Clinical trial results:
Proof of concept study to evaluate single and chronic dosing effects of ultra-long acting bronchodilator therapy on mannitol challenge in asthmatic patients taking inhaled corticosteroids

Summary

EudraCT number	2013-001953-28
Trial protocol	GB
Global end of trial date	15 July 2016

Results information

Result version number	v1 (current)
This version publication date	29 July 2017
First version publication date	29 July 2017

Trial information

Trial identification

Sponsor protocol code	2012RC15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02039011
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee - NHS Tayside
Sponsor organisation address	Residency Block, Level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, b.j.lipworth@dundee.ac.uk
Scientific contact	Professor Brian Lipworth, Scottish Centre for Respiratory Research, 44 01382 383188, 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	15 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2016
Global end of trial reached?	Yes
Global end of trial date	15 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare first and last dose protection against mannitol challenge for indacaterol alone versus indacaterol plus tiotropium given once daily as add-on therapy to pre-existing inhaled corticosteroids.

Protection of trial subjects:

The study was approved the Tayside committee for medical ethics (reference: 13/ES/0072) and full informed consent was obtained from all patients. Participants were only selected if they fulfilled the pre-determined inclusion criteria. Medical histories were obtained and physical examinations conducted prior to randomisation into the study, and a medically qualified person confirmed that it was safe for participants to receive the study drug. A screening blood sample was taken at screening with tests appropriate to the risk of the study. An emergency card was issued to each subject, detailing the study, fthe Chief Investigator, the drug under investigation and emergency contact numbers. An emergency mobile was kept 24 hours a day by the study doctor, and participants were advised to phone if they felt that their asthma was worsening during the step-down/run-in period. Only subjects deemed clinically stable were recruited into the study. They received a written PIS detailing the trial requirements and the extent of their participation before attending for a screening visit. They had the PIS for at least 24 hours and were encouraged to discuss the study and their potential involvement with both study staff and others, such as family and friends If participant becomes clinically unstable as assessed by the study physician then they will revert to their usual asthma medication and be withdrawn from the study
A pre-Sponsorship study risk assessment was carried out by the TASC Research Governance Manager prior to Sponsorship approval being granted.

Background therapy:

After initial screening, any LABA therapy was first withdrawn for 2 weeks followed by halving the ICS dose, to a minimum of 400µg/day (as beclometasone equivalent dose). If patients were on secondary controllers such as leukotriene receptor antagonists, these were also stopped. Participants then entered a 2 week run in on this dose of ICS, which was then continued throughout the study.

Evidence for comparator:

Tiotropium (TIO) is a long acting muscarinic antagonists (LAMA), which is functionally selective for the post junctional M3 muscarinic receptor, found on airway smooth muscle. TIO reduces asthma exacerbations by 21% in patients when used as add on therapy in patients receiving inhaled corticosteroids and long-acting beta-agonists (ICS/LABA). TIO exhibits only modest improvements in FEV1, which amounts to approximately 100ml at trough, which is less than the minimally important difference of 230ml. It is therefore hard to explain the protective effect on exacerbations on solely the basis of this small improvement in airway calibre alone.

No studies have looked at effects of TIO on AHR assessed by bronchial challenge using non cholinergic agents. One study showed that as expected TIO produced prolonged functional antagonism of M3 mediated smooth muscle constriction induced by the cholinergic agonist methacholine. As TIO is only currently indicated as add-on therapy to ICS/LABA , the objective of this study was to evaluate the impact of adding TIO to ICS/LABA on AHR, in patients with persistent asthma and whether TIO might also prevent against LABA induced subsensitivity. We chose an indirect bronchial challenge, namely mannitol, as this is thought to more closely reflect physiological stimuli and acts by release of pro-inflammatory mediators. Moreover mannitol challenge has been shown to be related to an inflammatory phenotype in asthma.

Actual start date of recruitment	24 March 2014
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from March 2014 to May 2016. Of the 39 patients screened, 18 were randomised, and 14 completed per protocol.

Pre-assignment

Screening details:

Males & females, non-smokers, >18 years, persistent asthma on ICS or ICS/LABA, FEV1 >50% predicted, mannitol responsive, no chest infections or oral steroids in the last 3 months. After screening, LABAs were stopped for 2 weeks, then ICS dose halved to a minimum of 400µg/day BDP, which continued thoughout study. Secondary controllers were stopped.

Pre-assignment period milestones

Number of subjects started	39
Intermediate milestone: Number of subjects	Screening Visit: 39
Number of subjects completed	18

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion criteria: 17
Reason: Number of subjects	Inability to comply with protocol: 4

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	INDACATEROL

Arm description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) alone at a dose of 150µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

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

Arm type	Experimental
Investigational medicinal product name	Indacaterol
Investigational medicinal product code	
Other name	Onbrez Breezhaler
Pharmaceutical forms	Capsule, hard
Routes of administration	Inhalation use

Dosage and administration details:

Indacaterol (Onbrez Breezhaler) 150µg OD was taken for 4 weeks.

Arm title	TIOTROPIUM + INDACATEROL

Arm description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) at a dose of 150µg OD, combined with tiotropium (Spiriva Handihaler) 18µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

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

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	Spiriva Handihaler
Pharmaceutical forms	Capsule, hard
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium (Spiriva Handihaler) 18µg OD was taken for 4 weeks.

Investigational medicinal product name	Indacaterol
Investigational medicinal product code	
Other name	Onbrez Breezhaler
Pharmaceutical forms	Capsule, hard
Routes of administration	Inhalation use

Dosage and administration details:

Indacaterol (Onbrez Breezhaler) 150µg OD was taken for 4 weeks.

Number of subjects in period 1	INDACATEROL	TIOTROPIUM + INDACATEROL
Started	18	17
Completed	15	17
Not completed	3	0
Adverse event, non-fatal	2	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups[1]

Reporting group title	Randomised Treatment (overall period)

Reporting group description:

Inclusion Criteria: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

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 (39).

The number of subjects in the baseline period is the number who were then randomised into the study (18).

Of these 18 subjects, 14 completed both arms of the cross-over trial and were able to be analysed.

Reporting group values	Randomised Treatment (overall period)	Total	
Number of subjects	18	18	
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)	17	17	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	48		
standard deviation	± 15	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	6	6	

Subject analysis sets

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

Subject analysis set description:

Inclusion Criteria: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

Reporting group values	Completed Subjects		
Number of subjects	14		
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	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	46		
standard deviation	± 15		
Gender categorical Units: Subjects			
Female	9		
Male	5		

End points

End points reporting groups

Reporting group title	INDACATEROL

Reporting group description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) alone at a dose of 150µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

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

Reporting group title	TIOTROPIUM + INDACATEROL

Reporting group description:

Patients received 4 weeks of indacaterol (Onbrez Breezhaler) at a dose of 150µg OD, combined with tiotropium (Spiriva Handihaler) 18µg OD as add-on to pre-existing ICS.

There was a 2 week washout in between treatments while continuing to take the same dose of ICS.

Including screening, there were 7 visits in total. Visits were performed, in the mornings, at baseline after run-in and washout, and at 24 hours (i.e. trough) after the first and last doses of each randomised treatment period. Patients were allowed short acting beta-2 agonists (SABAs) as a reliever during the study, but were asked to abstain from SABA use at least 6 hours before each visit. The visits were conducted in the mornings (8am-10am).

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: Non-smoking male or female patients, aged at least 18 years, with persistent asthma already receiving ICS or ICS/LABA. Minimum FEV1 of > 50% predicted, and mannitol responsive (i.e., provocative dose required to reduce FEV1 by 15% (PD15) <635 mg.

Exclusion Criteria: History of respiratory tract infection or oral corticosteroid use in the last three months prior to screening.

Primary: Mannitol PD15 (mg)

End point title	Mannitol PD15 (mg)

End point description:

single dose vs chronic dosing

End point type	Primary

End point timeframe:

1 day to 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mg				
arithmetic mean (confidence interval 95%)				
baseline	390 (291 to 521)	390 (291 to 521)		
single	537 (438 to 619)	487 (329 to 624)		
chronic	455 (342 to 606)	388 (255 to 593)		

Statistical analyses

Statistical analysis title	per protocol

Statistical analysis description:

The study was powered at 80% to detect a minimal important difference of one doubling dose in mannitol PD 15 (the primary outcome), as change from baseline, comparing indacaterol alone with indacaterol plus tiotropium, after single and chronic dosing, and a within-subject SD of 1.3 doubling dose, requiring a sample size of 14 using a crossover design, with alpha error of 0.05 (2 tailed). All data were first examined for normality and distribution. Repeated measures analysis of variance (ANO

Comparison groups	INDACATEROL v TIOTROPIUM + INDACATEROL
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA

Secondary: FEV1 (L)

End point title	FEV1 (L)

End point description:

single (1 day) vs chronic (28 day) dosing

End point type	Secondary

End point timeframe:

1 day - 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
baseline	2.56 (2.18 to 2.95)	2.56 (2.18 to 2.95)		

single	2.69 (2.28 to 3.1)	2.78 (2.38 to 3.19)		
chronic	2.64 (2.26 to 3.02)	2.71 (2.33 to 3.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 Predicted (%)

End point title	FEV1 Predicted (%)
End point description: single (1 day) vs chronic (28 day) dosing	
End point type	Secondary
End point timeframe: 1 day - 28 days	

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: percent				
arithmetic mean (confidence interval 95%)				
baseline	87 (78 to 97)	87 (78 to 97)		
single	91 (82 to 100)	95 (85 to 105)		
chronic	90 (81 to 100)	93 (83 to 102)		

Statistical analyses

No statistical analyses for this end point

Secondary: FEF25-75 (L)

End point title	FEF25-75 (L)
End point description: single (1 day) vs chronic (28 day) dosing	
End point type	Secondary
End point timeframe: 1 day - 28 days	

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: litre(s)				
arithmetic mean (confidence interval 95%)				
baseline	1.79 (1.22 to 2.36)	1.79 (1.22 to 2.36)		
single	2.02 (1.93 to 2.65)	2.22 (1.49 to 2.95)		
chronic	1.91 (1.25 to 2.57)	1.94 (1.38 to 2.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: R5 (kPA/l.s)

End point title	R5 (kPA/l.s)

End point description:

Single (1 day) vs chronic (28 days) dosing

End point type	Secondary

End point timeframe:

1 day - 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: kPA/l.s				
arithmetic mean (confidence interval 95%)				
baseline	0.54 (0.44 to 0.64)	0.54 (0.44 to 0.64)		
single	0.45 (0.37 to 0.52)	0.39 (0.34 to 0.43)		
chronic	0.44 (0.37 to 0.5)	0.45 (0.39 to 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: R5-R20 (kPA/l.s)

End point title	R5-R20 (kPA/l.s)

End point description:

Single (1 day) vs chronic (28 days) dosing

End point type	Secondary

End point timeframe:

1 - 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: kPa/l.s				
arithmetic mean (confidence interval 95%)				
baseline	0.14 (0.07 to 0.22)	0.14 (0.07 to 0.22)		
single	0.07 (0.03 to 0.11)	0.05 (0.03 to 0.07)		
chronic	0.07 (0.04 to 0.1)	0.08 (0.04 to 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: AX (kPa/l)

End point title	AX (kPa/l)

End point description:

Single (1 day) vs chronic (28 days) dosing

End point type	Secondary

End point timeframe:

1- 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: kPa/l				
arithmetic mean (confidence interval 95%)				
baseline	1.63 (0.58 to 2.68)	1.63 (0.58 to 2.68)		
single	0.76 (0.34 to 1.19)	0.44 (0.25 to 0.63)		
chronic	0.68 (0.43 to 0.92)	0.78 (0.48 to 1.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: RDR (%/mg)

End point title	RDR (%/mg)

End point description:

Single (1 day) vs chronic (28 days) dosing

End point type	Secondary

End point timeframe:

1- 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: %/mg				
arithmetic mean (confidence interval 95%)				
baseline	0.037 (0.025 to 0.055)	0.037 (0.025 to 0.055)		
single	0.011 (0.005 to 0.026)	0.015 (0.008 to 0.029)		
chronic	0.037 (0.023 to 0.061)	0.035 (0.018 to 0.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: FeNO (ppb)

End point title	FeNO (ppb)

End point description:

Single (1 day) vs chronic (28 days) dosing

End point type	Secondary

End point timeframe:

1- 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: ppb				
arithmetic mean (confidence interval 95%)				
baseline	30 (20 to 45)	30 (20 to 45)		
single	30 (20 to 44)	32 (23 to 45)		
chronic	30 (20 to 45)	29 (19 to 44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Salbutamol Recovery (%.min)

End point title	Salbutamol Recovery (%.min)
End point description:	
Single (1 day) vs chronic (28 days) dosing	
End point type	Secondary
End point timeframe:	
1- 28 days	

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: %/min				
arithmetic mean (confidence interval 95%)				
baseline	47 (-79 to 172)	47 (-79 to 172)		
single	33 (-47 to 113)	77 (19 to 136)		
chronic	259 (196 to 322)	239 (177 to 300)		

Statistical analyses

No statistical analyses for this end point

Secondary: ACQ-7

End point title	ACQ-7
End point description:	
Single (1 day) vs chronic (28 days) dosing	
End point type	Secondary

End point timeframe:

1- 28 days

End point values	INDACATEROL	TIOTROPIUM + INDACATEROL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: units				
arithmetic mean (confidence interval 95%)				
baseline	0.72 (0.48 to 0.95)	0.72 (0.48 to 0.95)		
chronic	0.44 (0.24 to 0.63)	0.5 (0.27 to 0.73)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs 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 CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

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 / 14 (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	11 / 14 (78.57%)		
Investigations			
Delayed Recovery following Mannitol Challenge			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Surgical and medical procedures			
Root Canal			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Feeling Shaky			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hangover			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Elevated INR			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Rhinovirus infection			

subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 5		
Pharyngitis subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 5		
Sleep apnoea syndrome subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Chest pain subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Cough subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Rhinitis subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 2		
Musculoskeletal and connective tissue disorders Foot Cramps subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 3		
Hand Cramps subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Painful Finger Joint subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		
Jaw Pain			

subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Metabolism and nutrition disorders Toothache subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 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.
19 March 2015	REC Amendment (AM02) Amendment for use of additional sources for patient recruitment.
20 October 2015	REC Amendment (AM03) Amendment for prospective approval of patient diaries and emergency contact card

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/28665534