Clinical trial results:
Randomised controlled single and chronic dosing crossover comparison of extra fine particle formoterol and coarse particle salmeterol in asthmatic patients with persistent small airways dysfunction

Summary

EudraCT number	2013-001103-36
Trial protocol	GB
Global end of trial date	17 December 2014

Results information

Result version number	v1 (current)
This version publication date	20 July 2016
First version publication date	20 July 2016

Trial information

Trial identification

Sponsor protocol code	2013RC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01892787
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Tayside Medical Sciences Centre on behalf of the University of Dundee & NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie Way , Dundee, United Kingdom, DD1 9SY
Public contact	Prof Brian Lipworth, Scottish Centre for Respiratory Research University of Dundee , 44 01382 383188, b.j.lipworth@dundee.ac.uk
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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 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2014
Global end of trial reached?	Yes
Global end of trial date	17 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects of extra fine particle formoterol (Atimos) with coarse particle salmeterol (Serevent) on small airway function

Protection of trial subjects:

Subjects were recruited from a database of volunteers who had agreed to be contacted with regard to participating in departmental research. Subjects received a written information sheet (PIS) with details of trial requirements, and had this for at least 24 hours before attending for a screening visit. They were encouraged to discuss the possibility of participation with study staff and others.

Informed consent was obtained before any protocol-specific procedures were carried out. Subjects were given every opportunity to clarify points they did not understand, and ask for more information. It was emphasised that the subject could withdraw consent to participate at any time without loss of benefits to which they otherwise would be entitled. The Chief Investigator could also withdraw a participant at any point if they felt it would be unsafe or inappropriate for the subject to continue. An informed consent form was signed and dated by the subject and the person taking consent, and the volunteer received a copy.

Subjects were only selected if they met the pre-determined inclusion criteria. Only subjects deemed clinically stable were recruited.
Medical history and concomitant medications were reviewed by a medically qualified person to confirm it was safe for the subject to receive the study drug. A physical examination was conducted before randomisation. A screening blood sample was taken at screening with tests appropriate to the risk of the study. Participants received an emergency mobile phone number, carried by a study doctor 24 hours a day, to contact if they experienced any problems, and were advised to contact the department if they felt their asthma was worsening during the study.

Participants on long-acting beta agonists (LABAs) or combination inhalers with a LABA component had to withhold the LABA during the run-in/washout period. The washout periods were for a very short duration (1-2 weeks), and reliever inhalers could be used as required.

Background therapy:

At Screening, all subjects were on inhaled corticosteroid (ICS), either alone, or in a combination inhaler

After screening, subjects were converted to a reference ICS therapy (Clenil Modulite) at an equivalent dose.
LABAs were stopped during the run-in period, and subjects taking a LABA / ICS combination inhaler were switched to Clenil Modulite at an equivalent dose.

Short acting beta-agonists (SABAs) were withheld for 6 hours prior to each visit Other second line controller drugs were permitted (e.g., LTRAs, theophyllines, cromones, and LAMAs)

The average ICS dose for subjects was 500µg/day (74 SEM)

Evidence for comparator:

This was an open label study comparing Atimos Modulite with Serevent Accuhaler
Pathological abnormalities in the small airways have been demonstrated regardless of asthma severity and seem to persist even in patients with stable asthma.
There is a lack of information on the potential benefits of extra fine formoterol on the small airways.
The comparators selected represent the two extremes of available long-acting beta-agonist formulations – i.e. extra fine HFA formoterol (Atimos) versus coarse particle DPI salmeterol (i.e. Serevent

Accuhaler). and their effects on the small airway function was assessed via impulse oscillometry (IOS).

Actual start date of recruitment	08 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	34
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from July 2013 until November 2014. Sufficient numbers were recruited to ensure 16 subjects completed.

Pre-assignment

Screening details:

Subjects were assessed at screening against pre-defined inclusion and exclusion criteria. Eligible subjects entered a 1 to 2 week run-in period during which their ICS dose was converted to a reference inhaler (Clenil Modulite) at an equivalent dose, and any LABAs were stopped.

Pre-assignment period milestones

Number of subjects started	37
Intermediate milestone: Number of subjects	Screening Visit: 37
Intermediate milestone: Number of subjects	Run-In Period: 19
Number of subjects completed	17

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion criteria: 18
Reason: Number of subjects	Did not attend after screening visit: 2

Period 1

Period 1 title	Randomised Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	HFA Formoterol (Cross-Over Design)

Arm description:

Subjects randomised to HFA-formoterol solution 12µg bid, At start of treatment arm, baseline IOS, spirometry, ACQ & FeNO recorded. First IMP dose administered in department, and IOS & spirometry measured at 5,15,30,45 & 60 minutes post-dose.
After 1 to 2 weeks on IMP, subjects returned to department, 12 hours post-dose. Baseline IOS, spirometry, ACQ & FeNO recorded. Final IMP dose administered in department. IOS and spirometry recorded at 5, 15, 30, 45 and 60 minutes post-dose
Cross-over design - Participants received both IMPs (participated in both arms) during the course of the study.

Arm type	Experimental
Investigational medicinal product name	HFA Formoterol
Investigational medicinal product code	
Other name	Atimos Modulite
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

Formoterol 12µg bid

Arm title	DPI Salmeterol (Crossover design)

Arm description:

Subjects randomised to either DPI salmeterol 50µg bid.
At start of treatment arm, baseline IOS, spirometry, ACQ & FeNO recorded.
First IMP dose administered in department, and IOS & spirometry measured at 5,15,30,45 & 60 minutes post-dose.
After 1 to 2 weeks on IMP, subjects returned to department, 12 hours post-dose. Baseline IOS, spirometry, ACQ & FeNO recorded. Final IMP dose administered in department. IOS and spirometry recorded at 5, 15, 30, 45 and 60 minutes post-dose
Cross-over design - Participants received both IMPs (participated in both arms) during the course of the study.

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

Dosage and administration details:

Salmeterol 50µg bid

Number of subjects in period 1	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)
Started	16	17
Completed	16	16
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups[1]

Reporting group title	Randomised Treatment

Reporting group description:

Inclusion Criteria: Male or female, aged > 16 years, with persistent asthma. R5 > 150% predicted, R5-R20 > 0.05 kPa·L·s-1, on ICS or ICS/LABA, with a FEV1 > 60%.
Exclusion Criteria: other significant respiratory diseases, an asthma exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 3 months of the study commencement and smoking within one year or > 10 pack year history.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: The worldwide number enrolled is the number of subjects screened into the study (37).

The number of subjects in the baseline period is the number who were then randomised into the study (17).

Of these 17 subjects, 16 of them completed both arms of the cross-over trial per protocol and were able to be analysed.

Total number of subjects analysed: 16

Reporting group values	Randomised Treatment	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	43		
standard deviation	± 4.2	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	9	9	

Subject analysis sets

Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol

Subject analysis set description:

Inclusion Criteria: Male or female, aged > 16 years, with persistent asthma. R5 > 150% predicted, R5-R20 > 0.05 kPa·L·s-1, on ICS or ICS/LABA, with a FEV1 > 60%.

Exclusion Criteria: other significant respiratory diseases, an asthma exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 3 months of the study commencement and smoking within one year or > 10 pack year history.

Reporting group values	Completed Subjects		
Number of subjects	16		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	13		
From 65-84 years	3		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female	7		
Male	9		

End points

End points reporting groups

Reporting group title	HFA Formoterol (Cross-Over Design)

Reporting group description:

Subjects randomised to HFA-formoterol solution 12µg bid, At start of treatment arm, baseline IOS, spirometry, ACQ & FeNO recorded. First IMP dose administered in department, and IOS & spirometry measured at 5,15,30,45 & 60 minutes post-dose.
After 1 to 2 weeks on IMP, subjects returned to department, 12 hours post-dose. Baseline IOS, spirometry, ACQ & FeNO recorded. Final IMP dose administered in department. IOS and spirometry recorded at 5, 15, 30, 45 and 60 minutes post-dose
Cross-over design - Participants received both IMPs (participated in both arms) during the course of the study.

Reporting group title	DPI Salmeterol (Crossover design)

Reporting group description:

Subjects randomised to either DPI salmeterol 50µg bid.
At start of treatment arm, baseline IOS, spirometry, ACQ & FeNO recorded.
First IMP dose administered in department, and IOS & spirometry measured at 5,15,30,45 & 60 minutes post-dose.
After 1 to 2 weeks on IMP, subjects returned to department, 12 hours post-dose. Baseline IOS, spirometry, ACQ & FeNO recorded. Final IMP dose administered in department. IOS and spirometry recorded at 5, 15, 30, 45 and 60 minutes post-dose
Cross-over design - Participants received both IMPs (participated in both arms) during the course of the study.

Subject analysis set title	Completed Subjects
Subject analysis set type	Per protocol

Subject analysis set description:

Inclusion Criteria: Male or female, aged > 16 years, with persistent asthma. R5 > 150% predicted, R5-R20 > 0.05 kPa·L·s-1, on ICS or ICS/LABA, with a FEV1 > 60%.
Exclusion Criteria: other significant respiratory diseases, an asthma exacerbation or respiratory tract infection requiring systemic steroids and/or antibiotics within 3 months of the study commencement and smoking within one year or > 10 pack year history.

Primary: % change in R5-R20 from baseline

End point title	% change in R5-R20 from baseline

End point description:

Effects on R5-R20 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as % change from baseline.

End point type	Primary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Percentage				
number (not applicable)				
5 minutes	53.05	37.87		
60 minutes	31.12	18.36		

Statistical analyses

Statistical analysis title	% change in R5-R20 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: change in R5 from baseline

End point title	change in R5 from baseline
End point description:	
Effects on R5 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.	
End point type	Secondary
End point timeframe:	
Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)	

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percentage				
number (not applicable)	13.6	6.11		

Statistical analyses

Statistical analysis title	change in R5 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
Variability estimate	Standard error of the mean

Secondary: change in R20 from baseline

End point title	change in R20 from baseline

End point description:

Effects on R20 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percentage				
number (not applicable)	6.82	1.45		

Statistical analyses

Statistical analysis title	change in R20 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
Variability estimate	Standard error of the mean

Secondary: Change in X5 from baseline

End point title	Change in X5 from baseline

End point description:

Effects on X5 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percent				
number (not applicable)	20.48	9.29		

Statistical analyses

Statistical analysis title	change in X5 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: change in RF from baseline

End point title	change in RF from baseline

End point description:

Effects on RF with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percent				
number (not applicable)	18.04	8.7		

Statistical analyses

Statistical analysis title	change in RF from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: change in AX from baseline

End point title	change in AX from baseline

End point description:

Effects on AX with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percent				
number (not applicable)	38.27	18.81		

Statistical analyses

Statistical analysis title	change in AX from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %

Secondary: change in FEV1 from baseline

End point title	change in FEV1 from baseline

End point description:

Effects on FEV1 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percent				
number (not applicable)	5.81	3.15		

Statistical analyses

Statistical analysis title	change in FEV1 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: change in FEF25-75 from baseline

End point title	change in FEF25-75 from baseline

End point description:

Effects on FEF25-75 with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: percent				
number (not applicable)	13.5	9.93		

Statistical analyses

Statistical analysis title	change in FEF25-75 from baseline
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: mean ACQ

End point title	mean ACQ

End point description:

Effects on ACQ with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: units				
number (not applicable)	0.48	0.52		

Statistical analyses

Statistical analysis title	Change from baseline in ACQ
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: Change from baseline in FeNO.

End point title	Change from baseline in FeNO.

End point description:

Effects on FeNO with either small particle formoterol or large particle salmeterol over a 60 minute period after acute and chronic dosing of the IMP, reported as change from baseline.

End point type	Secondary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 1 – 2 weeks

until last visit of treatment period (chronic dosing)

End point values	HFA Formoterol (Cross-Over Design)	DPI Salmeterol (Crossover design)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: ppb				
number (not applicable)	22.5	23.6		

Statistical analyses

Statistical analysis title	Change from baseline in FeNO
Comparison groups	HFA Formoterol (Cross-Over Design) v DPI Salmeterol (Crossover design)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs were recorded from the time a participant consented to join the study until the last study visit.

Adverse event reporting additional description:

Subjects were asked about the occurrence of AEs at each study visit and received training on how to record AEs and concomitant medications. All AEs were recorded on subject-specific logs in the CRFs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Completed Subjects

Reporting group description: -

Serious adverse events	Completed Subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Completed Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Migraine			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Immune system disorders			
Allergic Reaction			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Ear and labyrinth disorders			
earache			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Lightheaded			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Reflux gastritis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Wheeze			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	2		
Worsening of respiratory symptoms			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Dry Cough			

subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all) pain in shoulder subjects affected / exposed occurrences (all) Muscle strain (back) subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 3 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		
Infections and infestations Rhinovirus infection subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2014	REC Amendment (AM01) / MHRA Amendment AM01 Amendment to Inclusion / Exclusion criteria intended to help with recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26220533