. Batch numbers will be indicated in the CSR.

For training purposes, each patient will receive an empty DPI that will be used on Visit 3, 6 and 9 if considered necessary.

7.2 Dose and treatment regimens

At Visit 1, patients will be provided with salbutamol, to be used as rescue medication during the study, until the Follow-up Visit. Salbutamol should be held at least 6 hours before any pulmonary function tests.

7.2.1 Run-in period

At Visit 2, if the reversibility test and FEV_1 predicted values are fulfilled, the patient will start a run-in period for 14 to 28 days. All patients will receive ipratropium following the approved dosage and regimen during the run-in period.

7.2.2 Treatment periods

The first dose of IP is to be taken at the clinic at 9:00 AM ±2 hours on Day 1 of each treatment period (Visits 3, 6 and 9) after the pre-dose specified procedures and randomisation. On subsequent days of each treatment period, IP is to be taken within ±1 hour of dosing time of Day 1 (and between 7 am and 11 am).

The Day 2 dose of IP will also be taken on site. Doses from Day 3 to Day 7 will be taken at home. IP administration on Day 8 and Day 14 will be done at the site and the rest of the doses (Day 9 to Day 13) will be taken at home.

During each treatment period, each patient will receive one of the 3 possible treatments, with every patient receiving placebo in one of the treatment periods. Patients will receive 2 kits (one to cover treatment from Day 1 to Day 7 and one to cover treatment from Day 8 to Day 14) containing IP for one of the 3 following treatments for 14 days in any given period:

- AZD8871 100 μg

- AZD8871 600 μg

- Placebo

Further information regarding IP kit will be provided in the Investigator drug manual.

7.2.3 Wash-out periods

Wash-out periods of 28 up to 35 days will occur between each treatment period (after last administration of IP). All patients will receive ipratropium following the approved dosage and regimen during the wash-out periods.

7.3 Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The IP will be provided in individual patient kit labelled with study-specific label.

To allow drug reconciliation and dispensation control, research personnel will record patient ID on the labels of the patient kit, every period kit dispensed, as well as on the aluminium bag labels and inhaler labels.

Patients participating in the study will be provided with an identification card where the Investigator's details including telephone number are included and will be instructed to keep this identification card with them at all times.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the study drug specifies: "No special storage conditions. Do not refrigerate or freeze".

Further information regarding IP storage at the site will be provided in the Investigator drug manual.

7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF (date, time, number of inhalations).

Patients will be provided with an e-Diary to record their intake of the IP on a daily basis.

7.6 Accountability

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

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

All used and unused supplies of the IP will be destroyed by PAREXEL at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instructions by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

7.7 Concomitant and other treatments

Any treatment taken during the 2 weeks prior to signing of the ICF, must be recorded in the Previous and Concomitant Medication eCRF page to ensure proper wash-out of prohibited medications.

Patients will be withdrawn from their usual COPD therapy after signing the ICF and maintained on their usual ICS therapy, if any. In addition, salbutamol will be provided as rescue medication for the duration of the study.

From the first IP administration, any new treatments taken or any change in ongoing medications during the participation in the study, apart from the IP, will be transcribed onto the corresponding eCRF page by the Investigator or designee.

Patients must be instructed to inform the Investigator of plans to take any new treatment during the participation in the study, including over-the-counter medicinal and herbal products.

In the interest of patient safety and acceptable standards of medical care, patients may be allowed to take any medications not listed as either permitted or not permitted (see below) at the discretion of the Investigator. All treatments must be recorded in the patients' eCRF. Any medication taken for medical reasons deemed acceptable by the Investigator prior to study entry will be continued at the same dose and conditions during the entire experimental phase of the study.

Table 4 and Table 5 summarise different possible treatments for COPD and other indications which are allowed and prohibited, respectively, with example of medication and applicable restrictions.

Table 4   Medications allowed as concomitant medications

Medications	Restrictions
Oral anti-histamines, intranasal corticosteroids and sympathomimetics and intranasal anticholinergics	Allowed but avoid for 12 hours prior and up to 36 hours post IP dosing at each period
ICSs mono-component	Allowed but if taken, dosage and regimen must be stable during all study duration
Rescue medication: Salbutamol 100 μg (2 puffs)	Allowed but avoid for 6 hours prior to any spirometry test for the study
Ipratropium at the approved dosage and regimen	Mandatory during run-in and wash-out periods but should be held at least 8 hours before Visits 3,

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| | | 6 and 9 (before any pulmonary function test) and during all treatment periods (until last pulmonary function test at Visits 5, 8 and 11) |

ICS=Inhaled corticosteroid; QID=Four times a day.

Table 5   **Medications prohibited as concomitant medications**

Drug Class	Medications	Restrictions
ANTICHOLINERGICS		
Oral or parenteral	-	Wash-out of 72 hours required before Visit 2
Inhaled short-acting, SAMAs	Oxitropium	Wash-out of 12 hours required before Visit 2
Inhaled long-acting, LAMAs	Tiotropium	Wash-out of 72 hours before Visit 2
B$_2$-ADRENERGIC AGONISTS		
Inhaled short-acting, SABAs (except Salbutamol-rescue medication)	Fenoterol, Terbutaline	Wash-out of 6 hours before starting first pulmonary function test at each study visit
Inhaled long-acting, LABAs (BID or QD)	Formoterol, Salmeterol, Vilanterol, Indacaterol	BID: Wash-out of 48 hours required before Visit 2 QD: Wash-out of 7 days required before Visit 2.
Oral short-acting	Terbutaline, Metaprotenerol	Wash-out of 24 hours required before Visit 2
COMBINATIONS (INHALED)		
LABA + ICS fixed-dose combinations	-	Interrupt combination at least 48 hours before Visit 2. Must be switched to ICS mono-component at Visit 1
SABA + anticholinergic agent		Wash-out of 72 hours required before Visit 2
CORTICOSTEROIDS		
Continuous oral or parenteral		Wash-out of 6 weeks required before Visit 2
OTHERS		
Methyl-xanthines	Theophylline, Aminophylline	Patients with these medications should not be enrolled into the study
Mast cell stabilisers	Cromolyn sodium/nedocromil sodium	Wash-out of 5 days required before Visit 2

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Drug Class	Medications	Restrictions
Leukotriene modifiers	Montelukast, Zafirlukast, Zileuton	Wash-out of 48 hours required before Visit 2
Selective and non-selective β-blocking agents (oral or topical including eye drops)	Acebutolol, Celiprolol, Xamoterol, Practolol, Propanolol	Patients with these medication should not be enrolled into the study
Phosphodiesterase IV inhibitors	Roflumilast	Wash-out of 4 weeks required before Visit 2
Anti-IgE and anti-IL-5 antibody therapies	Omalizumab, Mepolizumab	Wash-out of 6 months required before Visit 2
Medications that prolong the QT/QTc interval (other than inhaled β_2 agonist) eg, anti-arrhythmics, anti-psychotics and fluoroquinolones	-	Stable at least 4 weeks prior to Visit 2
"Experimental", non-approved medications		Wash-out of 3 months before Visit 1
Strong inhibitors of carboxyl esterase 2	Loperamide	Wash-out of 5 days required before Visit 2
Live attenuated vaccine		Wash-out of 30 days before Screening
Inactivated vaccine	Inactivated influenza vaccination, pneumococcal vaccination, or any other inactivated vaccine	Wash-out of 7 days before Screening or randomisation Visit Wash-out of 7 days before each treatment period Inactivated vaccines are not allowed during the treatment periods

BID=Twice a day; ICS=Inhaled corticosteroid; LAMA=Long-acting muscarinic antagonist; QID=Four times a day; SABA=Short-acting β_2-agonist; SAMA=Short-acting muscarinic antagonist.

7.7.1   Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

8.   STATISTICAL ANALYSES BY ASTRAZENECA

8.1   Statistical considerations

All data analyses will be performed by the Global programming lead from AstraZeneca except the derivation of the PK parameters, which will be performed by Covance.

A fully detailed Statistical Analysis Plan (SAP) will be prepared by the Global Project Statistician from AstraZeneca before the database lock.

All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables. Demographic and baseline characteristics will be presented. For continuous variables, the number of non-missing observations, mean, standard deviation (SD), standard error (SE) of the mean, 95% confidence interval (CI) of the mean (except safety data), median, first and third quartiles, minimum and maximum will be presented. For categorical variables: counts (n) and percentages (%) (where specified) will be presented. These summaries will be provided by time point of assessment as appropriate.

The SAS® version 9.3 or later will be used for the data analysis. A complete set of raw data listings will be appended to the final CSR. All tables, figures and listings will be presented in Word and PDF documents without any manual editing, ie, they will appear unmodified as programmed by means of the statistical package.

In general, there will be no imputation of missing data for the safety or efficacy analyses. Additional details will be provided in the SAP.

8.2 Sample size estimate

The study will be powered to demonstrate superiority of AZD8871 100 µg and 600 µg versus placebo for the primary efficacy endpoint. With a total of 30 patients, there is 80% power to detect a difference between actives and placebo for the change from baseline to trough FEV_1 at Day 15 equal to 100 mL, assuming a within-patient SD of 135 mL, 2-sided 5% significance level and a normal distribution. Assuming an approximate 25% dropout, the total sample size will be approximately 42 (multiple of 6 sequences). From previous studies, the screening failure rate is estimated to be approximately 55%, therefore approximately 93 screened patients will be required to achieve the goal of approximately 42 randomised patients.

Due to the exploratory nature of the study, there will be no adjustment for multiple comparisons.

8.3 Definitions of analysis sets

8.3.1 Full analysis set

The Full Analysis Set (FAS) population is defined as all patients randomised and receiving IP, irrespective of their protocol adherence and continued participation in the study. Patients will be assigned according to their randomised treatment, irrespective of whether or not they have prematurely discontinued. Patients who withdraw consent to participate in the study will be included up to the date of their study termination. All efficacy analyses will be based on the FAS and analysed according to the intent to treat principle.

8.3.2 Safety analysis set

The safety analysis set consists of all randomised patients who received at least one dose of IP. Patients will be analysed according to the randomised treatment assignment in each

period. Any important deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

8.3.3 Pharmacokinetic analysis set

The PK analysis set is defined as all randomised patients participating in the subset of PK patients, who took at least one dose of IP and have at least one of the parameters, C_{max}, AUC or AUC_{last} evaluable and are assumed not to be affected by factors such as protocol deviations (eg, disallowed medication, or incorrect study medication received). All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to the PK analysis sets.

The exclusion of any patients or time points from the calculation of the PK parameters will be documented by the PK scientist including the reason(s) for exclusion. The available concentration data and PK parameter data for any patients excluded from the PK analysis set will be listed only, and presented in the individual figures of concentration-time plots.

8.3.4 Per-protocol analysis set

The Per-Protocol (PP) population is defined as a subset of FAS population constituted by those patients who did not present important deviations of the protocol that may affect efficacy (eg. met all inclusion/exclusion criteria liable to affect the efficacy assessment).

8.3.5 Protocol deviations

Deviations from the protocol will be assessed as "important" or "not-important". Important deviations from the protocol may lead to the exclusion of patients from the PP set and/or other analysis sets. Deviations will be defined before database hard lock and unblinding. Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria.

- Administration of prohibited concomitant medications that are expected to influence the measurement of the primary endpoint.

All important protocol deviations will be listed by patient for all randomised patients. Further details will be described in the SAP.

A Blind Data Review Meeting (BDRM) will be held before opening randomisation codes in order to assign the patients to the different analysis populations according to the specified definitions. The precise reasons for excluding patients from the study populations will be fully defined in the SAP and documented in the BDRM Report.

8.4 Outcome measures for analyses

8.4.1 Primary efficacy variable

The primary efficacy variable is the change from baseline in trough FEV_1 at Day 15 (ie, after 14 days of treatment).

Baseline for FEV_1 will be defined as the mean of the 2 measured values for the corresponding variable (2 measurements 45 min apart, at -1 hour and -15 min), prior to the morning IP administration on Day 1 of each treatment period. If both are missing, the Visit 2 pre-bronchodilator value will be used instead.

Trough is defined as the mean of the FEV_1 values obtained at 23 hours and 23 hours and 45 min after the morning IP administration on Day 1 and Day 14 (ie, obtained on Day 2 and Day 15). On Day 8, trough is defined as the mean of the FEV_1 pre-dose values (-1 hour and -15 min). If one of the values is missing, just the available value will be used as trough.

8.4.2 Secondary variables

8.4.2.1 Efficacy variables

The secondary efficacy variables are the following:

- Change from baseline in Trough FEV_1 on Day 2, and Day 8

- Change from baseline in Peak FEV_1 on Day 1, Day 8, and Day 14

- Change from baseline in Trough FEV_1 over treatment duration (Day 8 to Day 15)

- Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14)

- Change from baseline in Total Score BCSS questionnaire and cough, breathlessness and sputum individual domain scores from Day 1 to Day 8 after treatment, from Day 8 to Day 14 after treatment and during the whole treatment duration

- Rescue medication use

8.4.2.2 Pharmacokinetic variables

When possible, the following PK parameters will be assessed for AZD8871 and its metabolites, LAS191861 and LAS34850 on plasma concentrations:

- Day 1:

  - C_{max} - Observed maximum concentration, taken directly from the individual concentration-time curve

  - t_{max} - Time to reach maximum concentration, taken directly from the individual concentration-time curve

  - AUC_{last} - Area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration

  - $AUC_{(0-24)}$ - Area under the plasma concentration-curve from time 0 to 24 hours post-dose

- Day 14:

    - C_{max} - Observed maximum concentration, taken directly from the individual concentration-time curve

    - t_{max} - Time to reach maximum concentration, taken directly from the individual concentration-time curve

    - AUC_{last} - Area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration

    - $AUC_{(0-24)}$ - Area under the plasma concentration-curve from time 0 to 24 hours post-dose

    - C_{max}/D - Observed maximum concentration divided by dose

    - AUC_{0-24}/D - Area under the concentration-time curve 0 to 24 h divided by the dose

    - C_{avg} - Average plasma concentration during a dosing interval, estimated as $AUC_{0-24}/24$

    - %Fluctuation - Fluctuation index during a dosing interval estimated as $100*(C_{max} - C_{min})/C_{avg}$ (%), where C_{min} is the minimum concentration at the end of the dosing interval

    - Rac (C_{max}) - Accumulation ratio for C_{max} estimated as (C_{max} on Day 14/C_{max} on Day 1)

    - Rac (AUC_{0-24}) - Accumulation ratio for AUC_{0-24} estimated as (AUC_{0-24} on Day 14/AUC_{0-24} on Day 1)

Additional parameters may be determined where appropriate.

Calculation or derivation of the pharmacokinetic parameters

The PK analyses of the plasma concentration data for AZD8871 and its metabolites will be performed at Covance, UK, on behalf of AstraZeneca. The actual sampling times will be used in the plasma PK parameter calculations.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.2, or higher and/or SAS® Version 9.3 or later. Pharmacokinetic analyses will be conducted according to AstraZeneca SOPs for PK analyses, if not otherwise indicated.

For AUC derivation, plasma concentrations below the lower limit of quantification (BLQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration

will be set to a value of 0. After this point, BLQ plasma concentrations will be set to missing for all concentration profiles. Also, if 2 or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration-curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so, this is documented in the PK analysis notes.

AUC will be calculated using trapezoidal methods when concentration is increasing and logarithmic trapezoidal method when concentrations are decreasing.

Three concentrations higher than the lower limit of quantification (LLOQ) are required as a minimum for the AUC parameter to be summarised.

If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

8.4.3 Safety variables

The safety variables are:

- AEs/SAEs

- Vital signs

- ECG

- Clinical laboratory assessments

8.4.4 Exploratory variable

- Taste assessment

8.5 Methods for statistical analyses

8.5.1 Demographic and baseline characteristics

Analyses of demographic and baseline characteristics will be performed on the Safety population.

Demographic characteristics to be assessed are age, sex, race, height, weight and BMI.

Baseline characteristics to be assessed include:

- Smoking status (current and former smokers), smoking duration (years) and smoking consumption (total pack-years) at Screening.

- Medical history and physical findings classified by system organ class and preferred term.

- COPD duration (years).

- COPD severity. COPD severity will be based on the post-bronchodilator FEV_1 at Screening and will be defined as follows:

    – Stage II (Moderate): $FEV_1/FVC < 0.70$ and $50\% \le FEV_1 < 80\%$ predicted

    – Stage III (Severe): $FEV_1/FVC < 0.70$ and $30\% \le FEV_1 < 50\%$ predicted

- Absolute values of the FEV_1 and FVC (pre- and post-bronchodilator test) at Screening.

- Percent of predicted FEV_1 and FVC (pre- and post-bronchodilator test) at Screening.

- Ratio FEV_1/FVC (post-bronchodilator test) at Screening.

- Mean bronchodilator reversibility (change from pre-bronchodilator test value) at Screening.

- Percentage of bronchodilator reversibility (% increase over pre-bronchodilator test value) at Screening.

- Number of patients who meet the reversibility criteria (at least 12% increase in FEV_1 post-bronchodilator and at least 200 mL increase from pre-test in FEV_1).

- Time since last exacerbation (days) during last 12 months.

- The number and percentage of patients who used any prior medication (14 days before ICF) will be summarised overall by Anatomical Therapeutic Code (ATC) code (to a maximum of 3rd level), and preferred name. (Including also those medications taken before the ICF administration and continue afterwards, this will be classified in both prior and concomitant medication groups). Patients with multiple drug usage in the same preferred name will be counted only once.

- Additionally, a subset of the previous summary will be produced presenting the number and percentage of patients who used any prior medication for COPD by the following therapeutic categories; ICS, LABA, LABA+ICS combination, LAMA, short-acting β_2-agonists (SABA), SABA+ICS combination, short-acting muscarinic antagonist (SAMA), SABA+SAMA combination, Influenza Vaccine, Oxygen, Xanthines and PDE4 inhibitors. If a patient has LABA+ICS followed by ICS (as monotherapy), then this patient will be counted only once in the LABA+ICS category.

Screening values for ECGs, laboratory assessments, and blood pressure will not be presented in the tables corresponding to demographic and Screening characteristics but together with the corresponding assessments after baseline and with the changes from baseline to ease the interpretation of these safety outcomes.

Appropriate descriptive statistics according to the nature of each variable will be provided for these variables. No statistical tests will be performed.

8.5.2 Concomitant and rescue medication

The number and percentage of patients with:

- Any medication taken during wash-out periods (those medications being taken after 24 h of IP intake on Day 14 and before the following treatment period).

- Any medication taken during the treatment periods (those medications being taken between the first IP administration and 24 h after the last IP administration of each treatment period) will be tabulated by ATC code (third level), preferred term and treatment.

- Any rescue medication (ie, salbutamol) taken during the treatment periods.

Additionally, the number and percentage of patients with any of these medications versus those not taking medication will be tabulated by treatment. Listings with concomitant medication will also be produced.

Concomitant medication will be summarised for the Safety population. Additionally, the number and percentage of patients with any of these medications versus those not taking medication will be tabulated by treatment for each study part. Listings with prior, concomitant and reliever medication will also be produced.

8.5.3 Analysis of the primary efficacy variable

The primary efficacy variable will be analysed by means of a mixed model; a random effects model with fixed effects for treatment, sequence, and period. The patient will be fitted as a random effect and the pre-dose FEV_1 of each period will be included as a covariate.

Each treatment effect and treatment differences will be estimated by the Least Square (LS) means along with their SE and 95% CI, and the p-value corresponding to the between-treatment group difference.

The main treatment comparisons that will be evaluated are:

- AZD8871 100 µg versus Placebo

- AZD8871 600 µg versus Placebo

Treatment comparisons among active treatments will be also explored.

8.5.4 Analysis of the secondary variables

8.5.4.1 Analysis of the efficacy variables

All secondary efficacy variables will be analysed using the same mixed model as that for the primary efficacy variable adjusting for the corresponding baselines.

All baselines will be the pre-dose values of each treatment period except for the Total BCSS questionnaire score where the run-in period baseline will be used for all treatments in each sequence.

Peak FEV_1 will be defined as the maximum value from 0 to 4 hours.

The same treatment comparisons as those for the primary variable will be performed for the secondary variables.

8.5.4.2 Analysis of pharmacokinetic variables

Descriptive statistics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. A listing of individual sample collection dates and times, AZD8871 and metabolites concentrations, and comments will be provided.

Plasma concentrations will be summarised by dose level of AZD8871 using descriptive statistics (n, geometric mean, geometric SD, geometric coefficient of variation [CV%], arithmetic mean, arithmetic SD, minimum, median and maximum) based on the PK analysis set.

For descriptive statistics for plasma concentrations that are below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.

- At a time point where more than half (but not all) of the values are BLQ, the arithmetic mean, arithmetic SD, geometric mean and CV% will be set to Not Determined (ND). The maximum value will be reported from the individual data, and the minimum and median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be calculated for that time point. Not applicable (NA) will be written in the field for arithmetic SD and geometric CV% and BLQ will be written in fields for arithmetic mean, geometric mean, minimum, median, and maximum.

- The number of BLQ values (n above LLOQ) will be reported for each time point.

All plasma PK parameters will also be listed and summarised using similar descriptive statistics. For t_{max} only n, median, minimum and maximum will be reported.

Data from patients excluded from the PK analysis set will be included in the data listings, but not in the summaries or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale, with separate plots for each patient and concentrations for Day 1 and

Day 14 (where applicable) overlaid on the same plot. Combined individual plasma concentration per dose level of AZD8871 will also be presented in linear and semi-logarithmic scale with separate plots for each dose level and day (Day 1 and Day 14).

Figures for the geometric mean (± geometric SD) concentration-time data will be presented for all doses overlaid on the same plot, in both a linear and semi-logarithmic scale (SD only on the linear scale).

All plots will be provided for AZD8871 and its metabolites.

Additional graphical presentations of PK data may be added at the discretion of the PK Scientist. More details will be provided in the SAP.

Analysis of accumulation

Product accumulation will be evaluated by comparing $AUC_{(0-24)}$ (Day 14) with $AUC_{(0-24)}$ (Day 1) and C_{max} (Day 14) with C_{max} (Day 1). A linear mixed-effect model will be used with the logarithm of the PK parameters as the response variable and dose, day and dose by day interaction as fixed effects. Day will be treated as a repeated effect within-patient. From these models, LS means together with 95% CI for Day 1 and Day 14, and LS means together with 90% CI for the difference for Day 14 versus Day 1 will be obtained. The results will be transformed back to the original scale by exponentiation to provide estimates of geometric LS means, geometric LS mean ratios for Day 14/Day 1 and corresponding CI.

8.5.5 Sensitivity analysis

The primary efficacy variable is the change from baseline in trough FEV_1 at Day 15 (ie, after 14 days of treatment).

A sensitivity analysis will be performed computing the baseline for FEV_1 as the mean of the 2 measured values for the corresponding variable (2 measurements 45 min apart, at -1 hour and -15 min), prior to the morning IP administration on Day 1 of the first treatment period. If both are missing, the Visit 2 pre-bronchodilator value will be used instead.

This "modified" primary efficacy variable will be analysed by means of a mixed model; a random effects model with fixed effects for treatment, sequence, and period. The patient will be fitted as a random effect and the pre-dose FEV_1 of first period will be included as a covariate.

8.5.6 Exploratory analysis

Each question of the taste questionnaire will be analysed using descriptive statistics. In addition, the overall evaluation of taste will be compared among treatment groups using an analysis of variance (ANOVA) model for crossover designs adjusting for sequence, patient within sequence, period, and inhaler type as fixed effects factors. The difference in taste between devices (estimated by differences between LS means), the SE and 95% CI will be presented.

8.5.7 Analyses of safety variables

All analyses of safety and tolerability outcomes will be performed on the Safety population. Individual safety and tolerability data will be provided in data listings and summarised as appropriate by treatment. Continuous variables (laboratory parameters [including i-STAT], vital signs and ECG) will be summarised using descriptive statistics (n, mean, SD, minimum, median, and maximum) as appropriate by scheduled assessment time point. Where applicable, data will be summarised for the observed value, and for the corresponding change from baseline/Screening. Categorical variables will be summarised in frequency tables (counts and percentage). Change from baseline will be calculated as the differences between the post-dose value at each time point and the morning value prior to administration of the IP.

For all variables, 12-lead ECG parameters, vital signs and laboratory tests (including i-STAT), baseline values will be defined as the values obtained prior to the morning IP administration on Day 1 of Visit 3.

Any clinically relevant new physical examination findings or worsening of a pre-existing physical examination finding that were to be recorded as an AE will be presented with the AEs.

AEs: The number and percentage of patients who experienced 1 or more TEAEs, and the number of TEAE occurrences will be tabulated by treatment group. Adverse events occurring before administration of IP (ie, not treatment-emergent) and the number of occurrences will be reported in the same way as TEAEs. An AE will be considered a TEAE if it was not present prior to the date of the first dose of IP or was present prior to the date of the first dose of IP, but increased in severity after IP administration. A TEAE that occurs during a wash-out period will be associated to the last treatment taken. An AE that occurs more than 30 days after the last IP administration will not be counted as a TEAE. TEAEs tables will be tabulated by system organ class, preferred term, intensity, causality, action taken, outcome, seriousness criteria and treatment group using descriptive statistics.

12-lead ECG: Descriptive statistics will be produced at each schedule assessment time point for all quantitative ECG parameters (heart rate, PR, RR, QRS, QT, QTcB and QTcF intervals) for both observed absolute values and changes from baseline.

For the QT, QTcB and QTcF parameters, the normalised $AUC_{(0-4)}$, and $AUC_{(0-24)}$ will be calculated as the value of each AUC (computed using the trapezoidal rule) divided by its corresponding time (4, and 24 h, respectively) on Days 1 and Day 14 (no AUCs will be computed for Day 8). Heart rate and QT data will be analysed using mixed models for repeated measures. More details will be given in the SAP.

Electrocardiogram findings in rhythm, ectopy, conduction, morphology, myocardial infarction, ST segment, T wave, and U wave will be presented with counts and percentages by treatment.

Electrocardiogram findings will also be listed. A listing of AEs for patients with abnormal ECG findings will also be performed.

An analysis of potentially clinically significant ECG values on QT, QTcB, QTcF, QRS and PR interval, and heart rate will be performed. The number and percentage of patients with potentially clinically significant ECG values will be tabulated across time and treatment group. The criteria based on severity will be defined in the SAP.

Blood Pressure: SBP and DBP (mmHg) will be analysed at each scheduled assessment time point using descriptive statistics for both observed absolute values and changes from baseline.

Additionally, the number and percentage of patient with notable changes from pre-dose at each post-dose time point for SBP and DBP will be presented by treatment group. The criteria for notable changes in blood pressure will be detailed in the SAP.

Laboratory tests (including i-Stat): Observed absolute values and changes from baseline in haematology, serum biochemistry and urinalysis parameters, will be summarised by treatment group using descriptive statistics at each scheduled assessment time point.

Out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented.

Additionally, treatment-emergent abnormalities, defined as newly occurring or worsening as well as notable abnormalities in laboratory parameters will be summarised by means of shift contingency tables comparing the values (post-dose versus pre-dose Day1 and follow-up versus pre-dose Day 1). Newly occurring or worsening of abnormalities in laboratory parameters will be identified using the expanded normal ranges that will be specified in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

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

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

9.2 Monitoring of the study

During the study, a PAREXEL representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).

- Confirm that facilities remain acceptable.

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

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

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

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

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

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

The study is expected to start in Quarter 4, 2016 and to end by Quarter 2, 2017.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (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 AZD8871.

9.4 Data management by PAREXEL

Data management of the study will be performed by PAREXEL and supervised by Data Management at AstraZeneca.

The main data management activities and procedures will be described in the Data Management Plan (DMP), created by PAREXEL using the AstraZeneca Redacted template.

Database and Data Validation

DataLabs (an EDC system) will be used to collect and manage clinical data.

The Data Validation Specification (DVS) will contain details of consistency and structural checks to be run against the data as well as listings required for PAREXEL data cleaning and review. The DVS will be created by PAREXEL to meet Sponsor requirements and standards.

Automated edit checks with DataLabs are available once the data have been entered. Additional queries may also be identified during the study via further edit checks, listing review by PAREXEL personnel, data coding, etc.

Database, edit checks, listings (programmed for data review) and any programming implying data conversions will be appropriately validated by PAREXEL.

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

The data will be validated as defined in the DMP. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Clinical Coding

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO-Drug Enhanced plus Herbal Dictionary. Classification coding will be performed by PAREXEL.

Serious adverse event (SAE) reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Mapping

Data will be collected during the study execution and will be mapped into Study Data Tabulation Model (SDTM) datasets in an ongoing basis.

Transfers of SDTM datasets will be periodically received at Sponsor during the study and after database lock. Frequency of these transfers will be agreed between Sponsor and PAREXEL and documented within the DMP.

Management of external data

In addition to the eCRF data, PAREXEL will receive electronic records for external data processed by vendors (Covance for PK, and ERT for e-Diary, and local laboratory for safety laboratory tests). A reconciliation process will be performed by PAREXEL of eCRF data and against the rest of the data sources to ensure consistency of the common data.

Audit trail of all databases will be maintained in order to protect the authenticity and integrity of the clinical data.

When all data have been coded, validated, and electronically signed, the database will be locked. Any treatment revealing data (such as the treatment information and the PK data) will be added to the set of data to be transferred after the database has been locked and the populations' definition has been completed.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients.

The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

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

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

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

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

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

AstraZeneca will handle the distribution of any of these documents to the national Regulatory Authorities.

AstraZeneca will provide Regulatory Authorities, ECs and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the ECs with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4   Informed consent

The PI(s) at each centre will:

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

- Ensure each patient is notified that they are free to discontinue from the study at any time

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

- Ensure each patient provides signed and dated ICF before conducting any procedure specifically for the study

- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed ICF is given to the patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5   Changes to the protocol and Informed Consent Form

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

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

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

10.6   Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC 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 ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11.   LIST OF REFERENCES

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Wielders PL, Ludwig-Sengpiel A, Locantore N, Baggen S, Chan R, Riley JH. A new class of bronchodilator improves lung function in COPD: a trial with GSK961081. Eur Respir J. 2013; 42(4):972–81.

Appendix A   Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment

- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine

- Intensive treatment in an emergency room or at home for allergic bronchospasm

- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

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

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

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

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

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

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

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

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

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

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

Appendix B   International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

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

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

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

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

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

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

Appendix C   Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.3.7 of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) **together with** total bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3x ULN **together with** TBL ≥2xULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3xULN

- AST $\geq$3xULN

- TBL $\geq$2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met and will:

- Notify the AstraZeneca representative

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits. If the criteria are met, assess if the patient meets study-specific withdrawal criteria (Section 3.9).

- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the 3 Liver CRF forms as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

- Assess if the patient meets study-specific withdrawal criteria (Section 3.9).

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

   – The 'Medically Important' serious criterion should be used if no other serious criteria apply

   – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D   Breathlessness, Cough Sputum Scale

The BCSS was used in clinical trials as part of a patient daily diary card and is highlighted in bold below in this sample instruction page from the diary card.

PLEASE COMPLETE IN THE EVENING (Prior to going to bed)

PLEASE ENTER DAY, e.g. Mon, Tues, Wed

PLEASE RECORD THE DATE (Day/Month)

HOW MUCH DIFFICULTY DID YOU HAVE BREATHING TODAY?

0 = None – unaware of any difficulty

1 = Mild – noticeable during strenuous activity (e.g. running)

2 = Moderate – noticeable during light activity (e.g. bedmaking)

3 = Marked – noticeable when washing or dressing

4 = Severe – almost constant, present even when resting

HOW WAS YOUR COUGH TODAY?

0 = None – unaware of coughing

1 = Rare – cough now and then

2 = Occasional – less than hourly

3 = Frequent – one or more times an hour

4 = Almost constant – never free of cough or need to cough

HOW MUCH TROUBLE WAS YOUR SPUTUM TODAY?

0 = None – unaware of any difficulty

1 = Mild – rarely caused problem

2 = Moderate – noticeable as a problem

3 = Marked – caused a great deal of inconvenience

4 = Severe – an almost constant problem

Appendix E   Taste questionnaire

TASTE

ID: ☐☐   Age: ☐☐

Sex: ○ male   ○ female

TASTE vers 1.2 Eng. Used by permission
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102 (107)

Assessment date ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋
Yyyy-mm-dd

Assessment time ☐☐ : ☐☐

Below are questions about the taste of the medicine you received. Answer each question by ticking the box, please mark only one alternative.

Sweet

0	1	2	3	4	5	6	7	8	9	10

Not at all sweet — Extremely sweet

Salty

0	1	2	3	4	5	6	7	8	9	10

Not at all salt — Extremely salt

Sour

0	1	2	3	4	5	6	7	8	9	10

Not at all sour — Extremely sour

Bitter

0	1	2	3	4	5	6	7	8	9	10

Not at all bitter — Extremely bitter

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Metallic

0	1	2	3	4	5	6	7	8	9	10

Not at
all
metallic

Extremely
metallic

Hot/spicy

0	1	2	3	4	5	6	7	8	9	10

Not at all
hot/spicy

Extremely
hot/spicy

Overall, how would you rate the taste of this medicine?

0	1	2	3	4	5	6	7	8	9	10

I dislike it
extremely
much

I like it
extremely
much

Do you think this medicine smells?

Yes	No

If Yes, how does it smell?

0	1	2	3	4	5	6	7	8	9	10

Extremely
bad

Extremely
nice

Could you consider taking this medicine again?

0	1	2	3	4	5	6	7	8	9	10

Never –
under no
circumstances

Yes,
definitely

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Please add any additional comments you have regarding the taste/smell of this medicine.

_____

_____

_____

_____

_____

_____

_____

_____

_____

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Clinical Study Protocol Appendix E
Drug Substance AZD8871
Study Code D6640C00004
Version 3.0
Date 16 December 2016

TASTE_1

ID: ☐☐   Age: ☐☐

Sex: ○ male   ○ female

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106 (107)

Assessment time ☐☐ : ☐☐
HH　　MM

For how long did the taste of the medicine stay in your mouth?

Less than 1 minute	1 – 2 minutes	3 – 5 minutes	6 – 10 minutes	11 – 20 minutes	21 – 30 minutes	31 – 60 minutes	1 – 2 hours	More than 2 hours