Clinical trial results:
A multiple dose, randomised, double-blind, placebo controlled, parallel clinical trial to assess the effect of aclidinium bromide/formoterol fumarate fixed-dose combination on lung hyperinflation, exercise capacity and physical activity in patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Summary

EudraCT number	2014-005318-50
Trial protocol	HU DE ES
Global end of trial date	25 July 2016

Results information

Result version number	v1 (current)
This version publication date	30 July 2017
First version publication date	30 July 2017

Trial information

Trial identification

Sponsor protocol code	M-40464-33

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02424344
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Karlebyhus, Astraallén, Södertälje, Sweden, SE-151 85
Public contact	Study Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Study Director, AstraZeneca, 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	25 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2016
Global end of trial reached?	Yes
Global end of trial date	25 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to assess the effect of the aclidinium bromide/formoterol fumarate 400/12 µg BID on lung hyperinflation, exercise endurance and physical activity in patients with moderate to severe COPD. Additionally, the effect of a behavioural intervention on top of aclidinium bromide/formoterol fumarate 400/12 µg were assessed both on the exercise endurance and the physical activity.

Protection of trial subjects:

This study was conducted in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly of Helsinki (1964), revised at Tokyo (1975), Venice (1983), Hong-Kong (1989), Somerset West (1996) and Edinburgh (2000), including the Notes of clarification made by the World Medical Assembly of Washington (2002) and Tokyo (2004), 59th World Medical Association (WMA) General Assembly, Seoul (2008) and 64th WMA General Assembly, Fortaleza, Brazil (2013) as well as in compliance with ICH GCP guidelines and local regulations. Patients were provided with relief medication, salbutamol pressurised metered dose inhaler (pMDI), 100 µg/puff, which could be used from the time of signing the informed consent until the end of the treatment period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 April 2015
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	Canada: 9
Country: Number of subjects enrolled	Germany: 223
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Spain: 19
Worldwide total number of subjects	267
EEA total number of subjects	258

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)	158
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 26 study centers, 15 in Germany, 4 in Hungary, 3 in Spain and 4 in Canada. The first patient was enrolled in April 2015 and the last patient visit was in July 2016.

Pre-assignment

Screening details:

This was a randomised, double-blind, parallel-group, placebo-controlled study. 335 patients were screened; 267 were assessed as eligible and were randomized into the study.

68 patients failed screening. The main reason for screening failure was non-fulfilment of inclusion or exclusion criteria (n=56; 16.7%).

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

Are arms mutually exclusive?	Yes
Arm title	AB/FF 400/12 µg

Arm description:

Aclidinium Bromide/Formoterol Fumarate 400/12µg

Arm type	Experimental
Investigational medicinal product name	Aclidinium bromide/formoterol fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

400/12 µg twice daily (BID)

Arm title	Placebo

Arm description:

Placebo to Aclidinium Bromide/Formoterol Fumarate 400/12µg

Arm type	Placebo
Investigational medicinal product name	Placebo to Aclidinium/Formoterol 400/12 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Twice-daily (BID)

Number of subjects in period 1	AB/FF 400/12 µg	Placebo
Started	134	133
Completed	127	123
Not completed	7	10
Consent withdrawn by subject	2	1
Adverse event, non-fatal	4	8
Lost to follow-up	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AB/FF 400/12 µg
Reporting group description:	
Aclidinium Bromide/Formoterol Fumarate 400/12µg	
Reporting group title	Placebo
Reporting group description:	
Placebo to Aclidinium Bromide/Formoterol Fumarate 400/12µg	

Reporting group values	AB/FF 400/12 µg	Placebo	Total
Number of subjects	134	133	267
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	79	79	158
From 65-84 years	55	54	109
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	62.6	62.1	
standard deviation	± 7.9	± 7.7	-
Gender, Male/Female Units: Subjects			
Female	53	54	107
Male	81	79	160

End points

End points reporting groups

Reporting group title	AB/FF 400/12 µg
Reporting group description:	
Aclidinium Bromide/Formoterol Fumarate 400/12µg	
Reporting group title	Placebo
Reporting group description:	
Placebo to Aclidinium Bromide/Formoterol Fumarate 400/12µg	

Primary: Change from baseline in trough Functional Residual capacity (FRC) after 4 weeks of treatment

End point title	Change from baseline in trough Functional Residual capacity (FRC) after 4 weeks of treatment
End point description:	
Baseline values in FRC were defined as the corresponding values just before randomization on Day 1 of treatment (Week 0). Trough values were obtained prior to study drug administration.	
End point type	Primary
End point timeframe:	
Baseline and Week 4	

End point values	AB/FF 400/12 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	125		
Units: Liters				
least squares mean (standard error)	-0.162 (± 0.05)	-0.037 (± 0.05)		

Statistical analyses

Statistical analysis title	AB/FF 400/12µg v Placebo
Statistical analysis description:	
Adjusted by baseline and age as covariates, and treatment group, sex and smoking-status as fixed effect factors	
Comparison groups	AB/FF 400/12 µg v Placebo
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.069
Method	ANCOVA
Parameter estimate	Least Square mean difference
Point estimate	-0.125

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.259
upper limit	0.01

Secondary: Change from baseline in Endurance Time (ET) during constant work rate cycle ergometry at Week 8

End point title	Change from baseline in Endurance Time (ET) during constant work rate cycle ergometry at Week 8

End point description:

The ET was the time from the increase in work rate to 75% Wmax to the point of symptom limitation.

Baseline measurements were taken prior to the IP dose on Day 1. Measurements at Week 8 were taken at 3 hours post-dose. Participants underwent a behavioural intervention (consisting of a telecoaching programme to enhance physical activity) between Week 4 and Week 8.

End point type	Secondary

End point timeframe:

Baseline to Week 8

End point values	AB/FF 400/12 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	121		
Units: Seconds				
least squares mean (standard error)	50.7 (± 18.1)	-4.6 (± 18.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of inactive patients (mean of <6000 steps per day) at Week 8

End point title	Percentage of inactive patients (mean of <6000 steps per day) at Week 8

End point description:

Physical activity was assessed by means of measurement of activity paramenters (e.g. number of steps) through a Dynaport MoveMonitor and completion of the Daily ProActive Physical Activity in COPD questionnaire.

Compliant criterion based on at least 8 hours per day, and at least 3 days per week. Participants underwent a behavioural intervention (consisting of a telecoaching programme to enhance physical activity) between Week 4 and Week 8.

Baseline was defined as mean of steps/day assessed during the week before the randomisation visit.

End point type	Secondary

End point timeframe:

Week 8

End point values	AB/FF 400/12 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	117		
Units: Percent				
number (not applicable)	41.53	50.43		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 70+3	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Aclidinium Bromide/Formoterol Fumarate FDC 400/12µg
Reporting group description: 8 weeks, double blind treatment period	
Reporting group title	Placebo to Aclidinium/Formoterol
Reporting group description: 8 weeks, double blind treatment period	

Serious adverse events	Aclidinium Bromide/Formoterol Fumarate FDC 400/12µg	Placebo to Aclidinium/Formoterol	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 134 (1.49%)	3 / 133 (2.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Pubis fracture			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	1 / 134 (0.75%)	0 / 133 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Lens dislocation			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 134 (0.00%)	1 / 133 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Aclidinium Bromide/Formoterol Fumarate FDC 400/12µg	Placebo to Aclidinium/Formoterol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 134 (10.45%)	24 / 133 (18.05%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 134 (2.99%)	12 / 133 (9.02%)	
occurrences (all)	4	24	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 134 (10.45%)	13 / 133 (9.77%)	
occurrences (all)	14	13	

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