Clinical trial results:
A proof of concept study in allergic rhinitis, to evaluate the differential effects of doxazosin between single and chronic dosing on nasal airway calibre

Summary

EudraCT number	2012-005035-85
Trial protocol	GB
Global end of trial date	02 June 2015

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	01 June 2016

Trial information

Trial identification

Sponsor protocol code	2012RC14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01946035
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 , 44 01382383188, b.j.lipworth@dundee.ac.uk
Scientific contact	Prof Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382383188, b.j.lipworth@dundee.ac.uk

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	18 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2015
Global end of trial reached?	Yes
Global end of trial date	02 June 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

What are the effects of chronic alpha blocker use on nasal blockage in patients with allergic rhinitis(allergic inflammation of the nose)?

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 emphasized 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.

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 the screening with tests appropriate to the risk of the study. Blood pressure was taken at each visit.

Participants received an emergency mobile phone number, carried by a study doctor 24 hours a day, to contact if they experienced any problems.

Background therapy:

Antihistamines and / or intranasal corticosteroids were withheld for 7 days prior to the first study visit, and were not permitted for the duration of the study.

If required, participants were given sodium cromoglycate 2% nasal spray if required for relief of symptoms on demand.

Evidence for comparator:

Current management guidelines for allergic rhinitis advocate the use of nasal corticosteroids and antihistamines as first line therapy. However, despite such treatment, there is an unmet need with many patients remaining symptomatic in terms of persistent nasal blockage. Alpha-receptor agonists such as oxymetazoline are available without prescription and provide effective acute decongestant relief, mediated by direct venoconstriction of the nasal sinusoids and by vasoconstriction of afferent arterioles and arteriovenous shunts, leading to a reduction in blood flow to the sinusoids. However, their repeated use is associated with a rapid tachyphylaxis of response due alpha-receptor down-regulation and G protein uncoupling, resulting in desensitization of response. In addition to tachyphylaxis of the vasoconstrictor response, there is also an associated increase in nasal airway hyper-reactivity and rebound worsening of nasal congestion, resulting in the so-called syndrome of rhinitis medicamentosa. Hence, alpha-agonists are only recommended for decongestant use on a temporary short-term basis in patients with allergic rhinitis, for example to aide nasal breathing during an acute viral episode.

These data have in turn led to a novel paradoxical pharmacological hypothesis, namely that chronic dosing with a selective alpha-1 receptor antagonist doxazosin might be beneficial in allergic rhinitis by producing alpha-1 receptor up-regulation and associated resensitization of alpha-receptor-mediated

responsiveness. Doxazosin exhibits strong inverse agonist activity at the alpha-1 receptor and may therefore be able to inhibit constitutive unliganded receptor activity in addition to its antagonist activity by inhibiting the receptor when activated by ligand. The presence of inverse agonist activity also appears to be related to the propensity for inducing up-regulation of alpha-1.

Actual start date of recruitment	04 September 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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	37
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from September 2013 until April 2015. A total of 15 subjects completed the study.

Pre-assignment

Screening details:

Subjects were assessed at screening against pre-defined inclusion and exclusion criteria. Eligible subjects entered a 1-3 week run-in period.

Pre-assignment period milestones

Number of subjects started	40
Intermediate milestone: Number of subjects	Screening Visit: 40
Intermediate milestone: Number of subjects	Run-In Period: 18
Number of subjects completed	17[1]

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion criteria: 22
Reason: Number of subjects	Adverse event, non-fatal: 1

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: The number of subjects who started the pre-assignment period (40) is the number of subjects screened into the study. 17 subjects completed the pre-assignment period and were randomised into the study.

Of these 17 subjects, 15 completed both arms of the cross-over trial and were able to be analysed. There are thus 15 subjects in the arms in Period 1.

Period 1

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

Blinding implementation details:

Blinding was performed under the direct supervision of the affiliated NHS Tayside Clinical Trials Pharmacist, Ninewells Hospital, Dundee. This was GCP compliant with a clear audit trail. Participants were allocated randomised treatment chronologically as they entered the trial. The IMP was double-blinded so that neither the study team nor participants knew whether the treatment was active or placebo at any given point.

Arms

Are arms mutually exclusive?	No
Arm title	Doxazosin

Arm description:

Subjects randomized to prolonged released Doxazosin (Cardozin XL) 4mg once daily in the evening for 3 - 5 weeks. There was a 1- to 3- week run-in and washout period in between randomized treatments.

Baseline measures after run-in and washout were performed at visits 2 of 6, while single-dose effects were measured at visits 3 of 7 and chronic dose effects at visits 4 of 8 (at 12 h post-dose). At each of these visits, an oxymetazoline dose-response curve was also performed. At visits 5 of 9 after the last

dose, a bolus histamine challenge was performed along with subsequent recovery in response oxymetazoline (at 36 h 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	Doxazosin
Investigational medicinal product code	
Other name	Cardozin XL
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Doxazosin 4mg was taken once daily for 3 - 5 weeks.

Arm title	Placebo

Arm description:

Subjects randomized to identical (over-encapsulated) placebo once daily in the evening for 3 - 5 weeks. There was a 1- to 3- week run-in and washout period in between randomized treatments.

Baseline measures after run-in and washout were performed at visits 2 of 6, while single-dose effects were measured at visits 3 of 7 and chronic dose effects at visits 4 of 8 (at 12 h post-dose). At each of these visits, an oxymetazoline dose-response curve was also performed. At visits 5 of 9 after the last dose, a bolus histamine challenge was performed along with subsequent recovery in response oxymetazoline (at 36 h post-dose).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo was taken once daily for 3 - 5 weeks.

Number of subjects in period 1	Doxazosin	Placebo
Started	16	16
Completed	15	15
Not completed	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups[1]

Reporting group title	Randomised Treatment

Reporting group description:

Inclusion Criteria: Physician-based diagnosis of mild allergic rhinitis, at least one positive skin prick test to a panel of common aeroallergens, at least a 20L/min and 20% reversibility in PNIF during DRF to oxymetaozoline using a diluent (baseline) followed by cumulative doses of 25 mcg, 50 mcg, and 100 mcg (sum of both nostrils) at 15-min intervals, able to withhold nasal steroids and antihistamines for the duration of the study.

Exclusion Criteria: Deviated nasal septum (>50%), obstructive inferior turbinate hypertrophy, obstructive adenoidal hypertrophy, nasal polyposis, systolic blood pressure less than 100 mmHg, taking vasodilators which might interact with doxazosin to adversely lower blood pressure.

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 (40).

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

Of these 17 subjects, 15 completed both arms of the cross-over trial and were able to be analysed.

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)	16	16	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	37		
standard deviation	± 3	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	7	7	

Subject analysis sets

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

Subject analysis set description:

Inclusion Criteria: Diagnosis of mild allergic rhinitis, at least one positive skin prick test to a panel of common aeroallergens. At least a 20 L/min and 20% reversibility in PNIF during a DRC to oxymetazoline

using a diluent (baseline) followed by cumulative doses of 25 mcg, 50 mcg and 100 mcg (sum of both nostrils) at 15 minute intervals. Able to withhold nasal steroid and anti-histamines for the duration of the study.
Exclusion Criteria: Deviated Nasal Septum (>50%), obstructive inferior turbinate hyeprtrophy, obstructive adenoidal hypertrophy, or nasal polyposis. Systolic blood pressure less than 100 mmHg. Taking any vasodilators which might interact with doxazosin to adversely lower blood pressure.

Reporting group values	Completed Subjects		
Number of subjects	15		
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)	14		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female	8		
Male	7		

End points

End points reporting groups

Reporting group title	Doxazosin

Reporting group description:

Subjects randomized to prolonged released Doxazosin (Cardozin XL) 4mg once daily in the evening for 3 - 5 weeks. There was a 1- to 3- week run-in and washout period in between randomized treatments.

Baseline measures after run-in and washout were performed at visits 2 of 6, while single-dose effects were measured at visits 3 of 7 and chronic dose effects at visits 4 of 8 (at 12 h post-dose). At each of these visits, an oxymetazoline dose-response curve was also performed. At visits 5 of 9 after the last dose, a bolus histamine challenge was performed along with subsequent recovery in response oxymetazoline (at 36 h post-dose).

Cross-over design - Participants received both IMPs (participated in both arms) during the course of the study.

Reporting group title	Placebo

Reporting group description:

Subjects randomized to identical (over-encapsulated) placebo once daily in the evening for 3 - 5 weeks. There was a 1- to 3- week run-in and washout period in between randomized treatments.

Baseline measures after run-in and washout were performed at visits 2 of 6, while single-dose effects were measured at visits 3 of 7 and chronic dose effects at visits 4 of 8 (at 12 h post-dose). At each of these visits, an oxymetazoline dose-response curve was also performed. At visits 5 of 9 after the last dose, a bolus histamine challenge was performed along with subsequent recovery in response oxymetazoline (at 36 h post-dose).

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

Subject analysis set description:

Inclusion Criteria: Diagnosis of mild allergic rhinitis, at least one positive skin prick test to a panel of common aeroallergens. At least a 20 L/min and 20% reversibility in PNIF during a DRC to oxymetazoline using a diluent (baseline) followed by cumulative doses of 25 mcg, 50 mcg and 100 mcg (sum of both nostrils) at 15 minute intervals. Able to withhold nasal steroid and anti-histamines for the duration of the study.
Exclusion Criteria: Deviated Nasal Septum (>50%), obstructive inferior turbinate hyeprtrophy, obstructive adenoidal hypertrophy, or nasal polyposis. Systolic blood pressure less than 100 mmHg. Taking any vasodilators which might interact with doxazosin to adversely lower blood pressure.

Primary: PNIF

End point title	PNIF

End point description:

Peak nasal inspiratory flow

End point type	Primary

End point timeframe:

Timeframe started at the first visit of the treatment period (acute dosing) and extended 3 - 5 weeks until the last visit of the treatment period (chronic dosing).

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: L/min				
arithmetic mean (standard error)				
single dosing	137 (± 14)	155 (± 16)		

chronic dosing	185 (± 14)	170 (± 17)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

The study was powered at 80% to detect a minimal important difference of 5 L/min [25] (within-subject SD 7 L/min) in the primary end-point of PNIF with an alpha error of 0.05 (two tailed). Baseline values after run-in and washout were compared paired Student's ttests. An overall repeated-measures analysis of variance (ANOVA) was applied to evaluate visit-based effects for PNIF and other secondary outcomes, followed by paired Student's t-tests to compare different time-points. An overall

Comparison groups	Doxazosin v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA
Confidence interval	
level	95 %
sides	2-sided

Secondary: VAS

End point title	VAS

End point description:

Visual Analogue Scale (0-10)

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: units				
arithmetic mean (standard error)				
single dosing	34 (± 5)	25 (± 6)		
chronic dosing	19 (± 4)	20 (± 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nasal Blockage Score

End point title	Nasal Blockage Score
End point description: Symptom score, range 0-3	
End point type	Secondary
End point timeframe: 3-5 weeks	

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: units				
arithmetic mean (standard error)				
single dosing	2.1 (± 0.3)	1.4 (± 0.3)		
chronic dosing	1.1 (± 0.2)	1.3 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall TNS4

End point title	Overall TNS4
End point description: Symptom score 0-12	
End point type	Secondary
End point timeframe: 3-5 weeks	

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Units				
arithmetic mean (standard error)				
single dosing	4.3 (± 0.8)	3.5 (± 0.7)		
chronic dosing	2.8 (± 0.5)	3.2 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supine Heart Rate

End point title	Supine Heart Rate

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: BPM				
arithmetic mean (standard error)				
single dosing	80 (± 4)	74 (± 3)		
chronic dosing	72 (± 4)	71 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erect Heart Rate

End point title	Erect Heart Rate

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: BPM				
arithmetic mean (standard error)				
single dosing	96 (± 5)	84 (± 3)		
chronic dosing	83 (± 3)	82 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supine Systolic BP

End point title	Supine Systolic BP

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mmHg				
arithmetic mean (standard error)				
single dosing	131 (± 4)	135 (± 4)		
chronic dosing	133 (± 3)	133 (± 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erect Systolic BP

End point title	Erect Systolic BP

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mmHg				
arithmetic mean (standard error)				
single dosing	125 (± 3)	129 (± 4)		
chronic dosing	130 (± 4)	133 (± 4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Supine Diastolic BP

End point title	Supine Diastolic BP

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mmHg				
arithmetic mean (standard error)				
single dosing	78 (± 2)	78 (± 3)		
chronic dosing	80 (± 3)	79 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Erect Diastolic BP

End point title	Erect Diastolic BP

End point description:

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mmHg				
arithmetic mean (standard error)				
single dosing	79 (± 2)	80 (± 3)		
chronic dosing	84 (± 3)	84 (± 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: change in Mini-RQLQ Scores

End point title	change in Mini-RQLQ Scores
End point description: compared to baseline	
End point type	Secondary
End point timeframe: 3-5 weeks	

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: units				
arithmetic mean (confidence interval 95%)	-0.3 (-0.7 to 0.1)	-0.09 (-0.72 to 0.54)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nasal NO

End point title	Nasal NO
End point description:	
End point type	Secondary
End point timeframe: 3-5 weeks	

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ppb				
geometric mean (geometric coefficient of variation)	376 (± 1.28)	304 (± 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Oxymetazoline DRC

End point title	Oxymetazoline DRC

End point description:

dose response curve comparing single vs chronic dosing

End point type	Secondary

End point timeframe:

3-5 weeks

End point values	Doxazosin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: L/min				
arithmetic mean (confidence interval 95%)	-17 (-30 to -4)	-4 (-16 to 7)		

Statistical analyses

No statistical analyses for this end point

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 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Completed Subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)		
Injury, poisoning and procedural complications			
Painful Left Nostril Post-Rhinoscopy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sore Left Arm from Skin Prick Test			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vascular disorders			
Palpitations			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	19		
Paresthesia (Hands)			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Fever			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Eye disorders			
Itchy Eyes			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Abdominal Cramps			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Dry mouth			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastric Reflux			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Menstrual Cramps			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Itchy Throat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasal Congestion			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	7		
Chest Tightness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Sore Throat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dry throat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Itchy nose			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nose Bleed			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders			
Stiff Neck			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Shoulder Calcification			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Ankle Strain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Rhinovirus infection			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	11		
Chest Infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thrush			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2014	REC Amendment (AM01) Amendment to notify REC of changes made in response to MHRA's grounds for non-acceptance and right to amend request during initial application process. MHRA Amendment (AM01) Amendment to notify MHRA of temporary halt of the study pending REC approval of AM01.
09 April 2014	REC Amendment (AM02) Amendment to restart the study following a temporary halt. MHRA Amendment (AM02) Amendment to restart the study following a temporary halt.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 December 2013	The study was temporarily halted on 19.12.2013 pending the approval of substantial amendment AM01 by REC. This was approved by REC 15.01.2014. AM02 was submitted to REC & MHRA to permit study re-start, and received final approvals on 15.04.2014.	15 April 2014

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26741127