Clinical trial results:
A Phase IIa, Randomised, Multi-centre, Double-blind, Placebo and Active-controlled, 3 Periods, Crossover Study to Investigate the Efficacy, Pharmacokinetics, Safety and Tolerability of Inhaled AZD8871 Administered Once Daily for 2 Weeks in Patients with Moderate to Severe COPD

Summary

EudraCT number	2018-001722-25
Trial protocol	GB DE
Global end of trial date	07 August 2019

Results information

Result version number	v1 (current)
This version publication date	12 August 2020
First version publication date	12 August 2020

Trial information

Trial identification

Sponsor protocol code	D6640C00006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03645434
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Södertälje, Sweden, 151 85
Public contact	AstraZeneca AB, AstraZeneca AB, 001 18774004656, clinicaltrialtransparency@astrazeneca.com
Scientific contact	AstraZeneca AB, AstraZeneca AB, 001 18774004656, clinicaltrialtransparency@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	17 October 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of inhaled AZD8871 600 µg 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 Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2018
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	United Kingdom: 31
Country: Number of subjects enrolled	Germany: 42
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	28
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who met all the inclusion and none of the exclusion criteria were enrolled at 3 sites in Germany and 2 sites in the United Kingdom (UK).

Pre-assignment

Screening details:

Subjects attended Screening Visit within a 14 to 28-days Screening Period, before receiving their first dose of AZD8871. All subjects underwent inclusion exclusion criteria assessment and all eligible subjects signed the informed consent before undergoing any study related procedures.

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

Arms

Arm title	All participants

Arm description:

Subjects received AZD8871 inhalation powder 600 µg, 1 inhalation per day; umeclidinium 55 µg / vilanterol 22 µg as oral inhalation once per day; Placebo to AZD8871 via oral inhalation, 1 inhalation per day and Placebo to Anoro® Ellipta® via oral inhalation, 1 inhalation per day.

Arm type	Experimental
Investigational medicinal product name	AZD8871 600 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received AZD8871 (as saccharinate) inhalation powder 600 µg, 1 inhalation per day.

Investigational medicinal product name	Anoro® Ellipta®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received umeclidinium 55 µg / vilanterol 22 µg. as oral inhalation once per day.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received Placebo to AZD8871via oral inhalation, 1 inhalation per day

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Inhalation powder
Routes of administration	Oral use

Dosage and administration details:

Subjects received Placebo to Anoro® Ellipta® via oral inhalation, 1 inhalation per day.

Number of subjects in period 1	All participants
Started	73
Completed	66
Not completed	7
Participant did not meet FEV1 stability check	1
COPD exacerbation	1
Adverse event, non-fatal	1
Stability criteria not met	4

Baseline characteristics

Reporting groups	
Reporting group title	All participants
Reporting group description:	
Subjects received AZD8871 inhalation powder 600 µg, 1 inhalation per day; umeclidinium 55 µg / vilanterol 22 µg as oral inhalation once per day; Placebo to AZD8871 via oral inhalation, 1 inhalation per day and Placebo to Anoro® Ellipta® via oral inhalation, 1 inhalation per day.	

Reporting group values	All participants	Total	
Number of subjects	73	73	
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)	28	28	
From 65-84 years	45	45	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	66.0		
standard deviation	± 7.6	-	
Sex: Female, Male Units: Participants			
Female	23	23	
Male	50	50	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	73	73	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	All participants
Reporting group description:	
Subjects received AZD8871 inhalation powder 600 µg, 1 inhalation per day; umeclidinium 55 µg / vilanterol 22 µg as oral inhalation once per day; Placebo to AZD8871 via oral inhalation, 1 inhalation per day and Placebo to Anoro® Ellipta® via oral inhalation, 1 inhalation per day.	
Subject analysis set title	AZD8871 600 µg
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received AZD8871 (as saccharinate) inhalation powder 600 µg, 1 inhalation per day.	
Subject analysis set title	Anoro® Ellipta®
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received umeclidinium 55 µg / vilanterol 22 µg. as oral inhalation once per day.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Subjects received Placebo to AZD8871via oral inhalation, 1 inhalation per day	

Primary: Change from baseline in Trough FEV1

End point title	Change from baseline in Trough FEV1
End point description:	
To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe chronic obstructive pulmonary disease (COPD).	
End point type	Primary
End point timeframe:	
Day 15	

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)	0.1904 (± 0.2052)	0.2260 (± 0.2275)	-0.0222 (± 0.1404)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Placebo
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001

Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.151
upper limit	0.253

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0746
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	0.005

Statistical analysis title	Anoro® Ellipta® vs Placebo
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.248
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.197
upper limit	0.3

Primary: Change from baseline in chronic obstructive pulmonary disease (COPD) assessment test (CAT)

End point title	Change from baseline in chronic obstructive pulmonary disease (COPD) assessment test (CAT)

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD. At each visit, patients are asked to evaluate the impact of COPD on their wellbeing and daily life on a 6-point Likert scale ranging from 0 to
5, with higher scores indicating a higher impact of COPD. The CAT is expressed as a total score, which is a sum of the 8 questions, ranging from 0 to 40.

End point type	Primary

End point timeframe:

Day 1 to Day 8, Day 9 to Day 14, Day 1 to Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Total Score				
arithmetic mean (standard deviation)				
Day 1 to Day 8	-2.11 (± 4.34)	-2.78 (± 4.34)	-0.57 (± 4.69)	
Day 9 to Day 14	-2.87 (± 5.01)	-3.29 (± 4.94)	-0.52 (± 5.06)	
Day 1 to Day 14	-2.42 (± 4.49)	-3.01 (± 4.51)	-0.59 (± 4.81)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®

Statistical analysis description:

Day 1 to Day 8

Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2049
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.637
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.352
upper limit	1.626

Statistical analysis title	Anoro® Ellipta® vs Placebo

Statistical analysis description:

Day 1 to Day 8

Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	

P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.212
upper limit	-1.203

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 1 to Day 8	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0022
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.563
upper limit	-0.579

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5317
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.369
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.795
upper limit	1.533

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.755
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.924
upper limit	-1.585

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.386
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.541
upper limit	-1.23

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description: Day 1 to Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2906
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.546
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.472
upper limit	1.565

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 1 to Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.459
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.482
upper limit	-1.435

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 1 to Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.912
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.923
upper limit	-0.901

Secondary: Area under the curve for the change in FEV1 from baseline to 4h, normalised by the time window(FEV1 AUC(0-4)/4h)

End point title	Area under the curve for the change in FEV1 from baseline to 4h, normalised by the time window(FEV1 AUC(0-4)/4h)

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1, Day 8, and Day 14.

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1	0.3604 (± 0.1753)	0.2912 (± 0.1677)	0.0430 (± 0.0783)	
Day 8	0.4296 (± 0.2197)	0.3796 (± 0.2133)	0.0808 (± 0.2117)	
Day 14	0.4060 (± 0.2448)	0.3358 (± 0.2011)	0.0209 (± 0.1210)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve for the change in FEV1 from baseline to 8h, normalised by the time window (FEV1 AUC(0-8)/8h)

End point title	Area under the curve for the change in FEV1 from baseline to 8h, normalised by the time window (FEV1 AUC(0-8)/8h)

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

Day 1 and Day 14.

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1	0.3072 (± 0.1565)	0.2798 (± 0.1695)	0.0230 (± 0.0923)	
Day 14	0.3394 (± 0.2462)	0.3102 (± 0.1998)	0.0021 (± 0.1204)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve for the change in FEV1 from baseline to 12h, normalised by the time window (FEV1 AUC(0-12)/12h)

End point title	Area under the curve for the change in FEV1 from baseline to 12h, normalised by the time window (FEV1 AUC(0-12)/12h)

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

Day 1 and Day 14.

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1	0.2668 (± 0.1494)	0.2720 (± 0.1697)	0.0096 (± 0.0946)	
Day 14	0.3024 (± 0.2141)	0.2919 (± 0.2027)	-0.0032 (± 0.1150)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve for the change in FEV1 from baseline to 24h, normalised by the time window (FEV1 AUC(0-24)/24h)

End point title	Area under the curve for the change in FEV1 from baseline to 24h, normalised by the time window (FEV1 AUC(0-24)/24h)

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

Day 1 and Day 14.

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				

Day 1	0.1832 (± 0.1399)	0.2333 (± 0.1742)	-0.0132 (± 0.0920)	
Day 14	0.2223 (± 0.2154)	0.2417 (± 0.2012)	-0.0324 (± 0.1104)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Trough FEV1 on Day 2, and Day 8.

End point title	Change from baseline in Trough FEV1 on Day 2, and Day 8.
End point description:	
To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD	
End point type	Secondary
End point timeframe:	
Day 2 and Day 8.	

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				
Day 2	0.1359 (± 0.1672)	0.2249 (± 0.1897)	0.0339 (± 0.1139)	
Day 8	0.2161 (± 0.1613)	0.2748 (± 0.1894)	0.0121 (± 0.1240)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description:	
Day 2	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	-0.044

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 2	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
upper limit	0.237

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 2	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.146

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description:	
Day 8	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0066
Method	Mixed models analysis

Parameter estimate	Mean difference (final values)
Point estimate	-0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	-0.018

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 8	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.213
upper limit	0.306

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 8	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.242

Secondary: Change from baseline in Peak FEV1 on Day 1, Day 8 and Day 14.	
End point title	Change from baseline in Peak FEV1 on Day 1, Day 8 and Day

	14.

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1, Day 8, and Day 14.

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Liters				
arithmetic mean (standard deviation)				
Day 1	0.403 (± 0.182)	0.333 (± 0.176)	0.092 (± 0.086)	
Day 8	0.511 (± 0.240)	0.454 (± 0.227)	0.120 (± 0.130)	
Day 14	0.464 (± 0.255)	0.391 (± 0.215)	0.066 (± 0.131)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description:	
Day 1	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.107

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 1	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified

Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.239
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.199
upper limit	0.279

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 1	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.346

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description:	
Day 8	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0734
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.096

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 8	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.328
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.278
upper limit	0.379

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 8	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.374
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.324
upper limit	0.425

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description:	
Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0385
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.062
Confidence interval	

level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.121

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.326
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.266
upper limit	0.385

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.388
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.329
upper limit	0.447

Secondary: Change from baseline in Breathlessness, Cough and Sputum Scale (BCSS) Total Score

End point title	Change from baseline in Breathlessness, Cough and Sputum Scale (BCSS) Total Score

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD. The BCSS questionnaire is a 3-item, patient-reported outcome (PRO)
measure. On a daily basis, patients are asked to evaluate each of their 3 symptoms (breathlessness, cough, and sputum) on a 5-point Likert scale ranging from 0 to 4,
with higher scores indicating a higher severity of the symptom. The BCSS questionnaire is expressed as a daily total score, which is the sum of the 3 symptom scores, ranging from 0 to 12.

End point type	Secondary

End point timeframe:

Day 1 to Day 8, Day 9 to Day 14, Day 1 to Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Total Score				
arithmetic mean (standard deviation)				
Day 1 to Day 8	-0.37 (± 1.27)	-0.61 (± 1.31)	0.16 (± 1.11)	
Day 9 to Day 14	-0.35 (± 1.58)	-0.63 (± 1.49)	0.53 (± 1.43)	
Day 1 to Day 14	-0.36 (± 1.33)	-0.63 (± 1.32)	0.36 (± 1.26)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®

Statistical analysis description:

Day 1 to Day 8

Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1362
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.078
upper limit	0.563

Statistical analysis title	Anoro® Ellipta® vs Placebo

Statistical analysis description:

Day 1 to Day 8

Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	

P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.794
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	-0.468

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 1 to Day 8	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.551
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.876
upper limit	-0.226

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.131
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.291
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.669

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.539
upper limit	-0.776

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.248
upper limit	-0.486

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description: Day 1 to Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.096
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.273
Confidence interval	

level	95 %
sides	2-sided
lower limit	-0.049
upper limit	0.596

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description: Day 1 to Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.996
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.321
upper limit	-0.67

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 1 to Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.722
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.047
upper limit	-0.397

Secondary: Number of participants with adverse events.

End point title	Number of participants with adverse events.

End point description:

To evaluate the safety and tolerability of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

From Screening to folow-up or discontinuation (42 days after last study drug)

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Participants				
Any AE	39	38	35	
Any AE with outcome=death	0	0	0	
Any SAE (including events with outcome=death)	0	2	2	
Any AE leading to discontinuation of treatment	0	1	0	
Any AE leading to withdrawal from study	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Rescue medication use

End point title	Rescue medication use

End point description:

To evaluate the efficacy of inhaled AZD8871 600 µg in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

Day 1 to Day 8 and Day 9 to Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: unit on a scale				
arithmetic mean (standard deviation)				
Day 1 to Day 8	-1.00 (± 1.83)	-0.95 (± 2.03)	0.18 (± 2.13)	
Day 9 to Day 14	-0.78 (± 1.97)	-0.87 (± 1.96)	0.52 (± 1.80)	

Statistical analyses

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®

Statistical analysis description:

Day 1 to Day 8

Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6566
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.578
upper limit	0.365

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description:	
Day 1 to Day 8	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.642
upper limit	-0.681

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description:	
Day 1 to Day 8	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.268
Confidence interval	
level	95 %
sides	2-sided

lower limit	-1.741
upper limit	-0.794

Statistical analysis title	AZD8871 600 µg vs Anoro® Ellipta®
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Anoro® Ellipta®
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.802
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.441
upper limit	0.569

Statistical analysis title	Anoro® Ellipta® vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	Anoro® Ellipta® v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.366
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.875
upper limit	-0.857

Statistical analysis title	AZD8871 600 µg vs Placebo
Statistical analysis description: Day 9 to Day 14	
Comparison groups	AZD8871 600 µg v Placebo
Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	

P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.302
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.804
upper limit	-0.8

Secondary: maximum plasma concentration (Cmax)

End point title	maximum plasma concentration (Cmax)

End point description:

To investigate the Cmax of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1 and Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871 - Day 1	310.4 (± 61.30)	0 (± 0)	0 (± 0)	
AZD8871 - Day 14	532.9 (± 46.58)	0 (± 0)	0 (± 0)	
LAS191861- Day 1	26.64 (± 53.33)	0 (± 0)	0 (± 0)	
LAS191861- Day 14	63.29 (± 52.12)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: time to reach maximum plasma concentration (Tmax)

End point title	time to reach maximum plasma concentration (Tmax)

End point description:

To investigate the Tmax of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Hours				
median (full range (min-max))				
AZD8871- Day 1	0.99 (0.38 to 2.02)	0 (0 to 0)	0 (0 to 0)	
AZD8871- Day 14	0.98 (0.45 to 2.05)	0 (0 to 0)	0 (0 to 0)	
LAS191861 - Day 1	2.00 (0.98 to 4.00)	0 (0 to 0)	0 (0 to 0)	
LAS191861 - Day 14	2.00 (0.98 to 4.03)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: time to reach last quantifiable plasma concentration (Tlast)

End point title	time to reach last quantifiable plasma concentration (Tlast)

End point description:

To investigate the Tlast of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1 and Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Hours				
median (full range (min-max))				
AZD8871 -Day 1	23.93 (7.98 to 24.05)	0 (0 to 0)	0 (0 to 0)	
AZD8871-Day 14	24.03 (23.90 to 24.37)	0 (0 to 0)	0 (0 to 0)	
LAS191861 - Day 1	23.92 (1.97 to 24.05)	0 (0 to 0)	0 (0 to 0)	
LAS191861 - Day 14	24.03 (23.90 to 24.37)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration (AUClast)

End point title	Area under the plasma concentration-curve from time 0 to the time of last quantifiable concentration (AUClast)

End point description:

To investigate the AUClast of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1 and Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: h*pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871- Day 1	1655 (± 85.24)	0 (± 0)	0 (± 0)	
AZD8871-Day 14	4001 (± 55.64)	0 (± 0)	0 (± 0)	
LAS191861 -Day 1	251.9 (± 97.81)	0 (± 0)	0 (± 0)	
LAS191861 -Day 14	943.3 (± 63.08)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-curve from time 0 to 24 hours post-dose [AUC(0-24)]

End point title	Area under the plasma concentration-curve from time 0 to 24 hours post-dose [AUC(0-24)]

End point description:

To investigate the AUC(0-24) of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 1 and Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: h*pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871- Day 1	1661 (± 83.55)	0 (± 0)	0 (± 0)	
AZD8871- Day 14	3996 (± 55.66)	0 (± 0)	0 (± 0)	
LAS191861 - Day 1	289.5 (± 57.83)	0 (± 0)	0 (± 0)	
LAS191861 - Day 14	941.7 (± 63.11)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average plasma concentration during a dosing interval (Cavg)

End point title	Average plasma concentration during a dosing interval (Cavg)

End point description:

To investigate the Cavg of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
AZD8871 -Day 14	166.5 (± 55.63)	0 (± 0)	0 (± 0)	
LAS191861 - Day 14	39.23 (± 63.06)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Fluctuation index during a dosing interval (%Fluctuation)

End point title	Fluctuation index during a dosing interval (%Fluctuation)

End point description:

To investigate the %Fluctuation of AZD8871 600 µg and its primary metabolite after multiple dose

administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: percentage				
median (full range (min-max))				
AZD8871- Day 14	273.1 (128 to 514)	0 (0 to 0)	0 (0 to 0)	
LAS191861 - Day 14	91.03 (39.3 to 174)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation ratio for Cmax (Rac(Cmax))

End point title	Accumulation ratio for Cmax (Rac(Cmax))

End point description:

To investigate the Rac (Cmax) of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Ratio				
geometric mean (geometric coefficient of variation)				
AZD8871 -Day 14	1.725 (± 44.77)	0 (± 0)	0 (± 0)	
LAS191861 - Day 14	2.377 (± 40.02)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: accumulation ratio for AUC(0-24) Rac(AUC(0-24))

End point title	accumulation ratio for AUC(0-24) Rac(AUC(0-24))

End point description:

To investigate the Rac(AUC(0-24) of AZD8871 600 µg and its primary metabolite after multiple dose administration of inhaled AZD8871 in patients with moderate to severe COPD

End point type	Secondary

End point timeframe:

At Day 14

End point values	AZD8871 600 µg	Anoro® Ellipta®	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	70	69	68	
Units: Ratio				
geometric mean (geometric coefficient of variation)				
AZD8871 - Day 14	2.406 (± 50.37)	0 (± 0)	0 (± 0)	
LAS191861 -Day 14	3.443 (± 47.15)	0 (± 0)	0 (± 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From screening to follow-up visit or treatment discontinuation (48 days after last dose)	
Adverse event reporting additional description:	
An adverse event was the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition might be symptoms, signs or the abnormal results of an investigation.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	AZD8871 600 µg
Reporting group description:	
Subjects received AZD8871 (as saccharinate) inhalation powder 600 µg, 1 inhalation per day.	
Reporting group title	Anoro® Ellipta®
Reporting group description:	
Subjects received umeclidinium 55 µg / vilanterol 22 µg. as oral inhalation once per day.	
Reporting group title	Placebo
Reporting group description:	
Subjects received Placebo to AZD8871via oral inhalation, 1 inhalation per day	

Serious adverse events	AZD8871 600 µg	Anoro® Ellipta®	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 70 (0.00%)	2 / 69 (2.90%)	2 / 68 (2.94%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 68 (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			

Tooth abscess			
subjects affected / exposed	0 / 70 (0.00%)	1 / 69 (1.45%)	0 / 68 (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
Vestibular neuronitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 69 (0.00%)	1 / 68 (1.47%)
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 600 µg	Anoro® Ellipta®	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 70 (27.14%)	19 / 69 (27.54%)	17 / 68 (25.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 70 (20.00%)	13 / 69 (18.84%)	14 / 68 (20.59%)
occurrences (all)	28	22	21
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 70 (8.57%)	8 / 69 (11.59%)	3 / 68 (4.41%)
occurrences (all)	7	9	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2018	Removal of reversibility criterion for study eligibility. Reversibility testing continued to take place but did not impact a patient's eligibility for entering the study. The screening failure rate was revised downwards from 60% to 50%; the number of patients to be screened is revised downwards from 180 to 145 patients. The ipratropium dose was changed from 34 µg to 20 µg. The ECG parameters were updated to remove QRS complexes.
08 August 2018	Section 5.1: Inclusion criterion #12 Clarifications were added regarding true sexual abstinence under the contraception criterion. Section 6.3 Measures to minimise bias: randomisation and blinding Description of unblinding processes was revised as follows: In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator is asked to contact the Sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. The changes were made in response to MHRA feedback.
13 September 2018	The below changes were made in response to MHRA feedback. Section 5.1: Inclusion criterion #12 Clarifications were added regarding true sexual abstinence under the contraception criterion. Section 6.3 Measures to minimise bias: randomisation and blinding Description of unblinding processes was revised as follows: In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator is asked to contact the Sponsor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. The below changes were made in response to BfArM feedback. Section 5.2: Exclusion criteria #12 Maximum heart rate was lowered from >120 to >100 bpm. Section 5.2: Exclusion criteria #13 Maximum blood pressure was lowered from >180 to >160 mmHg. Section 7.3: Withdrawal from the study Description of processes to withdraw patients enrolled in error was revised as follows: Any patient that has been initiated on treatment and subsequently found not to meet all the eligibility criteria must stop the treatment and be excluded from the study.

11 December 2018	Clarification was added that heart rate for pre-dose timepoints on visits 4, 7 and 10 was to be taken from vital signs. Clarification was added that ECGs were to be done as single measurements and not as triplicates. Description of triple ECGs was removed. Clarification was added that ECGs and vital signs were to be measured after 5-minute rest in a supine position. Clarification was added that vital signs were to be done as single measurements and not as triplicates. Clinical Stability Check was added in the schedule of activities at Visit 6 and Visit 9. Clarification was added that screening results for drugs of abuse and alcohol were to be used to determine exclusion criterion #21 prior to randomisation due to the logistically accessibility of the results. Clarification was added regarding the timing of Cough Monitoring for home and site assessments. The following clinical safety laboratory parameters were added:• aPTT,• INR,• PTT. The following clarification was made: For Placebo and active comparator treatments immediately following an AZD8871 treatment period, only Day 1 pre-dose samples will be analysed unless specified. For any other Placebo and active comparator treatments, samples will not be analysed unless specified. Hy's law SOP updated. Pregnancy test was added to Follow-Up Visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported