



Clinical trial results:

Efficacy and safety of acclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo when administered to patients with stable chronic obstructive pulmonary disease

Summary

EudraCT number	2011-001524-38
Trial protocol	GB SE SK HU CZ ES FI BE DE AT DK PL IT
Global end of trial date	04 January 2013

Results information

Result version number	v1 (current)
This version publication date	30 September 2016
First version publication date	30 September 2016

Trial information

Trial identification

Sponsor protocol code	M/40464/30
-----------------------	------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462942
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	2 Kingdom St, London, United Kingdom, W2 6BD
Public contact	Esther Garcia, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Esther Garcia, 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	04 January 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2013
Global end of trial reached?	Yes
Global end of trial date	04 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To assess the long-term bronchodilation of acclidinium bromide/formoterol fixed dose combinations compared to individual components and placebo, when administered BID via inhalation to COPD patients
2. To assess the benefits of acclidinium bromide/formoterol fixed dose combinations in COPD symptoms, disease-related health status and COPD exacerbations compared to individual components and placebo, when administered BID via inhalation to COPD patients
3. To evaluate the long-term safety and tolerability of acclidinium bromide/formoterol fixed dose combinations compared to individual components and placebo when administered BID via inhalation to COPD patients

Protection of trial subjects:

This study was performed according to the local regulations of each country where the study was conducted, the directives of the Declaration of Helsinki for biomedical research in humans adopted by the 18th World Medical Assembly, Helsinki (1964), revised at Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996) and Edinburgh (2000) including the Note of Clarification in paragraph 29, Washington (2002), Tokyo (2004) and Seoul (2008), as well as in compliance with the guidelines of the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP)

Salbutamol pMDI (100 µg/puff) was allowed during the study as relief medication provided the 6 hours washout was maintained prior to any scheduled visit

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 October 2011
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	Austria: 3
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Croatia: 13
Country: Number of subjects enrolled	Czech Republic: 134
Country: Number of subjects enrolled	Denmark: 30
Country: Number of subjects enrolled	Finland: 27
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 303
Country: Number of subjects enrolled	Hungary: 88
Country: Number of subjects enrolled	Italy: 14

Country: Number of subjects enrolled	Netherlands: 24
Country: Number of subjects enrolled	Poland: 244
Country: Number of subjects enrolled	Romania: 119
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Slovakia: 36
Country: Number of subjects enrolled	South Africa: 141
Country: Number of subjects enrolled	Korea, Republic of: 50
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 34
Country: Number of subjects enrolled	Ukraine: 210
Country: Number of subjects enrolled	United Kingdom: 120
Worldwide total number of subjects	1729
EEA total number of subjects	1289

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)	965
From 65 to 84 years	763
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 22 countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Sweden, Ukraine and UK). The first patient was screened in October 2011 and the last patient visit was in January 2013

Pre-assignment

Screening details:

In total 2443 patients were screened, of whom, 1729 patients were considered eligible and were randomised into the study. In total, 714 (29.2%) patients were considered screen failures, the main reason being non-fulfilment of inclusion/exclusion criteria (88.9%)

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	Placebo

Arm description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

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:

Administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm title	Acclidinium/Formoterol 400/12 µg
------------------	----------------------------------

Arm description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm type	Experimental
Investigational medicinal product name	Acclidinium bromide / Formoterol fumarate 400/12 µg fixed-dose combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Acclidinium bromide / Formoterol fumarate 400/12 µg administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm title	Acclidinium/Formoterol 400/6 µg
------------------	---------------------------------

Arm description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm type	Experimental
Investigational medicinal product name	Acclidinium bromide / Formoterol fumarate 400/6 µg fixed-dose combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Acclidinium bromide / Formoterol fumarate 400/6 µg administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm title	Acclidinium 400 µg
------------------	--------------------

Arm description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm type	Active comparator
Investigational medicinal product name	Acclidinium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

400 µg administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm title	Formoterol 12 µg
------------------	------------------

Arm description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Arm type	Active comparator
Investigational medicinal product name	Formoterol fumarate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

12 µg administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Number of subjects in period 1	Placebo	Acclidinium/Formoterol 400/12 µg	Acclidinium/Formoterol 400/6 µg
Started	194	385	381
Completed	160	351	341
Not completed	34	34	40
Other, including COPD exacerbation	3	5	2
Consent withdrawn by subject	14	10	14

Adverse event, non-fatal	7	12	10
Lost to follow-up	-	1	1
Lack of efficacy	6	-	4
Protocol deviation	4	6	9

Number of subjects in period 1	Acclidinium 400 µg	Formoterol 12 µg
Started	385	384
Completed	335	339
Not completed	50	45
Other, including COPD exacerbation	8	5
Consent withdrawn by subject	16	19
Adverse event, non-fatal	11	11
Lost to follow-up	1	1
Lack of efficacy	5	3
Protocol deviation	9	6

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium/Formoterol 400/12 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium/Formoterol 400/6 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium 400 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Formoterol 12 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	

Reporting group values	Placebo	Acclidinium/Formoterol 400/12 µg	Acclidinium/Formoterol 400/6 µg
Number of subjects	194	385	381
Age categorical Units: Subjects			
Adults (18-64 years)	94	230	222
From 65-84 years	100	155	158
85 years and over	0	0	1
Age Continuous Units: Years			
arithmetic mean	64.2	62.7	62.9
standard deviation	± 8	± 8.1	± 7.7
Gender, Male/Female Units: Participants			
Female	56	124	122
Male	138	261	259

Reporting group values	Acclidinium 400 µg	Formoterol 12 µg	Total
Number of subjects	385	384	1729
Age categorical Units: Subjects			
Adults (18-64 years)	208	211	965
From 65-84 years	177	173	763

85 years and over	0	0	1
-------------------	---	---	---

Age Continuous Units: Years arithmetic mean standard deviation	63.1 ± 8.2	63.4 ± 7.8	-
Gender, Male/Female Units: Participants			
Female	129	129	560
Male	256	255	1169

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium/Formoterol 400/12 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium/Formoterol 400/6 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Acclidinium 400 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Reporting group title	Formoterol 12 µg
Reporting group description: Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)	
Subject analysis set title	Placebo (ITT population)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population defined as all randomised patients who took at least one administration of study medication and had a baseline and at least one post-baseline FEV1 assessment	
Subject analysis set title	Acclidinium/Formoterol 400/12 µg (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population defined as all randomised patients who took at least one administration of study medication and had a baseline and at least one post-baseline FEV1 assessment	
Subject analysis set title	Acclidinium/Formoterol 400/6 µg (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population defined as all randomised patients who took at least one administration of study medication and had a baseline and at least one post-baseline FEV1 assessment	
Subject analysis set title	Acclidinium 400 µg (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population defined as all randomised patients who took at least one administration of study medication and had a baseline and at least one post-baseline FEV1 assessment	
Subject analysis set title	Formoterol 12 µg (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) population defined as all randomised patients who took at least one administration of study medication and had a baseline and at least one post-baseline FEV1 assessment	

Primary: Change from baseline in 1-hour morning post-dose forced expiratory volume in one second (FEV1)

End point title	Change from baseline in 1-hour morning post-dose forced expiratory volume in one second (FEV1)
End point description:	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Placebo (ITT population)	Acclidinium/Formoterol 400/12 µg (ITT)	Acclidinium/Formoterol 400/6 µg (ITT)	Acclidinium 400 µg (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	157	347	339	327
Units: Liters				
least squares mean (standard error)	-0.03 (± 0.018)	0.269 (± 0.013)	0.213 (± 0.013)	0.144 (± 0.013)

End point values	Formoterol 12 µg (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	335			
Units: Liters				
least squares mean (standard error)	0.129 (± 0.013)			

Statistical analyses

Statistical analysis title	Acclidinium/Formoterol 400/12 µg v Acclidinium
Comparison groups	Acclidinium/Formoterol 400/12 µg (ITT) v Acclidinium 400 µg (ITT)
Number of subjects included in analysis	674
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.16

Statistical analysis title	Acclidinium/Formoterol 400/6 µg v Acclidinium
Comparison groups	Acclidinium/Formoterol 400/6 µg (ITT) v Acclidinium 400 µg (ITT)
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.105

Primary: Change from baseline in morning pre-dose (trough) forced expiratory volume in one second (FEV1)

End point title	Change from baseline in morning pre-dose (trough) forced expiratory volume in one second (FEV1)
End point description:	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Placebo (ITT population)	Acclidinium/Formoterol 400/12 µg (ITT)	Acclidinium/Formoterol 400/6 µg (ITT)	Acclidinium 400 µg (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	159	349	340	332
Units: Liters				
least squares mean (standard error)	-0.061 (± 0.018)	0.083 (± 0.012)	0.05 (± 0.012)	0.056 (± 0.012)

End point values	Formoterol 12 µg (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	337			
Units: Liters				
least squares mean (standard error)	-0.002 (± 0.012)			

Statistical analyses

Statistical analysis title	Acclidinium/Formoterol 400/12 µg v Formoterol 12 µg
Comparison groups	Acclidinium/Formoterol 400/12 µg (ITT) v Formoterol 12 µg (ITT)
Number of subjects included in analysis	686
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.119

Statistical analysis title	Acclidinium/Formoterol 400/6 µg v Formoterol 12 µg
Comparison groups	Acclidinium/Formoterol 400/6 µg (ITT) v Formoterol 12 µg (ITT)
Number of subjects included in analysis	677
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.087

Secondary: Improvement in Transition Dyspnoea Index (TDI) focal score

End point title	Improvement in Transition Dyspnoea Index (TDI) focal score
End point description:	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Placebo (ITT population)	Acridinium/Formoterol 400/12 µg (ITT)	Acridinium/Formoterol 400/6 µg (ITT)	Acridinium 400 µg (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	156	344	333	331
Units: Total score				
least squares mean (standard error)	1.215 (± 0.241)	2.508 (± 0.162)	2.377 (± 0.165)	2.112 (± 0.165)

End point values	Formoterol 12 µg (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	333			
Units: Total score				
least squares mean (standard error)	2.062 (± 0.164)			

Statistical analyses

Statistical analysis title	Acridinium/Formoterol 400/12 µg v Placebo
Comparison groups	Placebo (ITT population) v Acridinium/Formoterol 400/12 µg (ITT)
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	1.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.728
upper limit	1.859

Statistical analysis title	Acridinium/Formoterol 400/6 µg v Placebo
Comparison groups	Placebo (ITT population) v Acridinium/Formoterol 400/6 µg (ITT)

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Least Squares Mean Difference
Point estimate	1.162
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.593
upper limit	1.73

Secondary: Change from baseline in St. George ´s Respiratory Questionnaire (SGRQ) total score

End point title	Change from baseline in St. George ´s Respiratory Questionnaire (SGRQ) total score
End point description:	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Placebo (ITT population)	Acclidinium/Formoterol 400/12 µg (ITT)	Acclidinium/Formoterol 400/6 µg (ITT)	Acclidinium 400 µg (ITT)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	154	338	332	327
Units: Total score				
least squares mean (standard error)	-6.511 (± 1.029)	-7.164 (± 0.703)	-8.339 (± 0.706)	-5.801 (± 0.71)

End point values	Formoterol 12 µg (ITT)			
Subject group type	Subject analysis set			
Number of subjects analysed	332			
Units: Total score				
least squares mean (standard error)	-5.579 (± 0.706)			

Statistical analyses

Statistical analysis title	Acidinium/Formoterol 400/12 µg v Placebo
Comparison groups	Placebo (ITT population) v Acidinium/Formoterol 400/12 µg (ITT)
Number of subjects included in analysis	492
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.598
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-0.653
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.082
upper limit	1.776

Statistical analysis title	Acidinium/Formoterol 400/6 µg v Placebo
Comparison groups	Placebo (ITT population) v Acidinium/Formoterol 400/6 µg (ITT)
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1406
Method	Mixed models analysis
Parameter estimate	Least squares mean difference
Point estimate	-1.828
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.259
upper limit	0.604

Adverse events

Adverse events information

Timeframe for reporting adverse events:

26 Weeks

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.1
--------------------	------

Reporting groups

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Reporting group title	Acclidinium/Formoterol 400/12 µg
-----------------------	----------------------------------

Reporting group description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Reporting group title	Acclidinium/Formoterol 400/6 µg
-----------------------	---------------------------------

Reporting group description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Reporting group title	Acclidinium 400 µg
-----------------------	--------------------

Reporting group description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Reporting group title	Formoterol 12 µg
-----------------------	------------------

Reporting group description:

Safety population defined as all randomised patients who took at least one administration of study medication - medication administered BID by inhalation, in the mornings and evenings using a multi-dose dry powder inhaler (Genuair®)

Serious adverse events	Placebo	Acclidinium/Formoterol 400/12 µg	Acclidinium/Formoterol 400/6 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 194 (6.19%)	24 / 385 (6.23%)	20 / 381 (5.25%)
number of deaths (all causes)	0	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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

Bladder transitional cell carcinoma subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Lung neoplasm malignant subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung squamous cell carcinoma stage unspecified subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Metastatic gastric cancer subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal cancer stage unspecified subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer stage			

unspecified			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemi			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic oedema			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Allergy to arthropod sting			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food allergy			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary diseases			
subjects affected / exposed	5 / 194 (2.58%)	4 / 385 (1.04%)	4 / 381 (1.05%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary embolism			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Brain contusion			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Concussion			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Femur fracture			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal injury			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Humerus fracture			

subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Traumatic shock			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Congenital, familial and genetic disorders			
Diverticulum Meckel's			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Angina pectoris			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardio-respiratory arrest			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 194 (0.00%)	2 / 385 (0.52%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Torsade de pointes			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			

subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Episcleritis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer hemorrhage			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer hemorrhage			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			

subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Pancreatitis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Cholelithiasis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			

subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious peritonitis			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 194 (0.52%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal abscess			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 194 (0.52%)	3 / 385 (0.78%)	4 / 381 (1.05%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Tonsillitis			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	0 / 381 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 194 (0.00%)	1 / 385 (0.26%)	0 / 381 (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
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	0 / 194 (0.00%)	0 / 385 (0.00%)	1 / 381 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Acclidinium 400 µg	Formoterol 12 µg	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 385 (4.16%)	15 / 384 (3.91%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage unspecified			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic gastric cancer			

subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal cancer stage unspecified			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer stage unspecified			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemi			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic oedema			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Allergy to arthropod sting subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food allergy subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary diseases			
subjects affected / exposed	7 / 385 (1.82%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			

subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal injury			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic shock			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Diverticulum Meckel's			

subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 385 (0.26%)	2 / 384 (0.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Episcleritis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Duodenal ulcer hemorrhage subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer hemorrhage subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders Bile duct obstruction subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious peritonitis			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lobar pneumonia			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 385 (0.26%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			

subjects affected / exposed	0 / 385 (0.00%)	1 / 384 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 385 (0.00%)	0 / 384 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Acclidinium/Formoterol 400/12 µg	Acclidinium/Formoterol 400/6 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 194 (21.65%)	82 / 385 (21.30%)	84 / 381 (22.05%)
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 194 (8.25%)	29 / 385 (7.53%)	27 / 381 (7.09%)
occurrences (all)	22	50	48
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	23 / 194 (11.86%)	33 / 385 (8.57%)	36 / 381 (9.45%)
occurrences (all)	24	38	45
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	9 / 194 (4.64%)	18 / 385 (4.68%)	13 / 381 (3.41%)
occurrences (all)	12	21	15

Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 194 (7.22%) 15	30 / 385 (7.79%) 32	30 / 381 (7.87%) 43
--	------------------------	------------------------	------------------------

Non-serious adverse events	Acclidinium 400 µg	Formoterol 12 µg	
Total subjects affected by non-serious adverse events subjects affected / exposed	94 / 385 (24.42%)	105 / 384 (27.34%)	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	35 / 385 (9.09%) 67	43 / 384 (11.20%) 114	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	39 / 385 (10.13%) 45	59 / 384 (15.36%) 71	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	20 / 385 (5.19%) 32	19 / 384 (4.95%) 27	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	22 / 385 (5.71%) 67	26 / 384 (6.77%) 114	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2012	Amendments included: MACE adjudication was to be assessed during the study; Statistical analyses updated according to the CHMP scientific advice; COPD exacerbations according to Health Resource Utilisation updated; An additional analysis population added, ITT-Exacerbations; Pooled analysis adjusted for EU and US filing purposes; Sensitivity analysis to assess the robustness of the MMRM model was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported