Clinical trial results:
Does allopurinol reduce right ventricular mass in lung disease associated pulmonary hypertension?

Summary

EudraCT number	2014-002305-38
Trial protocol	GB
Global end of trial date	16 June 2017

Results information

Result version number	v2 (current)
This version publication date	02 November 2018
First version publication date	09 June 2018
Version creation reason	• Correction of full data set Noticed mistake in the results of the primary outcome

Trial information

Trial identification

Sponsor protocol code	2013CV11

Additional study identifiers

ISRCTN number	ISRCTN11081180
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Reference : 2013CV11

Notes:

Sponsors

Sponsor organisation name	University of Dundee - NHS Tayside
Sponsor organisation address	George Pirie Way, Dundee, United Kingdom,
Public contact	Stephen McSwiggan, University of Dundee, Tayside Clinical Trials Unit, 0044 1382383233, s.j.mcswiggan@dundee.ac.uk
Scientific contact	Stephen McSwiggan, University of Dundee, Tayside Clinical Trials Unit, 0044 1382383233, s.j.mcswiggan@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	22 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2017
Global end of trial reached?	Yes
Global end of trial date	16 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective will be to see if Allopurinol can improve right ventricular hypertrophy in patients with pulmonary hypertension associated with COPD or interstitial lung disease(ILD). This will be done by measuring the size of the right side of the heart muscle with an MRI scan before and after one years of treatment with allopurinol or placebo.

Protection of trial subjects:

All adverse events (AEs) and serious adverse events (SAEs) will be recorded from the time a participant consents to join the study until the last study visit. Participants with unresolved AEs at the last study visit will be followed up until resolution or 30 days after last patient, last visit (LPLV), whichever is sooner. SUSARS will be followed until resolution.

Background therapy:

All the patients currently prescribed medication for their lung disease will continue as normal.

Evidence for comparator:

A possible new way to treat lung disease related pulmonary hypertension (PH) is Allopurinol (Xanthine Oxidase Inhibitor) which decreases both uric acid and oxidative stress. The case for allopurinol is based on several different factors. Firstly, in primary
pulmonary hypertension serum uric acid independently predicts mortality. Furthermore, when vasodilator therapy is given, the change in urate correlates very well (r= 0·68 p<0·0011) with the change in total pulmonary resistance. This accords well with experimental evidence that uric acid decreases NO production in cultured pulmonary artery endothelial cells. Secondly,
both hypoxia and tobacco smoke are known from many studies to up-regulate xanthine oxidase and therefore to increase its production of both uric acid and oxidative stress. Thirdly, and most importantly, there are five experimental studies all showing that allopurinol inhibits hypoxia induced pulmonary vasoconstriction, pulmonary hypertension, endothelial dysfunction and
vascular remodelling. Fourthly, there is one human study where allopurinol improved endothelial function in hypoxic patients.However, this study looked at the brachial artery. Indeed, there is a wealth of data that allopurinol improves systemic endothelial function in many other diseases characterised by oxidative stress. Although this is supportive to some
extent, the pulmonary vasculature is clearly very different from the systemic vasculature. Fifthly, allopurinol profoundly reduces oxidative stress (OS) and OS is known to directly promote RV hypertrophy as well as cause pulmonary vascular abnormalities. There is a sixth, albeit, fairly speculative further reason for studying allopurinol in lung disease. Allopurinol
blocks an oxidase enzyme which “wastes” molecular oxygen by converting it into oxygen free radicals. Therefore in theory blocking this oxidase should boost tissue oxygen.

Actual start date of recruitment	01 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 72

Worldwide total number of subjects	72
EEA total number of subjects	72

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)	9
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 191 patients screened, 72 were randomised, and 66 completed per protocol.

Pre-assignment

Screening details:

Aged 18 years or over, previously diagnosed with COPD or ILD, screening echocardiography based diagnosis of PH, stable lung disease medication for at least two weeks prior to consent, no contraindications to MRI, no allergy or intolerance to allopurinol, LVEF > 45% on echocardiography, CKD class 3B or greater, severe hepatic disease

Period 1

Period 1 title	Overall trial (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:

Double blind medication (allopurinol or placebo) will be prepared, packaged and labelled by Tayside Pharmaceuticals.
Randomisation was carried out by Tayside Pharmaceuticals using block randomisation in twelve groups of six (with three active/three placebo in each block). They used a validated randomisation program and securely backed up both the randomisation seed and the
randomisation allocation. A copy of the allocation was supplied to the Clinical Trials Pharmacy at Ninewells Hospital.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Received placebo tablets

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

Dosage and administration details:

100mg once daily for 2 weeks, then 300mg once daily for 4 weeks and then 300mg twice daily for 10.5 weeks

Arm title	Allopurinol

Arm description:

Received allopurinol tablets

Arm type	Active comparator
Investigational medicinal product name	Allopurinol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg once daily for 2 weeks, 300mg once daily for 4 weeks and then 300mg twice daily for 10.5 weeks

Number of subjects in period 1	Placebo	Allopurinol
Started	36	36
Completed	32	31
Not completed	4	5
Adverse event, serious fatal	1	-
Physician decision	1	-
Consent withdrawn by subject	1	3
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	72	72	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	63	63	
Age continuous Units: years			
arithmetic mean	71		
standard deviation	± 6	-	
Gender categorical Units: Subjects			
Female	28	28	
Male	44	44	
Long-term oxygen use Units: Subjects			
Yes	5	5	
No	67	67	
Chronic lung disease Units: Subjects			
COPD	67	67	
ILD	5	5	
BMI Units: kg/m2			
arithmetic mean	29		
standard deviation	± 5	-	
Smoking history Units: Pack-years			
arithmetic mean	48.6		
standard deviation	± 27.8	-	
FEV1 Units: % predicted			
arithmetic mean	60		
standard deviation	± 21	-	
Pulmonary acceleration time Units: ms			
arithmetic mean	96.0		
standard deviation	± 10.9	-	

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Received placebo tablets	
Reporting group title	Allopurinol
Reporting group description: Received allopurinol tablets	

Primary: Change in right ventricular mass (RVM)	
End point title	Change in right ventricular mass (RVM)
End point description:	
End point type	Primary
End point timeframe: 12 months	

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: gram(s)				
arithmetic mean (standard error)	0.97 (± 1.20)	1.85 (± 1.56)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Comparison groups	Allopurinol v Placebo
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	t-test, 2-sided

Primary: Change in right ventricular mass index (RVMI)	
End point title	Change in right ventricular mass index (RVMI)
End point description:	
End point type	Primary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: gram(s)/square meter				
arithmetic mean (standard error)	0.50 (± 0.60)	0.70 (± 0.75)		

Statistical analyses

Statistical analysis title	Intention-to-treat analysis
Comparison groups	Placebo v Allopurinol
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83
Method	t-test, 2-sided

Secondary: Change in left ventricular mass (LVM)

End point title	Change in left ventricular mass (LVM)

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: gram(s)				
arithmetic mean (standard error)	-1.9 (± 2.8)	0.8 (± 3.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in left ventricular mass index (LVMI)

End point title	Change in left ventricular mass index (LVMI)

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: gram(s)/square meter				
arithmetic mean (standard error)	-1.1 (± 1.2)	0.1 (± 1.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SGRQ total score

End point title	Change in SGRQ total score

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	-1.3 (± 2.0)	-0.9 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: BDI-TDI score

End point title	BDI-TDI score

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	-0.1 (± 0.9)	-0.7 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in six minute walk distance (6MWD)

End point title	Change in six minute walk distance (6MWD)

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: meter				
arithmetic mean (standard error)	-10.0 (± 12.5)	8.8 (± 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NT-ProBNP

End point title	Change in NT-ProBNP

End point description:

End point type	Secondary

End point timeframe:
12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: picogram(s)				
arithmetic mean (standard error)	289.4 (± 213.3)	-87.6 (± 127.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in right ventricular end-systolic volume (RVESV)

End point title	Change in right ventricular end-systolic volume (RVESV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	3.8 (± 2.8)	4.8 (± 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in right ventricular end-diastolic volume (RVEDV)

End point title	Change in right ventricular end-diastolic volume (RVEDV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	5.6 (± 4.2)	8.8 (± 4.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in right ventricular stroke volume (RVSV)

End point title	Change in right ventricular stroke volume (RVSV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	1.6 (± 2.7)	3.0 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in right ventricular ejection fraction (RVEF)

End point title	Change in right ventricular ejection fraction (RVEF)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: percent				
arithmetic mean (standard error)	1.7 (± 1.7)	1.3 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in left ventricular end-systolic volume (LVESV)

End point title	Change in left ventricular end-systolic volume (LVESV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	2.9 (± 2.6)	1.3 (± 2.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in left ventricular end-diastolic volume (LVEDV)

End point title	Change in left ventricular end-diastolic volume (LVEDV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	3.8 (± 4.1)	7.2 (± 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in left ventricular stroke volume (LVSV)

End point title	Change in left ventricular stroke volume (LVSV)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: millilitre(s)				
arithmetic mean (standard error)	0.4 (± 2.6)	5.8 (± 3.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in left ventricular ejection fraction (LVEF)

End point title	Change in left ventricular ejection fraction (LVEF)

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: percent				
arithmetic mean (standard error)	0.0 (± 1.3)	3.0 (± 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for physical functioning

End point title	Change in SF-36 score for physical functioning

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	2.9 (± 2.4)	-1.1 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for physical role limitations

End point title	Change in SF-36 score for physical role limitations

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	8.2 (± 6.4)	1.7 (± 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for emotional role limitations

End point title	Change in SF-36 score for emotional role limitations

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	1.5 (± 8.5)	-5.8 (± 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for energy/fatigue

End point title	Change in SF-36 score for energy/fatigue

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	4.5 (± 3.8)	-0.8 (± 2.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for emotional well-being

End point title	Change in SF-36 score for emotional well-being

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	0.3 (± 3.1)	4.6 (± 2.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for social functioning

End point title	Change in SF-36 score for social functioning

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	-1.6 (± 4.0)	-2.4 (± 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for pain

End point title	Change in SF-36 score for pain

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	1.1 (± 4.7)	-4.1 (± 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for general health

End point title	Change in SF-36 score for general health

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	0.0 (± 3.3)	0.1 (± 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SF-36 score for health change

End point title	Change in SF-36 score for health change

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo	Allopurinol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	36		
Units: unit(s)				
arithmetic mean (standard error)	7.0 (± 5.3)	5.6 (± 4.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were recorded from the time the participants consented to join the study until the last study visit. Participants with unresolved AEs at the last study visit were followed up until resolution or 30 days after last patient, last visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Randomised & analysed subjects

Reporting group description: -

Serious adverse events	Randomised & analysed subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 71 (25.35%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Transitional cell cancer of renal pelvis and ureter metastatic			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prostate cancer			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Toxicity to various agents	Additional description: Drug-induced syncope		

subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal obstruction				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal wall haematoma				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Urinary retention				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Lower respiratory tract infection				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pneumonia			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Randomised & analysed subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 71 (88.73%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 71 (8.45%)		
occurrences (all)	6		
Intermittent claudication			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		

Peripheral swelling			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Testicular swelling			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	5		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Blood cholesterol increased			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	5		
Blood glucose increased			
subjects affected / exposed	8 / 71 (11.27%)		
occurrences (all)	8		
Blood urea increased			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Mean cell volume increased			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Laceration			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Overdose			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Procedural vomiting	Additional description: Intermittent vomiting due to post-nasal drip		
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Rib fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Skin injury	Additional description: Injury to left leg - cut to left shin		
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	5		
Drug withdrawal convulsions			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Dysgeusia	Additional description: Metallic taste		
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Paraesthesia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eye disorders			
Macular degeneration			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Visual acuity reduced			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Retinal detachment			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all)	3 / 71 (4.23%) 3		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 71 (8.45%) 7		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Irritable bowel syndrome subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Nausea subjects affected / exposed occurrences (all)	3 / 71 (4.23%) 3		
Rectal haemorrhage subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Vomiting subjects affected / exposed occurrences (all)	3 / 71 (4.23%) 3		
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	1 / 71 (1.41%) 1		
Dry skin			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Hyperhidrosis	Additional description: Increased sweating		
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Groin pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal chest pain			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	6 / 71 (8.45%)		
occurrences (all)	6		
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Eye infection			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Furuncle			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Hordeolum			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Laryngitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		

Nail infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Oral candidiasis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Viral infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	5		
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2015	Amendment to seek approval for patients suffering from interstitial lung disease to be eligible for recruitment in the study.
05 October 2015	Amendment to seek approval to - Change exclusion criteria from 'already had gout' to ' - Change the timing of six minute walk test from doing two at randomisation visit to doing one as a practice test at screening visit and a second one at randomisation. - Remove the measurement of diffusion capacity of lung for carbon monoxide - Add an additional patient identification centre using SPCRN - Allow study visits 3, 4, 6 and 8 to be done at the location of participant's convenience such as their home
21 April 2016	Amendment to seek approval for adding NHS Grampian as another centre for recruitment for the study.
21 December 2016	Amendment to seek approval to: - Change the follow-up period from 12 months to a minimum of 9 months - Change software for the analysis of MRI images to Circle Cardiovascular Imaging (Calgary, Canada)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: