Clinical trial results:
A randomised, double-blind, placebo controlled, parallel study to assess the benefits of aclidinium bromide in the relief of COPD symptoms including cough when administered to patients with COPD

Summary

EudraCT number	2014-004715-37
Trial protocol	DE GB HU IT ES
Global end of trial date	17 November 2015

Results information

Result version number	v1 (current)
This version publication date	12 November 2016
First version publication date	12 November 2016

Trial information

Trial identification

Sponsor protocol code	M-34273-46

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02375724
WHO universal trial number (UTN)	-
Other trial identifiers	Alternative sponsor identifier: D6560C00001

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	2 Kingdom St, London, United Kingdom, W2 6BD
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	17 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2015
Global end of trial reached?	Yes
Global end of trial date	17 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of aclidinium bromide 400 µg administered twice a day on COPD symptoms including cough and on cough-related quality of life measures in patients with moderate COPD compared to placebo

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics

Before enrolment into the study, all patients were comprehensively informed by the investigator (or the personnel identified as designated staff) orally and by means of the patient information sheet about the characteristics of the investigational medicinal products to be administered, the nature of the clinical investigation, the risks and the discomfort that could reasonably be expected as a result of their participation and about their right to withdraw at any time from the study, without prejudice and without any need to specify the reasons

Patients documented their willingness to participate in the study by giving their written consent by signing the Informed Consent Form before the start of any study procedure

Salbutamol pMDI (100 µg/puff) was allowed as relief medication

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 March 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	Germany: 115
Country: Number of subjects enrolled	Hungary: 88
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 36
Worldwide total number of subjects	269
EEA total number of subjects	269

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)	163
From 65 to 84 years	105
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were randomized in 30 study sites in 5 countries Germany (10 sites), Hungary (6), Italy (2), Spain (9) and the United Kingdom (3)

First patient was enrolled in March 2015 and last patient last visit was in November 2015

Pre-assignment

Screening details:

300 patients were screened; 269 were assessed as eligible and were randomized into the study

Thirty-one patients failed screening, with the main reason for screening failure being non-fulfilment of the inclusion or exclusion criteria (24 patients)

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	Aclidinium 400 µg

Arm description:

Aclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler

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

Dosage and administration details:

1 puff of 400 µg in the morning (09:00±1 hour) and in the evening (21:00±1 hour)

Arm title	Placebo

Arm description:

Placebo BID administered by Genuair® multidose dry powder inhaler

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

Dosage and administration details:

1 puff of 400 µg in the morning (09:00±1 hour) and in the evening (21:00±1 hour)

Number of subjects in period 1	Aclidinium 400 µg	Placebo
Started	135	134
Completed	129	128
Not completed	6	6
Consent withdrawn by subject	1	1
Adverse event, non-fatal	2	4
Lost to follow-up	1	-
Lack of efficacy	1	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Aclidinium 400 µg
Reporting group description:	
Aclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler	
Reporting group title	Placebo
Reporting group description:	
Placebo BID administered by Genuair® multidose dry powder inhaler	

Reporting group values	Aclidinium 400 µg	Placebo	Total
Number of subjects	135	134	269
Age categorical Units: Subjects			
Adults (18-65 years)	89	81	170
From 66-84 years	45	53	98
85 years and over	1	0	1
Age Continuous | Units: Years			
arithmetic mean	62	62	
standard deviation	± 8.4	± 9.1	-
Gender, Male/Female Units: Participants			
Female	57	50	107
Male	78	84	162

End points

End points reporting groups

Reporting group title	Aclidinium 400 µg
Reporting group description:	
Aclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler	
Reporting group title	Placebo
Reporting group description:	
Placebo BID administered by Genuair® multidose dry powder inhaler	

Primary: Change from baseline in overall Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) total score

End point title	Change from baseline in overall Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) total score

End point description:

The EXACT-Respiratory Symptoms (E-RS) questionnaire was completed every evening
The E-RS scale is an instrument comprising a subset of EXACT items to test the effect of treatment on the severity of respiratory symptoms in stable COPD
Eleven of the 14-items of the EXACT questionnaire provides information about COPD symptoms: The E-RS Total Score is an aggregate of three domains: chest symptoms (derived sum of 3 items), cough and sputum (derived sum of 3 items) and RS-breathlessness (derived sum of 4 items)
Individual scores are rated from 0 to 4

End point type	Primary
End point timeframe:	
Week 8	

End point values	Aclidinium 400 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	133		
Units: Score				
least squares mean (standard error)	-1.75 (± 0.342)	-0.73 (± 0.342)		

Statistical analyses

Statistical analysis title	Aclidinium v Placebo
Comparison groups	Aclidinium 400 µg v Placebo

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0306
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	-0.1

Secondary: Change from baseline in overall E-RS cough and sputum domain score

End point title	Change from baseline in overall E-RS cough and sputum domain score

End point description:

End point type	Secondary

End point timeframe:

Week 8

End point values	Aclidinium 400 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	133		
Units: Score				
least squares mean (standard error)	-0.54 (± 0.09)	-0.33 (± 0.09)		

Statistical analyses

Statistical analysis title	Aclidinium v Placebo
Comparison groups	Aclidinium 400 µg v Placebo
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0793
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-0.22

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	0.03

Secondary: Change from baseline in the Leicester Cough Questionnaire (LCQ) total score

End point title	Change from baseline in the Leicester Cough Questionnaire (LCQ) total score

End point description:

The LCQ is a self-administered questionnaire that assesses cough related quality of life
The LCQ comprises 19 items and 3 domains (physical, psychological and social)
The total score ranges from 3 to 21 and each domain scores range from 1 to 7; a higher score indicates a better quality of life

End point type	Secondary

End point timeframe:

Week 8

End point values	Aclidinium 400 µg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	128		
Units: Score				
least squares mean (standard error)	1.18 (± 0.214)	1.24 (± 0.214)		

Statistical analyses

Statistical analysis title	Aclidinium v Placebo
Comparison groups	Aclidinium 400 µg v Placebo
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.844
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	0.52

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 70±3	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo BID administered by Genuair® multidose dry powder inhaler	
Reporting group title	Aclidinium 400 µg
Reporting group description:	
Aclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler	

Serious adverse events	Placebo	Aclidinium 400 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 134 (1.49%)	2 / 135 (1.48%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Aclidinium 400 µg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 134 (14.93%)	11 / 135 (8.15%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 134 (9.70%)	7 / 135 (5.19%)	
occurrences (all)	25	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 134 (6.72%)	4 / 135 (2.96%)	
occurrences (all)	10	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2014	Correction included, as the Investigator Brochure was not provided along with the protocol and was available on request; Modification of the clarification note of inclusion criteria 1, as a serum pregnancy test was not performed in the study, but a urine pregnancy test was performed; Correction on the number of digits for site identification, as the first 5 digits representing the investigator identifier was replaced by the first 4 digits representing the site identifier

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported