Clinical Study Report Appendix 16.1.9

Drug Substance AZD8871

Study Code D6640C00006

Appendix 16.1.9
Documentation of Statistical Methods and Supporting Statistical Analysis

Statistical Analysis Plan Number	Date	Page Number
Statistical Analysis Plan, Version 2.0	08 Feb 2019	3
Data Review Meeting Report Minutes	29 Aug 2019	60

Files embedded in the Data Review Meeting Report Minutes are archived in the Trial Master File and available upon request.

Statistical Analysis Plan

Drug Substance	AZD8871
Study Code	D6640C00006
Date	08 February 2019

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

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Study Statistician PPD

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Global Product Statistician PPD

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PK Specialist

PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase, also named SGPT
AST	Aspartate aminotransferase, also named SGOT
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}24h)}$	Area under the plasma concentration-time curve from time zero to 24 hours post-dose
$AUC_{0\text{-}t/th}$	Area under curve from time zero to specified time t hours normalized by t hours
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BCSS	Breathlessness, Cough, Sputum Score
BDR	Blind data review
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
C_{avg}	Average plasma concentration during a dosing interval
C_{max}	Maximum plasma concentration
COPD	Chronic obstructive pulmonary disease
CV%	Coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
CCI	[redacted]
ENR	Expanded normal range
FAS	Full analysis set
FEV_1	Forced expiratory volume in 1 second

Abbreviation or special term	Explanation
%Fluc	Fluctuation index
FVC	Forced vital capacity
gCV(%)	Geometric coefficient of variation
GGT	Gamma glutamyl transferase
gmean	Geometric mean
gSD	Geometric standard deviation
ICF	Informed consent form
ICS	Inhaled Corticosteroids
IP	Investigational product
LABA	Long-Acting Beta2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
max	Maximum value
min	Minimum value
$MRAUC_{(0-24)}$	Metabolite to parent ratio for $AUC_{(0-24)}$
$MRAUC_{last}$	Metabolite to parent ratio for AUC_{last}
MRC_{max}	Metabolite to parent ratio for C_{max}
N	Total number of subjects
n	Total number of values
NA	Not applicable
NC	Not calculated
NQ	Not quantifiable
NR	Not reported
NS	No sample

Abbreviation or special term	Explanation
PCS	Potentially clinically significant
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PP	Per protocol analysis set
PR interval	Duration in milliseconds from the beginning of wave P to onset of ventricular depolarization (Q and R)
PT	Preferred term
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
QTcF interval	QT interval corrected, Fridericia formulae
Rac($AUC_{(0-24)}$)	Accumulation ratio for $AUC_{(0-24)}$
Rac(C_{max})	Accumulation ratio for C_{max}
REML	Restricted maximum likelihood
RR interval	Duration in milliseconds between two R peaks of two consecutive QRS complexes
SAE	Serious adverse event
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxalacetic transaminase, also named AST
SGPT	Serum glutamic pyruvic transaminase, also named ALT
SI	International system of units
SOC	System organ class
SS	Safety set
TEAE	Treatment-emergent adverse event
t_{last}	Time to reach last quantifiable plasma concentration
t_{max}	Time to reach maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
25 Jan 2019	Text updated as per Protocol Amendment 4 Values for the CompEx algorithm corrected

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary and secondary objective

Primary objective:	Endpoints:
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. • FEV1 $AUC_{(0-8)/8h}$, $AUC_{(0-12)/12h}$, 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.

Secondary objective:	Endpoints:
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}), time to reach last quantifiable plasma concentration (t_{last}), 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}, tlast, AUC_{last}, $AUC_{(0-24)}$, average plasma concentration during a dosing interval (Cavg,), fluctuation index during a dosing interval (%Fluc), 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 (e.g. metabolite to parent ratios).

1.1.2 Safety objectives

Safety objectives:	Endpoints:
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.

1.1.3 Exploratory objectives

Exploratory objectives:	Endpoints:
To evaluate patient's response to inhaled AZD8871 600 µg in patients with moderate to severe COPD	• COPD exacerbations. • Cough VAS. • Cough monitoring. • CCI

1.2 Study 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 using a DPI device once daily, for 2 weeks, in patients with moderate to severe COPD. This multi-centre study will be conducted at approximately 5 sites in Germany and United Kingdom (UK). It is planned that approximately 72 men and non-childbearing female aged 40 to 85 years (both inclusive) with moderate to severe COPD will be randomised in a 1:1:1:1:1:1 ratio to 1 of 6 treatment sequences. A subset of 36 patients, who will have specifically consented for pharmacokinetics (PK), will also undergo PK assessments. 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.

Screening period: This will last up to 28 days and consists of a Screening Visit (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 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). The study will consist of a Screening period, 3 treatment periods (each separated by a wash-out period), and a Follow-up Visit.

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: This must be performed at Visit 2 due to wash-out requirements.

Only patients who fulfil FEV_1 predicted values (FEV_1 ≥40% and <80% from predicted normal value and FEV_1/forced vital capacity (FVC) ratio <70%) postsalbutamol at Visit 2, will be started on the run-in period to assess clinical stability.

If the FEV_1 predicted values is not met, pulmonary function tests may be repeated 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 x 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 medications 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. During the treatment periods, patients will receive all 3 possible treatments, with every patient receiving placebo in one of the periods in addition to their ICS mono-component therapy, if any. In each period, patients will receive two devices to ensure the double blindness of the study. Patients will receive one of the 3 following possible treatments in any given period, in a randomised manner:

- AZD8871 600 µg once daily
- Anoro® Ellipta® (55µg UMEC/ 22 µg VI) once daily
- Placebo once daily

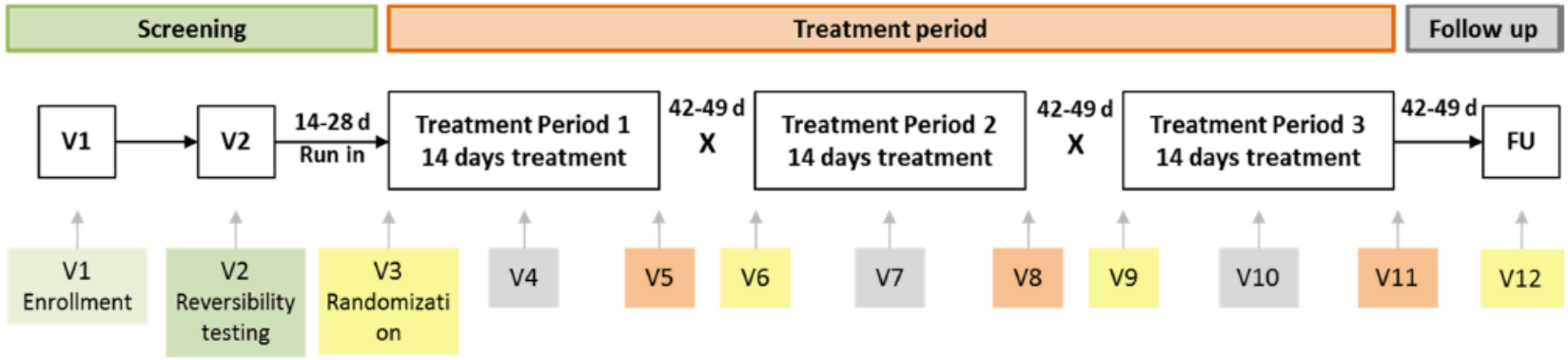
Each of the 3 treatment periods will last for 14 days and will include 2 overnight stays at the study site and one ambulatory visit at the study site.

Each 14-day treatment period (except the last one) will be followed by a wash-out period of 42 to 49 days, during which patients will receive ipratropium 20 µg x 2 puffs 4 times per day (must be discontinued 8 hours before any pulmonary function test), in addition to their usual ICS therapy, if any.

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

There will be a Follow-up Visit scheduled to take place 42 up to 49 days after last administration of the IP.

Figure 1 Study flow chart



d=day; FU=follow-up; V=visit.
During treatment periods 1 to 3, each patient will randomly receive one of the 3 possible treatments (AZD8871 600 µg, Anoro® Ellipta® or placebo).

1.3 Number of patients

The study was 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 FEV1 at Day 15 equal to 100 mL, assuming a SD of 220 mL, 2-sided 5% significance level and a normal distribution. Assuming an approximate 25% dropout, the total sample size required is 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.

No adjustment of the Type I error for multiple comparisons will be made in the study due to the exploratory nature of the study.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

The Full Analysis Set (FAS) 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 are included up to the date of their study termination. All efficacy analyses are based on the FAS and analysed according to the intent to treat principle.

2.1.2 Safety analysis set

The Safety Analysis Set (SS) consists of all randomised patients who receive at least one dose of IP. For summaries based on the SS, patients are included for a treatment only if they received at least one dose of that treatment (e.g. a patient who discontinues prior to taking the study treatment for period 2 will not be included in the safety set for that treatment).

The SS will be used for all summaries of safety data, and patients will be analysed according to the randomised treatment assignment for a given study period. Any important deviations from the randomised treatment assignment and any patients who received IP without being randomised for a given study period will be listed and considered when interpreting the safety data. Relevant safety summaries presented by actual treatment received will be considered if there are a considerable number of patients receiving another treatment than the one they were randomised to.

2.1.3 Pharmacokinetic analysis set

The Pharmacokinetic (PK) Analysis Set (PKS) will consist of all patients participaiting in the subset of the PK patients, who received at least 1 dose of AZD8871 and have at least 1 of the

parameters C_{max}, $AUC_{(0-24)}$ or AUC_{last} evaluable for AZD8871 and are assumed not to be affected by factors such as protocol deviations (e.g., prohibited concomitant medications which are thought to impact on the PK data, or incorrect study medication received).

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to the PK analysis sets. The exclusion of any patients or time-points from the calculation of the PK parameters and/or from the PK summary statistics will be agreed at the blinded data review meeting and it will be documented by the PK Scientist including the reason(s) for exclusion. The available concentration data and PK parameter data for any patients excluded from the PK analysis set for a given study period will be listed only. Concentration data for patients excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

2.1.4 Per-Protocol Analysis Set

The Per-Protocol Analysis Set (P-PS) 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).

2.2 Violations and deviations

Only important protocol deviations that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, efficacy, safety, or well-being will be summarised and listed.

Important protocol deviations include:

- Key eligibility criteria not fulfilled but patient randomised
- Disallowed concomitant medication taken during the study
- Developed discontinuation criteria but not withdrawn from study or discontinued investigational product, as appropriate
- Received incorrect study drug

A sensitivity analysis based on the P-PS will be conducted for internal validity purposes, whereby patients with important deviations from protocol deemed to affect efficacy will be excluded from the analysis.

Table 1 shows the protocol deviations which will lead to exclusion from P-PS, PKS, SS, or FAS. During the blind data review (BDR) the final list of the important protocol deviations affecting efficacy will be finalyzed and documented prior to unblinding of the study data.

Table 1 Major protocol deviations and population classification

		Excluded from analysis set			
Item #	**Event description**	**P-PS**	**SS**	**PKS**	**FAS**
1.	Provision of informed consent not performed before any study specific procedures.	Yes	No	No	No
2.	ICF source document not available at site, or any issue with the ICF document.	Yes	No	No	No
3.	Subject must be able to read, speak and understand local language.	Yes	No	No	No
4.	Female Patient has childbearing potential	Yes	No	No	No
5.	Male patient did not prevent pregnancy and drug exposure of a partner.	Yes	No	No	No
6.	Patient has alpha-1 antitrypsin deficiency as the cause of COPD (laboratory results will be used in combination with smoking and medical history).	Yes	No	No	No
7.	Patient is less than 40 or more than 85 years of age	Yes	No	No	No
8.	Patient has no established clinical history of moderate to severe COPD for more than 1 year at Screening	Yes	No	No	No
9.	Patient is not current or former smoker with a history of ≥10 pack-years of cigarette smoking and/or not smoking other types of tobacco (including e-cigarettes).	Yes	No	No	No
10	Patient has post-bronchodilator FEV_1/FVC ratio is >=70% based on the value reached after inhalation of salbutamol (400 µg) at Visit 2	Yes	No	No	No
11	Patient with post-bronchodilator FEV_1 <40% or > =80% predicted normal value at Visit 2.	Yes	No	No	No
12	Patient with body mass index (BMI) >=40 kg/m^2 at the time of Screening	Yes	No	No	No
13	Patient has a clinically significant disease, other than COPD, that may impact study outcome, as determined by medical history, physical examination, laboratory testing, and 12-lead ECG findings, at Screening.	Yes	No	No	No
14	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.	Yes	No	No	No
15	Patient has undergone lung volume reduction surgery, lung transplantation, lobectomy, or bronchoscopic lung volume reduction within 1 year of Screening.	Yes	No	No	No
16	Patient is using nocturnal positive pressure	Yes	No	No	No
17	Patient has been hospitalised due to poorly controlled COPD within 3 months of Screening.	Yes	No	No	No
18	Patient has acute worsening of COPD that required antibiotics or corticosteroids in the 6-week interval prior to Screening (Visit 1), or during the Screening Period (between Visits 1 and 2).	Yes	No	No	No
19	Patient has lower respiratory tract infections that required antibiotics within 6 weeks prior to Screening.	Yes	No	No	No
20	Patient has changed their smoking status (ie, restart or stop smoking) or initiation of a smoking cessation program within 6 weeks of Screening.	Yes	No	No	No
21	Subject with significant cardiovascular disease that may be vulnerable to cardiovascular instability.	Yes	No	No	No
22	Patient with QT interval corrected using Fridericia's formula (QTcF) value at Screening >450 ms for male and >470 ms for female or an ECG that is not suitable for QT measurements (eg, poorly defined termination of the T wave).	Yes	No	No	No
23	Patient with heart rate <50 or >100 bpm at Screening.	Yes	No	No	No
24	Patient has clinically significant uncontrolled hypertension as assessed by the investigator.	Yes	No	No	No
25	Patient with seizures or history of seizures requiring anticonvulsants within 12 months prior to Screening.	Yes	No	No	No
26	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.	Yes	No	No	No

		Excluded from analysis set			
Item #	**Event description**	**P-PS**	**SS**	**PKS**	**FAS**
27	Patient with symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.	Yes	No	No	No
28	Patient has a serum potassium value <3.5 mmol/L at Screening and on repeat testing, uncontrolled diabetes and any clinically relevant lab abnormality. Note: however potassium replacement and rescreening is allowed once if serum potassium concentration was <3.5 mmol/L at Screening.	Yes	No	No	No
29	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.	Yes	No	No	No
30	Patient has known narrow-angle glaucoma.	Yes	No	No	No
31	Patient has a history of hypersensitivity to β_2-agonists, muscarinic anticholinergics or lactose/milk protein. Lactose intolerance is not an exclusion criterion.	Yes	No	No	No
32	The patient has a history of drug of abuse within the past 2 years or consuming more than 14 (female patients) or 21 (male patients) units of alcohol a week, or shows positive for drugs of abuse and alcohol tests at Screening and/or prior to randomisation.	Yes	No	No	No
33	Patient received a live attenuated vaccination within 30 days prior to Screening.	Yes	No	No	No
34	Patient donated or lost >500 mL of blood and plasma within the previous 3 months prior to Screening	Yes	No	No	No
35	Vulnerable patients (who has been placed in an institution due to a regulatory or court order)	Yes	No	No	No
36	Patient is unlikely to co-operate with the requirements of the study, instructions of the Principal Investigator (PI), or have e-dairy completion rate of <70% during the run-in period..	Yes	No	No	No
37	Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).	Yes	No	No	No
38	Patient previously enrolled in the present study	Yes	Yes	Yes	Yes
39	Patient has participate 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.	Yes	No	Yes	Yes
40	Patient non-compliance with study procedures, unable to change current COPD therapy as required by the protocol and not willing to use ipratropium following the approved dosge and regimen – as judged by the investigator.	Yes	No	Yes	Yes
41	Patient is unwilling to remain at the study centre as required per protocol to complete all visit assessments.	Yes^{+++}	No	Yes^{+++}	No
42	Participation in another clinical study with investigational drug or device within the last 30 days or 5 half-lives (whichever is longer) prior to Screening.	Yes^{+++}	No	Yes^{+++}	No
43	Patient with known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C infection.	Yes	No	No	No
44	Patient did not fulfill fasting requirements on Day 1, 8, and 14 before IP administration and following dose administration.	Yes^{++}	No	No	No
45	Salbutamol not withheld at least 6 hours prior to any spirometry test for the study.	Yes	No	No	No
46	Ipratropium not withheld at least 8 hours before visits 3, 6, and 9 and during all treatment periods.	Yes	No	No	No
47	Patient could not abstain from list in protocol section 5.3	Yes	No	No	No
48	Patient who had 2 or more exacerbations of COPD within the last year prior to Screening	Yes	No	No	No
49	Patient unable to abstain from protocol-defined prohibited medications during the study, in the opinion of the investigator.	Yes^{++}	No	Yes^{++}	No
50	Patient is screening failure, but received study drug.	Yes	Yes	Yes	Yes
51	Incorrect study medication received.	Yes^{++}	No	Yes^{++}	No

		Excluded from analysis set			
Item #	**Event description**	**P-PS**	**SS**	**PKS**	**FAS**
52	Incorrect dose of study medication received.	Yes++	No	Yes++	No
53	Patient did not take any IP	Yes++	Yes	Yes++	Yes++
54	IP not taken at the study site at 9:00 AM±2 hours on Day 1 (Visits 3, 6 and 9).	Yes++	No	Yes+++	No
55	IP not taken within ±1 hours of dosing time of Day 1 and between 7 AM and 11AM on subsequent days of each treatment period.	Yes++	No	Yes+++	No
56	Patient has taken any of the restricted medications on a different regim than the described in the protocol (Table 5, section 6.5).	Yes++	No	Yes+++	No
57	Procedure not performed (missing PK samples to prevent calculation of PK parameters).	No	No	Yes++	No
58	Study assessments (For example cough monitoring, spirometry, CCI i-Stat, 12 Lead ECG and/or vital signs) are not performed at the scheduled timepoints.	No	No	No	No
59	Missing baseline data for the spirometry (FEV1 main variable)	Yes++	No	No	No
60	FEV1 and FVC measurements performed outside tolerance window	No	No	No	No
61	Fulfilling withdrawal criteria during the study but not withdrawn.	Yes	No	No	No
62	Fatal or life-threatening AE was not reported to the appropriate AstraZeneca representatives within 1 calendar day of initial receipt.	No	No	No	No
63	Non-fatal, and non-life-threatening SAE was not reported to the appropriate AstraZeneca representatives within 5 calendar days of initial receipt.	No	No	No	No
64	Date of Screening Visit 1 is after date of Screening Visit 2.	No	No	No	No
65	Visit date is after the Completed date.	No	No	No	No
66	Any of the study visits not performed within the allowed time as per protocol.	No	No	No	No
67	Other protocol deviations	Yes+++	No	Yes+++	No

++Excluded from the specific timepoint or period only. +++ To be confirmed at the DRM; timepoint specific, global P-PS/PKS exclusion or no exclusion.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

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. If one of the values is missing, the available value will be used as baseline.

All baseline values for efficacy analysis will be the pre-dose values of each treatment period except for the Total BCSS questionnaire score, where the last 14 days of the run-in period baseline will be used for all treatments in each sequence.

The baseline for daily rescue medication use will be the daily average of puffs recorded in the e-Diary during the last 14 days of the run-in period; this baseline will be used as baseline for all treatment periods.

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

The cough VAS measurement done at pre-dose on Day 1 of each treatment period will be used as a baseline. For cough monitoring, the assessment done starting 24 hours prior to dosing on Day 1 will be regarded as a baseline of each treatment period.

For COPD assessments (CAT), baseline is defined as the value obtained at Screening (Visit 1 or Visit 2).

3.1.1 Handling of missing or partial dates

For date of COPD diagnosis, partial dates will be imputed as follows.

- For dates with missing day and month (year is present), January 1 will be assigned to the missing fields.
- For dates with missing day only (month and year are present), the first day of the month will be assigned to the missing day.

For date of most recent COPD exacerbation, partial dates will be imputed as follows.

- For dates with missing day and month (year is present), December 31 will be assigned to the missing fields provided it does not result in a date post screening visit, in which case last day of month preceding month of screening visit will be used.
- For dates with missing day only (month and year are present), the last day of the month will be assigned to the missing day.

3.1.1.1 Imputation for concomitant medication start and stop dates

For prior or concomitant medications, including relief medications, incomplete (ie, partial or completely missing) start dates and/or stop dates will be imputed.

When the start date and the stop date are both incomplete for a patient, impute the start date first.

Incomplete start date

The following rules will be applied to impute the missing numerical fields. In addition, if the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date. If the stop date is present and implies that the medication is concomitant (ie, stop date is on or after the date of first dose of IP in the study), but the start date is completely missing, then the start date of the medication will be imputed with the date of first dose of IP.

For start dates with missing day and month (year is present):

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP in the study, then the day and month of the date of the first dose will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the date of the first dose of IP in the study, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of IP in the study, then January 1 will be assigned to the missing fields.

For start dates with missing month only (day and year are present):

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

For start dates with missing day only (month and year are present):

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of IP, then the day of the date of the first dose of IP will be assigned to the missing day;
- If either the year of the incomplete start date is before the year of the date of the first dose of IP or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day;
- If either the year of the incomplete start date is after the year of the date of the first dose of IP or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

Incomplete stop date

The following rules will be applied to impute the missing numerical fields. If the stop date is completely missing, replace it with the last dose date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

For stop dates with missing day and month (year is present):

- If the year of the incomplete stop date is the same as the year of the date of the last dose of IP, then the day and month of the date of the last dose will be assigned to the missing fields.
- If the year of the incomplete stop date is prior to the year of the date of the last dose of IP, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of IP, then January 1 will be assigned to the missing fields.

For stop dates with missing month only (day and year are present):

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

For stop dates with missing day only (month and year are present):

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of IP, then the day of the date of the last dose will be assigned to the missing day.
- If either the year of the incomplete stop date is before the year of the date of the last dose of IP or if both years are the same but the month is before the month of the date of the last dose of IP, then the last day of the month will be assigned to the missing day.
- If either the year of the incomplete stop date is after the year of the date of the last dose of IP or if both years are the same but the month is after the month of the date of the last dose of IP, then the first day of the month will be assigned to the missing day.

Incomplete time in start or stop date

Note that when dates are recorded using time (from 00:00 until 23:59) and if time is missing in a start date record, time = 00:01 will be assigned; if time is missing in a stop date record, then time = 23:59 will be assigned.

3.1.1.2 Imputation for adverse event start dates

The following imputation rules apply to cases in which the start date is incomplete (ie, partial or completely missing) for adverse events.

In addition to the following rules, if the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date. If the stop date is present and implies that the adverse event (AE) is treatment-emergent (ie, stop date is on or after the date of first dose of IP in the study), but the start date is completely missing, then the start date will be imputed with the date of first dose of IP. If the stop date is present and does not imply that the AE is treatment-emergent (ie, stop date is prior to the date of first dose of IP in the study), but the start date is completely missing, then the start date will be imputed with the stop date.

For start dates with missing day and month (year is present):

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of IP will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the date of the first dose of IP, then December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of the first dose of IP, then January 1 will be assigned to the missing fields.

For start dates with missing month only (day and year are present):

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

For start dates with missing day only (month and year are present):

- If the month and year of the incomplete start date are the same as the year and month of the date of the first dose of IP, then the date of the first dose of IP will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of IP or if both years are the same but the month is before the month of the date of the first dose of IP, then the last day of the month will be assigned to the missing day.
- If either the year of the incomplete start date is after the year of the date of the first dose of IP or if both years are the same but the month is after the month of the date of the first dose of IP, then the first day of the month will be assigned to the missing day.

For incomplete time in start date

- Note that when dates are recorded using time (from 00:00 until 23:59) and if time is missing in a start date record, time = 00:01 will be assigned; if time is missing in a stop date record, then time = 23:59 will be assigned.

3.1.1.3 Imputation for adverse event stop dates

- The following rules will be applied to partial stop dates:
- If only the month and year are specified, then the last day of the month will be used.
- If only the year is specified, then December 31 of the known year will be used.
- If the stop date is completely unknown, the stop date will not be imputed.

Missing or partially missing dates and/or times will be imputed as for the calculation of duration of each AE.

3.1.2 Repeated and unscheduled visits

All repeated and unscheduled measurements will be presented in the listings. Repeated and unscheduled measurements will not be used for statistical analysis or summary tables, unless the repeated measurement was performed due to unreliable values/technical reasons, or the repeated measurement occurred prior to IP administration and is defined as the 'baseline'. The following general rules will apply to all repeated and unscheduled measurements (the below section describes a different approach for spirometry variables):

- For repeated measurements obtained prior to the first dose of IP in each period, the latest reliable value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics
- For repeated measurements obtained at the designated Baseline visit, the latest reliable value (which may be scheduled or unscheduled) will be defined as the Baseline in each period. Repeated measurements designated Baseline will be used in descriptive statistics rather than the planned measurement they replace
- For repeated measurements obtained at any time point after the first dose of IP, the first reliable value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics.

3.1.2.1 Spirometry variables

For repeated spirometry measurements that are taken on the same day and time as a scheduled visit and time point, the latest nonmissing- result will be used for that visit and time point.

Spirometry data from unscheduled and End of Study visits for patients who discontinue from the study will not be included in the analyses, but all data (from scheduled and unscheduled visits) will be listed.

3.2 Assessment of study population

3.2.1 Demographic and baseline characteristic variables

Demographic characteristics (including country, age, sex, race and ethnicity), baseline characteristics (including height, weight, body mass index [BMI]) and baseline disease characteristics (including COPD history, smoking history, time from diagnosis of COPD to randomisation, time from most recent exacerbation to randomisation, number of exacerbations in previous 12 months and FEV1, FVC variables defined in 4.2.1.2) will be assessed.

3.2.2 Surgical and medical history

Surgical and medical histories will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA, 21.0 or later).

3.2.3 Prior and concomitant medications

All medications will be classified into anatomical therapeutic chemical (ATC) drug classes using the latest version of the World Health Organization (WHO DD+HD March 2017 or later) Drug Dictionary.

Any medications taken by the patient between 15 days prior to signing the ICF and prior to the first dose date of IP will be considered prior medication. The medications taken by the patient more than 15 days before signing the ICF will be not considered prior medication but will be listed in the general listing of all medications for the patient.

Any medication taken by the patient at any time between the date of the first dose (including the date of the first dose) of IP up to 24h after the last IP administration of each treatment period will be considered concomitant medication.

A medication is considered concomitant for a treatment if the start date of the medication is on or after the date of first dose in that treatment period and prior to or at 24h post last IP intake of the treatment period, or the start date is prior to the date of first dose in that treatment period and a stop date on or after the date of first dose in that treatment period (the medication is ongoing). If a medication is taken over multiple periods of treatment, it will be considered concomitant for all treatments taken in the different periods.

A medication is considered to be taken during wash-out periods if it is taken after 24h of IP intake on Day 14 and before the following treatment period.
Medications that start after one day post the date of last dose of IP during the overall study will not be considered concomitant.

For the purpose of inclusion in prior or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 3.1.1.1.

Medications that start during the follow-up period (ie, that start after one day post the date of the last dose of IP during the study) will only be displayed in listings.

3.2.4 Duration of exposure

Exposure (in days) will be calculated as the treatment duration, from the first dose to the last dose (inclusive), separately for each treatment:

$$\begin{aligned}\text{Treatment duration} \\ &= (\text{last dose date in treatment period} \\ &- \text{first dose date in treatment period}) + 1\end{aligned}$$

3.2.5 Treatment compliance

Treatment compliance will be calculated separately for each treatment received by a patient.

For all treatments, treatment compliance will be calculated as follows, using the drug accountability data

$$\text{Treatment compliance (\%)} = \frac{\text{Number of puffs taken during treatment period}}{\text{Number of puffs expected during treatment period}} \times 100.$$

3.3 Efficacy variables

3.3.1 Pulmonary function variables

Pulmonary function will be assessed using spirometry performed as follows:

- Pre-dose spirometry is performed before the morning daily dose at Day 1, Day 8, and Day 14 of each treatment period. Two sets of measurements will be performed during

the hour preceding the scheduled morning study drug administration, allowing approximately 45 min between them.

- Trough FEV_1 values are defined as the mean of the values obtained at 23 hours and 23 hours 45 minutes after the morning IP administration on Day 1 and Day 14 (i.e. obtained on Day 2 and Day 15). On Day 8, $TFEV_1$ value is defined as the mean of the FEV_1 pre-dose values (-1 hour and -15 min).

  If one of the two measurements is missing, the non-missing measurement will be used as the trough value.

- Definition above also applies to FVC measurements.

- 4 hour serial spirometry is performed at Day 8 of each treatment period; spirometry will be performed post-dose at 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours.

- 8 hour and 24 hour serial spirometry is performed at Day 1 and 14 of each treatment period; spirometry will be performed post-dose at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 23 hours and 23:45 hours.

- The FEV_1 peak value at a visit is defined as the highest value observed during the 4 hour period immediately following the morning study drug administration at that visit (ie, the maximum value observed at 15 minutes, 30 minutes, 1 hour, 2 hours or 4 hours post-dose).

AUC is defined as the area under the curve.

For t= 4, 8, 12 and 24 AUC is calculated from zero time to t hours ($AUC_{0\text{-}t}$), using the trapezoidal method, divided by the corresponding duration (ie, 4, 8 and 24 hours, respectively) to give the $AUC_{0\text{-}t/th}$ values (where t is either 4, 8 or 24) in litres. Non-missing FEV_1, at the following time points are required in order to calculate the normalised $AUC_{0\text{-}4/4h}$: pre-dose; at least one value between 0 and 2 hours and the value at 4 hours post-dose. Similarly, nonmissing- FEV_1 values at the following time points are required in order to calculate the normalised $AUC_{0\text{-}8/8h}$: predose-; at least one value between 0 and 4 hours and the value at 8 hours post-dose. For $AUC_{0\text{-}24/24h}$, nonmissing- FEV_1 values at the following time points are required in order to calculate the normalised $AUC_{0\text{-}24/24h}$: predose-; at least one value between 0 and 8 hours and at least one value post 8 hours post-dose; otherwise the normalised $AUC_{0\text{-}t/th}$ will be missing.

Notice that in case that the 23:45 timepoint is missing and only the 23h timepoint is used, the $AUC_{0\text{-}24}$ will still be normalized by 24 and $AUC_{0\text{-}24/24h}$ computed. The raw AUC will be used (rather than the logs), since the distribution of the FEV_1 data is expected to approximate to a normal distribution.

3.3.1.1 Primary outcome variable

The primary variable to assess the primary objective is the change from baseline (pre-dose) in Trough FEV_1 at Day 15 (ie, after 14 days of treatment).

3.3.1.2 Secondary FEV_1 -related variables

Secondary efficacy variables that will be assessed are the following:

- Change from baseline in Trough FEV_1 on Day 2, and Day 8
- Change from baseline in Peak FEV_1 on Day 1, Day 8, and Day 14
- Change from baseline in Trough FEV_1 over treatment duration (Day 1 to Day 15)
- Change from baseline in Peak FEV_1 over treatment duration (Day 1 to Day 14)

3.3.1.3 Other FEV_1 -related variables

- Change from baseline in FEV_1 $AUC_{(0\text{-}4/4h)}$ (area under the curve for the change in FEV1 from baseline to 4h, normalised by the time window) on Day 1, Day 8, and Day 14
- FEV_1 $AUC_{(0\text{-}8/8h)}$ on Day 1, and Day 14
- FEV_1 $AUC_{(0\text{-}12/12h)}$ on Day 1, and Day 14
- FEV_1 $AUC_{(0\text{-}24/24h)}$ on Day 1, and Day 14

3.3.2 Other efficacy variables

3.3.2.1 Total Breathlessness, Cough Sputum Scale (BCSS) score questionnaire and cough, breathlessness and sputum individual domain scores

The daily change from baseline obtained after treatment in Total BCSS score and cough, breathlessness and sputum individual domain scores will be averaged

- over Day 1 to Day 8 to construct the Day 8 endpoints
- over Day 9 to Day 14 to construct the Day 14 endpoints
- over Day 1 to Day 14 to construct the Day 14 endpoints for the analysis of the whole treatment

3.3.2.2 COPDCompEx, Cough VAS and Cough Monitoring

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 the different 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.
- Dropouts: Dropouts due to lack of efficacy (if possible to judge) occurring during treatment periods.

The following COPD and cough variables will be assessed:

- Change from baseline in cough VAS on Day 8 and Day 15
- Change from baseline in number of coughs as measured by cough monitoring on Day 14
- Time to first COPDCompEx.

3.3.2.3 COPD Assessment Test (CAT)

Change from baseline in CAT from Day 1 to Day 8, from Day 9 to Day 14 and during the whole treatment duration will be described.

3.3.2.4 Rescue medication use (Salbutamol)

The daily change from baseline obtained after treatment in rescue medication will be averaged

- over Day 1 to Day 8 to construct the Day 8 endpoint
- over Day 9 to Day 14 to construct the Day 14 endpoint

3.4 Pharmacokinetic variables

The PK analyses of the plasma concentration data for AZD8871 and its primary metabolite LAS191861 will be performed by the Covance Clinical Pharmacology Alliance (CPKA) 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 6.4. or higher. PK analyses will be conducted according to AstraZeneca SOPs for PK analyses, if not otherwise indicated.

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. 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 will be documented in the PK analysis notes. If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

Area under the plasma concentration-curve will be calculated using trapezoidal methods when concentrations are 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 an AUC parameter to be determined, with at least one of these concentrations following C_{max}.

When possible, the following PK parameters will be determined for AZD8871 and its primary metabolite, LAS191861 from plasma concentration-time data:

Day 1:

C_{max} - Maximum observed plasma concentration, taken directly from the individual concentration-time curve

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

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

t_{last} - Time to reach last quantificable concentration

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

For metabolite LAS191861 only:

MRC_{max} - Metabolite to parent ratio for C_{max}

$MRAUC_{(0-24)}$ - Metabolite to parent ratio for $AUC_{(0-24)}$

$MRAUC_{last}$ - Metabolite to parent ratio for AUC_{last}

Day 14:

C_{max} - Maximum observed plasma concentration, taken directly from the individual concentration-time curve

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

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

t_{last} - Time to reach last quantificable concentration

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

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

%Fluc - 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)

For metabolite LAS191861 only:

MRC_{max} - Metabolite to parent ratio for C_{max}

$MRAUC_{(0-24)}$ - Metabolite to parent ratio for $AUC_{(0-24)}$

$MRAUC_{last}$ - Metabolite to parent ratio for AUC_{last}

3.5 Safety variables

3.5.1 Adverse events

AEs: The number and percentage of patients who experienced 1 or more treatment-emergent adverse event (TEAE), and the number of TEAE occurrences will be tabulated by treatment group. An AE is considered TEAE if the event occurs after first dose of IMP up to 42 days after the administration of the last dose of IMP or was present prior to the date of the first dose of IP, but increased in intensity after IP administration. All events present before first IMP are considered non-TEAEs.
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 in a different Table.

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.

3.5.2 Serious adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Any SAE occurring before the first dose of IP, or more than 42 days after the last dose of IP, is considered non-TEAE , it will be included in the data listings but will not be included in the summary tables of SAEs.

3.5.3 COPD exacerbations

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.

All COPD exacerbations will be captured using a COPD exacerbation eCRF and will not be reported as AEs unless considered an SAE

3.5.4 Laboratory variables

Laboratory parameters will be recorded at Visit 1, pre-dose at visits 3, 6, 9, and at 24h post-dose at visits 5, 8, 11, and at follow-up. Safety laboratory tests will be done after 8 hours of fasting. Serology parameters will be measured at Visit 1 only.

The laboratory variables detailed in Table 2 will be recorded. In addition, urine pregnancy tests will be performed for women of childbearing potential. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. This last values will not be transferred to the Sponsor, if there are relevant abnormalities it will be reported as TEAE. Laboratory values of the form of "< x" (ie, below the lower limit of quantification) or > x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics, but the original value (ie, "< x" or "> x") will be displayed in the listings.

Table 2 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haematocrit	S/P-Glucose (fasting)
B-Haemoglobin	S/P-Cholesterol, total
B-Erythrocytes (red blood cells)	S/P-Triglycerides
B-MCV	S/P-Creatinine
B-MCH	S/P-Bilirubin, total
B-MCHC	S/P-Protein, total
B-Leukocyte count (white blood cells)	S/P-Albumin
B- differential blood count (neutrophils, lymphocytes, monocytes, eosinophils and basophil)	S/P-Uric acid and BUN
B-thrombocytes	S/P-Sodium
B-Platelet	S/P-Potassium
aPTT	S/P-Calcium, total
INR	S/P-Chloride
PTT	Alpha-1 antitrypsin
Urinalysis (dipstick)	S/P-Phosphorus, inorganic
U-pH	S/P-AST
U-Blood	S/P-ALT
U-leucocytes	S/P-ALP
U-Protein	S/P-GGT
U-Glucose	S/P-LDH
U-Bilirubin	S/P-Creatine kinase
U-Urobilinogen	S/P-Bicarbonate
U-Ketones	S/P-Magnesium
U-Nitrites	

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

3.5.5 ECG

Electrocardiogram will be performed during Screening Visit, and then at pre-dose and 1, 2, 4, and 24 hours post-dose on Visits 3, 5, 6, 8, 9 and 11. At Visits 4, 7 and 10 measurements will be done at 1 and 4 hours post-dose. ECG will also be performed at follow-up. ECG should be performed before spirometry.

Number of ECG abnormalities in each category of conduction defects, rhythm, myocardial infarction and others will be reported at each timepoint from each day within each treatment.

The following ECG parameters will be analyzed:

- Heart rate (except pre-dose on Visits 4, 7 and 10, which will be taken from vital signs).
- RR interval: Duration in milliseconds between two R peaks of two consecutive measurements
- QRS complexes
- PR interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: Duration in milliseconds of the QRS complex
- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T wave
- QTc interval: QT interval corrected by heart rate:
  - QTcF interval: QT interval corrected using Fridericia's formula ($QT[msec]/RR[sec]^{1/3}$)
- Sinus rhythm
- Overall evaluation (normal/abnormal)

For HR, and QTcF parameters, between-group differences will be presented at each timepoint (day, timepoint (hours) within day).

3.5.6 Vital signs

Systolic and diastolic blood pressure (BP) will be recorded at screening, 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. BP will also be recorded at follow-up. 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).

CCI [redacted]

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Statistical testing

This study is exploratory in nature. The main comparisons of interest are

- AZD8871 600 µg versus Anoro® Ellipta® and
- AZD8871 600 µg versus Placebo.

No adjustment of the Type I error for multiple comparisons will be made in the study, as the primary purpose is estimation rather than hypothesis testing.

4.1.2 Presentation of results

All analyses will use SAS® version 9.3 or higher. Unless otherwise specified, summary tables will be presented by treatment group, labelled as follows: AZD8871 600 µg, Anoro® Ellipta®, and Placebo.

All data will be presented in listings, sorted by sequence, patient number, and treatment. Continuous variables will be summarised by the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median and standard deviation will be reported to one more decimal place than the raw data recorded in the database. The maximum number of decimal places presented for any statistic shall be four, except for pulmonary function variables, where the maximum shall be three. Decimals to be used for PK analysis is described in section 4.3.

Percentages will be presented to one decimal place.

All confidence intervals (CIs) will be two-sided 95% CIs, unless stated otherwise, and presented to one more decimal place than the raw data recorded in the database. If a model is used to estimate the treatment difference, the corresponding CI according to the model will be presented. Otherwise, the unadjusted CI will be used. Nominal p-values may also be presented. Care should be taken when interpreting CIs and p-values since no correction for

multiple testing is done for the endpoints. The presentation of pvalues- will be to four decimal places unless a p-value is less than 0.0001, in which case "<0.0001" will be displayed.

A month and a year are operationally defined to be 30.4 and 365.25 days respectively.

4.2 Analysis methods

4.2.1 Analyses of study population

4.2.1.1 Patient disposition

The reason for screen failure (i.e., patients screened but not randomised) will be listed.

The number and percentage of patients enrolled, randomised, receiving IP, completing the study and prematurely discontinuing from the study (as recorded on the End of Study eCRF page), including the reasons for premature discontinuation, in addition to the number of patients included in each analysis set, will be summarised overall and by treatment for enrolled patients.

The number and percentage of patients completing the treatment period and prematurely discontinuing during the treatment period, including the reasons for premature discontinuation, will be summarised by treatment for the FAS. For patients who discontinue from the study, the discontinuation will be assigned to the last treatment period prior to their discontinuation. Patients who do not discontinue during a treatment period will be as counted as completing the treatment period.

A summary of important protocol deviations will be provided. Important protocol deviations will be listed by centre and treatment.

4.2.1.2 Demographic and baseline characteristics

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

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m2), calculated as follows (where height is in metres): $\frac{\text{weight}}{\text{height}^2}$
- Time from diagnosis of COPD to randomisation (years), calculated as:

$$\frac{\text{date of randomisation} - \text{date of diagnosis of COPD}}{365.25}$$

- Time from most recent exacerbation to randomisation (months), calculated as:

$$\frac{\text{date of randomisation} - \text{date of most recent exacerbation}}{30.4}$$

- Number of exacerbations in previous 12 months
- Pre-bronchodilator FEV_1 at screening (L)
- Pre-bronchodilator FEV_1 % predicted at screening
- Pre-bronchodilator FVC at screening (L)
- Pre-bronchodilator FVC % predicted at screening
- Post-bronchodilator FEV_1 at screening (L)
- Post-bronchodilator FEV_1 % predicted at screening
- Post-bronchodilator FVC at screening (L)
- Post-bronchodilator FVC % predicted at screening
- Post-bronchodilator FEV_1/FVC (%) at screening
- FEV_1 absolute reversibility at screening (mL)
- FEV_1 percentage reversibility at screening

The total counts and percentages of patients will be presented for the categorical variables of:

- Age categorized (18-64 years, 65-84 years, 85 years and older)
- Country
- Sex
- Race
- Ethnicity
- Smoking status (Current smoker, Former smoker)
- Smoking history (number of pack-years)
- Severity of airflow limitation at screening, defined as:

- Stage II (moderate): post-bronchodilator $FEV_1/FVC < 70\%$ and post-bronchodilator FEV_1 % predicted $\geq 50\%$ and $< 80\%$
- Stage III (severe): post-bronchodilator $FEV_1/FVC < 70\%$ and post-bronchodilator FEV_1 % predicted $\geq 30\%$ and $< 50\%$

- Reversible at screening (Yes, No). A patient is defined as being reversible if the post-salbutamol spirometry increases (post-bronchodilator FEV_1) with at least 12% (percentage reversibility) and at least 200 mL (absolute reversibility) compared to the pre-salbutamol spirometry.

Medical history will be listed and the number and percentage of patients with any relevant medical history will be summarised overall, by SOC and PT. Surgical history will be listed and summarised similarly.

The following summaries will be produced:

- Summary of prior medications received (15 days prior to signing the ICF), by ATC level 3 code and PT, overall. Prior medications that continue after the date of first dose will be reported as well and classified in both prior and concomitant medication groups..
- Summary of disallowed medications will be reported.

Additionally, a subset of the previous summary will be produced presenting the number and percentage of patients who used any prior medication for COPD by the following therapeutic categories; Inhaled Corticosteroids (ICS), Long-Acting Beta2-Agonists (LABA), LABA+ICS combination, Long-Acting Muscarinic Antagonist (LAMA), Short-Acting Beta2-Agonists (SABA), SABA+ICS combination, Short-Acting Muscarinic Antagonist (SAMA), SABA+SAMA combination, Influenza Vaccine, Oxygen, Xanthines and PDE4 inhibitors. If a patient has LABA+ICS followed by ICS (as monotherapy), then this patient will be counted only once in the LABA+ICS category.

Multiple records for a patient in the same ATC level 3 category and PT will be counted only once.

All concomitant and other treatment data will be listed.

4.2.1.3 Exposure

Treatment duration (days) will be summarised by treatment for the SS, using descriptive statistics.

4.2.1.4 Treatment compliance

Treatment compliance (%) will be summarised by treatment for the FAS, using continuous type descriptive statistics.

Treatment compliance will also be presented using the following compliance status categories: <70%, >=70%-130%, >130%.

4.2.2 Analysis of the primary variable: change from baseline in Trough FEV_1 at Day 15

All analyses will be based on the FAS and P-PS populations.

The primary efficacy variable will be analysed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence), the pre-dose FEV_1 of each period being included as covariate.

Each treatment effect and treatment differences will be estimated by the Least Square means along with their standard errors (SE) and 95% CI, and the p-value corresponding to the between-treatment group difference. Differences between least squares means, the SE of the difference, 95% CIs, and the p-values corresponding to between-treatment differences will also be presented for each comparison of interest.

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 using as baseline FEV_1 the mean of the 2 measured values prior to the morning IP administration on Day 1 of the first treatment period (see Section 3.1 for the baseline FEV_1 derivation on Day 1 of the first treatment period in case of missing value). This sensitivity analysis will be performed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence), the pre-dose FEV_1 of the first period being included as a covariate to capture carry-over effects.

For all mixed models, the estimation method used will be Restricted Maximum Likelihood (REML). The Kenward and Roger method for computing degrees of freedom will be used.

4.2.3 Analysis of the FEV_1-related secondary variables

- 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

The analyses of the above endpoints will be performed using the FAS and will be based on the same model as described in 4.2.2.

- Change from baseline in Trough FEV_1 over treatment duration (Day 1 to Day 15)
- Change from baseline in Peak FEV_1 over treatment duration (Day 1 to Day 14)

The analyses of the 2 above endpoints will be performed using the FAS. These 2 efficacy variables will be analysed by means of a mixed repeated model: fixed effects for treatment, sequence, period, and day as a repeated factor within period (Day 1, Day 8 and Day 15 (Day 14 for Peak FEV_1)) and day-by-treatment interaction; a random effect for patient (nested within sequence) will be included also. The repeated covariance structure for day will be compound symmetry; the pre-dose FEV_1 of each period being included as a covariate.

For all mixed models, the estimation method used will be Restricted Maximum Likelihood (REML). The Kenward and Roger method for computing degrees of freedom will be used. The same treatment comparisons as those for the primary variable will be performed for the secondary variables.

4.2.4 Analysis of the other FEV_1-related variables

All analyses below will be based on the FAS and will be based on the same model as described in 4.2.2.

- Change from baseline in FEV_1 $AUC_{0\text{-}4/4h}$ (area under the curve for the change in FEV_1 from baseline to 4h, normalised by the time window) on Day 1, Day 8, and Day 14
- FEV_1 $AUC_{0\text{-}8/8h}$ on Day 1, and Day 14
- FEV_1 $AUC_{0\text{-}12/12h}$ on Day 1, and Day 14
- FEV_1 $AUC_{0\text{-}24/24h}$ on Day 1, and Day 14

In addition, statistical analyses on the change from baseline in FEV_1 15 min, 30 min, 1, 2, 4, 8, 23, and 23:45 hours post-dose will be presented by treatment group at Day 1 and Day 15. Also, analyses on the change from baseline in FEV_1 15 min, 30 min, 1, 2, and 4 hours post-dose will be presented by treatment group at Day 8. All analyses will be using the FAS and will be based on the same model as described in 4.2.2.

Mean changes from baseline for FEV_1 will be displayed in a longitudinal plot by treatment group, where the least squares means and corresponding 95% CI from the mixed model at each time point will be displayed, separately for Day 1, Day 8, and Day 14.

Absolute FEV_1 values will be summarised by visit and time point, by treatment group using descriptive statistics. The same treatment comparisons as those for the primary variable will be performed for the secondary variables.

4.2.5 Analysis of the other efficacy variables

The change from baseline in Total BCSS score and cough, breathlessness and sputum individual domain scores assessed at Day 8 and at Day 14 (see Section 3.3.2.1 for definition) will be analysed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence); the baseline will be included as a covariate.

The change from baseline in use of rescue medication at Day 8, and at Day 14 (see Section 3.3.2.4 for definition) will be analysed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence); the baseline will be included as a covariate.

Change from baseline in CAT from Day 1 to Day 8, from Day 9 to Day 14 and during the whole treatment duration will be analysed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence); the baseline will be included as a covariate. The same treatment comparisons as those for the primary variable will be performed for the secondary variables.

4.2.6 Exploratory outcome variables

The change from baseline in cough VAS at Day 8, and at Day 15 will be analysed by means of a mixed model: fixed effects for treatment, sequence, and period and random effect for patient (nested within sequence); baseline will be included as a covariate. The change from baseline in number of coughs as measured by cough monitoring at Day 14 will be analysed in a similar model after data transformation (a square root transformation will be applied to the counts). A summary of raw counts should also be produced.

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 and dropout events.

[redacted]

[redacted]

The analysis of this composite endpoint for exacerbations will be time to first COPDCompEx event and, for each period, it will be calculated as follows:

$$Time\ to\ first\ COPDCompEx\ (of\ each\ period) = Date\ of\ first\ COPDCompEx\ (in\ that\ period) - Date\ of\ Day\ 1\ (of\ each\ period)+1$$

For each period, if a patient presents either an exacerbation as described above, or any diary event meeting the threshold and slope criteria, or drops out, COPDCompEx will be 1 (otherwise it will be 0). For those patients with COPDCompEx=1 the date when the event (either exacerbations, diary events or dropouts) occurred will be also recorded. Patients with COPDCompEx=0 in a particular period, will be considered as censored in that period. The date of censoring will be defined as last day of treatment in that period (or date of withdrawal if not judged to be a dropout due to lack of efficacy, whichever is sooner).

Time to to first COPDCompEx event will be analysed using a Cox's proportional hazards model with factors for treatment, sequence, and period. Patient will be fitted as as a clustering factor. Hazard ratios with 95% CIs will be presented, for the comparisons of AZD8871 600 µg to Anoro® Ellipta® and to Placebo.

Time to to first COPDCompEx event will be summarized in a table including the following summary statistics: the number of subjects in the analysis, the percentage of patients with events, the mean time to event, and the median time to event with 95% CI, for each treatment (AZD8871 600 µg Anoro® Ellipta® and Placebo). In addition, a Kaplan-Meier plot will be provided.

4.3 Analysis of pharmarcokinetic variables

4.3.1.1 Descriptive statistics

All PK summary statistics and inferential statistics will be based on the PKS.

A listing of all available PK blood sample collection times as well as derived sampling time deviations will be provided.

AZD8871 and LAS191861 plasma concentrations will be listed by subject and time-point for the relevant treatment period and treatment sequence.

Plasma concentrations for AZD8871 and its primary metabolite (LAS191861) will be summarised after the first dose of AZD8871 on Day 1 and after QD multiple doses on Day 14 using descriptive statistics (n, n below LLOQ, geometric mean (gmean), gmean +gSD, gmean –gSD, geometric coefficient of variation [gCV%], minimum, median and maximum) based on the PKS.

The statistics for geometric mean, geometric mean+/-geometric SD and geometric CV% will be calculated as follows:

Geometric mean: Calculated as $\exp[\mu]$

Geometric mean +/- geometric SD: Calculated as $\exp[\mu +/- s]$

Geometric CV% : Calculated as $100 \times \text{sqrt}[\exp(s^2) - 1]$

For the geometric mean, geometric mean +/- geometric SD and geometric CV%, the following holds:

- s is the arithmetic standard deviation of the natural log-transformed variable
- μ is the arithmetic mean of the natural log-transformed variable
- exp denotes the power function based on the natural base e

Individual concentrations below the Lower Limit of Quantification (LLOQ) of the bioanalytical assay will be reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reports as NR or NS will be excluded from the summary tables and figures.
- At a time point where less than or equal to 50% of the values are NQ, all NQ 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 NQ, the gmean, gmean + gSD, gmean – gSD and gCV% will be set to Not Calculated (NC). 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. The gmean, minimum, median and maximum will be reported as BLQ and the gCV% and gmean + gSD and gmean – gSD as NC.

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

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

Plasma conentrations that are NQ will be handled as follows for display in figures:

- For gmean concentration-time plots: NQ concentrations will be handled as described for the descriptive statistics. If this handling results in a geometric mean of "NQ", then the value plotted at that time-point will be zero for linear plots and set to missing for semi-logarithmic plots. Any gmean±gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots

- For individual plots and combined individual plots: NQ values prior to the first quantifiable concentration in that profile will be set to zero (linear plots only); after the first quantifiable concentration of the profile any NQ values will be set to missing

Subjects who reported Day 1 pre-dose concentrations > 5% of Cmax may be excluded from the Day 1 PK analysis and/or statistical analyses.

Plasma PK parameters for AZD8871 and its primary metabolite (LAS191861) will be summarised using descriptive statistics as follows:

- C_{max}, C_{avg}, $AUC_{(0\text{-}24)}$ and AUC_{last}: present n, gmean, gmean+gSD, gmean-gSD, gCV(%), median, min and max.

- All parameter ratios (i.e. Rac values and metabolite to parent ratios): present n, gmean, gCV(%), mean, SD, median, min and max.

- %Fluc: present n, mean, SD, median, min and max.

- t_{max} and t_{last} : present n, median, min and max.

Three values are required as a minimum for PK parameters to be summarized. Two values are presented as a min and max with the other summary statistics as NC.

For concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- C_{max} will be presented to the same number of significant figures as received from the bioanalytical laboratory.

- t_{max} and t_{last} will be presented as received in the data, usually to 2 decimal places

- AUC_{last}, $AUC_{(0-24)}$, C_{avg}, accumulation ratios and metabolite to parent ratios and %Fluc and will be presented to 3 significant figures

For concentration data all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures. For PK parameter data the descriptive statistics will be presented according to the following rules:

- C_{max}, AUC_{last}, $AUC_{(0-24)}$, C_{avg}, Rac ratios, metabolite to parent ratios and %Flucdescriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

- t_{max} and t_{last} all descriptive statistics will be presented as received in the data, usually to 2 decimal places

PK concentration and parameter data for patients excluded from the PKS will be included in the data listings, but not in the descriptive or inferential statistics or in mean figures or combined individual figures.

Individual plasma concentrations versus actual elapsed time after dose will be plotted on both linear and semi logarithmic scales for AZD8871 and LAS191861 separately with the Day 1 and Day 14 data overlaid on the same plot. Combined individual plasma concentrations will be presented on both linear and semi logarithmic scales with separate plots for each analyte and PK day (Day 1 and Day 14).

Figures for the gmean concentration-time data (with gSD error bars) will be presented, on both a linear and semi-logarithmic scales by analyte, with Day 1 and Day 14 overlaid on the same plot.

To evaluate any potential carryover effect in the study due to AZD8871 treatment, Day 1 predose concentrations for AZD8871 and LAS191861 in those periods preceded by AZD8871 treatment will be also listed. These data however, will not be summarized.

4.3.1.2 Statistical analysis of accumulation in AZD8871 exposure (C_{max} and $AUC_{(0-24)}$) following multiple doses

$AUC_{(0-24)}$ and C_{max} at Day 1 and Day 14 will be analysed by means of a linear mixed-effect model with the logarithm of the PK parameters as the response variable and sequence, period,

and day as fixed effects, random effect for patient nested within sequence and day being treated as a repeated effect within patient, the covariance structure being assumed to be compound symmetry. ADZ8871 accumulation will be evaluated by comparing $AUC_{(0-24)}$ (Day 14) with $AUC_{(0-24)}$ (Day 1) and C_{max} (Day 14) with C_{max} (Day 1) in the same model. From these models, least squares (LS) means together with 95% CI for Day 1 and Day 14, and LS means together with 90% CI for the difference for Day 14 versus Day 1 will be obtained. The results will be transformed back to the original scale by exponentiation to provide estimates of geometric LS means, geometric LS mean ratios for Day 14/Day 1 and corresponding CI.

4.4 Safety

All safety summaries will be based on the SS. Any important deviations from the randomised treatment assignment will be listed and considered when interpreting the safety data.

4.4.1.1 Adverse events

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of intensity, outcome, action taken with IMP, and possible relationship to study drug.

Any AE occurring before the first dose of IP, or more than 42 days after the last dose of IP, will be considered as non-TEAE, it will be included in the data listings but will not be included in the summary tables of AEs.

Multiple occurrences of a TEAE in the same patient will only be counted once overall considering start date as the first day of first occurrence and stop date the last day of the last occurrence and the TEAE will assigned to the treatment of the first occurrence period study drug. Multiple occurrences of a TEAE in the same patient for the same treatment will only be counted once for that treatment.

The number of patients/event will be tabulated also by preferred term, and treatment.

In the case that, within a treatment period, a patient has more than one episode of the same preferred term with different levels of intensity, action taken, outcome causality or seriousness, then the maximum intensity level, action taken (i.e. withdrawn) and outcome (i.e. fatal), causality level (i.e. related), or seriousness level (i.e. serious), respectively will be used. The following ordering will be used to define maximum intensity level, action taken, outcome causality level, or seriousness level :

- Intensity: Mild < Moderate < Severe
- Causality: No < Yes
- Seriousness: No < Yes

- Action taken: Unknown < Not applicable < Dose not changed < Drug interrupted < Drug withdrawn

- Outcome: Unknown < Recovered/resolved < Recovered/resolved with sequelae < Recovering/resolving < Not recovered/not resolved < Fatal

A general summary of all TEAEs will show the number and percentage of patients with

- Any TEAE

- Any TEAE with outcome = death

- Any TESAE (including events with outcome = death)

- Any TEAE leading to discontinuation of IP

- Any TEAE leading to withdrawal from study

The total number of TEAEs will be presented for the following categories;

- All TEAE

- All TEAE with outcome = death

- All TESAE (including events with outcome = death)

- All TEAE leading to discontinuation of IP

- All TEAE leading to withdrawal from study

The number and percentage of patients who experience one or more TEAEs will be tabulated by treatment and by:

- SOC and PT .

- PT, and maximum reported intensity

- PT, and causality with the IP judged by investigator

- SOC and PT with outcome of death

Additionally, a subset with the number and percentage of patients with any non-serious treatment emergent adverse event (TEAE) by system organ class, and preferred term by treatment with common incidence >=5% will also be produced (ordered by frequency).

Key patient information (age/sex/race) for patients experiencing SAEs and discontinuation of study drug due to AEs will be presented in a listing.

4.4.1.2 Laboratory data

All laboratory data recorded in the eCRF will be listed. Flags will be applied to values falling outside the expanded normal ranges (which will be explicitly noted on these listings where applicable). Individual patient data where ALT and/or AST and total bilirubin are elevated at any time will be listed (ie, ALT and/or AST ≥ 3 × the upper limit of normal [ULN] and total bilirubin ≥ 2 × ULN, at any time) to evaluate potential Hy's Law cases.

Change from baseline to 24h post-dose assessment will be calculated.

For i-STAT glucose and potassium at Day 1 and 14, mean absolute values at baseline, 1, 2, 4, and 24 hours postdose as well as mean changes from baseline at 1, 2, 4, and 24 hours post-dose will be will be presented by treatment.

Mean absolute values and mean change from baseline for all clinical chemistry and haematology laboratory parameters (in international system of units [SI]) will be presented by treatment and timepoint.

A figure summarizing the mean change from baseline (and SE) in i-STAT glucose and potassium by treatment and timepoint will also be provided.

Shift from baseline tables will be presented by treatment overall and by timepoint, separately for haematology, clinical chemistry and iSTAT measurements, showing the number and percentage of subjects with shifts from baseline for each laboratory variable.

Shift is defined as the change in category based on the expanded normal ranges (low, normal or high as above) at baseline to a post-baseline timepoint. The number and percentage of patients with laboratory test values:

- lower than the lower limit of the expanded normal range (ENR),
- within the ENR limits, and
- larger than the upper limit of the ENR

will be provided for post baseline timepoints, the ENR being calculated by multiplying the LLN and ULN of the laboratory by the factor shown in Table 3.

Moreover, treatment-emergent abnormalities, defined as newly occurring or clinically relevant worsening, as well as notable abnormalities in laboratory parameters will be summarised by means of shift contingency tables comparing the values assessed at post-baseline timepoints to the baseline values; values at baseline are "Low", "Normal", "High" according to Table 3; values post-baseline are "New", "Worsened", "Notable". Newly occurring or clinically relevant worsening laboratory abnormalities in laboratory parameters will be identified using the ENR. A laboratory result lying outside the ENR will be considered abnormal.

A laboratory parameter will be defined as showing a "New" abnormality if the observed lab test value is within the ENR at baseline but not at post-baseline timepoints, or it is outside the ENR at baseline and outside the ENR at endpoint at different extreme limits (from expanded lower limit to expanded upper limit, or vice versa).

A laboratory parameter will be defined as "Worsened" if the baseline lab test value is above the expanded upper limit of the corresponding normal range (xULN) specified in Table 3 and the ratio of endpoint value to baseline value is also greater than the corresponding coefficient (multiplying factor) specified in Table 3, or alternatively if the baseline laboratory test value is below the expanded lower limit of the corresponding normal range (xLLN) specified in the above table and the ratio of endpoint value to baseline value is also lower than the corresponding coefficient specified in Table 3.

The laboratory abnormality will be also classified as a "Notable" abnormality if it satisfies the criteria detailed in Table 3.

A listing of all treatment-emergent AEs recorded for patients with laboratory parameters outside of the ENR limits (at baseline or post-baseline) will also be provided including the assessment of clinical relevance by investigator.

Pregnancy test results will be listed only.

Table 3 Expanded normal ranges and notable abnormalities for laboratory parameters

Laboratory Parameter	***Expanded Normal Ranges***		***Notable Abnormalities***	
	Lower Limit	*Upper Limit*	*Lower Limit*	*Upper Limit*
HAEMATOLOGY				
Hemoglobin	0.85 × LLN	1.15 × ULN	< 60 g/L	> 230 g/L
Hematocrit	0.85 × LLN	1.15 × ULN	< 0.24	NA
Red Blood cells	0.85 × LLN	1.15 × ULN	NA	NA
MCV	0.85 × LLN	1.15 × ULN	NA	NA
MCH	0.85 × LLN	1.15 × ULN	NA	NA
MCHC	0.85 × LLN	1.15 × ULN	NA	NA
Platelets	0.85 × LLN	1.15 × ULN	$< 100 \times 10^9$/L	NA
White Blood cells				
Total	0.85 × LLN	1.15 × ULN	$< 1 \times 10^9$/L	$> 30 \times 10^9$/L
Neutrophils	0.85 × LLN	1.15 × ULN	$< 0.5 \times 10^9$/L	NA
Eosinophils	NA	1.15 × ULN	NA	NA
Basophils	NA	1.15 × ULN	NA	NA
Lymphocytes	0.85 × LLN	1.15 × ULN	NA	NA
Monocytes	NA	1.15 × ULN	NA	NA

Table 3 Expanded normal ranges and notable abnormalities for laboratory parameters

Laboratory Parameter	*Expanded Normal Ranges*		*Notable Abnormalities*	
	Lower Limit	*Upper Limit*	*Lower Limit*	*Upper Limit*
BIOCHEMISTRY				
Aspartate aminotransferase	NA	1.15 × ULN	NA	> 3 × ULN
Alanine aminotransferase	NA	1.15 × ULN	NA	> 3 × ULN
Alkaline phosphatase	NA	1.15 × ULN	NA	> 3 × ULN
Gamma-glutamyltranspeptidase	NA	1.15 × ULN	NA	> 3 × ULN
Total bilirubin	NA	1.15 × ULN	NA	> 51.3 µmol/L
Creatine-kinase	NA	1.15 × ULN	NA	> 10 × ULN
Lactate dehydrogenase	NA	1.15 × ULN	NA	> 3 × ULN
Blood urea nitrogen	NA	1.15 × ULN	NA	> 17.9 mmol/L
Creatinine	NA	1.15 × ULN	NA	> 265 µmol/L
Uric acid	NA	1.15 × ULN	NA	> 714 µmol/L
Total cholesterol	NA	1.15× ULN	NA	NA
Triglycerides	NA	1.15× ULN	NA	NA
Glucose	0.85 × LLN	1.15 × ULN	< 2.22 mmol/L	> 22.2 mmol/L
Sodium	0.95 × LLN	1.05 × ULN	<115 mmol/L	> 165 mmol/L
Potassium	0.95 × LLN	1.05 × ULN	< 2.6 mmol/L	> 6.9 mmol/L
Calcium	0.85 × LLN	1.15 × ULN	< 1.25 mmol/L	> 3.25 mmol/L
Chloride	0.95 × LLN	1.05 × ULN	NA	NA
Inorganic phosphorus	0.85 × LLN	1.15 × ULN	NA	NA
Total Protein	0.85 × LLN	1.15 × ULN	< 20 g/L	> 90 g/L
Albumin	0.85 × LLN	1.15 × ULN	NA	NA
URINALYSIS				
pH	0.85 × LLN	1.15 × ULN	NA	> 1.15 × ULN

MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume; LLN = lower limit of normal; ULN = upper limit of normal (LLN and ULN values are provided by the laboratory). NA = Not applicable

4.4.1.3 ECG

All ECG data collected will be listed.

Mean absolute values and mean change from baseline for continuous ECG parameters will be summarised by treatment, day (Day 1, 8, and 14) and timepoint within day, 95% CIs for the change from baseline will be provided in addition to the usual descriptive statistics parameters.

Graphical presentation of mean change from baseline (and SE) for ECG parameters by treatment and timepoint will also be pprovided.

For HR, and QTcF parameters, change from baseline at each timepoint within Day 1, Day 8, and Day 14 will be analysed by means of a mixed model; a random effect model with fixed effects for treatment, sequence, and period. The patient will be fitted as a random effect and the pre-dose value of the parameter obtained at visit 3 will be included as a covariate. Between-groups difference in LSMeans will be provided with their 90% CI. A Figure presenting the LSMeans and 90% CI across time will be presented as well.

QTcF exceeding ICH boundaries are defined in Table 4**.** Other ECG values (HR, QRS interval, and PR interval) are defined to be PCS if they meet criterion 1 or criterion 2 displayed in Table 5. Number and percentages of patients with post-baseline QTcF exceeding ICH boundaries and PCS ECG values will be presented for each category, each criterion defined in Table 4 and Table 5.

These numbers and percentages of patients with post-baseline QTcF exceeding ICH boundaries and PCS ECG values will be summarised by treatment overall and by timepoint within each day (Day 1, 8, and 14).

A listing of individual data for all patients with PCS ECG values will be provided, and will include treatment sequence, patient number, and all ECG values (baseline and post-baseline values), clinical relevance of PCS assessed by the PI will also be in the listing.

A listing of all treatment-emergent AEs recorded for patients with PCS ECG values (at baseline or post-baseline) will also be provided.

The number and percentage of patients with post-baseline abnormal ECG findings (Rhythm, Extra Systoles, Conduction, ST-Changes, ST Segment, T Wave Observations, and U Wave Observations) will be summarised by treatment, overall and and by timepoint within each day (Day 1, 8, and 14).

Percentages will be based on the number of patients with at least one post-baseline ECG assessment.

A listing of all ECG abnormal findings will be provided.

Table 4 PCS ECG criteria: QTcF exceeding ICH boundaries

Category 1: QTcF value above the following cut-off at any time during treatment Criteria: >450 (ms) >480 (ms) >500 (ms) Category 2: QTcF increase by more than following cut-off at any time during treatment Criteria: >30 (ms) >60 (ms) >90 (ms) Category 3: QTcF value above cut-off and QTcF increase by more than cut-off at any time during treatment Criterions: Value >450(ms) and Increase >30(ms) Value >500(ms) and Increase >60(ms)

Table 5 PCS ECG criteria: Heart Rate and QRS interval

ECG parameter	Category	Criterion 1	Criterion 2
Heart rate	Tachycardia event	≥ 110 bpm and an increase of ≥ 15% over baseline value	≥ 120 bpm if baseline is < 100 bpm
	Bradycardia event	≤ 50 bpm and a decrease of ≥ 15% over baseline value	≤ 40 bpm if baseline is > 40 bpm
QRS interval		≥ 100 msec and an increase of ≥ 25% over baseline value	≥ 150 msec if baseline is < 150 msec
PR interval		≥ 200 msec and an increase of ≥ 25% over baseline value	≥ 250 msec if baseline is < 250 msec

bpm = beats per minute.

4.4.1.4 Vital signs

All vital sign data collected will be listed.

Mean absolute values and mean change from baseline for BP will be summarised by treatment, and time point; graphical presentation of mean change from baseline and SE will be provided also.

High and low PCS vital signs values will be identified. Vital sign values will be PCS if they meet both the PCS criteria for the observed value and the PCS criteria for the change from baseline value for criterion 1, or if they meet the PCS criteria for the observed value for criterion 2; the 2 criteria should not be combined. The criteria for PCS vital signs values are displayed in Table 6.

Table 6 PCS vital sign criteria

		Criterion 1		Criterion 2
Vital sign		**Observed value**	**Change from baseline**	**Observed value**
Systolic BP (mmHg)	High	≥ 180	Increase of ≥ 20	≥ 200, if baseline < 160
	Low	≤ 90	Decrease of ≥ 20	≤ 75, if baseline > 75
Diastolic BP (mmHg)	High	≥ 105	Increase of ≥ 15	≥ 115, if baseline < 115
	Low	≤ 50	Decrease of ≥ 15	≤ 40, if baseline > 40

BP = Blood pressure.

The number and percentage of patients with post-baseline PCS vital sign values will be summarised for each criteria by treatment, day and timepoint within day. Percentages will be based on the number of patients with baseline vital sign values and at least one post-baseline vital sign assessment.

A listing of individual data for all patients with PCS vital sign values will be provided, and will include treatment sequence, patient number, and all vital sign values (baseline and post-baseline values).

A listing of all treatment-emergent AEs recorded for patients with PCS vital sign values (at baseline or post-baseline) will also be provided.

CCI [redacted]

[redacted]

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CCI

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

Change in the analysis set used:
All demographic and baseline characteristics will be analysed using the full analysis set instead of the safety population.

Change in definition of baseline for vital signs, laboratory variables including i-STAT glucose and potassium and ECG variables:
Baseline is defined as the last assessment made before the first dose of IP in each period instead of the value obtained prior to the morning IP administration on day 1 of Visit 3

For HR, and QTcF parameters:
Analyses of change from baseline at each day and timepoint within day will be perfomed instead of the analysis of AUC_{0-4} at Day 1, Day 8, and Day 14 and AUC_{0-24} at Day 1 and Day 14. No formal analysis of other ECG parameters will be performed.

Dropouts due to lack-of-efficacy during treatment periods added as a COPDCompEx event.

Additional analysis on FEV1:
Statistical analyses on the change from baseline in FEV1 15 min, 30 min, 1, 2, 4, 8, 23, and 23:45 hours post-dose will be presented by treatment group at Day 1 and Day 15.

Also, analyses on the change from baseline in FEV1 15 min, 30 min, 1, 2, and 4 hours post-dose will be presented by treatment group at Day 8.

7. REFERENCES (NOT APPLICABLE)

8. APPENDIX

Appendix A Statistical supporting documentation

CCI [redacted]

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	[redacted]	[redacted]				
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