Clinical Study Report Appendix 16.1.1

Drug Substance AZD8871

Study Code D6640C00006

Appendix 16.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Global Document Name	**Version No**	**Version Date**
First final version of the protocol prior to any amendments	1.0	29 May 2018
Amended CSP	2.0	13 Jun 2018
Amended CSP	3.0	13 Sep 2018
Amended CSP	4.0	11 Dec 2018
Local Document Name		
Country Name: United Kingdom	**Version No**	**Version Date**
First final version of the protocol prior to any amendments	1.0	08 Aug 2018

Clinical Study Protocol	
Drug Substance	AZD8871
Study Code	D6640C00006
Version	4.0
Date	11 December 2018

A Phase IIa, Randomised, Multi-centre, Double-blind, Placebo and Active-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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

EudraCT number: 2018-001722-25

VERSION HISTORY

Version 1.0, 29 May 2018
Initial creation
Version 2.0, 13 June 2018 Changes to the protocol are summarised below.
Removal of reversibility criterion for study eligibility as it is an unnecessary constraint for the conduct of this study. Reversibility testing will continue to take place but will not impact a patient's eligibility for entering the study. The screening failure rate has been revised downwards from 60% to 50% due to removal of the reversibility criterion for study eligibility; the number of patients to be screened is revised downwards from 180 to 145 patients. The ipratropium dose has been changed from 34 µg to 20 µg. The ECG parameters have been updated to remove QRS complexes.
Version 3.0, 13 September 2018 Changes to the protocol are summarised below. Added text is shown in italic font and deleted text is shown with strikethrough.
Version 3.0 implements changes requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the German Federal Institute for Drugs and Medical Devices (BfArM). **In response to MHRA feedback the following changes have been made:** Section 5.1: Inclusion criterion #12: Male patients should use a condom and spermicide *(or sexual abstinence*)* 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. In addition to a condom with spermicide, a second highly effective method of contraception (oral, intravaginal or transdermal hormonal contraceptives, intrauterine device, *or* intrauterine hormone-releasing system~~, or sexual abstinence~~ until 3 months after the last administration of the IP) should be used with female partners of childbearing potential. Double barrier methods (a combination of male condom with either a cap, diaphragm or sponge with spermicide) are not considered to be highly effective methods of contraception. Male patients with a pregnant partner should use a condom and spermicide *or sexual abstinence**. **True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods],*

declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

Section 6.3 Measures to minimise bias: randomisation and blinding:

The IVRS/IWRS will be programmed with blind-breaking instructions. ~~The blind may be broken if, in the opinion of the Investigator, it is in the patient's best interest for the Investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote available).~~ *In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator is asked to contact the Sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient.*

In response to BfArM feedback the following change has been made:

Section 5.2: Exclusion criteria:

12. Patient with a heart rate <50 or ~~>120~~ *>100* beats per minute (bpm).

13. Patient has clinically significant uncontrolled hypertension (~~>180~~ *>160* mmHg) as assessed by the Investigator.

Section 7.3: Withdrawal from the study

When 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~~. *Any patient that has been initiated on treatment and subsequently found not to meet all the eligibility criteria must stop the treatment and be excluded from the study.* The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

Version 4.0, 11 December 2018
Changes to the protocol are summarised below.

Heart Rate for pre-dose time points on visits 4, 7 and 10 will be taken from Vital Signs.

As per protocol there is no pre-dose ECG for visits 4, 7 and 10.

ECGs will be done as single measurements and not as triplicates.

8.2.4 Electrocardiogram: Triple 12-lead ECG will be obtained as specified in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures

PR, QRS, QT, and QTc intervals. Table 1 does not specify any triplicate ECG time points and therefore the section on triplicate ECG measurement is also irrelevant. Single measurement has been confirmed by sponsor.

ECGs and Vital signs will be measured after 5min rest in a supine position (as flat as possible and what is comfortable for the patient) to ensure consistency between measurements.

Use of supine position **(as flat as possible and what is comfortable for the patient)** for the ECG and vital signs. The same position should be used for all time-points.

Vital Signs will be done as single measurement and not as triplicates.

8.2.3 Vital signs: Vital signs will be measured in a supine position after 5 min rest and will include temperature, SBP and diastolic blood pressure (DBP). Three readings of BP will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the eCRF.

Clinical Stability Check will be done at Screening and before the start of each period.

This is to confirm that stability check will be done before the start of each treatment period.

Drugs of abuse and Alcohol

Screening results for Drugs of abuse and Alcohol will be used to determine Exclusion criterion #21 prior to randomisation due to the logistically accessibility of the results.

Cough Monitoring for Visits 5, 8 and 11 will start on Day 14, just before dosing at site, for 24hours recording

The recording for Visits 3, 6 and 9 are home recordings and will start at least 24 hours before the dosing and will finish pre-dose. Table 1, footnote r. Cough monitoring for Visits 5, 8, and 11 will start on Day 14, just before, for 24 hours recording.

Table 8: "Laboratory safety variables" in section 8.2.1

Clinical safety laboratory assessments of the protocol the following parameters were omitted in the table by error: aPTT=Activated partial thromboplastin time, INR=International normalised ratio; PTT=Partial thromboplastin time.

These parameters are only mentioned in the footnote but will be considered as part of the lab analysis in the table.

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.

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Table 1 Schedule of Assessments

	Screening		Treatment periods (Period 1-Period 3)									Follow-up or Discontinuation	Details in CSP section or Appendix
			Period 1			Period 2			Period 3				
Visit	**1[a]**	**2[a]**	**3[b,d]**	**4[c]**	**5[b]**	**6[b,d]**	**7[c]**	**8[b]**	**9[b,d]**	**10[c]**	**11[b]**	**42 days after Visit 11**	
Day	**-28 to -14**	**-28 to -14**	**1**	**8**	**14**	**1**	**8**	**14**	**1**	**8**	**14**	**(or last IP admin)**	
Informed consent	X												Section 5.1
Inclusion/exclusion criteria	X	X	X[e]										Section 5.1 and 5.2
Routine clinical procedures													
Demography	X												Section 5.1
Smoking history	X												Section 5.1
Physical examination[f]	X		X		X	X		X	X		X	X	Section 5.1
Medical/surgical history	X												Section 5.1
Vital signs (BP)[g]	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.3
Height	X												Section 8.2.2
Weight	X											X	Section 8.2.2
12-lead ECG[h]	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.4
Previous and concomitant medication	X	X	At every visit and may be conducted by phone if not tied to a visit										Section 6.5
Routine safety measurements													
Adverse events and COPD exacerbations	X	X	At every visit and may be conducted by phone if not tied to a visit									X	Section 8.3
Pregnancy test (urine)	X[w]		X			X			X			X	Section 5.1
Drugs of abuse and alcohol screen[i]	X		X			X			X				Section 5.1
Safety laboratory assessments (clinical chemistry, haematology and urinalysis)[j]	X		X		X	X		X	X		X	X	Section 8.2.1

Table 1 Schedule of Assessments

	Screening		Treatment periods (Period 1-Period 3)									Follow-up or Discontinuation	Details in CSP section or Appendix
			Period 1			Period 2			Period 3				
Visit	**1[a]**	**2[a]**	**3[b,d]**	**4[c]**	**5[b]**	**6[b,d]**	**7[c]**	**8[b]**	**9[b,d]**	**10[c]**	**11[b]**	**42 days after Visit 11**	
Day	**-28 to -14**	**-28 to -14**	**1**	**8**	**14**	**1**	**8**	**14**	**1**	**8**	**14**	**(or last IP admin)**	
i-STAT measurement [k]			X		X	X		X	X		X		Section 8.2.1
[redacted]													
[redacted]			[redacted]										[redacted]
Pharmacokinetic measurements [m]													
Pre-dose PK blood sample			X	X	X	X	X	X	X	X	X		Section 8.5
30 min post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
1 hour post-dose PK blood sample			X	X	X	X	X	X	X	X	X		Section 8.5
2 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
4 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
6 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
8 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
12 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
24 hours post-dose PK blood sample			X		X	X		X	X		X		Section 8.5
Efficacy measurements													
Reversibility testing [n]		X											Section 8.1.3
Clinical stability check	X		X			X			X				Section 8.1.2
FEV_1 stability check [o]						X			X				Section 8.1.2
Spirometry [p]		X	X	X	X	X	X	X	X	X	X		Section 8.1.1
BCSS questionnaire	X		X	X	X	X	X	X	X	X	X		Section 8.1.1

Table 1 Schedule of Assessments

	Screening		Treatment periods (Period 1-Period 3)									Follow-up or Discontinuation	Details in CSP section or Appendix
			Period 1			Period 2			Period 3				
Visit	**1[a]**	**2[a]**	**3[b,d]**	**4[c]**	**5[b]**	**6[b,d]**	**7[c]**	**8[b]**	**9[b,d]**	**10[c]**	**11[b]**	**42 days after Visit 11**	
Day	**-28 to -14**	**-28 to -14**	**1**	**8**	**14**	**1**	**8**	**14**	**1**	**8**	**14**	**(or last IP admin)**	
COPD assessment test (CAT)	X		X	X	X	X	X	X	X	X	X		Section 8.1.1
Cough VAS[q]			X	X	X	X	X	X	X	X	X		Section 8.1.1
Cough monitoring[r]			X		X	X		X	X		X		Section 8.1.1
Study treatment administration													
Ipratropium dispensed[s]	X				X			X			X		
Salbutamol dispensed	X		X	X	X	X	X	X	X	X	X		
Randomisation			X										Section 6.3
Inhaler training[t]			X			X			X				
Study treatment kit dispensed (daily dosing)[u]			X			X			X				
Dispense/Check e-Diary/paper diaries[v]	X		X	X	X	X	X	X	X	X	X		

AE=Adverse event; BCSS=Breathlessness, Cough, Sputum Scale; BP=Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; CSP=Clinical Study Protocol; ECG=Electrocardiogram; e-Diary= Electronic Diary; [redacted] FEV_1=Forced Expiratory Volume in 1 second; IP=Investigational Product; PK=Pharmacokinetics; [redacted].

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) Informed Consent Form (ICF) must be completed at Visit 1 before any study-specific assessments are performed.

(ii) Reversibility test with salbutamol and spirometry (to confirm inclusion criterion #6) 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 of 5 hours.

d. Interval between randomised treatment periods (wash-out period) will be 42 to 49 days (from the last IP administration).

e. Eligibility for study inclusion will be assessed from Screening Visit data for exclusion criterion #17.

f. Physical examination will be a complete examination at Screening and at the Follow-up Visit. Brief physical examinations will be performed pre-dose at Visits 3, 6, 9, and 24 hours post-dose at Visits 5, 8 and 11.

g. Vital signs: Blood pressure will be assessed pre-dose and 1, 2, 4, and 24 hours post-dose 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 at the Follow-up Visit. Heart rate will be assessed by ECG (except pre-dose on Visits 4, 7 and 10, which will be taken from Vital Signs).

h. 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 ECG measurements will be done at 1 and 4 hours post-dose. ECG should be performed before spirometry.

i. The alcohol screen may be performed using a urine sample or a breath test. Screening results for drugs of abuse will be used to determine exclusion criterion #21 prior to randomisation due to the logistically accessibility of the results.

j. 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.

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

[redacted]

m. PK blood samples will be collected from patients who will have specifically consented to the PK assessments at pre-dose and at 30 minutes (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.

n. Reversibility test includes a pre-salbutamol spirometry and then at 20-30 min post-salbutamol.

o. FEV_1 stability will be done at Visits 6 and 9 based on the pre-best test review (BTR).

p. Spirometry measurements will be done at -1 h and -15 min pre-dose and then 15 min, 30 min, 1, 2, 4, 8, 12, 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.

q. Cough VAS will be done pre-dose at Visits 3, 4, 6, 7, 9, and 10, and 24 hours post-dose at Visits 5, 8, and 11.

r. Cough monitoring will be done starting 24 hours prior to dosing on Visits 3, 6, and 9, and pre-dose at Visits 5, 8, and 11. The recording for Visits 3, 6 and 9 are home recordings and will start at least 24 hours before the dosing and will finish pre-dose. Cough monitoring for Visits 5, 8 and 11 will start on Day 14, just before dosing at site, and will finish 24 hours later. Patients may attend the site between visits to collect the cough monitor prior to the recording start.

s. All patients will receive ipratropium (20 µg × 2 puffs 4 times per day) during the run-in and wash-out periods. In addition, those patients that were taking any LAMA and/or LABA 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).

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

u. 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 of each treatment period - doses will be taken at home.

v. E-Diary will be used to collect daily BCSS and daily use of rescue medication (salbutamol 100 µg as needed) during the run-in and treatment periods. E-Diary will be used to collect CAT once at screening and daily during 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. Paper diary is also used to collect rescue medication intake during the wash-out phase.

w. Pregnancy results at Screening will be used to check the eligibility of the patient for participation in the study.

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).

1.2 Synopsis

International co-ordinating Investigators:

Protocol Title:

A Phase IIa, Randomised, Multi-centre, Double-blind, Placebo and Active-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

Rationale:

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 as an inhalation powder and delivered by dry powder inhaler (DPI).

Objectives and Endpoints

Primary objective:	Endpoint/variable:
To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD	**Primary** • Change from baseline in Trough FEV_1 on Day 15. **Secondary** • FEV_1 $AUC_{(0-4)/4h}$ (area under the curve for the change in FEV_1 from baseline to 4h, normalised by the time window) at Day 1, Day 8, and Day 14. • FEV_1 $AUC_{(0-8)/8h}$, $AUC_{(0-12)/12h}$, and $AUC_{(0-24)/24h}$ at Day 1 and Day 14. • 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. • Change from baseline in Peak FEV_1 over treatment duration. • 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, from Day 9 to Day 14 and during the whole treatment duration. • Change from baseline in CAT from Day 1 to Day 8, from Day 9 to Day 14 and during the whole treatment duration. • Rescue medication use from Day 1 to Day 8 and from Day 9 to Day 14.

Objectives and Endpoints

Secondary objective:	Endpoint/variable:
To investigate the PK of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD	On serial PK sampling days, the following PK parameters will be calculated for AZD8871 and its primary metabolite LAS191861 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:	**Endpoint/variable:**
To evaluate the safety and tolerability of inhaled AZD8871 600 µg in patients with moderate to severe COPD	• Adverse events (AEs)/Serious Adverse Events (SAEs). • Vital signs. • Electrocardiogram (ECG). • Clinical laboratory assessments.
Exploratory objective:	**Endpoint/variable:**
To evaluate patient's response to inhaled AZD8871 600 µg in patients with moderate to severe COPD	• COPD exacerbations. • Cough VAS. • Cough monitoring. • CCI

Overall design:

This is a randomised, placebo-controlled, double-blind, 3-way complete crossover William's design, international, multi-centre Phase IIa multiple dose study of 1 dose level of AZD8871, an active comparator (Anoro® Ellipta®) and placebo administered by DPI devices.

The study will be performed in adult male and non-childbearing female patients aged 40 to 85 years (both inclusive) with moderate to severe COPD as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2018) guidelines.

The study will be conducted at approximately 5 sites in Germany and the United Kingdom (UK). Estimated study duration is 12 months.

Treatment will be assigned via a computer generated randomisation schedule after the Screening period (at Visit 3).

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

Study Period:

Estimated date of first patient enrolled: Q3 2018

Estimated date of last patient completed: Q3 2019

Number of Patients:

Approximately 145 patients will be screened in order to randomise 72 patients into the study (previous studies estimate the screening failure rate to be approximately 50%). Screening failures are defined as patients who signed the informed consent form (ICF) to participate in the clinical trial but are not subsequently randomly assigned to study treatment. It is anticipated that 54 patients will be evaluable (study completers) assuming an approximate 25% dropout rate. A subset of 36 patients, who will have specifically consented for pharmacokinetics (PK), will undergo PK assessments.

Treatments and treatment duration:

The entire study period is scheduled to take from a minimum of 6.5 months (182 days) to a maximum of 7.5 months (217 days) for each individual patient.

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

Patients will be requested to stop their usual COPD therapy after signing the ICF at Visit 1 and will be maintained on a mono-component inhaled corticosteroid (ICS) therapy, if required. Patients that were taking any LAMA and/or LABA will be maintained with ipratropium (20 µg × 2 puffs 4 times per day) between Visit 1 and Visit 2. In addition, salbutamol 100 µg will be provided as rescue medication during the study as needed (rescue medication has to be discontinued 6 hours before 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 (to confirm inclusion criterion #6); this must be performed at Visit 2 due to wash-out requirements.

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

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 20 µg × 2 puffs 4 times per day (must be discontinued 8 hours prior to previous any pulmonary function test). A paper diary will be used to collect AEs and concomitant medication during run-in and wash-out periods.

Treatment periods: After the screening period, patients must fulfil all inclusion and none of the exclusion criteria prior to being randomised at Visit 3. Eligibility results will be used from the Screening period for any assessments that cannot be completed within Visit 3 (eg, laboratory assessments).

The duration of each treatment period will be 14 days. In each treatment period, patients will receive 1 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 600 µg once daily (double-blind).
- Anoro® Ellipta® (55 µg UMEC/ 22 µg VI) once daily (double-blind).
- Placebo (double-blind).

Each of the 3 treatment periods will include 2 overnight stays at the study site and 1 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 in each period) 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.

Study treatment 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 36 patients will undergo PK assessments. Blood samples will be collected pre-dose and up to 24 hours post-dose.

On Day 1 of treatment periods 2 and 3, a FEV_1 stability test will be performed pre-dose. FEV_1 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).

Study treatment administration compliance will be recorded in the e-Diary of the patient when the patient is not at the site. No dose modification is planned for this study.

Wash-out periods: Between each treatment period, there will be a wash-out period of 42 to 49 days. During this period, all patients will receive ipratropium 20 µg × 2 puffs 4 times per day (must be discontinued 8 hours before any pulmonary function test). A paper diary will be used to collect AEs and concomitant medication during run-in and wash-out periods.

Follow-up Visit: Patients will come to the site for a Follow-up Visit, 42 days (up to 49 days) after the last IP administration, for AE assessment, safety laboratory, ECG, vital signs and physical examination.

Statistical methods:

The analysis of all the efficacy variables will be performed on the Full Analysis Set (FAS) 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 36 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 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 efficacy variables: All continuous variables defined as change from baseline or observed values will be analysed using similar mixed models as for the primary efficacy variable adjusted for the corresponding baselines. Modifications compared to the primary analysis model to covariance structures and included covariates may be done as appropriate. 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 primary metabolite LAS191861 per day using appropriate descriptive statistics.

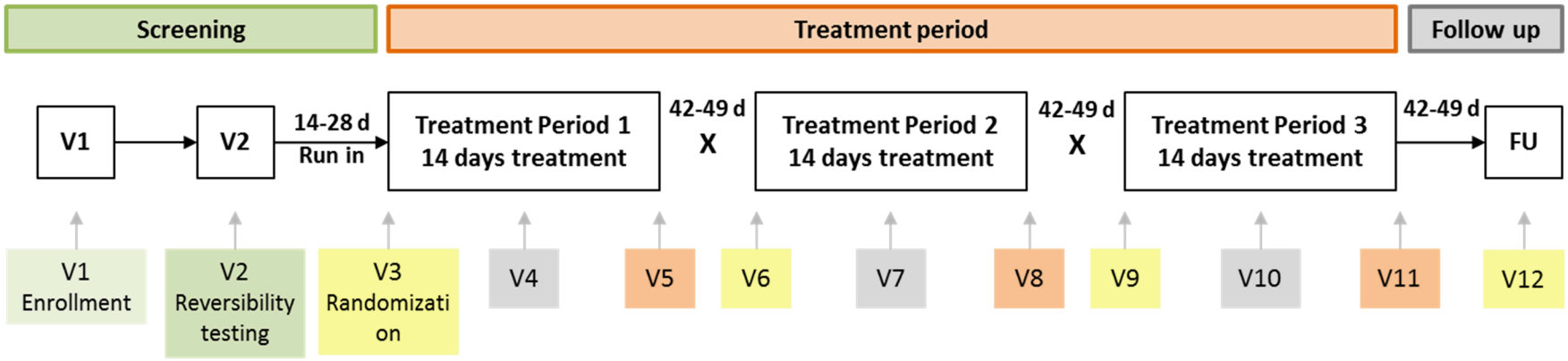
Safety analyses: Safety will be assessed by descriptive analysis of AEs, vital signs, ECGs and clinical laboratory assessments. Heart rate and QT data will be analysed using mixed models.

The study will be powered to demonstrate superiority of AZD8871 600 µg versus Anoro® Ellipta® for the primary efficacy endpoint. With a total of 54 patients, there is 90% power to detect a difference between AZD8871 and Anoro® Ellipta® treatments for the change from baseline to Trough FEV_1 at Day 15 equal to 100 mL, assuming a standard deviation (SD) of differences of 220 mL, 2-sided 5% significance level and a normal distribution.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



d: day; FU: Follow-up; V: Visit.

2. INTRODUCTION

2.1 Study rationale

AZD8871 is a new chemical entity, a muscarinic receptor antagonist and β_2 adrenoceptor agonist (MABA), with the combined properties of a LAMA and a LABA in a single molecule. AZD8871 is being developed as an inhaled long-acting bronchodilator for the maintenance treatment of COPD, formulated as an inhalation powder and delivered by DPI. 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.

The purpose of this study is to provide efficacy and safety data for AZD8871 in subjects with moderate to severe COPD. This study will determine the 24-hour efficacy (lung function) profile of AZD8871 600 µg relative to placebo DPI based on Trough FEV_1 following repeated dosing (2 weeks). Anoro® Ellipta® once daily is included as an active control.

2.2 Background

Chronic obstructive pulmonary disease is a significant cause of morbidity and mortality worldwide (Global Initiative for Chronic Obstructive Lung Disease [GOLD 2018]). It is a common, preventable and treatable disease characterised by persistent airflow limitations. 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 2018 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. This will also be evaluated by directly comparing AZD8871 to the best-in-class once daily LAMA and LABA fixed-dose combination, Anoro® Ellipta®. Out of 3 fixed-dose combination products available on the market for the treatment of COPD, Anoro® Ellipta® was shown to be the most effective and will serve as the benchmark for this study (Feldman et al, 2017).

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD8871 is provided in the Investigator's Brochure (IB).

2.3 Benefit/risk assessment

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 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.

Study D6640C00001 was a 2-part, randomised, placebo-controlled, safety, tolerability, pharmacokinetic and pharmacodynamic study of AZD8871 delivered by inhalation in asthmatic and COPD patients. In Part 1, single doses of AZD8871 from 50 up to 2100 µg were administered to asthma patients. Efficacy of the compound was apparent with Peak and

Trough FEV_1 ranging from 427-694 mL to 267-414 mL at doses of 200-2100 µg (respectively). AZD8871 was safe and well tolerated, no SAEs were reported during this part of the study; no AEs led to study discontinuation or met any of the stopping criteria.

In Part 2, single doses of AZD8871 of 400 and 1800 µg were administered to COPD patients in a randomised crossover design. The evaluation of FEV_1 showed that AZD8871 at 400 and 1800 µg induced bronchodilation in COPD patients with a quick onset and the effect was sustained up to 36 hours. Both doses of 400 and 1800 µg AZD8871 were observed to be safe and well tolerated, and no deaths were observed.

Study D6640C00003 reported data on multiple doses of 300, 600 and 900 µg in healthy subjects. Neither SAEs, nor AE leading to discontinuation were reported in this study. No clinically relevant laboratory or ECG results were reported. With the exception of heart rate, no dose response effects were seen in any of the other safety outcomes. This effect needs further exploration in future studies. Overall, multiple doses of AZD8871 administered to healthy male subjects in this study were well tolerated and no safety concerns were noted for any of the dosages investigated, and stopping criteria were not met.

Study D6640C00004 was 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 (100 and 600 µg) and placebo, administered using a DPI device once daily, for 2 weeks, in patients with moderate to severe COPD. A total of 42 patients were randomised; 31 completed all 3 treatments periods and the relevant follow up assessments. Both dose levels of AZD8871 had a positive, dose dependent effect on FEV_1 at Day 14-15 of treatment compared with placebo, with the highest effect observed for the AZD8871 600 µg dose level. Overall, AZD8871 was well tolerated in COPD patients and no safety concerns were raised in the study.

Study D6640C00005 was a Phase I, randomised, multiple ascending dose (MAD) study to investigate safety, tolerability and PK of AZD8871 in healthy male Japanese subjects. This study entailed 3 dose levels: 300 µg (cohort 1), 600 µg (cohort 2) and 900 µg (cohort 3). In this study, the administration schedule for AZD8871 or placebo was a single dose on Day 1, followed by once daily dosing from Day 5 to Day 16 (12 consecutive daily doses). Safety stopping criteria or pre-set exposure limits were not reached. Overall, single and multiple doses of AZD8871 administered to healthy male subjects in this study were well tolerated and no safety concerns were noted for any of the dosages investigated.

To limit the risks for the patients enrolled in this study D6640C00006 and who will be required to stop their usual COPD therapy and to assess IP efficacy, patients will be maintained on a mono-component ICS, if required. They will also be provided with salbutamol 100 µg to be used as rescue medication. In addition, patients that were taking any LAMA and/or LABA will be maintained with ipratropium between Visit 1 and Visit 2. All patients will receive ipratropium (20 µg × 2 puffs 4 times per day) during run-in and wash-out period to ensure stability of the patient.

Potential risks have been evaluated through review of the literature regarding β_2-agonists and muscarinic antagonists, AZD8871 non-clinical studies, and data from completed or ongoing

AZD8871 clinical studies. Relevant potential risks include cardiac effects (such as tachycardia, PR interval prolongation and 1st and 2nd degree atrio-ventricular blocks); other potential risks are metabolic effects (such as hyperglycemia and hypokalaemia) and hypersensitivity. No treatment-related serious or severe AEs have been reported in the completed or ongoing clinical studies. No clinically significant ECG abnormalities or laboratory abnormalities were observed to date in human trials. Thus, AZD8871 was well tolerated in firsts in human trials and its safety profile is acceptable for continuing further investigations.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of AZD8871 may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Table 2 Study objectives and endpoints

Primary Objective:	**Endpoint/Variable:**
To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD	**Primary** • Change from baseline in Trough FEV_1 on Day 15. **Secondary** • FEV_1 $AUC_{(0-4)/4h}$ (area under the curve for the change in FEV_1 from baseline to 4h, normalised by the time window) at Day 1, Day 8, and Day 14. • FEV_1 $AUC_{(0-8)/8h}$, $AUC_{(0-12)/12h}$, and $AUC_{(0-24)/24h}$ at Day 1 and Day 14. • 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. • Change from baseline in Peak FEV_1 over treatment duration. • Change from baseline in Total Score of BCSS questionnaire and cough, breathlessness and sputum individual domain scores from Day 1 to Day 8, from Day 9 to Day 14 and during the whole treatment duration. • Change from baseline in CAT from Day 1 to Day 8, from Day 9 to Day 14 and during the whole treatment duration. • Rescue medication use from Day 1 to Day 8 and from Day 9 to Day 14.
Secondary Objective:	**Endpoint/Variable:**
To investigate the PK of AZD8871 600 µg and its primary metabolite 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 primary metabolite LAS191861 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:	**Endpoint/Variable:**

To evaluate the safety and tolerability of inhaled AZD8871 600 µg in patients with moderate to severe COPD	• AEs/SAEs. • Vital signs. • ECG. • Clinical laboratory assessments.
Exploratory objective:	**Endpoint/variable:**
To evaluate patient's response to inhaled AZD8871 600 µg in patients with moderate to severe COPD	• COPD exacerbations. • Cough VAS. • Cough monitoring. • CCI

4. STUDY DESIGN

4.1 Overall design

This is a randomised, placebo-controlled, double-blind, 3-way complete crossover William's design, international, multi-centre Phase IIa multiple dose study of 1 dose level of AZD8871, an active comparator (Anoro® Ellipta®) and placebo administered by DPI devices. Approximately 72 eligible male and non-childbearing female patients with moderate to severe COPD before randomisation and fulfilling all of the eligibility criteria will be randomised in a 1:1:1:1:1:1 to 1 of 6 treatment sequences. The study includes 12 visits and the entire study period is scheduled to take from a minimum of 6.5 months (182 days) to a maximum of 7.5 months (217 days) for each individual patient. The aim is to ensure at least 54 patients complete the study.

A subset of 36 patients, who will have specifically consented for pharmacokinetics (PK), will undergo PK assessments.

The study will be conducted at approximately 5 sites in Germany and the UK. Estimated study duration is 12 months.

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

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

Patients will be requested to stop their usual COPD therapy after signing the ICF at Visit 1 and will be maintained on a mono-component ICS therapy, if required. Patients that were taking any LAMA will be maintained with ipratropium (20 µg × 2 puffs 4 times per day) between Visit 1 and Visit 2. In addition, salbutamol 100 µg will be provided as rescue medication during the study as needed (rescue medication has to be discontinued 6 hours before 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 (to confirm inclusion criterion #6); this must be performed at Visit 2 due to wash-out requirements.

If the FEV_1 predicted value is fulfilled according to inclusion criteria, the patient will be started on run-in period to assess clinical stability. If the FEV_1 predicted value is not met, pulmonary function tests could be rescheduled at the latest, up to Day -14.

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 20 µg × 2 puffs 4 times per day (must be discontinued 8 hours prior to previous any pulmonary function test). A paper diary will be used to collect AEs and concomitant medication during run-in and wash-out periods.

Treatment periods: After the screening period, patients must fulfil all inclusion criteria and no exclusion criteria prior to being randomised at Visit 3. Eligibility results will be used from the Screening period for any assessments that cannot be completed within Visit 3 (eg, laboratory assessments).

The duration of each treatment period will be 14 days. In each treatment period, patients will receive 1 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 600 µg once daily (double-blind).
- Anoro® Ellipta® (55 µg UMEC/ 22 µg VI) once daily (double-blind).
- Placebo (double-blind).

Each of the 3 treatment periods will include 2 overnight stays at the study site and 1 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 in each period) 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.

Study treatment 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 36 patients will undergo PK assessments. Blood samples will be collected pre-dose and up to 24 hours post-dose.

On Day 1 of treatment periods 2 and 3, a FEV_1 stability test will be performed pre-dose. FEV_1 stability check will be based on the pre-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).

Study treatment administration compliance will be recorded in the e-Diary of the patient when the patient is not at the site. No dose modification is planned for this study.

Wash-out periods: Between each treatment period, there will be a wash-out period of 42 to 49 days. During this period, all patients will receive ipratropium 20 µg × 2 puffs 4 times per day (must be discontinued 8 hours before any pulmonary function test).

A paper diary will be used to collect AEs and concomitant medication during run-in and wash-out periods.

Follow-up Visit: Patients will come to the site for a Follow-up Visit, 42 days (up to 49 days) after the last IP administration, for AE assessment, safety laboratory, ECG, vital signs and physical examination.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

The objective of the study is to assess the efficacy, safety and pharmacokinetics (PK) of AZD8871 600 µg after a 14-day treatment period 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. Based on the information of terminal elimination half-lives observed for AZD8871 and LAS191861 from previous clinical studies, the wash-out period proposed for this current study is a minimum of 42 days and up to 49 days in order to avoid any carry-over effect between periods.

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).

AZD8871 will be evaluated by directly comparing it against Anoro® Ellipta®; the best-in-class once daily LAMA and LABA fixed-dose combination (Feldman et al, 2017).

Since COPD patients present with multiple comorbidities, a placebo arm has been added to better characterise the safety profile of the product. The inclusion of a placebo treatment will enhance the interpretation of the difference in safety and efficacy outcomes between active arms. This is due to the limited available data for Anoro® Ellipta® in this specific COPD patient population and the endpoints that will be assessed.

4.3 Justification for dose

The proposed dose level of AZD8871 in this study is 600 µg of AZD8871 given by inhalation once daily during 14 days through a multi-dose DPI device. The dose has been selected based on the safety, tolerability, efficacy, and PK information generated in previous clinical studies. The study drug released in this study will differ to previous trials due to the addition of Magnesium Stearate – required in multi-dose device setting - and slight changes in production processes. It is estimated these changes will have limited impact to the clinical outcome.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Patients will be recruited from early phase clinical unit sites via internal databases and local advertisement. Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study treatment. Under no circumstances can there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign informed consent. "Randomised" patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Provision of signed and dated, written ICF prior to any study-specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

2. Patient must be 40 to 85 years of age (both inclusive) at the time of signing the ICF (Screening; Visit 1).

Type of patient and disease characteristics

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

4. 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)* number 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.

   – Patient smoking other tobacco types (including e-cigarettes) will not be allowed, unless he/she meets the cigarette criterion as well.

5. Patient with post-bronchodilator FEV_1/forced vital capacity (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.

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

7. 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 to Visit 11.

8. Patient must be able to read, speak and understand local language, and be willing to remain at the study centre as required per-protocol to complete all visit assessments.

Weight

9. Body mass index (BMI) <40 kg/m^2 at the time of Screening.

Sex

10. Male and/or females of non-childbearing potential who are not pregnant or lactating.

Reproduction

11. Female patients must be of non-childbearing potential defined as:

    – 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.

12. Male patients should use a condom and spermicide (or sexual abstinence*) 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. In addition to a condom with spermicide, a second highly effective method of contraception (oral, intravaginal or transdermal hormonal contraceptives, intrauterine device, or intrauterine hormone-releasing system until 3 months after the last administration of the IP) should be used with female partners of childbearing potential. Double barrier methods (a combination of male condom with either a cap, diaphragm or sponge with spermicide) are not considered to be highly effective methods of contraception. Male patients with a pregnant partner should use a condom and spermicide or sexual abstinence*.

*True abstinence: When this is in line with the preferred and usual lifestyle of the subject. (periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

5.2 Exclusion criteria

Medical conditions

1. Patient has significant diseases other than COPD, (ie, clinically relevant disease or condition or an abnormality in prior ECGs, medical history or physical examinations) 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 (eg, severe hepatic impairment).

2. Patient has alpha-1 antitrypsin deficiency as the cause of COPD (laboratory results will be used in combination with smoking and medical history).

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

4. 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).

5. 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.

6. Patient who had 2 or more exacerbations of COPD (moderate or severe in intensity) within the last year prior to Screening (see Section 7.1 for definition of exacerbation of COPD).

7. Patient has been hospitalised due to poorly controlled COPD within 3 months of the Screening period.

8. Patient has acute worsening of COPD that requires treatment with corticosteroids or antibiotics in the 6 week interval prior to or during the Screening period.

9. Patient has had lower respiratory tract infection(s) that required antibiotics within 6 weeks prior to the Screening period.

Cardiac disease:

10. Patient has 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 which has required changes in the pharmacological therapy or other intervention within 12 months prior to Screening (Visit 1), or newly diagnosed arrhythmia within the previous 3 months prior to Screening (Visit 1).
    - Second degree atrio-ventricular block.
    - Use of pacemaker.
    - Hospitalisation within 12 months prior to Screening (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".

11. Patient with a QT interval corrected using Fridericia's formula (QTcF) value >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).

12. Patient with a heart rate <50 or >100 beats per minute (bpm).

13. Patient has clinically significant uncontrolled hypertension (>160 mmHg) as assessed by the Investigator.

Neurological:

14. Patient has seizures or a history of seizures requiring anticonvulsants within 12 months prior to Screening.

15. 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/Urogenital:

16. Patient has a symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.

Other:

17. Any laboratory abnormality or suspicion of any clinically relevant disease or disorder (on history or examination), including uncontrolled diabetes or hypokalaemia (serum potassium <3.5 mmol/L), 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 (eg, severe hepatic impairment) or any other safety concerns in the opinion of the Investigator. Note: Potassium replacement and re-test is allowed once if serum potassium concentration was <3.5 mmol/L at Screening or prior to randomisation.

18. Patient has known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C infection.

19. 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.

20. Patient has known narrow-angle glaucoma.

21. 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: 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.

22. Patient has a history of hypersensitivity (including paradoxical bronchospasm) to β_2-agonists, muscarinic anticholinergics or lactose/milk protein. Lactose intolerance is not an exclusion criterion.

Prior/concomitant therapy

23. Patient has 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 3).

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

Prior/concurrent clinical study experience

25. Patient was treated with an 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.

26. Previous participation or prior screen failure in the present study.

Other exclusions

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

28. Patient has changed their smoking status (ie, restarted or stopped smoking) or initiation of a smoking cessation program within 6 weeks of Screening.

29. 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.

30. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements. Inability to comply with requirements includes having an e-Diary completion rate of <70% during the run-in period.

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

32. Vulnerable patients (who has been placed in an institution due to a regulatory or court order).

Procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Patients enrolled in the study should adhere to the following fasting conditions for 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 according to the study centre's standard practice during their entire stay at the study centre each treatment visit. Meals should not include any xanthine-containing compounds (ie, caffeine) or grapefruit-containing foods or beverages. No food intake will be allowed between meals.

2. On Day 1, Day 8, and Day 14 of each treatment period, 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 IP administration on Day 1 and Day 14. On Day 8 a fasted condition of 1 hour after IP administration should be

observed. During 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' stays at the study centre, standardised meals will be served according to the study centre's standard practice.

4. 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.

5. Patients must abstain from consuming any of the following:

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

5.3.2 Caffeine, alcohol, and tobacco

1. Patients must abstain from any of the following:

   - Alcohol from 72 hours before each visit to the study centre and during the entire stay 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 the entire stay at the study centre. Decaffeinated drinks will be acceptable to be consumed during the study.

5.3.3 Activity

1. Patients should avoid exposure to dust or polluted air for at least 1 hour before conducting any respiratory procedures.

2. Patients must abstain from strenuous physical activity, which is not within the patient's normal daily routine, from 72 hours before the Screening Visit until the Follow-up Visit at the end of the study.

5.3.4 Medication and other restrictions

1. 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.

2. 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.

3. Patients must abstain from any of the following:

   - Blood or plasma donation from Screening (Visit 1) 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 6.5.

5.4 Screen failures

Screening failures are defined as patients who signed the ICF to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals may be rescreened only if the patient has not failed any assessment but was not randomised within the screening window (28 days of their first assessment). Individuals who do not meet the eligibility criteria (despite the repeated tests) will be screen failed. Repetition of the entire Screening Visit is not allowed. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These patients should have the reason for study withdrawal recorded in the electronic Case Report Form (eCRF).

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to AZD8871, Anoro® Ellipta®, and placebo.

6.1 Treatments administered

6.1.1 Investigational products

Table 3 Study Treatments

	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Study treatment name:	AZD8871 (as saccharinate) inhalation powder in SD3FL DPI	Anoro® Ellipta® (umeclidinium [UMEC]/ vilanterol [VI])	Placebo to AZD8871 in SD3FL DPI	Placebo to Anoro® Ellipta®
Dosage formulation:	600 µg	Predispensed: UMEC 62.5 µg, VI (as trifenatate) 25 µg. Delivered dose: UMEC 55 µg, VI (as trifenatate) 22 µg.	N/A	N/A
Route of administration	Oral inhalation	Oral inhalation	Oral inhalation	Oral inhalation
Dosing instructions:	1 inhalation per day	1 inhalation per day	1 inhalation per day	1 inhalation per day
Packaging and labelling	Study treatment will be provided in individual patient kit labelled with study-specific label. Each kit will be labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement. Label text will be translated into local language. The planned dose of AZD8871, Anoro® Ellipta®, or placebo will be administered via multi-dose DPI device. Each DPI device will be packed in an aluminium pouch including desiccant. Further information will be provided in the Investigator drug manual. For training purposes, each patient will receive an empty DPI device for SD3FL (a variant of the commercially available Genuair® or Pressair® DPI) that will be used on Visit 3, 6 and 9, if considered necessary.			

DPI: Dry powder inhaler; UMEC: umeclidinium; VI: vilanterol

6.2 Preparation/handling/storage/accountability

Study treatment will be provided in individual patient kit labelled with study-specific label. All IP should be kept in a secure place under appropriate storage conditions. The label on the IP specifies the appropriate storage.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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 pouch labels and inhaler labels.

The manufacturing, labelling, packaging and release of AZD8871 and placebo to AZD8871 will be conducted following GMP by AstraZeneca. Batch numbers will be indicated in the Clinical Study Report (CSR).

Further guidance and information for the final disposition of unused study treatment are provided in the Investigator drug manual.

6.3 Measures to minimise bias: randomisation and blinding

PAREXEL will be responsible for generating the randomisation scheme through the AZRand programme. The randomisation schedule will describe the link between the randomly assigned sequences of 3 treatments to each randomisation number.

At Visit 3, approximately 72 patients will be randomly assigned to 1 of the 6 possible treatment sequences, according to a William's design for crossover studies and using a balanced 1:1:1:1:1:1 randomisation ratio. Thus, 12 patients will be assigned to each treatment sequence (Table 4). To ensure random allocation, each patient will be given the IP bearing the lowest available randomisation number at the site.

Table 4 Treatment sequences

		Treatment Period 1	Treatment Period 2	Treatment Period 3
Sequence A (n=12)	AZD8871	600 µg	Placebo	Placebo
	Anoro® Ellipta®	Placebo	55 µg / 22 µg	Placebo
Sequence B (n=12)	AZD8871	600 µg	Placebo	Placebo
	Anoro® Ellipta®	Placebo	Placebo	55 µg / 22 µg
Sequence C (n=12)	AZD8871	Placebo	600 µg	Placebo
	Anoro® Ellipta®	55 µg / 22 µg	Placebo	Placebo
Sequence D (n=12)	AZD8871	Placebo	Placebo	600 µg
	Anoro® Ellipta®	55 µg / 22 µg	Placebo	Placebo
Sequence E (n=12)	AZD8871	Placebo	600 µg	Placebo
	Anoro® Ellipta®	Placebo	Placebo	55 µg / 22 µg
Sequence F (n=12)	AZD8871	Placebo	Placebo	600 µg
	Anoro® Ellipta®	Placebo	55 µg / 22 µg	Placebo

The Investigator(s) will:

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

2. Assign each 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 eCRF.

3. Determine patient eligibility; see Section 5.

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

Randomisation codes will be assigned strictly sequentially as patients become eligible for randomisation. The randomisation numbers will be grouped in blocks at an overall level. The block size will not be communicated to the Investigators.

All patients will be centrally assigned to randomised study treatment using an interactive voice/web response system (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Randomisation data will be kept strictly confidential. The randomisation list will only be provided to AstraZeneca personnel responsible for study IP preparation and to Covance Bioanalytical group responsible for PK analyses.

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.

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

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

AZD8871 and Anoro® IPs will be provided in the SD3FL (a variant of the commercially available Genuair® or Pressair® DPI) and Ellipta® DPI devices, respectively. Placebos will be provided in both the SD3FL and Ellipta® DPI devices with the same external appearance and containing lactose monohydrate; the Ellipta® placebo DPI device will also contain Magnesium Stearate.

For each treatment period patients will be provided with one SD3FL DPI device and one Ellipta® DPI device for daily administration of one of the 3 following combinations: AZD8871-placebo, placebo-Anoro®, or placebo-placebo.

Supplies of salbutamol and ipratropium will be open-label.

The IVRS/IWRS will provide to the Investigator(s) or pharmacists the kit identification number to be allocated to the patient at the dispensing visit.

Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The randomisation 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 the patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomisation 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.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator is asked to contact the Sponsor prior to unblinding a patient's

treatment assignment unless this could delay emergency treatment of the patient. In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable. Study unblinding should not occur until database lock and all decisions on the evaluability of the data from each individual patient have been made and documented.

6.4 Treatment compliance

Investigators will record patients' IP intake in the eCRF during site visits. For IP use between visits, patients will be provided with an e-Diary to record their intake of the IP on a daily basis. Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.5 Concomitant therapy

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 will be maintained on a mono-component ICS therapy, if required. Ipratropium will be provided during run-in and wash-out periods but should be held at least 8 hours before Visits 3, 6 and 9 (before any pulmonary function test) and during all treatment periods. 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 until completion of the Follow-up Visit.

Table 5 and Table 6 summarise different possible treatments for COPD and other indications which are allowed and prohibited, respectively, with example of medication and applicable restrictions.

Table 5 Restricted medications

Medications:	Usage (including limits for duration permitted and special situations in which it's allowed):
Oral anti-histamines, intranasal corticosteroids and sympathomimetics and intranasal anticholinergics	Allowed but avoid for 24 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 the study duration. Avoid for 12 hours prior to any spirometry test
Rescue medication: Salbutamol 100 µg	Allowed but avoid for 6 hours prior to any spirometry test for the study
Ipratropium 20 µg × 2 puffs 4 times per day	Mandatory during run-in and wash-out periods but 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)

ICS=Inhaled corticosteroid.

Table 6 Prohibited medications

Drug Class	Restrictions
ANTICHOLINERGICS	
Oral or parenteral	Wash-out of 72 hours required before Visit 2
Inhaled short-acting, SAMAs	Wash-out of 8 hours required before Visit 2
Inhaled long-acting, LAMAs	Wash-out of 72 hours before Visit 2
B_2-ADRENERGIC AGONISTS	
Inhaled short-acting, SABAs (except Salbutamol rescue medication)	Wash-out of 6 hours before starting first pulmonary function test at each study visit
Inhaled long-acting, LABAs (BID or QD)	BID: Wash-out of 48 hours required before Visit 2 QD: Wash-out of 7 days required before Visit 2
Oral short-acting	Wash-out of 24 hours required before Visit 2
COMBINATIONS (INHALED)	
Inhaled long-acting LABA/LAMA combinations (BID or QD)	BID: Wash-out of 48 hours required before Visit 2 QD: Wash-out of 7 days required before Visit 2
LABA + ICS fixed-dose combinations	Stop combination at least 48 hours before Visit 2 and switch to ICS mono-component at Visit 1

Table 6 Prohibited medications

Drug Class	Restrictions
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	Patients with these medications should not be enrolled into the study
Mast cell stabilisers	Wash-out of 5 days required before Visit 2
Leukotriene modifiers	Wash-out of 48 hours required before Visit 2
Selective and non-selective β-blocking agents (oral or topical including eye drops)	Patients with these medication should not be enrolled into the study
Phosphodiesterase IV inhibitors	Wash-out of 4 weeks required before Visit 2
Anti-IgE and anti-IL-5 antibody therapies	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	Wash-out of 5 days required before Visit 2
Live attenuated vaccine	Wash-out of 30 days before screening
Inactivated vaccine	Wash-out of 7 days before screening or randomisation (Visit 3) 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; IgE=Immunoglobulin E; IL-5=Interleukin-5; LABA=Long-acting β_2-agonist; LAMA=Long-acting muscarinic antagonist; QD=Once a day; SABA=Short-acting β_2-agonist; SAMA=Short-acting muscarinic antagonist.

6.5.1 Background medication

The IP will not be given as an "add-on" to another medication or class of medication.

6.5.2 Other concomitant treatment

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

6.5.3 Rescue medication

The study site will supply salbutamol rescue medication (Table 7) that will be provided by the Sponsor or PAREXEL. Patients will be provided with an e-Diary to collect their daily use of rescue medication during the run-in and treatment periods.

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 6 hours before any pulmonary function test. The date and time of rescue medication administration as well as the dosage regimen of the rescue medication must be recorded.

Table 7 Rescue medication

Rescue drug:	Usage:
Salbutamol 100 µg	As needed but avoid for 6 hours prior to any spirometry test for the study

6.6 Dose modification

N/A.

6.7 Treatment after the end of the study

N/A.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Patients may be discontinued from IP in the following situations.

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event.
- Severe non-compliance with the Clinical Study Protocol.
- Failure to meet randomisation criteria: Violations of inclusion and/or exclusion criteria detected after randomisation. See Section 7.3 for patients not fulfilling inclusion/exclusion criteria but detected after randomisation.
- Lost to follow-up: See Section 7.2 for details.
- Pregnancy: In case of pregnancy the female patient will be immediately discontinued from study treatment.

- 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.
- Withdrawal of consent to the use of donated biological samples.

(a) Vital signs (any time after randomisation; the test must be repeated to confirm that withdrawal criterion has been met)

- Systolic blood pressure (SBP) increase of >40 mmHg from pre-dose at Day 1 of each treatment period AND SBP >180 mmHg at any time within the 12-hour interval after taking study treatment.

(b) Laboratory findings (any time after randomisation; the 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×the upper limit of normal (ULN).
  - Confirmed isolated total bilirubin (TBL) increase to >2×ULN.
  - Confirmed ALT or AST increase to >2×ULN concurrent with an increase in TBL to >1.5×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 study treatment.

(c) ECG (within 4 hours of post-IP dosing; the test must be repeated to confirm that withdrawal criterion has been met):

- Symptomatic bradycardia defined as heart rate <45 bpm or asymptomatic bradycardia defined as resting supine pulse <30 bpm while awake, persisting for at least 10 min.

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

- QTcF interval prolongation exceeding >500 ms during the treatment period OR >60 ms change from pre-dose at Day 1 of each treatment period (within 4 hours post-dose), persisting for at least 5 min.

(d) Lung function

- FEV_1 decrease by>20% from pre-dose at Day 1 of each treatment period (ie, before first dose of study treatment) on 2 consecutive spirometry assessments obtained at least 15 min apart AND with associated symptoms of dyspnoea at any time within the first 2-hour interval after taking study treatment.

(e) Moderate to severe COPD exacerbation

- 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 colour 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 hospitalisation or death.

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

  - Severe: Exacerbations that result in hospitalisation or death.

(f) 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.

See the SoA (Table 1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation

Temporary discontinuation will not be permitted in this study.

7.1.2 Rechallenge

N/A.

7.1.3 Procedures for discontinuation of study treatment

The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment, the e-Diary, and paper diary should be returned by the patient at their next on-site study visit or unscheduled visit. Patients permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

A patient that has discontinued study treatment, for any reason, does not need to complete all planned visits for this study, however, they must attend a discontinuation Follow-up Visit 42 days (up to 49 days) after the last IP administration.

7.2 Lost to follow-up

A patient will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by eg, repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study the patient should be considered to be lost to follow-up with unknown vital status at end of study and censored at latest follow-up contact.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time (IP **and** assessments) at his/her own request, without prejudice to further treatment.

If a patient withdraws from the study they must attend a discontinuation Follow-up Visit 42 days (up to 49 days) after the last IP administration.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up patients as medically indicated. The patient will return the e-Diary and paper diary.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all patients is crucial for the integrity of the study.

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment should be returned by the patient.

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomised or receive study IPs. 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.

When 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. Any patient that has been initiated on treatment and subsequently found not to meet all the eligibility criteria must stop the treatment and be excluded from the study. The AstraZeneca Study Physician must ensure all decisions are appropriately documented.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

The Investigator will ensure that data are recorded on the eCRF. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

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

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed at Visit 1 or Visit 2 and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will not exceed 375 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 1).

8.1.1 Clinical outcome assessments

Pulmonary function test (spirometry)

The pulmonary function test uses a spirometer that 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).

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

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 American Thoracic Society (ATS) and European Respiratory Society (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 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 judgment 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-step 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 and then allow the patient 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 min prior to the test and comfortable; tight clothing should be loosened to allow the thorax to move freely. Each manoeuvre comprises one "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 one 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.

Breathlessness, cough, and sputum scale

The BCSS (Leidy et al, 2003) questionnaire is a 3-item, patient-reported outcome (PRO) measure (see Appendix E). 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.

COPD Assessment Test

The CAT (Jones et al, 2009) is an 8-item self-administered PRO designed to assess the condition of the patient and the overall impact of COPD (see Appendix F). Studies have shown the CAT to have good repeatability and discriminative properties, suggesting that it is sensitive to treatment effects at a group level. On a daily basis, patients are asked to evaluate the impact of COPD on their wellbeing and daily life on a 6-point Likert scale ranging from 0 to 5, with higher scores indicating a higher impact of COPD. The CAT is expressed as a total score, which is a sum of the 8 questions, ranging from 0 to 40. Patients will be provided with an e-Diary to collect their assessment in the evening on a daily basis.

Cough VAS

The VAS is a simple and reproducible PRO tool for the assessment of cough intensity as it provides an easy and rapid estimation (see Appendix G). It is a 10-cm long line (oriented horizontally or vertically) on which patients indicated the intensity of cough by crossing the line at the point that corresponded to their cough severity. The beginning of the scale refers to no cough (0 cm) and the end refers to the most severe cough they could imagine (10 cm).

Cough monitoring

Cough monitoring will be performed using the VitaloJAK wearable vitalograph device. Patients will be monitored for 24 hours, starting 24 hours prior to dosing on Day 1 and starting at pre-dose on Day 14. The VitaloJAK records coughs via an air-coupled Electret Condenser Microphone capacitive Cough Sensor on a single channel. A second channel uses a microphone to sense audio data to provide a monitoring or supervisory channel in order to determine the validity of the data recorded from the Cough Sensor channel. Patients will be trained on how to use the device after all pulmonary function tests have been completed at Visit 2.

8.1.2 FEV_1 and clinical stability check

This is not an outcome measure. FEV_1 stability check will be performed at Visits 6 and 9 (Day 1 of treatment periods 2 and 3). 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 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 (up to a maximum of 3 times), 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 the criteria of COPD exacerbation (as per Investigator's clinical judgment).
- No ongoing SAEs.
- No relevant AEs that potentially modify the absorption, distribution, metabolism, and excretion of IP.

8.1.3 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. Both percentage and absolute improvement will be captured.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Clinical safety laboratory assessments

See Table 8 for the list of clinical safety laboratory tests to be performed and to the SoA (Table 1) for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA. The results of tests performed at Screening (Visit 1 or Visit 2) will be regarded as baseline data.

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 8.3.7. Additional safety samples may be collected if clinically indicated at the

discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology and urinalysis will be performed at a central laboratory. The central laboratory will provide the centre with the necessary material and instructions for the sampling. In exceptional circumstances and upon discussion with the Sponsor, local laboratory assessments may have to be undertaken to collect key information supporting an AE or SAE. Information will be collected in eCRF as appropriate.

Table 8 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
aPTT	S/P-Calcium, total
INR	S/P-Chloride
PTT	Alpha-1 antitrypsin
Urinalysis (standard dipstick as a minimum)	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	S/P- Bicarbonate
U-Ketones	S/P- Magnesium
U-Nitrites	

ALP=Alkaline phosphatase; ALT=Alanine transaminase; AST=Aspartate transaminase; BUN=Blood urea nitrogen; GGT=Gamma glutamyl transferase; LDH=Lactate dehydrogenase; MCH=Mean cell haemoglobin; MCHC=Mean corpuscular

haemoglobin concentration; MCV=Mean corpuscular volume; aPTT=Activated partial thromboplastin time; INR=International normalised ratio; PTT=Partial thromboplastin time.

NB. In case a patient shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' for further instructions.

The following laboratory tests will be performed only at the Screening Visit (Visit 1 or Visit 2) 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 #11): Serum/plasma FSH and LH.

See the SoA (Table 1) for the timing and frequency of i-STAT measurements.

Drugs of abuse and alcohol screen (Table 9) will be performed as specified in the SoA (Table 1). The alcohol screen may be performed using a urine sample or a breath test.

Table 9 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	

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.

8.2.2 Physical examinations

A complete physical examination will be performed at Screening (Visit 1 or Visit 2) and at the Follow-up Visit and include an assessment of the following: general appearance, respiratory,

cardiovascular, abdomen skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

A brief physical examination will be performed at other visits which include 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 Screening (Visit 1 or Visit 2) for calculation of BMI. Patients should be in light indoor clothes without shoes.

Physical examination will be performed as specified in the SoA (Table 1), Investigators should pay special attention to clinical signs related to previous serious illnesses; new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital signs

- Temperature and blood pressure will be assessed by national standard methods.
- Blood pressure measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure measurements should be preceded by at least 5 min of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a supine position (as flat as possible and what is comfortable for the patient) after 5 min rest. The same position should be used for all timepoints and will include temperature, SBP and diastolic blood pressure (DBP). Vital Signs will be done as single measurement and are to be recorded in the eCRF. Heart rate will be assessed by ECG (except pre-dose on Visits 4, 7 and 10, which will be taken from Vital Signs).

8.2.4 Electrocardiograms

ECGs will be done as single measurement and will be obtained as specified in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1 for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

Standard 12-lead ECG evaluations will be recorded after approximately 5 min 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 performed according to the recommendations of the supplier.

Individual ECG analysis will be performed locally 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).

The following ECG parameters will be recorded:

- Time and date of the ECG.
- Heart rate (beats per minute). Except pre-dose on Visits 4, 7 and 10, which will be taken from Vital Signs.
- RR interval: Duration in milliseconds between 2 R peaks of 2 consecutive measurements.
- 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:
  - QTcF interval: QT interval corrected using Fridericia's formula (QT[msec]/RR[sec]1/3).
- Sinus rhythm (yes/no).
- Overall evaluation (normal/abnormal).

At Screening (Visit 1 or Visit 2), 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 at screening.

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 8.3.7.

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.

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the patient (or, when appropriate, by a caregiver or surrogate).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from time of signature of ICF throughout the treatment period and including the follow-up period (42 to 49 days after last dose of IP).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up.

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 (until resolution of a short-duration SAE or until chronic treatment is established in the scenario of a long-lasting SAE), 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.

8.3.4 Adverse event data collection

'The following variables will be collect for each AE:

- AE (verbatim).
- The date and time when the AE started and stopped.
- Maximum intensity.
- Whether the AE is serious or not.
- Investigator causality rating against the IP(s) (yes or no).
- Action taken with regard to IP(s).
- 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 serious AE.
- Date Investigator became aware of serious AE.
- AE is serious due to.
- Date of hospitalisation.
- Date of discharge.
- Probable cause of death.
- Date of death.
- Autopsy performed.
- Causality assessment in relation to study procedure(s).
- Causality assessment to other medications.

8.3.5 Causality collection

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

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

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

8.3.6 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 site staff: '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.

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and physical examination should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (DUS), see Sections 8.3.9 and 8.3.10.

8.3.8 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 TBL ≥2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

8.3.9 Disease under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of COPD. Events which are unequivocally due to DUS should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.10 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. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease.

All COPD exacerbations (see Section 7.1 for definition of exacerbation of COPD) will be captured using a COPD exacerbation eCRF and will not be reported as AEs unless considered an SAE.

8.4 Safety reporting and medical management

8.4.1 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 Investigators 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. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the electronic data capture (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 staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

For further guidance on the definition of a SAE, see Appendix B.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study patient has received any study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 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 data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.2) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 3 months after the last administration of the IP.

In case of pregnancy of the patient's partner, 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. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 3 months after the last administration of the IP and as indicated by previous studies (pre-clinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.4.3 Overdose

For this study, any dose of AZD8871 greater than 600 µg within 1 day will be considered an overdose.

AstraZeneca recommends symptomatic treatment and monitoring of vital functions should be performed in the event of an overdose; according to routine clinical practice.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then 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 data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error 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 completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.5 Pharmacokinetics

PK parameters will be derived using non-compartmental methods.

Definitions for the PK parameters are:

- 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_{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.

Blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of AZD8871 and its primary metabolite LAS191861 as specified in the SoA (Table 1). Instructions for the collection and handling of biological samples will be provided by the Sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1 Derivation of the pharmacokinetic parameters

The PK analyses of the plasma concentration data for AZD8871 and its primary metabolite LAS191861 will be performed at Covance 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.

8.5.2 Determination of drug concentration

For placebo and active comparator treatments immediately following an AZD8871 treatment period, only Day 1 pre-dose samples will be analysed unless specified. For any other placebo and active comparator treatments, samples will not be analysed unless specified.

Samples for determination of AZD8871 and its primary metabolite LAS191861 concentrations in plasma will be analysed by Covance on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

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.

8.5.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation 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 pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

CCI [redacted]

8.9 Health economics

Health economic parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The main comparison for the primary efficacy variable and for the key secondary efficacy variables is the efficacy of AZD8871 600 µg versus Anoro® Ellipta®. Due to the exploratory nature of this study, no adjustments for multiple testing will be made.

9.2 Sample size determination

The study will be powered to demonstrate superiority of AZD8871 600 µg versus Anoro® Ellipta® for the primary efficacy endpoint. With a total of 54 patients, there is 90% power to detect a difference between AZD8871 and Anoro® Ellipta® treatments for the change from baseline to Trough FEV_1 at Day 15 equal to 100 mL, assuming a SD of differences of 220 mL, 2-sided 5% significance level and a normal distribution. Assuming an approximate 25% dropout, the total sample size will be approximately 72 (multiple of 6 sequences). From previous studies, the screening failure rate is estimated to be approximately 50%; therefore approximately 145 screened patients will be required to achieve the goal of approximately 72 randomised patients.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	The 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 population and analysed according to the intent to treat principle.
Pharmacokinetic (PK)	The PK population is defined as all randomised patients participating in the subset of PK patients, who took at least 1 dose of IP and have at least 1 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 IP 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 population. 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 population will be listed only, and presented in the individual figures of concentration-time plots.
Per-Protocol (PP)	The 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).
Safety Population	The safety population consists of all randomised patients who received at least 1 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.

9.4 Statistical analyses

Analyses will be performed by PAREXEL except the derivation of the PK parameters, which will be performed by Covance. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

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, 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 Portable Document Format 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.

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

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 population and/or other populations. 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.

9.4.1 Efficacy analyses

The analysis of all efficacy variables will be performed on the FAS population. In addition, the primary efficacy variable will also be analysed using the PP population, and on the FAS population with a model including covariates to capture potential carry-over effects.

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 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 1 of the values is missing, the available value will be used as Trough.

This variable will be analysed by means of a mixed 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 600 µg versus Anoro® Ellipta®.
- AZD8871 600 µg versus Placebo.

A treatment comparison for Anoro® Ellipta® versus placebo will also be explored.

A sensitivity analysis will be performed for the primary efficacy variable; 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 (change from first period baseline in trough FEV_1) 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.

Analyses of secondary variables:

All continuous variables defined as change from baseline or observed values will be analysed using similar mixed models as for the primary efficacy variable adjusted for the corresponding baselines. Modifications compared to the primary analysis model to covariance structures and included covariates may be done as appropriate.

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

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

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

9.4.2 Safety analyses

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

Safety will be assessed by descriptive analysis of AEs, vital signs, ECGs and clinical laboratory assessments.

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 treatment-emergent AEs (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 42 days after the last IP administration will not be counted as a TEAE. TEAE 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 hours, and 24 hours, respectively) on Day 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.

9.4.3 Pharmacokinetic analysis

Pharmacokinetic parameters will be analysed in the PK population on the subset of 36 patients who will have specifically consented to participation in the PK assessments.

PK analyses will be described in the finalised SAP before database lock.

Plasma concentrations and PK parameters will be listed and summarised for AZD8871 and its primary metabolite LAS191861 per day using appropriate descriptive statistics.

The PK analyses described herein will be included in the CSR. Any additional analysis, such as PK population analyses, will be presented separately from the CSR.

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 primary metabolite concentrations, and comments will be provided.

Plasma concentrations of AZD8871 will be summarised by 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 population.

For descriptive statistics for plasma concentrations that are BLQ 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 population 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 for Day 1 and Day 14 (where applicable) overlaid on the same plot.

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 primary metabolite LAS191861.

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

9.4.4 Exploratory analysis

A composite endpoint for exacerbations (moderate or severe) in COPD (COPDCompEx) will be derived and analysed. COPDCompEx combines exacerbations with events defined from patient daily diaries. The definitions for both types of events are as follows:

- Exacerbations: episodes leading to one or more of the following; hospitalisation, emergency room visit, treatment with oral corticosteroids, or treatment with antibiotics.

- Diary events: defined by threshold and slope criteria using the following diary variables: individual domains of the breathlessness, cough, and sputum scale and rescue medication use.

The analysis of this endpoint will primarily be time to first COPDCompEx event, but the events may also be analysed with models addressing event rates or time to recurrent event. More details on the derivation and analysis of this variable will be given in the SAP.

9.4.5 Methods for multiplicity control

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

9.5 Interim analyses

No interim analysis is planned for this study.

10. REFERENCES

Bateman et al, 2013
Bateman ED, Kornmann O, Ambery C, Norris V. Pharmacodynamics of GSK961081, a bi-functional molecule, in patients with COPD. Pulm Pharmacol Ther. 2013; 26(5):581–7.

Feldman et al, 2017
Feldman GJ, Sousa AR, Lipson DA, Tombs L, Barnes N, Riley JH, et al. Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study. Adv Ther. 2017; 34(11):2518-2533

GOLD 2018
Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease updated 2018. Available from http://www.goldcopd.org. Accessed on 27 March 2018.

Jones et al, 2009
Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. Eur Respir J. 2009; 34(3):648-54.

Miller et al, 2005
Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

Leidy et al, 2003
Leidy NK, Schmier JK, Jones MKC, Lloyd J, Rocchiccioli K. Evaluating symptoms in chronic obstructive pulmonary disease: validation of the Breathlessness, Cough and Sputum Scale. Resp Med. 2003; 97(Suppl. A): S59-S70.

Tashkin and Ferguson 2013
Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res. 2013; 14:49.

Wielders et al, 2013
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.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an independent ethics committee (IEC) by the Investigator and reviewed and approved by the IEC before the study is initiated.

Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC.
- Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

If a patients' partner becomes pregnant during the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Subjects" and provide information about the pregnancy accordingly.

Patients who are rescreened (only if the patient has not failed any assessment but was not randomised within the screening window) are required to re-sign the same ICF.

A 4 Data Protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

There will be no steering committee, data monitoring committees or scientific advisory committee as this is a study of a drug intended to provide short-term symptom relief.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the source data agreement and computerised data check list for electronic source data.

A 9 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or wash-out periods, even if no study treatment has been administered.

B 2 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, wash-out, follow-up), that fulfils 1 or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent 1 of the outcomes listed above.

B 3 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).

B 4 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.

B 5 Important Medical Event or Medical Treatment

Medical and scientific judgment 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 treatment to prevent 1 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 judgment 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.

B 6 Intensity Rating Scale:

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 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 Appendix B 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 Appendix B 2.

B 7 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.

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

- 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 recognised 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 judgment. 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 DUS has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- occurred.

- was identified and intercepted before the participant received the drug.
- did not occur, but circumstances were recognise that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion.
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature.
- Wrong participant received the medication (excluding IVRS/IWRS errors).
- Wrong drug administered to participant (excluding IVRS/IWRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to 1 of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s) eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AZ product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody of Biological Samples

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

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

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

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

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

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

C 3 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations 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, 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- 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 D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

1 INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (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 Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

2 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 IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

3 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 subject who meets any of the following identification criteria in isolation or in combination:

ALT ≥ 3xULN
AST ≥ 3xULN
TBL ≥ 2xULN

When a subject meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

4 FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician **This includes deciding which tests available in the Hy's law lab kit should be used**
  - Complete the three Liver CRF Modules as information becomes available

5 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.

As soon as possible 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 IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

Where 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 CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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 IMP:

- Send updated 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 15 calendar days 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:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring

causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- 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 still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

6 LABORATORY TESTS

The list below represents the standard, comprehensive list of follow-up tests which are recommended when using a central laboratory. For individual studies, the list may be reduced to a subset of tests after consultation with the Hepatic Safety Knowledge Group.

Some of the tests may also be considered for use with local laboratories that have respective testing capabilities. Any test results need to be recorded in the CRF.

Hy's Law lab kit for central laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgM and IgG anti-HCV HCV RNA IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron

	Ferritin Transferrin Transferrin saturation

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

Appendix E Breathlessness, Cough, Sputum Scale Questionnaire

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 F COPD Assessment Test

Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

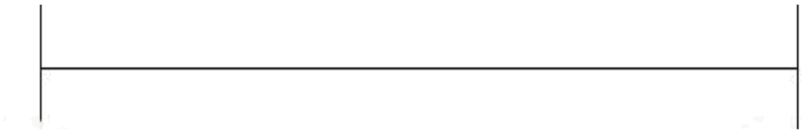
For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

Last Updated: February 24, 2012

Appendix G Cough Visual Analogue Scale



No cough Worse possible cough

Appendix H Abbreviations

Abbreviation or special term	Explanation
%Fluctuation	Fluctuation index during a dosing interval
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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
BP	Blood pressure
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
COPDCompEx	Composite endpoint for Exacerbations (moderate or severe) in COPD
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
CV%	Coefficient of variation
DBP	Diastolic blood pressure
DPI	Dry powder inhaler
DUS	Disease under study
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ERS	European Respiratory Society

Abbreviation or special term	Explanation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GMP	Good Manufacturing Practice
HBc	Hepatitis B core
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
IEC	Independent ethics committee IEC
IgM	Immunoglobulin antibodies
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally
IP	Investigational product
IVRS	Interactive voice response system
IWRS	Interactive web response system
LABA	long-acting β_2-agonist
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
µg	Microgram

Abbreviation or special term	Explanation
min	Minutes
NA	Not applicable
ND	Not determined
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-Protocol
PRO	Patient-reported outcome
QD	Once a day (quaque 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
SD	Standard deviation
SE	Standard error
SoA	Schedule of Activities
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach maximum plasma concentration
UK	United Kingdom
ULN	Upper limit of normal

SIGNATURE PAGE

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