Statistical Analysis Plan

Drug Substance	AZD8871
Study Code	D6640C00004
Date	26 June 2017

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

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Global Product Statistician Redacted 5/07/2017
Date

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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 curve
AUC_{0-x}	Area under curve from time 0 to x hours
$AUC_{0-x/xh}$	Area under curve from time 0 to x hours normalized by x hours
AUC_{last}	Area under the curve from time 0 to last quantifiable measurement
BCSS	Breathlessness, Cough, Sputum Score
BDR	Blind data review
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECG	Electrocardiogram
eCRF	electronic case report form
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICF	Informed consent form
IP	Investigational product
ITT	Intention-to-treat
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially clinically significant

Abbreviation or special term	Explanation
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
RR interval	Duration in milliseconds between two R peaks of two consecutive QRS complexes
SAE	Serious adverse event
SAP	Statistical analysis plan
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
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization
WO	Wash out

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary objective:	Endpoints:
To evaluate the efficacy of inhaled AZD8871 in patients with moderate to severe COPD	**Primary** • Change from baseline in Trough FEV_1 on Day 15 **Secondary** • Change from baseline in Trough FEV_1 on Day 2, and Day 8 • Change from baseline in Peak FEV_1 on Day 1, Day 8 and Day 14 • Change from baseline in Trough FEV_1 over treatment duration (Day 8 to Day 15) • Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14) • Change from baseline in FEV_1 $AUC_{0\text{-}4/4h}$ at Day 1, Day 8, and Day 14 • Change from baseline in FEV_1 $AUC_{0\text{-}8/8h}$ at Day 1, and Day 14 • Change from baseline in FEV_1 $AUC_{0\text{-}24/24h}$ at Day 1, and Day 14 • Change from baseline in Trough FVC on Day 2, Day 8, and Day 15 • Change from baseline in Peak FVC on Day 1, Day 8 and Day 14 • Change from baseline in Total Score of Breathlessness, Cough Sputum Scale (BCSS) questionnaire and cough, breathlessness and sputum individual domain scores on Day 8 and Day 14 of treatment • Change from baseline in average daily rescue medication use assessed on Day 8 and Day 14 of treatment
Secondary objective:	**Endpoints:**

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

1.1.2 Safety objectives

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

1.1.3 Exploratory objectives

Exploratory objectives:	**Endpoints:**
To evaluate the taste of inhaled AZD8871 in patients with moderate to severe COPD	• Taste assessment

1.2 Study design

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

This multi-centre study will be conducted at 2 sites in Europe (Germany and United Kingdom [UK]). It is planned that approximately 42 men and women of non-childbearing potential aged 40 to 80 years (both inclusive) with moderate to severe COPD will be randomised to the

study. A subset of 20 patients, who will have specifically consented, will also undergo PK assessments. The entire study period is scheduled to take from a minimum of 4.5 months (140 days) to a maximum of 5.6 months (175 days) for each individual patient. The study is anticipated to run for approximately 8 months and should not exceed 10 months.

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

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

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

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

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

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

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

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

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

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

- AZD8871 100 µg once daily

- AZD8871 600 µg once daily
- Placebo

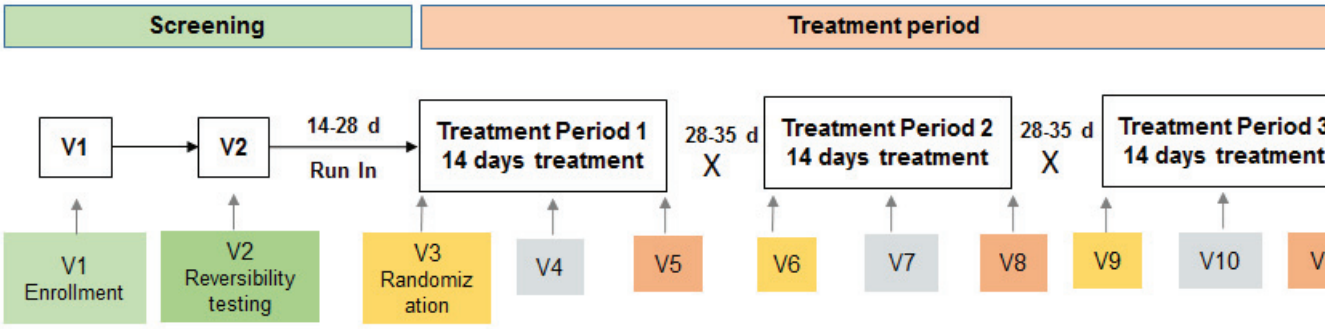
Each of the 3 treatment periods will last for 14 days and will include 2 overnight stays at the study site and one ambulatory visit at the study site.

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

From treatment period 2 onwards, on Day 1 of a new treatment period, a FEV_1 stability test will be performed pre-dose. FEV1 stability check will be based on the pre-best test review ., The mean of the pre-dose FEV_1 (mean of the 2 measured values) should be within (±)20% or (±)200 mL compared to the pre-dose FEV_1 (mean of the 2 measured values) of the first treatment period (Visit 3). If the FEV_1 stability criterion is not met, an additional measurement could be taken within 30 min of the second pre-dose measurement, and the mean of the last 2 measurements will be considered for the FEV_1 stability criterion. If the FEV_1 stability criterion is still not met, the test can be rescheduled as soon as possible, and if the FEV_1 stability criterion is not met after re-testing, the patient should be withdrawn.

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

Figure 1 Study flow chart



d=day; FU=follow-up; V=visit.
During treatment periods 1 to 3, each patient will randomly receive one of the 3 possible treatments (AZD8871 at the doses of 100

1.3 Number of patients

The study was powered to demonstrate superiority of AZD8871 100 µg and 600 µg versus placebo for the primary efficacy endpoint. With a total of 30 patients, there is 80% power to detect a difference between actives and placebo for the change from baseline to trough FEV_1 at Day 15 equal to 100 mL, assuming a within-patient SD of 135 mL, 2-sided 5% significance level and a normal distribution. Assuming an approximate 25% dropout, the total sample size as approximately 42 (multiple of 6 sequences).

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.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Screening analysis set

The screening analysis set will consist of all patients screened.

The screening analysis set will be used for reporting disposition and screening failures.

2.1.2 Full analysis set

The Full Analysis Set (FAS) population is defined as all patients randomised and receiving at least one dose of 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.

2.1.3 Safety analysis set

The safety analysis set consists of all randomised patients who receive at least one dose of IP. For summaries based on the safety set, 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 safety analysis set 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 major 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 non-randomised treatments.

2.1.4 PK analysis set

The PK analysis set (PKS) will consist of all patients in the safety analysis set who received at least 1 dose of AZD8871 (100 µg or 600 µg) and have at least 1 of the parameters Cmax, AUC or AUClast 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 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

2.1.5 Per Protocol Analysis Set

The Per Protocol (PP) analysis set (PPS) will consist of all patients who receive at least 1 dose of AZD8871 (100 µg or 600 µg) or placebo, who have at least 1 pre-dose and 1 post-dose measurement for forced expiratory volume in one second (FEV1) and who have no important protocol deviations thought to impact the analysis of the lung function data.
The available lung function data for any patients excluded from the PP analysis set for a given study period will be listed only. Only patients in the PP analysis set will be included in the descriptive statistics and statistical analyses.

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 PPS 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 PP set, PK set, safety set, or FAS set. 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 Important protocol deviations and population classification

		Excluded from analysis set			
Item #	**Event description**	**PPS**	**SAF**	**PKS**	**FAS**
1	Provision of informed consent not performed before any study specific procedures.	No	No	No	No
2	ICF source document not available at site, or any issue with the ICF document.	No	No	No	No
3	Female Patient is pregnant, lactating or is of childbearing potential	No	No	No	No
4	Patient has a current diagnosis of asthma	Yes	No	No	No
6	Patient has alpha-1 antitrypsin deficiency as the cause of COPD.	Yes	No	No	No
7	Patient is less than 40 or more than 80 years of age	No	No	No	No
8	Patient has no established clinical history of 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.	Yes	No	No	No
10	Patient has post-bronchodilator FEV_1/FVC ratio >=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 does not fulfil reversibility criteria to salbutamol at Visit 2. Reversibility is defined as ≥12% and ≥200 mL increase in FEV_1 after inhalation of 4 puffs of salbutamol (400 µg). If the criterion is not met, the test can be repeated at the latest, up to Day -14.	Yes	No	No	No
13	Patient with body mass index (BMI) >=40 kg/m^2 at the time of Screening	Yes	No	No	No
14	Patient is not free from any clinically active disease other than COPD that may impact study outcome, as determined by medical history, physical examination, laboratory testing, and 12-lead ECG findings, at Screening.	Yes	No	No	No
15	Patient has other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or uncontrolled sleep apnoea.	Yes	No	No	No
16	Patient has undergone lung volume reduction surgery, lobectomy, or bronchoscopic lung volume reduction	Yes	No	No	No
17	Patient is using nocturnal positive pressure	Yes	No	No	No
18	Patient has been hospitalised due to poorly controlled COPD within 3 months of Screening.	Yes	No	No	No
19	Patient has acute worsening of COPD or lower respiratory tract infections that required antibiotics or corticosteroids in the 6-week interval prior to Screening (Visit 1), or during the Screening Period (between Visits 1 and 3).	Yes	No	No	No
20	Patient has changed their smoking status (ie, start 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 (see protocol section 3.2, criteria 15).	No	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).	No	No	No	No
23	Patient with heart rate <50 bpm.	No	No	No	No
24	Patient has clinically significant uncontrolled hypertension	No	No	No	No

		Excluded from analysis set			
Item #	**Event description**	**PPS**	**SAF**	**PKS**	**FAS**
26	Patient with seizures or history of seizures requiring anticonvulsants within 12 months prior to Screening.	No	No	No	No
27	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.	No	No	No	No
28	Patient with symptomatic bladder neck obstruction, acute urinary retention or symptomatic non-stable prostate hypertrophy.	No	No	No	No
29	Patient has a serum potassium value <3.5 mmol/L at Screening and on repeat testing. Note: however potassium replacement and rescreening is allowed if serum potassium concentration was <3.5 mmol/L at Screening.	No	No	No	No
30	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.	No	No	No	No
31	Patient has known narrow-angle glaucoma.	No	No	No	No
32	Patient has a history of hypersensitivity to β_2-agonists, muscarinic anticholinergics or lactose/milk protein.	No	No	No	No
33	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.	No	No	No	No
34	Patient received a live attenuated vaccination within 30 days prior to Screening.	No	No	No	No
35	Patient donated or lost >500 mL of blood and plasma within the previous 3 months prior to Screening	No	No	No	No
34	Patient is unlikely to co-operate with the requirements of the study, instructions of the Principal Investigator (PI), or have e-dairy completion rate of <70% during the run-in period.	No	No	No	No
35	Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).	No	No	No	No
36	Patient previously enrolled in the present study	Yes	Yes	Yes	Yes
37	Participation in another clinical study with an IP within the last 30 days or 5 half-lives (whichever is longer) prior to Screening.	Yes^{+++}	No	Yes^{+++}	No
38	Patient with known human immunodeficiency virus (HIV) infection or chronic hepatitis B or C infection.	No	No	No	No
39	Patient did not fulfill fasting requirements on day 1, 8, and 14 before IP administration and following dose administration and prior to safety laboratory testing (protocol section 3.8, criteria 2 and 4)	No	No	No	No
40	Salbutamol not withheld at least 6 hours prior to each spirometry visit and ipratropium not withheld at least 8 hours before visits 3, 6, and 9.	Yes	No	No	No
41	Patient could not abstain from list in protocol section 3.8, criteria 7	No	No	No	No
42	Patient who had 2 or more exacerbations of COPD (moderate or severe in intensity) within the last year prior to Screening	Yes	No	No	No
43	Patient who took any concomitant medication not permitted by this protocol as described in Table 5 section 7.7 of the protocol and from the following class: Anticholinergics, B_2-adrenergic agonists, combinations(inhaled), corticosteroids, Methyl-xanthines, Mast-cell stabilizers, Leukotriene modifiers, Selective and non-selective β-blocking agents (oral or topical including eye drops), Phosphodiesterase IV inhibitors	Yes^{++}	No	Yes^{++}	No

		Excluded from analysis set			
Item #	**Event description**	**PPS**	**SAF**	**PKS**	**FAS**
44	The patient did not satisfy the FEV1 stability criterion at Visit 6 or 9: the mean of the pre-dose FEV1 should be within 20% or 200mL of the pre-best test review. (see secton 5.1.1 for details)	Yes	No	No	No
45	Incorrect study medication received.	Yes[++]	No	Yes[++]	No
46	Patient did not take any IP	Yes[++]	Yes	Yes[++]	Yes[++]
47	Overall treatment compliance < 70 % per treatment according to drug accountability	Yes[++]	No	Yes[++]	No
48	Subject was dispensed/administered the wrong kit of medication	Yes[++]	No	Yes[++]	No
49	Rescue medication (Salbutamol inhaler, 100 µg) used within 6 hours hours prior, and/or 36 hours post IP dosing in each period or ipatroprium used within 8 hours prior to first day within each period and during the treatment period	Yes[++]	No	Yes[++]	No
50	Procedure not performed (missing PK samples to prevent calculation of PK parameters).	No	No	Yes[++]	No
51	Missing baseline data for the spirometry (FEV1 main variable)	Yes[++]	No	No	No
52	Patient was not fasted for 8 hours prior to laboratory sampling	No	No	No	No
53	Patient was not fasted for 4 hours prior to iSTAT sampling per protocol specification	No	No	No	No
54	FEV1 and FVC measurements performed outside tolerance window	No	No	No	No
55	Fulfilling withdrawal criteria during the study but not withdrawn.	No	No	No	No
56	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
57	Other protocol deviations	Yes[+++]	No	Yes[+++]	No

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

3. PRIMARY AND SECONDARY VARIABLES

3.1 General definitions

Baseline will be calculated for each patient and each treatment period except for total score BCSS and for rescue medication which will have baseline calculated for each patient over the run-in period.

For spirometry variables, the baseline value for each treatment period is defined as the average of the two pre-dose values recorded on Day 1 of each period. If one of the values is missing, the available value will be used as baseline. If a patient's first period baseline value is missing, then the value at pre-bronchodilator at screening will be used. If the baseline value is missing for a subsequent treatment period (ie, the second, third treatment periods), then the average of the available baseline values for the other treatment periods for the patient will be used to impute the missing one. For example, if the third period baseline is missing, the average of the first, and second period baseline values will be imputed as the third period baseline value. Note that within a treatment period, for all FEV_1 endpoints, the same baseline FEV_1 value will be used; similarly for the FVC endpoints, the same baseline FVC value will be used.

Baseline for daily rescue medication use will be the daily average of puffs recorded in the e-Diary during the run-in period, prior to the first dose of double-blind investigational product; this baseline will be used as baseline for all treatments in each period. Baseline values will be computed only for those patients recording at least 4 diary entries during this period.

The average of the Total Score BCSS and cough, breathlessness and sputum individual domain scores obtained during the run-in period, prior to the first dose of double-blind investigational product, will be used as baseline for all treatments in each period. Baseline values will be computed only for those patients recording at least 4 diary entries during this period.

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.

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

Change from baseline for all spirometry variables, vital signs, laboratory variables including i-STAT, and ECG variables will be calculated as the value at the respective time point minus the value at baseline in the specific period.

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 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 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.

3.1.2 Repeated and unscheduled visits

In general, if a visit is repeated, at screening or at Day 1 visit, prior to first dose of IP in each Period, then all data collected at the repeated visit will be used in all analyses at Screening or Day 1.

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 non-missing 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.

3.1.2.2 Safety variables

For repeated laboratory tests, vital signs and ECG measurements that are taken on the same day and time as a pre-dose scheduled visit and time point (i.e. pre-dose at Day 1 of each Period), the latest non-missing result will be used for that visit and time point. For measurements that are taken on the same day and time as a post-dose scheduled visit and time point, the first non-missing result will be used for that visit and time point.

3.2 Assessment of study population

3.2.1 Demographic and baseline characteristic variables

- Demographic characteristics (including 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 FEV_1, 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, 20.0 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 parient.

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 24 h 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 considerd to be taken during wash-out periods if it is taken after 24 h 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 study overall will not be considered concomitant.

For the purpose of inclusion in prior or concomitant mediation summaries, incomplete medication start and stop dates will be imputed as detailed in Section 3.1.1.

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.

- The Day 1 and Day 14 FEV_1 trough value 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). The Day 8 FEV_1 trough 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.

- 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 30 minutes, 1 hour, 2 hours or 4 hours post-dose).
- Definition above also apply for 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 post-dose.

- 8 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, and 8 hours post-dose.

- 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, 23 hours, and 23.45 hours post-dose.

AUC is defined as the area under the curve, normalised for time.

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

$AUC_{0\text{-}24/24h}$, non-missing FEV_1 values at the following time points are required in order to calculate the normalised $AUC_{0\text{-}24/24h}$: pre-dose; 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 or 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 8 to Day 15)
- Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14)

3.3.1.3 Other FEV_1 -related variables

- Change from baseline in FEV_1 $AUC_{0\text{-}4/4h}$ on Day 1, Day 8, and Day 14
- Change from baseline in FEV_1 $AUC_{0\text{-}8/8h}$ on Day 1, and Day 14
- Change from baseline in FEV_1 $AUC_{0\text{-}24/24h}$ on Day 1, and Day 14
- Change from baseline in Trough FVC on Day 2, Day 8 and Day 14
- Change from baseline in Peak FVC on Day 1, Day 8, and Day 14
- Change from baseline in FEV_1 on Day 1, Day 8, and Day 14 at each timepoint

3.3.2 Other efficacy variables

3.3.2.1 Total Score BCSS and cough, breathlessness and sputum individual domain scores

The average of the Total Score BCSS and cough, breathlessness and sputum individual domain scores obtained the run-in period baseline will be used as baseline for all treatments in each period.

The daily change from baseline obtained after treatment in Total Score BCSS 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

3.3.2.2 Rescue medication use (Salbutamol)

The baseline for daily rescue medication use will be the daily average of puffs recorded in the e-Diary during the run-in period, prior to the first dose of double-blind investigational product; this baseline will be used as baseline for all treatments in each period.

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

3.3.2.3 Taste

For each evaluated item (Sweet, Salty, Sour, Bitter, Metallic, Hot/Spicy, Overall Rating,Smell, Would take again), the score (from 0 to 10) will be summarized by treatment. The answer (Y/N) to the question "Do you think this medicine smells?" and the duration of the taste of the medicine stays in the mouth will also be summarized by treatment.

3.4 Pharmacokinetic variables

The PK analyses of the plasma concentration data for AZD8871 and its metabolites (LAS191861 and LAS34850), will be performed at Covance, UK, on behalf of AstraZeneca.

The actual sampling times will be used in the plasma PK parameter calculations.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher. Pharmacokinetic 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 the AUC parameter to be summarised.

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

Day 1:

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

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

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

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

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

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

For metabolites LAS191861 and LAS34850 only:

MRCmax - Metabolite to parent ratio for Cmax

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

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

Day 14:

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

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

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

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

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

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

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

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

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

Rac (AUC_{0-24}) - Accumulation ratio for AUC_{0-24} estimated as (AUC_{0-24} on Day 14 / AUC0-24 on Day 1)

For metabolites LAS191861 and LAS34850 only:

MRCmax - Metabolite to parent ratio for C_{max}

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

3.5 Safety variables

3.5.1 Adverse events

AEs: The number and percentage of patients who experienced 1 or more TEAEs, and the number of TEAE occurrences will be tabulated by treatment group. An AE is considered TEAE if the event occurs after first dose of IMP. 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 30 days after the last IP administration will not be counted as a TEAE.

3.5.2 Serious adverse events

An 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 30 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 Laboratory variables

Laboratory parameters will be recorded at Visit 1, pre-dose at visits 3, 6, 9, and 24h postdose at visits 5, 8, 11, and at follow-up.

The laboratory variables detailed in

Table 2 Laboratory safety variables

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

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

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

will be recorded. In addition, serum 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
Coagulation parameters (INR, PTT and aPTT)[a]	S/P-Calcium, total
	S/P-Chloride
Urinalysis (dipstick)	S/P-Phosphorus, inorganic
U-pH	S/P-AST
U-Blood	S/P-ALT
U-leucocytes	S/P-ALP
U-Protein	S/P-GGT
U-Glucose	S/P-LDH
U-Bilirubin	S/P-Creatine kinase
U-Urobilinogen	
U-Ketones	
U-Nitrites	

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

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

3.5.4 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.

Number of ECG abnormalities in each category of conduction defects, rhythsm, MI signs and others will be reported at each timepoint from each day within each treatment.

The following ECG parameters will be analyzed:

- Heart rate
- RR interval: Duration in milliseconds between two R peaks of two consecutive
- QRS complexes
- PR interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: Duration in milliseconds of the QRS complex
- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T wave
- QTc interval: QT interval corrected by heart rate:
  - QTcB interval: QT interval corrected using Bazett formula (QT[msec]/RR[sec]1/2)
  - QTcF interval: QT interval corrected using Fridericia's formula (QT[msec]/RR[sec]1/3)

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

3.5.5 Vital signs

Systolic and diastolic blood pressure (BP) will be recorded at screening, pre-dose and 1, 2, 4, and 24 hours at Visits 3, 5, 6, 8, 9 and 11. On Visits 4, 7 and 10 blood pressure will be measured at pre-dose, 1 and 4 hours post-dose, and follow-up.

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 Placebo and
- AZD8871 100 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. As such, no formal hypothesis testing will be performed for this study and results from statistical analyses cannot be interpreted in terms of statistical significance.

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 100 µg, AZD8871 600 µg, 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, 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.

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 be presented, but these cannot be interpreted in terms of statistical significance. The presentation of p-values will be to three decimal places unless a p-value is less than 0.001, in which case "<0.001" will be displayed.

A month is operationally defined to be 30.4 days

4.2 Analysis methods

4.2.1 Analyses of study population

4.2.1.1 Patient disposition

The number and percentage of patients who are screen failures (i.e., patients screened but not randomised), will be summarised overall for the screening analysis set. The reson for screen failure will be listed.

The number and percentage of patients screened, 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 the screening analysis set.

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 analysis set. 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 Safety population.

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

- Age (years)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2), calculated as follows (where height is in metres): $\frac{weight}{height^2}$
- 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:
$$\frac{\text{date of most recent exacerbation} - \text{date of diagnosis of COPD}}{30.4}$$
- 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 (%)
- FEV_1 absolute reversibility at screening (mL)
- Bronchial reversibility at screening (%)
- Baseline FEV_1 (L)
- Baseline FVC (L)
- Baseline FEV_1 % predicted
- Baseline FVC % predicted

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

- 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 ≥ 50% and < 80%
    - Stage III (severe): post-bronchodilator FEV_1/FVC < 70% and post-bronchodilator FEV_1 % predicted ≥ 30% and < 50%
- Reversible at screening (Yes, No). A patient is defined as being reversible if bronchial reversibility ≥ 12% and FEV_1 absolute reversibility ≥ 200 mL.

Medical history will be listed and the number and percentage of patients with any medical history will be summarised for the safety analysis set 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 for the safety analysis set. Those medications continuing after ICF will be reported as well and classified in both prior and concomitant medication groups.

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 safety analysis set, using descriptive statistics.

4.2.1.4 Treatment compliance

Treatment compliance (%) will be summarised by treatment for the safety analysis set, 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 analysis set.

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 100 µg versus Placebo
- AZD8871 600 µg versus Placebo

Treatment comparison among active treatments will be also explored.

A sensitivity analysis will be conducted for internal validity purposes, whereby patients with important deviations from protocol deemed to affect efficacy will be excluded from the analysis (see Section 2.2). To confirm the achievement of the main objectives of this study, the above summary and analysis of change from baseline in trough FEV_1 at Day 15 will be

repeated for the PP analysis set, with those patients with any important protocol deviation affecting efficacy being excluded from the FAS set for the respective treatments.

An additional sensitivity analysis will be performed using for 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.

For all mixed models, the estimation method used will be Restricted Maximum Likelihood (REML). The Kenward and Roger version of the F-test 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 analysis set 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 8 to Day 15)
- Change from baseline in Peak FEV_1 over treatment duration (Day 8 to Day 14)

The analyses of the 2 above endpoints will be performed using the FAS analysis set. 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 8 and Day 15) 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 version of the F-test will be used.

4.2.4 Analysis of the other FEV_1 -related variables

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

- Change from baseline in FEV_1 $AUC_{0\text{-}4/4h}$ at Day 1, Day 8, and Day 14
- Change from baseline in FEV_1 $AUC_{0\text{-}8/8h}$ at Day 1, and Day 14

- Change from baseline in FEV_1 $AUC_{0\text{-}24/24h}$ at Day 1, and Day 14
- Change from baseline in Trough FVC on Day 2, Day 8, and Day 15
- Change from baseline in Peak FVC on Day 1, Day 8, 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 analysis set 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.

4.2.5 Analysis of the other efficacy variables

The change from baseline in Total Score BCSS 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 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.

4.2.6 Exploratory outcome variables

4.2.6.1 Taste Assessment

For each evaluated item (Sweet, Salty, Sour, Bitter, Metallic, Hot/Spicy, Overall Rating,Smell, Would take again), the score (from 0 to 10) will be summarized by treatment.

4.3 Analysis of pharmarcokinetic variables

4.3.1.1 Descriptive statistics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. AZD8871, LAS191861 and LAS34850 plasma concentrations will be listed by subject and time-point.

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

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

- Where there is NR, these will be set to missing.

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

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

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

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

For display in figures:

• For mean plots: BLQ values will be handled as described for the descriptive statistics. If this handling results in a geometric mean of "NA", "ND" or "BLQ", then the value plotted at that time-point will not be plotted (made missing)

• For individual plots and combined individual plots: BLQ values will be set to zero on Day1, pre-dose; at all other time-points, BLQ values will be set to missing

All plasma PK parameters for AZD8871 and metabolites will also be listed and summarised using using the same descriptive statistics as for the plasma concentrations, based on the PKS. Summaries will be presented by dose level of AZD8871, Day and parameter. For t_{max} only n, median, minimum and maximum will be reported.

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

Geometric mean: Calculated as exp[ML]

Geometric mean +/- geometric SD: Calculated as exp[ML +/- SDL]

Geometric CV% : Calculated as 100 x sqrt[exp(S_L^2) – 1]

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

• SDL is the arithmetic standard deviation of the natural log-transformed variable

• ML is the arithmetic mean of the natural log-transformed variable

• exp denotes the power function based on the natural base e

• The variable will not be calculated if one more of the raw values (prior to log-transform) is zero

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

Individual plasma concentrations versus actual time will be plotted in linear and semi logarithmic scale, with separate plots for each subject and concentrations for Day 1 and Day 14 (where applicable). Combined individual plasma concentration per dose level of AZD8871 will also be presented in linear and semi logarithmic scale with separate plots for each dose level and day (Day 1 and Day 14).

Figures for the geometric mean (± geometric SD) concentration-time data will be presented for all doses overlaid on the same plot, in both a linear and semi-logarithmic scale, with each Day (Day 1 and Day 16) overlaid on the same plot..

All plots will be repeated for AZD8871 and its metabolites. All mean and combined individual plots will be based on the PK analysis set. All individual plots will be based on the safety analysis set.

Additional graphical presentations of PK data may be added at the discretion of the PK Scientist.

4.3.1.2 Analysis of $AUC_{(0-24)}$, C_{max} at Day 1 and Day 14 and accumulation between Day 1 and Day 14

$AUC_{(0-24)}$ 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, dose, day and dose by day interaction 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. Product accumulation will be evaluated by comparing $AUC_{(0-24)}$ (Day 14) with $AUC_{(0-24)}$ (Day 1) and C_{max} (Day 14) with C_{max} (Day 1) 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 safety analysis set. 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 severity, outcome, action taken with IMP , and relationship to study drug.

Any AE occurring before the first dose of IP, or more than 30 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

If severity is missing for a TEAE, then a severity of severe will be assigned. The imputed values for severity will be used for the summary of TEAEs by severity; the actual values will be presented in the data listings.

If the relationship to treatment is missing for a TEAE, a relationship of related will be assigned. The imputed values for relationship to treatment will be used for the summary of TEAEs by relationship to treatment; the actual values will be presented in data listings.

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 causally related to treatment
- All TEAE with outcome = death
- All TEAE with outcome = death, causally related to treatment
- All TESAE (including events with outcome = death)
- All TESAE (including events with outcome = death), causally related to treatment
- 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, HLT, and PT (this table will also include the number and percentage of TEAEs episodes).
- SOC, PT, and intensity
- SOC, PT, and causality with the IMP
- SOC, PT and seriousness
- SOC, PT and action taken
- SOC, PT and outcome

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.

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 extended 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 $\geq 3 \times$ the upper limit of normal [ULN] and total bilirubin $\geq 2 \times$ 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 postdose 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 (±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 (low, normal or high as above) at baseline to a postbaseline 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 4 and the ratio of endpoint value to baseline value is also greater than the corresponding coefficient (multiplying factor) specified in Table 4, 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 × 10^9/L	NA
White Blood cells				
Total	0.85 × LLN	1.15 × ULN	< 1 × 10^9/L	> 30 × 10^9/L
Neutrophils	0.85 × LLN	1.15 × ULN	< 0.5 × 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
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

Table 3 Expanded normal ranges and notable abnormalities for laboratory parameters

Laboratory Parameter	***Expanded Normal Ranges***		***Notable Abnormalities***	
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 ECG parameters will be summarised by treatment, day (Day 1, 8, and 14) and timepoint within day, 95% confidence intervals for the change from baseline will be provided in addition to the usual descriptive statistics parameters.

Graphical presentation of mean change from baseline (±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 **Error! Reference source not found.**. 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
Criterions:
>450 (ms)
>480 (ms)
>500 (ms)

Category 2: QTcF increase by more than following cut-off at any time during treatment
Criterions:
>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 < 120 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	≥ 250 msec if baseline is < 250 msec

baseline value

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 ± 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 < 200
	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.

5. INTERIM ANALYSES (NOT APPLICABLE)

6. CHANGES OF ANALYSIS FROM PROTOCOL

Additional exploratory endpoints for efficacy were added

- Change from baseline in FEV_1 $AUC_{0\text{-}4/4h}$ at Day 1, Day 8, and Day 14
- Change from baseline in FEV_1 $AUC_{0\text{-}8/8h}$ at Day 1, and Day 14
- Change from baseline in FEV_1 $AUC_{0\text{-}24/24h}$ at Day 1, and Day 14
- Change from baseline in Trough FVC on Day 2, Day 8, and Day 15
- Change from baseline in Peak FVC on Day 1, Day 8 and Day 14
- Additional exploratory endpoints were added

Change in definition of TEAE:

An AE will be considered a TEAE if it was not present prior to the date of the first dose of IP. As opposed to what is presently written in the protocol, AE present prior to the date of the first dose of IP and that increased in severity after IP administration will not be considered TEAE.

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 $AUC_{0\text{-}4}$ at Day 1, Day 8, and Day 14 and $AUC_{0\text{-}24}$ at Day 1 and Day 14. No formal analysis of other parameter will be performed.

7. REFERENCES (NOT APPLICABLE)

8. APPENDIX (NOT APPLICABLE)