Clinical trial results:
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

Summary

EudraCT number	2016-002863-32
Trial protocol	GB DE
Global end of trial date	18 August 2017

Results information

Result version number	v1 (current)
This version publication date	01 July 2018
First version publication date	01 July 2018

Trial information

Trial identification

Sponsor protocol code	D6640C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	2 Kingdom Street, London, United Kingdom, W2 6BD
Public contact	Study Information Centre, AstraZeneca Clinical, Information.centre@astrazeneca.com
Scientific contact	Dr Ioannis Psallidas, MD, PhD, AstraZeneca, Information.centre@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study was to assess the efficacy, safety and pharmacokinetics (PK) of AZD8871 after a 14-day treatment period at 2 different doses in patients with moderate to severe COPD.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics. Informed consent was given freely after the subject was informed of the nature, significance, implications and risks of the study; and consent was evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his / her consent, prior to the start of participation in the study. The nature of the informed consent complied with the current version of the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation whichever provided the greater subject protection. Additional informed consent was obtained from the subset of patients enrolled for the PK analysis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	United Kingdom: 25
Worldwide total number of subjects	42
EEA total number of subjects	42

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at two centres, one each in Germany and the UK. The first patient was enrolled in December 2016 and the last patient last visit was in August 2017.

Pre-assignment

Screening details:

A total of 103 patients were screened. The screening period (lasting up to 28 days) consisted of a Screening Visit (Visit 1), Visit 2 and a run-in period (14–28 days) to assess clinical stability; 42 patients were eligible to participate and were randomised.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This study was performed in a double-blind manner. All IPs were supplied in identical packaging. Placebo-containing DPI devices were presented with the same external appearance and the same composition as the AZD8871-containing devices, except for the active ingredient.
Supplies of salbutamol and ipratropium were open-label.

Arms

Are arms mutually exclusive?	No
Arm title	AZD8871 100 µg

Arm description:

The subjects received AZD8871 100 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Arm type	Experimental
Investigational medicinal product name	AZD8871
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

100 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Arm title	AZD8871 600 µg

Arm description:

The subjects received AZD8871 600 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Arm type	Experimental
Investigational medicinal product name	AZD8871
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

600 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Arm title	Placebo

Arm description:

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

Arm type	Placebo
Investigational medicinal product name	AZD8871
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Placebo once daily by DPI device via single dose DPI that is an adaptation of the commercially available Genuair® with a smaller internal volume to enable delivery of single doses. To maintain blinding, each patient received one inhaled dose from placebo DPI provided to him/her on each day of the treatment period.

Number of subjects in period 1	AZD8871 100 µg	AZD8871 600 µg	Placebo
Started	34	39	36
Completed	33	32	33
Not completed	1	7	3
Adverse event, non-fatal	1	2	2
Development of study-specific withdrawal criteria	-	4	-
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	18	18	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	63.6		
standard deviation	± 6.6	-	
Sex/Gender, Customized Units: Subjects			
Female	14	14	
Male	28	28	

Subject analysis sets

Subject analysis set title	Overall study population
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised participants who received at least one dose of investigational product.

Reporting group values	Overall study population		
Number of subjects	42		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	24		

From 65-84 years	18		
85 years and over	0		

Age Continuous			
Units: Years			
arithmetic mean	63.6		
standard deviation	± 6.6		
Sex/Gender, Customized			
Units: Subjects			
Female	14		
Male	28		

End points

End points reporting groups

Reporting group title	AZD8871 100 µg
Reporting group description:	
The subjects received AZD8871 100 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.	
Reporting group title	AZD8871 600 µg
Reporting group description:	
The subjects received AZD8871 600 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.	
Reporting group title	Placebo
Reporting group description:	
The placebo was administered via single dose DPI that is an adaptation of the commercially available Genuair® with a smaller internal volume to enable delivery of single doses. To maintain blinding, each patient received one inhaled dose from placebo DPI provided to him/her on each day of the treatment period.	
Subject analysis set title	Overall study population
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised participants who received at least one dose of investigational product.	

Primary: Change from baseline in trough forced expiratory volume in 1 second (FEV1)

End point title	Change from baseline in trough forced expiratory volume in 1 second (FEV1)
End point description:	
The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in trough FEV1 on Day 15	
End point type	Primary
End point timeframe:	
On Day 15	

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	38	35	
Units: Litres				
least squares mean (standard error)	0.168 (± 0.037)	0.267 (± 0.035)	0.007 (± 0.036)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo

Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.246

Notes:

[1] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.176
upper limit	0.343

Notes:

[2] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.182

Notes:

[3] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Observed maximum plasma (Cmax) of AZD8871 and its metabolites

(single dose)	
End point title	Observed maximum plasma (Cmax) of AZD8871 and its metabolites (single dose)

End point description:

Observed maximum concentration, taken directly from the individual concentration-time curve, on Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[4]	18[5]	0[6]	
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	61.05 (± 47.47)	290.8 (± 36.30)	()	
LAS191861|	7.796 (± 38.67)	33.87 (± 33.05)	()	
LAS34850|	187.7 (± 55.41)	1016 (± 50.72)	()	

Notes:

[4] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=16
[5] - AZD8871 n=18
LAS191861 n=18
LAS34850 n=18
[6] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma (Cmax) of AZD8871 and its metabolites (multiple doses, Day 14)

End point title	Observed maximum plasma (Cmax) of AZD8871 and its metabolites (multiple doses, Day 14)

End point description:

Observed maximum concentration, taken directly from the individual concentration-time curve, on Day 14 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[7]	18[8]	0[9]	
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	72.52 (± 45.69)	381.8 (± 36.09)	()	
LAS191861|	11.89 (± 39.41)	63.17 (± 38.23)	()	
LAS34850|	221.4 (± 69.96)	1152 (± 55.11)	()	

Notes:

[7] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=16
[8] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17
[9] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration (tmax) of AZD8871 and its metabolites (single dose)

End point title	Time to reach maximum plasma concentration (tmax) of AZD8871 and its metabolites (single dose)

End point description:

Time to reach maximum concentration taken directly from the individual concentration-time curve on Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[10]	18[11]	0[12]	
Units: hours				
median (full range (min-max))				
AZD8871|	0.93 (0.42 to 2.00)	1.46 (0.48 to 2.03)	(to)	
LAS191861|	1.92 (0.93 to 4.83)	2.02 (1.00 to 4.03)	(to)	
LAS34850|	3.94 (1.92 to 6.00)	3.98 (3.92 to 6.03)	(to)	

Notes:

[10] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=16
[11] - AZD8871 n=18

LAS191861 n=18
LAS34850 n=18
[12] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration (tmax) of AZD8871 and its metabolites (multiple doses, Day 14)

End point title	Time to reach maximum plasma concentration (tmax) of AZD8871 and its metabolites (multiple doses, Day 14)

End point description:

Time to reach maximum concentration taken directly from the individual concentration-time curve on Day 14 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[13]	18[14]	0[15]	
Units: hours				
median (full range (min-max))				
AZD8871|	0.93 (0.42 to 1.00)	1.00 (0.50 to 2.22)	(to)	
LAS191861|	1.96 (0.98 to 3.95)	2.00 (0.98 to 3.98)	(to)	
LAS34850|	3.92 (0.00 to 4.00)	4.02 (3.90 to 6.05)	(to)	

Notes:

[13] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=16
[14] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17
[15] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of AZD8871 and its metabolites (single dose)

End point title	AUClast of AZD8871 and its metabolites (single dose)

End point description:

Area under the plasma concentration-curve from time zero to the last quantifiable time point (24 hours post-dose) calculated on Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[16]	18[17]	0[18]	
Units: pg.h/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	301.0 (± 54.52)	1777 (± 40.93)	()	
LAS191861|	60.06 (± 94.87)	358.5 (± 32.60)	()	
LAS34850|	1414 (± 69.31)	9299 (± 53.88)	()	

Notes:

[16] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=14
[17] - AZD8871 n=18
LAS191861 n=18
LAS34850 n=18
[18] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of AZD8871 and its metabolites (multiple doses, Day 14)

End point title	AUClast of AZD8871 and its metabolites (multiple doses, Day 14)

End point description:

Area under the plasma concentration-curve from time zero to the last quantifiable time point (24 hours post-dose) calculated on Day 14 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[19]	18[20]	0[21]	
Units: pg.h/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	539.2 (± 51.23)	3156 (± 42.51)	()	
LAS191861|	160.2 (± 64.39)	935.9 (± 46.56)	()	
LAS34850|	1964 (± 93.81)	13050 (± 52.49)	()	

Notes:

[19] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=15

[20] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17

[21] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24 of AZD8871 and its metabolites (single dose)

End point title	AUC0-24 of AZD8871 and its metabolites (single dose)

End point description:

Area under the plasma concentration-curve from time zero to 24 hours post-dose calculated on Day 1 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[22]	18[23]	0[24]	
Units: pg.h/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	326.1 (± 49.18)	1776 (± 40.95)	()	
LAS191861|	135.6 (± 25.79)	358.1 (± 32.56)	()	
LAS34850|	0 (± 0)	10440 (± 49.47)	()	

Notes:

[22] - AZD8871 n=14
LAS191861 n=7
LAS34850 n=1

[23] - AZD8871 n=18
LAS191861 n=18
LAS34850 n=15

[24] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-24 of AZD8871 and its metabolites (multiple doses, Day 14)

End point title	AUC0-24 of AZD8871 and its metabolites (multiple doses, Day 14)

End point description:

Area under the plasma concentration-curve from time zero to 24 hours post-dose calculated on Day 14 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[25]	18[26]	0[27]	
Units: pg.h/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	538.4 (± 51.16)	3152 (± 42.53)	()	
LAS191861|	179.4 (± 38.81)	933.8 (± 46.65)	()	
LAS34850|	3281 (± 66.13)	13030 (± 52.51)	()	

Notes:

[25] - AZD8871 n=16
LAS191861 n=15
LAS34850 n=7

[26] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17

[27] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation ratio for Cmax (RacCmax) of AZD8871 and its metabolites (Day 14)

End point title	Accumulation ratio for Cmax (RacCmax) of AZD8871 and its metabolites (Day 14)

End point description:

Accumulation ratio for Cmax estimated as (Cmax on Day 14 / Cmax on Day 1) in each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[28]	18[29]	0[30]	
Units: pg/mL				
arithmetic mean (full range (min-max))				
AZD8871|	1.263 (0.765 to 2.30)	1.385 (0.700 to 1.90)	(to)	
LAS191861|	1.594 (0.946 to 2.86)	1.968 (0.929 to 2.74)	(to)	
LAS34850|	1.257 (0.757 to 3.388)	1.133 (0.545 to 1.64)	(to)	

Notes:

[28] - AZD8871 n=16
LAS191861 n=16
LAS34850 n=16
[29] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17
[30] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation ratio for AUC0-24 (RacAUC[0-24]) of AZD8871 and its metabolites (Day 14)

End point title	Accumulation ratio for AUC0-24 (RacAUC[0-24]) of AZD8871 and its metabolites (Day 14)

End point description:

Accumulation ratio for AUC(0-24) estimated as (AUC0-24 on Day 14 / AUC0-24 on Day 1 in each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[31]	18[32]	0[33]	
Units: pg*h/mL				
arithmetic mean (full range (min-max))				
AZD8871|	1.893 (1.06 to 3.86)	1.878 (1.09 to 2.87)	(to)	
LAS191861|	1.576 (1.10 to 2.44)	2.721 (1.41 to 3.55)	(to)	
LAS34850|	1.24 (1.24 to 1.24)	1.326 (0.713 to 1.77)	(to)	

Notes:

[31] - AZD8871 n=14
LAS191861 n=7
LAS34850 n=1
[32] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=15
[33] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Cavg of AZD8871 and its metabolites during a dosing interval (Day 14)

End point title	Cavg of AZD8871 and its metabolites during a dosing interval (Day 14)

End point description:

Average plasma concentration during a dosing interval calculated on Day 14 of each treatment period.

End point type	Secondary

End point timeframe:

On Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16[34]	18[35]	0[36]	
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871|	22.44 (± 51.13)	131.4 (± 42.49)	()	
LAS191861|	7.478 (± 38.81)	38.94 (± 46.62)	()	
LAS34850|	136.7 (± 66.11)	543.3 (± 52.44)	()	

Notes:

[34] - AZD8871 n=16
LAS191861 n=15
LAS34850 n=7

[35] - AZD8871 n=17
LAS191861 n=17
LAS34850 n=17

[36] - Not included in the pharmacokinetic analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in trough FEV1 at Day 1 (single dose)

End point title	Change from baseline in trough FEV1 at Day 1 (single dose)

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in trough FEV1 on Day 1

End point type	Secondary

End point timeframe:

on Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.092 (± 0.029)	0.161 (± 0.027)	0.006 (± 0.028)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.14

Notes:

[37] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103
upper limit	0.207

Notes:

[38] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	= 0.011
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.121

Notes:

[39] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in trough FEV1 at Day 8 (pre-dose)

End point title	Change from baseline in trough FEV1 at Day 8 (pre-dose)

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in trough FEV1 on Day 8 (pre-dose)

End point type	Secondary

End point timeframe:

on Day 8 (pre-dose)

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.180 (± 0.033)	0.232 (± 0.030)	0.032 (± 0.031)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.067
upper limit	0.229

Notes:

[40] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.121
upper limit	0.278

Notes:

[41] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.201
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.131

Notes:

[42] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in trough FEV1 over the treatment duration (Days 1-15)

End point title	Change from baseline in trough FEV1 over the treatment duration (Days 1-15)

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in trough FEV1 over the treatment duration from Day 1 to Day 15

End point type	Secondary

End point timeframe:

Days 1-15

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.146 (± 0.029)	0.215 (± 0.027)	0.016 (± 0.027)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.071
upper limit	0.19

Notes:

[43] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	0.199
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	0.257

Notes:

[44] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.127

Notes:

[45] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in Peak FEV1 at Day 1 (single dose)

End point title	Change from baseline in Peak FEV1 at Day 1 (single dose)

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Peak FEV1

End point type	Secondary

End point timeframe:

on Day 1

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.376 (± 0.026)	0.469 (± 0.025)	0.076 (± 0.025)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.251
upper limit	0.35

Notes:

[46] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.394
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.442

Notes:

[47] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.141

Notes:

[48] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in Peak FEV1 at Day 8

End point title	Change from baseline in Peak FEV1 at Day 8

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Peak FEV1

End point type	Secondary

End point timeframe:

on Day 8

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.486 (± 0.040)	0.556 (± 0.037)	0.136 (± 0.038)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.349
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.433

Notes:

[49] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.338
upper limit	0.501

Notes:

[50] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg

Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[51]
P-value	= 0.092
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.152

Notes:

[51] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in Peak FEV1 at Day 14

End point title	Change from baseline in Peak FEV1 at Day 14

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Peak FEV1

End point type	Secondary

End point timeframe:

on Day 14

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	38	36	
Units: Litres				
least squares mean (standard error)	0.476 (± 0.037)	0.522 (± 0.035)	0.095 (± 0.036)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.38

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	0.467

Notes:

[52] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.427
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.342
upper limit	0.511

Notes:

[53] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.279
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.13

Notes:

[54] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in Peak FEV1 over the treatment duration (Days 1-15)

End point title	Change from baseline in Peak FEV1 over the treatment duration (Days 1-15)

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Peak FEV1

End point type	Secondary

End point timeframe:
over the treatment duration (Days 1-15)

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Litres				
least squares mean (standard error)	0.438 (± 0.028)	0.511 (± 0.027)	0.102 (± 0.028)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.336
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.297
upper limit	0.375

Notes:

[55] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.409
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.371
upper limit	0.447

Notes:

[56] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.111

Notes:

[57] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in BCSS questionnaire Total Score from Day 1 to Day 8 post-treatment

End point title	Change from baseline in BCSS questionnaire Total Score from Day 1 to Day 8 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Total score of the Breathlessness, Cough Sputum Scale (BCSS) questionnaire

End point type	Secondary

End point timeframe:

From Day 1 to Day 8 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Score points				
least squares mean (standard error)	-0.416 (± 0.216)	-0.920 (± 0.198)	-0.071 (± 0.205)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	= 0.205
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.345
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.882
upper limit	0.193

Notes:

[58] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.368
upper limit	-0.33

Notes:

[59] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	= 0.06
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.505
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.031
upper limit	0.022

Notes:

[60] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in BCSS questionnaire Total Score from Day 9 to

Day 14 post-treatment

End point title	Change from baseline in BCSS questionnaire Total Score from Day 9 to Day 14 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD was assessed by measuring the change from baseline in Total score of the Breathlessness, Cough Sputum Scale (BCSS) questionnaire

End point type	Secondary

End point timeframe:

From Day 9 to Day 14 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Score points				
least squares mean (standard error)	-0.491 (± 0.237)	-1.191 (± 0.219)	-0.030 (± 0.226)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.111
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.461
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.032
upper limit	0.109

Notes:

[61] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.162

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.713
upper limit	-0.61

Notes:

[62] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.015
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.259
upper limit	-0.142

Notes:

[63] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in cough individual domain score from Day 1 to Day 8 post-treatment

End point title	Change from baseline in cough individual domain score from Day 1 to Day 8 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire cough individual domain scores

End point type	Secondary

End point timeframe:

From Day 1 to Day 8 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: Score points				
least squares mean (standard error)	-0.186 (± 0.091)	-0.287 (± 0.084)	-0.134 (± 0.087)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 0.621
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.263
upper limit	0.158

Notes:

[64] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.138
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.357
upper limit	0.05

Notes:

[65] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 0.333
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.307
upper limit	0.105

Notes:

[66] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in cough individual domain score from Day 9 to Day 14 post-treatment

End point title	Change from baseline in cough individual domain score from Day 9 to Day 14 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire cough individual domain scores

End point type	Secondary

End point timeframe:

From Day 9 to Day 14 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: points				
least squares mean (standard error)	-0.160 (± 0.096)	-0.445 (± 0.088)	-0.123 (± 0.091)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	= 0.748
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.263
upper limit	0.19

Notes:

[67] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.103

Notes:

[68] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[69]
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.285
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.506
upper limit	-0.063

Notes:

[69] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in breathlessness individual domain score from Day 1 to Day 8 post-treatment

End point title	Change from baseline in breathlessness individual domain score from Day 1 to Day 8 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire breathlessness individual domain scores

End point type	Secondary

End point timeframe:

From Day 1 to Day 8 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: points				
least squares mean (standard error)	-0.122 (± 0.097)	-0.377 (± 0.089)	0.099 (± 0.092)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	= 0.064
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.455
upper limit	0.013

Notes:

[70] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.476
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.702
upper limit	-0.25

Notes:

[71] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg

Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.03
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.255
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.484
upper limit	-0.026

Notes:

[72] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in breathlessness individual domain score from Day 9 to Day 14 post-treatment

End point title	Change from baseline in breathlessness individual domain score from Day 9 to Day 14 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire breathlessness individual domain scores

End point type	Secondary

End point timeframe:

From Day 9 to Day 14 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: points				
least squares mean (standard error)	-0.202 (± 0.108)	-0.453 (± 0.100)	0.106 (± 0.103)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[73]
P-value	= 0.018
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.308

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.561
upper limit	-0.055

Notes:

[73] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.559
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.804
upper limit	-0.314

Notes:

[74] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[75]
P-value	= 0.047
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.499
upper limit	-0.003

Notes:

[75] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in sputum individual domain score from Day 1 to Day 8 post-treatment

End point title	Change from baseline in sputum individual domain score from Day 1 to Day 8 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire sputum individual domain scores

End point type	Secondary

End point timeframe:
From Day 1 to Day 8 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: points				
least squares mean (standard error)	-0.100 (± 0.070)	-0.255 (± 0.064)	-0.035 (± 0.066)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.477
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.245
upper limit	0.116

Notes:
[76] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[77]
P-value	= 0.014
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.393
upper limit	-0.046

Notes:

[77] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[78]
P-value	= 0.084
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.331
upper limit	0.022

Notes:

[78] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Secondary: Change from baseline in sputum individual domain score from Day 9 to Day 14 post-treatment

End point title	Change from baseline in sputum individual domain score from Day 9 to Day 14 post-treatment

End point description:

The efficacy of inhaled AZD8871 in patients with moderate to severe COPD will be assessed by measuring the change from baseline in BCSS questionnaire sputum individual domain scores

End point type	Secondary

End point timeframe:

From Day 9 to Day 14 post-treatment

End point values	AZD8871 100 µg	AZD8871 600 µg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	39	36	
Units: points				
least squares mean (standard error)	-0.122 (± 0.078)	-0.297 (± 0.073)	-0.011 (± 0.075)	

Statistical analyses

Statistical analysis title	AZD8871 100 µg vs Placebo
Comparison groups	AZD8871 100 µg v Placebo

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority[79]
P-value	= 0.213
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.286
upper limit	0.065

Notes:

[79] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.456
upper limit	-0.116

Notes:

[80] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Statistical analysis title	AZD8871 600 µg vs AZD8871 100 µg
Comparison groups	AZD8871 100 µg v AZD8871 600 µg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	= 0.046
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.347
upper limit	-0.003

Notes:

[81] - Analysis conducted in overall study population, 42 subjects. Subjects in this analysis field should be ignored due to reporting system limitations for statistical analysis of cross-over studies.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to Follow-up/early termination Visit, 28 to 35 days after the last administration of investigational product (IP)

Adverse event reporting additional description:

All reported AEs, date of onset/resolution, intensity, severity, outcome, action taken and relationship to IP were listed.
Non-Treatment-emergent AE (non-TEAE): Any AE occurring before first dose, or >30 days after last dose of IP
TEAE: any AE occurring after first dose or present prior to the first dose, but increasing in severity after IP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	AZD8871 100 µg

Reporting group description:

The subjects received AZD8871 100 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Reporting group title	AZD8871 600 µg

Reporting group description:

The subjects received AZD8871 600 µg once daily by DPI device via single dose DPI that is an adaptation of the multi-dose Genuair™ used in approved inhalation products.

Reporting group title	Placebo

Reporting group description:

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

Serious adverse events	AZD8871 100 µg	AZD8871 600 µg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 34 (0.00%)	1 / 39 (2.56%)	1 / 36 (2.78%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease exacerbation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 39 (2.56%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			

subjects affected / exposed	0 / 34 (0.00%)	0 / 39 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 39 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AZD8871 100 µg	AZD8871 600 µg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 34 (14.71%)	7 / 39 (17.95%)	5 / 36 (13.89%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 34 (11.76%)	3 / 39 (7.69%)	4 / 36 (11.11%)
occurrences (all)	5	3	7
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 34 (5.88%)	3 / 39 (7.69%)	0 / 36 (0.00%)
occurrences (all)	2	3	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 34 (2.94%)	2 / 39 (5.13%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Infections and infestations			
Viral upper respiratory tract infections			
subjects affected / exposed	0 / 34 (0.00%)	0 / 39 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 September 2016	High dose level was changed from 900 µg to 600 µg, based on exposure levels seen in the Phase I Study D6640C00003 (Sections 1.2, 1.4, 3.5, 7.1, 7.2.2, 8.2, 8.5.3). Dosage form for 300 µg removed and 2 Dry powder inhalers/administration changed to 1/administration (Section 7.1). New data from D6640C00003 added (Section 1.2). Update to serious adverse event reporting process (Section 6.3.6). Clarification of timing of taste assessment (Section 4.2.3).
16 December 2016	Update to exclusion criteria (Section 3.2) to exclude patients who had 2 or more exacerbations of COPD in the year prior to Screening and patients who were placed in an institution due to a regulatory or court order. Addition of study-specific withdrawal criteria (based on measurable parameters for vital signs, laboratory results, electrocardiograms, lung function, and worsening of COPD)(section 3.9). Appendix C updated to align with Section 3.9.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported