Clinical trial results:
A 12-week Phase IIa, Double-blind, Placebo-controlled, Randomised Study to Investigate the Efficacy and Safety of AZD7624 in COPD Patients with a History of Frequent Acute Exacerbations while on Maintenance Therapy

Summary

EudraCT number	2014-001053-16
Trial protocol	NL
Global end of trial date	04 April 2016

Results information

Result version number	v1 (current)
This version publication date	19 April 2017
First version publication date	19 April 2017

Trial information

Trial identification

Sponsor protocol code	D2550C00005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Stockholm, Sweden, 151 85
Public contact	Ziad Taib, AstraZeneca AB, 46 708 46 73 56, ziad.taib@astrazeneca.com
Scientific contact	Ziad Taib, AstraZeneca AB, 46 708 46 73 56, ziad.taib@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	03 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2016
Global end of trial reached?	Yes
Global end of trial date	04 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of AZD7624 versus placebo on the time to first event of moderate or severe COPD exacerbations or early drop-out related to worsening of COPD symptoms (i.e., composite endpoint referred to as "ExDo") in patients with COPD on maintenance treatment with at least ICS and LABA.

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 the International Council for Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.
Each subject was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and it was ensured that the Informed Consent Form (ICF) was signed and dated before any study specific procedure was performed.
Opportunity was given to ask questions and subjects were allowed time to consider the information provided. Subjects were also notified that they were free to discontinue from the study at any time. A copy of the signed ICF was provided to the subjects.
Written informed consent was obtained from all healthy subjects prior to initiation of the study.

Background therapy:

Stable COPD maintenance treatment with at least inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) for at least 2 months prior to enrolment (Visit 1), to be continued unchanged during the study.

Evidence for comparator:

A placebo comparator was used in this study.

Actual start date of recruitment	28 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 80
Country: Number of subjects enrolled	United States: 74
Country: Number of subjects enrolled	Chile: 14
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Peru: 19
Country: Number of subjects enrolled	South Africa: 13
Worldwide total number of subjects	213
EEA total number of subjects	13

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)	104
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the total 327 patients enrolled into the study, 114 were not randomised. The majority of these were due to screening failures.

Pre-assignment period milestones

Number of subjects started	327[1]
Number of subjects completed	213

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 6
Reason: Number of subjects	Consent withdrawn by subject: 10
Reason: Number of subjects	Protocol deviation: 97
Reason: Number of subjects	not specified: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The country of the subject was only databased and tabulated for subjects randomized into the study. The country for screening failures is not included in the table of Subject number per country.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD7624 1.0 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	AZD7624
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution, Inhalation solution
Routes of administration	Inhalation use, Inhalation use

Dosage and administration details:

2 x 0.5 mg inhalation once daily

Arm title	Placebo

Arm description: -

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

Dosage and administration details:
2 inhalations once daily

Number of subjects in period 1	AZD7624 1.0 mg	Placebo
Started	108	105
Completed	93	91
Not completed	15	14
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	7
Adverse event, non-fatal	7	3
Lost to follow-up	1	1
Protocol deviation	1	2
not specified	2	-
completion status not recorded	1	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment Period

Reporting group description: -

Reporting group values	Treatment Period	Total	
Number of subjects	213	213	
Age Categorical Units: Subjects			
Adults (18-64 years)	104	104	
From 65-84 years	109	109	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	64.8		
standard deviation	± 8.7	-	
Gender Categorical Units: Subjects			
Female	76	76	
Male	137	137	
Race Units: Subjects			
White	173	173	
Black or African American	9	9	
American Indian or Alaska Native	7	7	
Other	23	23	
Unknown	1	1	
Body Mass Index Units: kg/m^2			
arithmetic mean	27.74		
standard deviation	± 5.641	-	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The FAS was used as the primary population for reporting efficacy data and to summarise baseline characteristics. This set comprised all patients randomised into the study who received at least 1 inhalation of investigational product and was analysed according to randomised treatment (intention-to-treat principle).

Reporting group values	Full Analysis Set		
Number of subjects	212		
Age Categorical Units: Subjects			
Adults (18-64 years)	103		
From 65-84 years	109		

85 years and over	0		

Age Continuous Units: years			
arithmetic mean	64.8		
standard deviation	± 8.7		
Gender Categorical Units: Subjects			
Female	76		
Male	136		
Race Units: Subjects			
White	173		
Black or African American	9		
American Indian or Alaska Native	7		
Other	23		
Unknown	0		
Body Mass Index Units: kg/m^2			
arithmetic mean	27.74		
standard deviation	± 5.641		

End points

End points reporting groups

Reporting group title	AZD7624 1.0 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The FAS was used as the primary population for reporting efficacy data and to summarise baseline characteristics. This set comprised all patients randomised into the study who received at least 1 inhalation of investigational product and was analysed according to randomised treatment (intention-to-treat principle).

Primary: Time to first ExDo event

End point title	Time to first ExDo event

End point description:

the time to first event of moderate or severe COPD exacerbation or early drop-out related to worsening of COPD symptoms (ie, composite endpoint referred to as "ExDo")

End point type	Primary

End point timeframe:

up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[1]	105		
Units: Days				
median (not applicable)	-99 (± -99)	118 (± -99)		

Notes:

[1] - There were too few events to estimate median using Kaplan Meier methodology

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

Hazard ratios, 95% CIs for hazard ratios, and p-values are estimated using a Cox regression model with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex as covariates

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.2371
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	2.4

Notes:

[2] - A hazard ratio greater than 1 indicates a higher rate of incidence in the first of the two groups.

Secondary: Time to first moderate or severe COPD exacerbation or early drop-out

End point title	Time to first moderate or severe COPD exacerbation or early drop-out

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[3]	105		
Units: Days				
median (not applicable)	-99 (± -99)	118 (± -99)		

Notes:

[3] - There were too few events to estimate median using Kaplan Meier methodology

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

Hazard ratio, 95% CI for hazard ratio, and p-value are estimated using a Cox regression model with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.1261
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.5

Notes:

[4] - A hazard ratio greater than 1 indicates a higher rate of incidence in the first of the two groups.

Secondary: Time to first moderate or severe COPD exacerbation

End point title	Time to first moderate or severe COPD exacerbation

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[5]	105[6]		
Units: Days				
median (not applicable)	-99 (± -99)	-99 (± -99)		

Notes:

[5] - There were too few events to estimate median using Kaplan Meier methodology

[6] - There were too few events to estimate median using Kaplan Meier methodology

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

Hazard ratio, 95% CI for hazard ratio, and p-value are estimated using a Cox regression model with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.1529
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.76

Notes:

[7] - A hazard ratio greater than 1 indicates a higher rate of incidence in the first of the two groups.

Secondary: Time to first moderate or severe COPD exacerbation (Anthonisens criteria)

End point title	Time to first moderate or severe COPD exacerbation (Anthonisens criteria)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[8]	105[9]		
Units: Days				
median (not applicable)	-99 (± -99)	-99 (± -99)		

Notes:

[8] - There were too few events to estimate median using Kaplan Meier methodology

[9] - There were too few events to estimate median using Kaplan Meier methodology

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

Hazard ratio, 95% CI for hazard ratio, and p-value are estimated using a Cox regression model with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.8543
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.01

Notes:

[10] - A hazard ratio greater than 1 indicates a higher rate of incidence in the first of the two groups.

Secondary: Time to first symptom defined COPD exacerbation (EXACT daily diary)

End point title	Time to first symptom defined COPD exacerbation (EXACT daily diary)

End point description:

End point type	Secondary

End point timeframe:

up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[11]	105[12]		
Units: Days				
median (not applicable)	-99 (± -99)	-99 (± -99)		

Notes:

[11] - There were too few events to estimate median using Kaplan Meier methodology

[12] - There were too few events to estimate median using Kaplan Meier methodology

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

Hazard ratios, 95% CIs for Hazard ratios, and p-values are estimated using a Cox regression model with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.5381
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.38

Notes:

[13] - A hazard ratio greater than 1 indicates a higher rate of incidence in the first of the two groups.

Secondary: Frequency of ExDo events

End point title	Frequency of ExDo events

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Events / year				
least squares mean (standard error)	2.16 (± 0.8)	1.62 (± 0.63)		

Statistical analyses

Statistical analysis title	Frequency of ExDo events, negative binomial model

Statistical analysis description:

Analysis model: rates, rate ratios, and p-value are from a negative binomial regression analysis, with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex included in the model as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.249
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	2.16
Variability estimate	Standard error of the mean
Dispersion value	0.33

Secondary: Frequency of moderate or severe COPD exacerbations or early drop-out

End point title	Frequency of moderate or severe COPD exacerbations or early drop-out

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Exacerbations / year				
least squares mean (standard error)	2.17 (± 0.8)	1.55 (± 0.6)		

Statistical analyses

Statistical analysis title	negative binomial model

Statistical analysis description:

Analysis model: rates, rate ratios, and p-value are from a negative binomial regression analysis, with treatment, LAMA maintenance treatment, age group, baseline FEV1 and sex included in the model as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.21
Variability estimate	Standard error of the mean
Dispersion value	0.33

Secondary: Frequency of moderate or severe COPD exacerbations

End point title	Frequency of moderate or severe COPD exacerbations

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Exacerbations / year				
least squares mean (standard error)	2.12 (± 0.78)	1.42 (± 0.56)		

Statistical analyses

Statistical analysis title	Negative binomial model

Statistical analysis description:

Analysis model: rates, rate ratios, and p-value are from a negative binomial regression analysis, with treatment, country, LAMA maintenance treatment, age group, baseline FEV1 and sex included in the model as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.129
Method	Negative binomial regression
Parameter estimate	Risk ratio
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.52
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Frequency of moderate or severe COPD exacerbations (Anthonisens criteria)

End point title	Frequency of moderate or severe COPD exacerbations (Anthonisens criteria)

End point description:

End point type	Secondary

End point timeframe:

up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	105		
Units: exacerbations / year				
least squares mean (standard error)	1.23 (± 0.39)	1.09 (± 0.56)		

Statistical analyses

Statistical analysis title	Negative binomial model

Statistical analysis description:

Analysis model: rates, rate ratios, and p-value are from a negative binomial regression analysis, with treatment, LAMA maintenance treatment and sex included in the model as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo

Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.751
Method	negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.29
Variability estimate	Standard error of the mean
Dispersion value	0.41

Secondary: Frequency of symptom defined COPD exacerbations (EXACT daily diary)

End point title	Frequency of symptom defined COPD exacerbations (EXACT daily diary)

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: exacerbations / year				
least squares mean (standard error)	1.96 (± 0.54)	2.33 (± 0.64)		

Statistical analyses

Statistical analysis title	Negative binomial model

Statistical analysis description:

Analysis model: rates, rate ratios, and p-value are from a negative binomial regression analysis, with treatment, LAMA maintenance treatment, baseline FEV1 and sex included in the model as covariates.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: Transitional Dyspnoea Index - Total Daily Score

End point title	Transitional Dyspnoea Index - Total Daily Score
End point description:	
End point type	Secondary
End point timeframe:	
up to 12 weeks	

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	100		
Units: Score				
least squares mean (standard error)	1.29 (± 0.43)	1.58 (± 0.44)		

Statistical analyses

Statistical analysis title	Mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit and
treatment by visit interaction as fixed effects, patient as a random effect and baseline assessment as a continuous covariate. An unstructured covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.3468
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.32

Notes:

[14] - Positive values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Secondary: St George Respiratory Questionnaire for COPD patients (SGRQ-C)

End point title	St George Respiratory Questionnaire for COPD patients (SGRQ-C)

End point description:

Change from pre study-treatment baseline in Health related quality of life (as assessed by St George Respiratory Questionnaire for COPD patients [SGRQ-C] total score)

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Score				
least squares mean (standard error)	-5.7 (± 2.43)	-6.65 (± 2.48)		

Statistical analyses

Statistical analysis title	Mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit and
treatment by visit interaction as fixed effects, patient as a random effect and baseline assessment as a continuous covariate. An unstructured covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.5909
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	4.43

Notes:

[15] - Negative values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Secondary: Spirometry assessments - FEV1

End point title	Spirometry assessments - FEV1

End point description:

Pulmonary function measured as changes from baseline (post bronchodilator at Visit 3) in trough Forced Expiratory Volume in 1 second (FEV1)

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Litres				
least squares mean (standard error)	-0.07 (± 0.04)	-0.08 (± 0.04)		

Statistical analyses

Statistical analysis title	mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit,
sex, smoking history and treatment by visit interaction as fixed effects, patient as a random effect, and baseline assessment, age, BMI and height as continuous covariates. A compound symetry covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.5144
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.07

Notes:

[16] - Positive values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Secondary: Spirometry Assessments - FVC

End point title	Spirometry Assessments - FVC

End point description:

Pulmonary function measured as changes from baseline (post bronchodilator at Visit 3) in trough Forced Vital Capacity (FVC)

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: Litres				
least squares mean (standard error)	-0.07 (± 0.05)	-0.05 (± 0.06)		

Statistical analyses

Statistical analysis title	Mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit,
sex, smoking history and treatment by visit interaction as fixed effects, patient as a random effect, and baseline assessment, age, BMI and height as continuous covariates. A compound symmetry covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.5416
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.05

Notes:

[17] - Positive values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Secondary: Spirometry assessments - FEV1/FVC

End point title	Spirometry assessments - FEV1/FVC

End point description:

Pulmonary function measured as changes from baseline (post bronchodilator at Visit 3) in trough FEV1/FVC

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: L / L				
least squares mean (standard error)	-0.01 (± 0.01)	-0.01 (± 0.01)		

Statistical analyses

Statistical analysis title	Mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit,
sex, smoking history and treatment by visit interaction as fixed effects, patient as a random effect, and baseline assessment, age, BMI and height as continuous covariates. A compound symetry covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.1965
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.02

Notes:

[18] - Positive values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Secondary: EXACT for Respiratory Symptoms (E-RS)

End point title	EXACT for Respiratory Symptoms (E-RS)

End point description:

Symptoms of COPD (using the EXACT for Respiratory Symptoms [E-RS] Total Score, a subset of items from the EXACT diary)

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	AZD7624 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	105		
Units: Score				
least squares mean (standard error)	-0.21 (± 0.88)	0.17 (± 0.91)		

Statistical analyses

Statistical analysis title	Mixed model repeated measures analysis

Statistical analysis description:

Results obtained from mixed model repeated measures analysis, fitting treatment, country, LAMA maintenance treatment, visit and
treatment by visit interaction as fixed effects, patient as a random effect and baseline assessment as a continuous covariate. An unstructured covariance matrix has been used.

Comparison groups	AZD7624 1.0 mg v Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.5474
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	0.85

Notes:

[19] - Negative values for a difference show AZD7624 to have a favourable outcome compared to Placebo.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events occurring during the treatment period or 2-week follow-up period are reported	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	AZD7624 1.0 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Total
Reporting group description: -	

Serious adverse events	AZD7624 1.0 mg	Placebo	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 108 (10.19%)	11 / 105 (10.48%)	22 / 213 (10.33%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 108 (0.93%)	0 / 105 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Coronary artery occlusion			

subjects affected / exposed	1 / 108 (0.93%)	0 / 105 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 108 (0.93%)	0 / 105 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	7 / 108 (6.48%)	6 / 105 (5.71%)	13 / 213 (6.10%)
occurrences causally related to treatment / all	2 / 10	0 / 8	2 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 108 (0.93%)	0 / 105 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 108 (0.00%)	1 / 105 (0.95%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 108 (0.93%)	0 / 105 (0.00%)	1 / 213 (0.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AZD7624 1.0 mg	Placebo	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 108 (65.74%)	48 / 105 (45.71%)	119 / 213 (55.87%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 108 (2.78%)	2 / 105 (1.90%)	5 / 213 (2.35%)
occurrences (all)	3	2	5
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 108 (4.63%)	1 / 105 (0.95%)	6 / 213 (2.82%)
occurrences (all)	6	2	8
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 108 (2.78%)	0 / 105 (0.00%)	3 / 213 (1.41%)
occurrences (all)	3	0	3
Asthenia			
subjects affected / exposed	2 / 108 (1.85%)	4 / 105 (3.81%)	6 / 213 (2.82%)
occurrences (all)	2	5	7
Oedema peripheral			
subjects affected / exposed	0 / 108 (0.00%)	3 / 105 (2.86%)	3 / 213 (1.41%)
occurrences (all)	0	3	3
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	31 / 108 (28.70%)	23 / 105 (21.90%)	54 / 213 (25.35%)
occurrences (all)	40	30	70
Cough			
subjects affected / exposed	8 / 108 (7.41%)	2 / 105 (1.90%)	10 / 213 (4.69%)
occurrences (all)	8	2	10
Dyspnoea			
subjects affected / exposed	8 / 108 (7.41%)	4 / 105 (3.81%)	2 / 213 (0.94%)
occurrences (all)	11	5	16
Productive cough			
subjects affected / exposed	3 / 108 (2.78%)	0 / 105 (0.00%)	3 / 213 (1.41%)
occurrences (all)	3	0	3
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 108 (3.70%)	1 / 105 (0.95%)	5 / 213 (2.35%)
occurrences (all)	4	1	5
Pain in extremity			
subjects affected / exposed	0 / 108 (0.00%)	3 / 105 (2.86%)	3 / 213 (1.41%)
occurrences (all)	0	3	3
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 108 (4.63%)	3 / 105 (2.86%)	8 / 213 (3.76%)
occurrences (all)	5	3	8
Bronchitis			
subjects affected / exposed	4 / 108 (3.70%)	2 / 105 (1.90%)	6 / 213 (2.82%)
occurrences (all)	4	2	6
Nasopharyngitis			
subjects affected / exposed	4 / 108 (3.70%)	4 / 105 (3.81%)	8 / 213 (3.76%)
occurrences (all)	4	4	8
Sinusitis			
subjects affected / exposed	1 / 108 (0.93%)	3 / 105 (2.86%)	4 / 213 (1.88%)
occurrences (all)	2	3	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported