Clinical Study Report Synopsis

Drug Substance	AZD2115
Study Code	D3060C00003
Edition Number	1
EudraCT Number	NCT01498081

A Randomised, Double-Blind, Placebo- and Active-Controlled, Multi-Centre, 6-Way Cross-Over, Single-Dose Phase IIa Study to Investigate the Local and Systemic Effects of 3 Different Doses of Inhaled AZD2115 in Patients with Chronic Obstructive Pulmonary Disease (COPD)

Study dates: First patient enrolled: 22 March 2012
Last patient last visit: 23 October 2012

Phase of development: Therapeutic exploratory (IIa)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The objectives and criteria for evaluation are described in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacodynamic	To investigate the local bronchodilatory effects of 3 different doses of AZD2115 compared with placebo, with respect to peak and trough FEV_1, in patients with COPD	Primary variables: Peak FEV_1 (E_{max}) and trough FEV_1 ($E_{22\text{-}26h}$) Secondary variables: Average FEV_1 (E_{av}), peak FVC (E_{max}), average FVC (E_{av}), and trough FVC ($E_{22\text{-}26h}$)
Secondary	Pharmacodynamic	To investigate the local bronchodilatory effects of 3 different doses of AZD2115 compared with active comparators, in patients with COPD	Peak FEV_1 (E_{max}), trough FEV_1 ($E_{22\text{-}26h}$), and average FEV_1 (E_{av}), peak FVC (E_{max}), average FVC (E_{av}), and trough FVC ($E_{22\text{-}26h}$)
Secondary	Safety	To investigate the safety and tolerability of single doses of AZD2115	AEs, safety laboratory variables, physical examination, pulse, BP, dECG variables (HR and RR, PR, QRS, QT duration, QTcF), pECG (normal/abnormal), and spirometry (FEV_1, FVC)
Secondary	Pharmacodynamic	To investigate the systemic effects of 3 different doses of AZD2115	Peak and average value 0 to 4 hours for systolic BP, HR, QTcF, and glucose. Minimum and average value 0 to 4 hours for diastolic BP and potassium
Secondary	Pharmacodynamic	To investigate the dose-response pattern of AZD2115 within the tested dose range	Peak FEV_1 (E_{max}), trough FEV_1 ($E_{22\text{-}26h}$), and average FEV_1(E_{av})
Secondary	Pharmacokinetics	To investigate AZD2115 plasma exposure after single inhaled doses of AZD2115	Plasma concentrations of AZD2115, t_{max}, C_{max}, $AUC_{(0\text{-}24h)}$, and $AUC_{(0\text{-}t)}$

Note: Exploratory objectives are mentioned in the CSR, results of which will be reported separately.

AEs Adverse events; $AUC_{(0\text{-}24h)}$ Area under the plasma concentration-time curve from 0 to 24 hours; $AUC_{(0\text{-}t)}$ Area under plasma concentration curve from 0 to last time point with measurable concentration; BP Blood pressure; C_{max} Maximum plasma concentration observed; COPD Chronic obstructive pulmonary disease; CSR Clinical study report; dECG Digital electrocardiogram; $E_{22\text{-}26h}$ The average effect over 22 to 26 hours; E_{av} Average from 0 to 24 hours; E_{max} The maximum value over 24 hours post-dose; FEV_1 Forced expiratory volume in the first second; FVC Forced vital capacity; HR Heart rate; pECG Paper print-out electrocardiogram; QTcF QT interval corrected for heart rate using Fridericia's formula; t_{max} Time to reach maximum plasma concentration observed.

Study design

This was a double-blind, triple-dummy, placebo- and active-controlled, randomised, 6-way cross-over, single dose, Phase IIa study in patients with chronic obstructive pulmonary disease (COPD). The randomisation was done in balanced blocks across the study using Williams' design to control the sequences of the treatments. Randomisation codes (patient numbers) were assigned strictly sequentially as patients became eligible for randomisation.

Target subject population and sample size

The target population was patients aged ≥40 years with COPD for >1 year, (according to Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2010), current or ex-smokers with a smoking history of ≥10 pack-years, forced expiratory volume in the first second (FEV_1) ≥40 to <80% of the predicted normal value (post-bronchodilator), and post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.

Based on the results from previous studies with other bronchodilators, a coefficient of variation of 6% was expected for peak FEV_1 (E_{max}, the maximum value over 24 hours post-dose). Based on this assumption and using a 2-sided test at a 5% significance level, 36 patients were planned to be randomised, which would give an 80% power to detect a pair-wise difference of 4.1%. The variability in trough FEV_1 ($E_{22\text{-}26h}$, the average effect over 22 to 26 hours) was expected to be 7.5%, giving a detectable difference of 5.2%. This detection potential was considered sufficient for evaluating the primary objective and the dose-response pattern.

Investigational product and comparators: Dosage, mode of administration, and batch numbers

The details of the investigational products (IPs) are given in Table S2.

Table S2 Details of investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
AZD2115	Nebuliser solution, 0.13 mg/g, and 0.41 mg/g, 1.22 mg/g. The fill volume in the vials was 1 mL[a]	AstraZeneca	AZD2115 nebuliser solution 0.13 mg/g: 11-003213AZ AZD2115 nebuliser solution 0.41 mg/g: 11-003214AZ AZD2115 nebuliser solution 1.22 mg/g: 11-003215AZ
Placebo for AZD2115	Nebuliser solution, 1 mL	AstraZeneca	11-003212AZ

Table S2 Details of investigational products

Investigational product	Dosage form and strength	Manufacturer	Batch number
Onbrez® [1](indacaterol)	Inhalation powder, (hard capsule), 150 µg	Novartis	12-000401AZ
Placebo for Onbrez® (indacaterol)	Inhalation powder, (hard capsule)	AstraZeneca	11-003486AZ
Spiriva®[2] (tiotropium)	Inhalation powder, (hard capsule), 18 µg	Boehringer Ingelheim	11-003487AZ
Placebo for Spiriva® (tiotropium)	Inhalation powder, (hard capsule)	AstraZeneca	11-003489AZ

[a] For AZD2115, 0.25 mL of the vial content was given.

During the study, each patient received the following single doses of 6 different treatments according to the randomised, cross-over, triple-dummy design:

- AZD2115 25 µg (predicted lung-deposited dose) inhaled via I-neb® adaptive aerosol delivery (AAD) system
- AZD2115 80 µg (predicted lung-deposited dose) inhaled via I-neb® AAD system
- AZD2115 240 µg (predicted lung-deposited dose) inhaled via I-neb® AAD system
- Onbrez® (indacaterol) 150 µg inhaled via the Breezhaler® device plus Spiriva® (tiotropium) 18 µg inhaled via the HandiHaler® device
- Onbrez® (indacaterol) 150 µg inhaled via the Breezhaler® device
- Placebo matching AZD2115, Onbrez® (indacaterol), and Spiriva® (tiotropium) inhaled via I-neb® Breezhaler® and HandiHaler®, respectively.

The IP was given in the morning of each treatment visit (Visit 4 to Visit 9). To maintain blinding, patients were to inhale from I-neb®, Breezhaler®, and HandiHaler® at each visit.

[1] Onbrez® (indacaterol) is a registered trademark of Novartis.

[2] Spiriva® (tiotropium) is a registered trademark of Boehringer Ingelheim.

The predicted dose deposited in the lungs was based on *in vitro* data for the nebuliser and an assumed breathing pattern. The 25 µg, 80 µg, and 240 µg predicted lung-deposited dose of AZD2115 corresponds to 32 µg, 103 µg, and 308 µg delivered dose, respectively.

Ventolin®[3] (salbutamol, pressured metered dose inhaler [pMDI]) inhaler was used as reliever medication during the study visits; however, the investigator was to be consulted before using any reliever medication.

Duration of treatment

Each patient received single doses of 6 different treatments. The patients stayed at the clinic until 26 hours post-dose. The enrolment period was 3 days to 30 days. The aim was to have a wash-out period of 14 days to 21 days in between treatments. The planned total study duration for each patient was 13 weeks to 22 weeks.

Statistical methods

Efficacy/Pharmacodynamics (PD) analysis: The primary variables for the primary objective (peak FEV_1 [E_{max}] and trough FEV_1 [$E_{22\ to\ 26h}$]) were analysed using multiplicative analysis of covariance (ANCOVA) models adjusting for patient as random factor, treatment, period, and country as fixed factors and baseline FEV_1 (baseline FEV_1 was calculated as the mean value of the measurements at 30 minutes and 15 minutes prior to dose at each treatment) value as a covariate. A multiplicative model was used (ie, the FEV_1 variables were log-transformed prior to analysis and the result was then transformed back to the linear scale) and significance tests were 2-sided at a 5% significance level. Average FEV_1 (E_{av}, average FEV_1 from 0 to 24 hours) and FVC (peak, trough, and average) were used as secondary variables for evaluating the local effects of 3 doses of AZD2115 compared with placebo. Average FEV_1 was analysed and presented in the same way as the primary variables. As supportive analysis, tests were performed for the secondary variable, FVC, using the multiplicative ANCOVA model.

To evaluate secondary objective variables, local bronchodilatory effects were analysed using the same multiplicative ANCOVA models as in analysis of primary objective; systemic effects were analysed using an additive ANCOVA model (using untransformed data) with patient as random factor, treatment, period, and country as fixed factors and baseline value as a covariate. Dose-response was analysed using the multiplicative model.

Pharmacokinetics (PK) analysis: Plasma concentrations of AZD2115 and the following 4 PK parameters were computed:

- C_{max}: Maximum plasma concentration observed
- t_{max}: Time to reach maximum plasma concentration observed

[3] Ventolin® (salbutamol, pMDI) is a registered trademark of GlaxoSmithKline.

- $AUC_{(0-24h)}$: Area under the plasma concentration-time curve from 0 to 24 hours post-dose, calculated by the linear/log trapezoidal method

- $AUC_{(0-t)}$: Area under the plasma concentration-time curve from 0 to last time point with measurable concentration, calculated by the linear/log trapezoidal method.

Safety: The safety of AZD2115 was evaluated by assessment of the number and percentage of adverse events (AEs), clinical laboratory assessments (haematology, clinical chemistry, and urinalysis), physical examination, vital signs (pulse and blood pressure [BP]), heart rate (HR), electrocardiogram (ECG), and spirometry (FEV_1 and FVC).

PK and safety parameters were described using descriptive statistics. Shift tables and shift plots were also presented for the safety parameters.

Subject population

The number of patients allocated to each treatment period was similar. Of the 65 patients enrolled, 39 (60%) patients were randomised into the study and of these 33 (84.6%) patients completed the study. No patient discontinued the study due to an AE during the AZD2115 treatment periods (Table S3).

All the patients in this study were White, with a mean age of 65.9 years (range: 54 years to 80 years). A higher number of male patients (25 [64.1%]) were randomised in the study as compared with female patients (14 [35.9%]). There were more patients that were former smokers (24 [61.5%]) as compared with current smokers (15 [38.5%]) in the study. The average duration of COPD was 6.8 years (range: 1 year to 22 years). All the 39 randomised patients fulfilled the inclusion criterion of at least 12% reversibility to salbutamol at Visit 2 and 12% reversibility to ipratropium at Visit 3; thus, patients demonstrated bronchodilation through both the β-adrenergic pathway and the muscarinic pathway.

The demographic and baseline patient characteristics were reflective of the inclusion and exclusion criteria as defined in the Clinical Study Protocol (CSP). Thus, the study population was representative of the target population as defined in the CSP.

Table S3 Patient disposition (All Patients)

	Number (%) of patients Total
Patients enrolled[a]	65 (100.0)
Patients randomised	39 (60.0)
Patients who received treatment	
AZD2115 25 µg	33 (84.6)
AZD2115 80 µg	36 (92.3)
AZD2115 240 µg	35 (89.7)
Indacaterol 150 µg + tiotropium 18 µg	34 (87.2)

Table S3 Patient disposition (All Patients)

	Number (%) of patients Total
Indacaterol 150 µg	35 (89.7)
Placebo	35 (89.7)
Patients who completed treatment	
AZD2115 25 µg	33 (84.6)
AZD2115 80 µg	36 (92.3)
AZD2115 240 µg	35 (89.7)
Indacaterol 150 µg + tiotropium 18 µg	34 (87.2)
Indacaterol 150 µg	35 (89.7)
Placebo	35 (89.7)
Patients completed study	33 (84.6)
Patients withdrawn from study	6 (15.4)
Reason for discontinuation	
Patient decision	1 (2.6)
Eligibility criteria not fulfilled	2 (5.1)
Death	0 (0.0)
Adverse Event	1 (2.6)
Severe non-compliance to protocol	0 (0.0)
Development of study-specific withdrawal criteria	2 (5.1)
Subject lost to follow-up	0 (0.0)
Other	0 (0.0)

[a] Informed consent received.
Percent of patients randomised is based on number of patients enrolled; other percentages are based on number of patients randomised.
AZD2115 (25 µg, 80 µg, and 240 µg, predicted lung-deposited doses) nebuliser solution inhaled via I-neb®.
Indacaterol (Breezhaler®) 150 µg+tiotropium 18 µg (HandiHaler®).
Indacaterol (Breezhaler®) 150 µg.
Placebo: Placebo matching AZD2115, indacaterol, and tiotropium.

Summary of pharmacokinetic results

Based on visual inspection, the increase in AZD2115 plasma exposure (C_{max} and $AUC_{[0-t]}$) was dose-proportional for lung-deposited doses ranging from 25 µg to 240 µg. C_{max} occurred at approximately 22 minutes after inhaled dose and was independent of the dose.

The $AUC_{(0-24h)}$ could not be evaluated in the lowest dose as plasma concentrations were below the lower limit of quantification. The $AUC_{(0-24h)}$ increased in proportion to dose in the dose range of 80 µg to 240 µg of AZD2115.

Summary of pharmacodynamic results

Primary objective (local effects of the 3 doses of AZD2115 against placebo)

Primary variables

The results of the primary variables for primary objective, ie, peak FEV_1 and trough FEV_1, are summarised below.

Peak FEV_1 (E_{max}): Single doses of AZD2115 (240 µg, 80 µg, and 25 µg) demonstrated a statistically significant bronchodilatory effect compared with placebo. The geometric mean ratios (GMRs), 95% confidence intervals (CIs) and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.18, CI 1.13 to 1.22, p-value <0.001
- AZD2115 80 µg: GMR 1.15, CI 1.10 to 1.20, p-value<0.001
- AZD2115 25 µg: GMR 1.11, CI 1.06 to 1.16, p-value<0.001.

Trough FEV_1 ($E_{22\ to\ 26h}$): Only 240 µg of AZD2115 demonstrated a statistically significant bronchodilatory effect compared with placebo. The GMRs, 95% CIs, and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.07, CI 1.03 to 1.13, p-value=0.003
- AZD2115 80 µg: GMR 1.04, CI 0.99 to 1.09, p-value=0.135
- AZD2115 25 µg: GMR 1.00, CI 0.95 to 1.05, p-value=0.985

Secondary variables

The results of the secondary variables for the primary objective, average FEV_1 and FVC, are summarised below.

Average FEV_1 (E_{av}): The 3 doses of AZD2115 (240 µg, 80 µg, and 25 µg) demonstrated a statistically significant bronchodilatory effect compared with placebo. The GMRs, 95% CIs, and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.17, CI 1.12 to 1.22, p-value<0.001
- AZD2115 80 µg: GMR 1.11, CI 1.07 to 1.16, p-value<0.001
- AZD2115 25 µg: GMR 1.06, CI 1.02 to 1.11, p-value=0.002.

FVC (peak, average, and trough): For peak, average, and trough FVC, the results were similar to the results for the respective FEV_1 with an exception for trough FVC where the AZD2115 80 µg dose also reported a statistically significant bronchodilatory effect against placebo.

Secondary objectives

Local effects of the 3 doses of AZD2115 against active comparators

Peak FEV_1: The results of the secondary objective with regard to peak FEV_1 are summarised below.

Comparisons of peak FEV_1 between AZD2115 and indacaterol 150 µg+tiotropium 18 µg: Single doses (240 µg, 80 µg, and 25 µg) of AZD2115 did not demonstrate a statistically significant difference in bronchodilatory effect when compared with the combination of indacaterol 150 µg+tiotropium 18 µg. The GMRs, 95% CIs and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.02, CI 0.98 to 1.06, p-value=0.285
- AZD2115 80 µg: GMR 1.00, CI 0.96 to 1.04, p-value=0.952
- AZD2115 25 µg GMR 0.96, CI 0.92 to 1.00, p-value=0.070.

Comparisons of peak FEV_1 between AZD2115 and indacaterol 150 µg: Only the highest dose of AZD2115 (240 µg) demonstrated a statistically significant bronchodilatory effect compared with indacaterol 150 µg. The GMRs, 95% CIs, and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.06, CI 1.02 to 1.11, p-value=0.003
- AZD2115 80 µg: GMR 1.04, CI 1.00 to 1.08, p-value=0.057
- AZD2115 25 µg: GMR 1.00, CI 0.96 to 1.04, p-value=0.906.

Trough FEV_1: The results of the secondary objective with regard to trough FEV_1 are summarised below.

Comparisons of trough FEV_1 between AZD2115 and indacaterol 150 µg+tiotropium 18 µg: The highest dose of AZD2115 (240 µg) did not demonstrate statistically significant difference in bronchodilatory effect when compared with indacaterol 150 µg+tiotropium 18 µg combination. However, the 2 lower doses of AZD2115 (80 µg and 25 µg) showed statistically significantly lower effects. The GMRs, 95% CIs and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 0.96, CI 0.92 to 1.01, p-value=0.089
- AZD2115 80 µg: GMR 0.93, CI 0.88 to 0.97, p-value=0.001
- AZD2115 25 µg: GMR 0.89, CI 0.85 to 0.94, p-value<0.001.

Comparisons of trough FEV_1 between AZD2115 and indacaterol 150 µg: AZD2115 240 µg and AZD2115 80 µg did not demonstrate statistically significant

bronchodilatory effects when compared with indacaterol 150 µg. However, the lowest dose of AZD2115 (25 µg) showed a statistically significantly lower effect. The GMRs, 95% CIs and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.01, CI 0.97 to 1.06, p-value=0.566
- AZD2115 80 µg: GMR 0.98, CI 0.93 to 1.02, p-value=0.326
- AZD2115 25 µg: GMR 0.94, CI 0.90 to 0.99, p-value=0.015.

Average FEV_1: The results of the secondary objective with regard to average FEV_1 are summarised below.

Comparisons of average FEV_1 between AZD2115 and indacaterol 150 µg+tiotropium 18 µg: The highest dose of AZD2115 (240 µg) did not demonstrate statistically significant difference in bronchodilatory effect when compared with 150 µg+tiotropium 18 µg combination. However, the 2 lower doses of AZD2115 (80 µg and 25 µg) showed statistically significantly lower effects. The GMRs, 95% CIs, and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 0.98, CI 0.94 to 1.02, p-value=0.301
- AZD2115 80 µg: GMR 0.93, CI 0.90 to 0.97, p-value<0.001
- AZD2115 25 µg: GMR 0.89, CI 0.86 to 0.93, p-value<0.001.

Comparisons of average FEV_1 between AZD2115 and indacaterol 150 µg: The highest dose of AZD2115 (240 µg) demonstrated a statistically significantly higher bronchodilatory effect compared with indacaterol 150 µg. AZD2115 80 µg did not demonstrate statistically significant difference in bronchodilatory effect and the lowest dose of AZD2115 (25 µg) showed a statistically significantly lower effect when compared with indacaterol 150 µg. The GMRs, 95% CIs, and 2-sided p-values for these comparisons are as follows:

- AZD2115 240 µg: GMR 1.05, CI 1.01 to 1.09, p-value=0.011
- AZD2115 80 µg: GMR 1.00, CI 0.96 to 1.04, p-value=0.966
- AZD2115 25 µg: GMR 0.96, CI 0.92 to 1.00, p-value=0.029.

FVC (peak, average, and trough): The results for peak, average, and trough FVC were similar to the results for the respective FEV_1 with an exception for AZD2115 25 µg that did not demonstrate statistically significant difference in bronchodilatory effect against indacaterol 150 µg for trough and average FVC.

Systemic effects of the 3 different doses of AZD2115

Inhalation of a single dose of AZD2115 240 µg demonstrated statistical significance in least square mean differences compared with placebo during 0 to 4 hours with regard to:

- Decrease in minimum and average diastolic BP (-2.95 mmHg and -2.02 mmHg, respectively),
- Increase in maximum and average HR (5.12 beats/min and 4.40 beats/min, respectively),
- Increase in maximum and average QT interval corrected for heart rate using Fridericia's formula (QTcF) (5.70 ms and 4.14 ms, respectively),
- Increase in maximum and average glucose (0.85 mmol/L and 0.78 mmol/L, respectively) and
- Decrease in minimum potassium (-0.23 mmol/L) during 0 to 4 hours post-dose in patients with COPD.

No statistically significant differences in systemic effects were observed for AZD2115 (25 µg and 80 µg), when compared with placebo.

Dose response pattern

Single doses of AZD2115 demonstrated a dose-response relationship between 25 µg to 240 µg for peak, average, and trough FEV_1 in the studied COPD population.

Change in FEV_1 over time

Inhalation of single doses of AZD2115 (25 µg, 80 µg, and 240 µg) resulted in a rapid dose-related increase in FEV_1 with distinct peak within 2 hours post-dose followed by a progressive decrease. For the 2 lowest doses, the bronchodilatory effect was not sustained for 24 hours post-dose.

Summary of safety results

A summary of the AEs reported for this study is presented in Table S4. Overall, there were few AEs observed in the study. The proportion of patients with AEs was higher during AZD2115 240 µg and AZD2115 80 µg treatment periods as compared with AZD2115 25 µg, indacaterol 150 µg+tiotropium 18 µg, indacaterol 150 µg, and placebo treatment periods (Table S4). The most commonly reported AEs were dysgeusia (bitter taste) and headache. Except for indacaterol 150 µg, dysgeusia was reported during all the treatment periods, most of the cases being reported on AZD2115 80 µg and AZD2115 240 µg. Headache was reported during all the treatment periods except treatment with AZD2115 240 µg.

There were no AEs with fatal outcome in this study. One patient (E2002003) experienced an SAE (craniocerebral injury) in the wash-out period after placebo treatment period and 1

patient (E1002003) experienced an SAE (presyncope) before randomisation. One patient (E1001008) on indacaterol 150 µg discontinued the treatment due to ventricular extrasystoles, which was considered to be moderate in intensity with a reasonable possibility of a causal relationship to the IP as judged by the investigator.

A transient decrease in mean potassium value and an increase in mean glucose value were observed during the AZD2115 240 µg treatment period. The effects peaked at 2 hours post-dose and were almost reversed within 8 hours. No trends over time and between the treatment periods were observed for other laboratory measurements.

There were no clinically significant changes from baseline to 24 hours post-dose in vital signs during any of the treatment periods. For QTcF, a single dose of AZD2115 240 µg demonstrated statistically significant prolongation versus placebo 0 to 4 hours post-dose, but without pattern of abnormal individual outliers of >30 ms. In parallel, a transient increase in HR was observed for this dose.

There were no clinically relevant safety changes with respect to FEV_1 and FVC in the study. No case of post-dose bronchoconstriction was observed in this study.

AZD2115 was generally well tolerated at single inhaled predicted lung-deposited doses up to 240 µg in COPD patients.

Table S4 Adverse Events in any category (Safety Analysis Set)

	Number (%) of patients[a]					
AE category	**AZD2115 25 µg (N=33)**	**AZD2115 80 µg (N=36)**	**AZD2115 240 µg (N=35)**	**Indacaterol 150 µg+ tiotropium18 µg (N=34)**	**Indacaterol 150 µg (N=35)**	**Placebo (N=35)**
Any AE	3 (9.1)	8 (22.2)	8 (22.9)	4 (11.8)	4 (11.4)	5 (14.3)
Any AE with outcome = death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE (including events with outcome = death)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)
Any AE leading to discontinuation of IP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Any other significant AE[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as Other Significant AEs (OAEs).

AZD2115 (25 µg, 80 µg, and 240 µg, predicted lung-deposited doses) nebuliser solution inhaled via I-neb®.
Indacaterol (Breezhaler®) 150 µg + tiotropium 18 µg (HandiHaler ®).
Indacaterol (Breezhaler®) 150 µg.
Placebo: Placebo matching AZD2115, indacaterol and tiotropium.
Active study treatment and washout/follow-up are included in each treatment interval.
There were 2 SAEs in this study. Patient E1002003 experienced an SAE (presyncope) before randomisation.
AE Adverse event; IP Investigational product; N Number of patients; SAE Serious adverse event.