Clinical trial results:
Hyperpolarised xenon magnetic resonance imaging (Xe-129 MRI) lung imaging in COPD

Summary

EudraCT number	2011-002038-37
Trial protocol	GB
Global end of trial date	23 August 2017

Results information

Result version number	v1 (current)
This version publication date	25 September 2020
First version publication date	25 September 2020
Summary attachment (see zip file)	PUBLICATION (Matin_et_al-2016-Radiology.pdf)

Trial information

Trial identification

Sponsor protocol code	7.0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE
Public contact	Clinical Trials and Research Governance University of Oxford Boundary Brook House Churchill Drive, University of Oxford, +44 01865 616484, ctrg@admin.ox.ac.uk
Scientific contact	Najib Rahman, Oxford Respiratory Trials Unit University of Oxford Churchill Hospital, Najib Rahman, Oxford Respiratory Trials Unit University of Oxford Churchill Hospital, 01865 225205, najib.rahman@ndm.ox.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	02 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 January 2017
Global end of trial reached?	Yes
Global end of trial date	23 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our objective is to develop and use Xe-129 lung MRI, a regional non-ionising radiation based functional imaging tool for the evaluation of COPD. Specific aims are:
(1) Technique development
(2) Comparison to standard COPD assessment tools
(3) Effects of salbutamol
(4) Interval imaging
(5) To evaluate the changes in Xe-129 lung MRI imaging occurring in patients over time.

As a number of scans were used for technique development, the total number of scanned patients (50) is higher than those in whom outcomes for COPD are reported in the attached publication (22). However, safety information is reported for all 50 scanned patients.

Protection of trial subjects:

Patients were carefully monitored during Xenon inhalation and during MRI scanning, with an observation period post treatment. As the "intervention" (Xenon inhalation during an MRI scan) is extremely short lived (minutes), long term side effects beyond 24 hours post inhalatoin were not considered to be required. There is a significant amount of previous data on safety of Xenon inhalation at these doses and the side effect profile is well established; however, all safety data was collected in this study.

Background therapy:

All patients were optimised for treatment of their underlying COPD prior to inclusion in the study.

Evidence for comparator:

n/a - non comparative trial

Actual start date of recruitment	01 February 2012
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	22
From 65 to 84 years	27
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

COPD patients were prospectively enrolled from a tertiary referral center with: stage II–IV COPD on the basis of Global Initiative for Chronic Obstructive Lung Disease criteria (forced expiratory volume in 1 second [FEV1] ,80% predicted and FEV1/ forced vital capacity ,70%), substantial smoking history (>15 years)

Pre-assignment

Screening details:

Exclusion criteria included presence of coexistent cardiopulmonary disease that predominated over COPD (eg,asthma, bronchiectasis, cystic fibrosis). 15 patients did not fulfill inclusion criteria: 6 patients were classified as stage I COPD, 3 patients had inadequate smoking history, five had asthma and 1 heart failure.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	Scanned Patients

Arm description:

All patients received an MRI scan with Xenon (50), no comparator arm. Only those patients with an analysable MRI scan results are reported in the outcomes section = 22). For the purposes of adverse event reporting associated with the IMP (Xenon), all 50 cases are reported

Arm type	Experimental
Investigational medicinal product name	Xenon (Xe-129)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Xenon of approximately 100mL (hyper-polarised) is mixed with medical grade nitrogen for a total volume of 1L.

Number of subjects in period 1	Scanned Patients
Started	50
Completed	22
Not completed	28
COPD outcomes not available	28

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Baseline characteristics of all scanned patients	

Reporting group values	Overall Trial	Total	
Number of subjects	50	50	
Age categorical			
Age by categories			
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)	22	22	
From 65-84 years	27	27	
85 years and over	1	1	
Age continuous			
Age at baseline			
Units: years			
arithmetic mean	65.4		
standard deviation	± 8.5	-	
Gender categorical			
Units: Subjects			
Female	12	12	
Male	38	38	
Smoking Pack Years			
Pack year smoking History			
Units: Pack years			
arithmetic mean			
standard deviation	±	-	
FEV1/FVC ratio			
Ratio			
Units: % ratio			
arithmetic mean	43.2		
standard deviation	± 11.0	-	
FEV1			
Units: Litres			
arithmetic mean	1.34		
standard deviation	± 0.53	-	
FVC			
Forced vital capacity			
Units: Litres			

arithmetic mean	3.07		
standard deviation	± 0.89	-	

Subject analysis sets	
Subject analysis set title	Scanned Patients
Subject analysis set type	Full analysis
Subject analysis set description:	
Scanned patients	

Reporting group values	Scanned Patients		
Number of subjects	22		
Age categorical			
Age by categories			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age at baseline			
Units: years			
arithmetic mean	66.6		
standard deviation	± 7.3		
Gender categorical			
Units: Subjects			
Female	7		
Male	15		
Smoking Pack Years			
Pack year smoking History			
Units: Pack years			
arithmetic mean	66.3		
standard deviation	± 47.3		
FEV1/FVC ratio			
Ratio			
Units: % ratio			
arithmetic mean	43		
standard deviation	± 11		
FEV1			
Units: Litres			
arithmetic mean	.		
standard deviation	±		
FVC			
Forced vital capacity			

Units: Litres			
arithmetic mean	.		
standard deviation	±		

End points

End points reporting groups

Reporting group title	Scanned Patients

Reporting group description:

All patients received an MRI scan with Xenon (50), no comparator arm. Only those patients with an analysable MRI scan results are reported in the outcomes section = 22). For the purposes of adverse event reporting associated with the IMP (Xenon), all 50 cases are reported

Subject analysis set title	Scanned Patients
Subject analysis set type	Full analysis

Subject analysis set description:

Scanned patients

Primary: Xenon and CT scan measured lung paramters

End point title	Xenon and CT scan measured lung paramters[1]

End point description:

End point type	Primary

End point timeframe:

End of scanning

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an observational radiological study of the use of Xenon MRI in assessing lung disease, as compared with standard investigations including thoracic CT. As such, the statistical analyses were correlation of Xenon outcomes (129Xe MR imaging–derived ventilated volume (%) and 129Xe MR imaging–derived average ADC) with qualitative CT, and there are therefore no direct patient comparison groups. All results are in the attached publication.

End point values	Scanned Patients			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: See below	23			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Within 24 hours of inhaling Xenon	
Adverse event reporting additional description:	
All AEs were recorded for within the timeframe	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1.0

Reporting groups	
Reporting group title	All baseline patients

Reporting group description:

All patients undergoing inhaled Xenon and MRI scan (n=50) in which all AEs reported.

It should be noted that no SAE or SAR was reported. All AEs were grade 1 except for 2 which were grade 2 (Voice alteration and Tremor). These are both included within the AE reports.

Serious adverse events	All baseline patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (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	All baseline patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 50 (96.00%)		
Nervous system disorders			
Ataxia	Additional description: Transient		
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	22		
Vision blurred	Additional description: Transient bright lights in one patient, transient blurred vision in another		
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Dysaesthesia			

subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Dysgeusia			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	26		
Headache	Additional description: 3 of which reported "heavy head" rather than headache		
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Deafness	Additional description: Transient		
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Disorientation	Additional description: Transient and mild		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Oral dysaesthesia	Additional description: Transient		
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	15		
Sensory disturbance	Additional description: Warm sensation post intravenou gadolinium		
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Paraesthesia	Additional description: Transient		
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	10		
Tremor	Additional description: Transient and grade 1 in all but 1 case (grade 2). No specific treatment required, settled spontaneously.		
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Dizziness	Additional description: Transient		
subjects affected / exposed	48 / 50 (96.00%)		
occurrences (all)	114		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			

Vocal cord dysfunction	Additional description: Transient voice alteration (mild) and grade 1 in all cases except 1 case of grade 2 (settled spontaneously)		
subjects affected / exposed	25 / 50 (50.00%)		
occurrences (all)	52		
Skin and subcutaneous tissue disorders			
Ecchymosis	Additional description: At skin cannula site		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Pain	Additional description: Transient skin pain		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Pruritus	Additional description: Transient		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Psychiatric disorders			
Euphoric mood			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	17		
Musculoskeletal and connective tissue disorders			
Arthritis	Additional description: Transient		
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	Amendment 1.1.; Protocol v2.0 & 2.1 Patients with a known hypersensitivity to albumin should not undergo perfusion scanning: this exclusion criterion for perfusion scanning has been added to section 5.2. These volunteers may still undergo other components of the study. The duration of the observation period post scan should be indicated. Patients are observed for one hour following hyperpolarised xenon lung MRI. This observation period has now been highlighted in section 4.3. The duration of the study should be limited to two years: this has been highlighted in section 4.4. In section 8.6 the time frame in which SAEs are reported to ORTU should be consistent. Version 2.0 was submitted to the MHRA to state that the ORTU will assess SAEs that are reported to it within seven days (previously one day). This was approved by the MHRA. However on further review by Sponsor andthe Respiratory Trials Unit, this was actually incorrect. Version 2.1 was then submitted, in which the time frame was reverted back to the original of one day. The information that should have been changed, is to state that 'SAES occurring to a research participant during or within 24 hours (previously one hour) following Xe-129 lung MRI will be reported…'.
02 August 2012	Amendment 2.0; Protocol 3.2 Addition of salbutamol element. Study visits and target number of participants: With the addition of the salbutamol component of the study patients make at least two and up to nine visits over the course of two years. All patients undertake the first two visits (enrolment visit and baseline visit; target recruitment number is 30, which is slightly smaller than the previous target number of 40). The total number of visits has not been increased compared to the first submission, as we no longer plan to do three monthly imaging during the first year. Dyspnoea or 'breathlessness' is assessed at each visit using a visual analogue score (repeated after the salbutamol intervention) and Dyspnoea 12 questionnaire. Technical issues pertaining to Xe-129 lung MRI: Technological development suggests that it may be possible for a patient to breathe one litre of a lower concentration of xenon than 100% and still acquire good quality images. Wording in the protocol has therefore been changed from 'the patient breathes in from a bag containing 1L of xenon' to 'the patient breathes in from a 1L bag containing xenon'. The balance volume of gas in the 1L bag is nitrogen. Other amendments: In section 4.3 – correction to the radiation dose of a low dose CT as 1.7 mSv. The previous protocol had accidentally stated this was 0.3 to 0.5 mSv in error. The total number of low dose CT scans that a patient may have over two years is eight, which is in addition to the conventional CT chest at baseline (1.7 mSv). This scan thickness slice is actually 0.625 mm with t

24 July 2013	Protocol V4.0_24Jul2013, Amendment SA03 Clarification of precise name of nuclear medicine scan. The correct name of the scan to be performed is a ventilation/perfusion nuclear medicine scan. The salbutamol & placebo will now be delivered as a multidose inhaler (MDI) via a volumatic spacer rather than via a nebuliser. Each lung imaging visit will take longer than initially anticipated to allow for periods of rest between the different scans. Changes to the timing of patient monitoring following Xenon MRI from 1 hour to 30min. and the use of iodinated contrast for the baseline CT chest Longitudinal visit: lung function must be carried out if more than 6 weeks after Cohort visit. Clarification of timings for visit 3/reproducibility visit. Clarification to the total number of hyperpolarised xenon gas inhalations each participant will undertake during the two year study period. The process for screening participants for hypersensitivity/allergy to iodinated contrast added to the protocol. New wording added to the protocol to allow for completion of calibration prior to actual Xe129 lung MRI scanning. New wording has been added to allow for completion of Xe129 MR sequences in the case of technical failure or nonsynchronisation of patient breathing and scanning. The use of an MDI to deliver the salbutamol/placebo will ensure that the patient remains blinded to the treatment. Description of updated blinding procedure with use of MDI device. This wording was added to clarify the total number of hyperpolarised xenon gas inhalations each participant will undertake during a two year study period. Explanation of the quantity of salbutamol being delivered via a multidose inhaler. The original end of study referred to the COPD cohorts study; 2 years refers to this study. Clarification to AE, SAE and pregnancy reporting.
17 July 2014	SA04, Protocol V5.0_16May2014 Respiratory assessments (quality of life, exercise testing, lung function and daily diary cards) will now take place as part of this lung imaging protocol rather than the COPD Cohort from which these patients are recruited. The target sample size for this study of hyperpolarised xenon MRI lung imaging has also been increased from 30 to 100, to enable sub-group analysis, for example comparing imaging across different disease severities. A subgroup of patients undergoing lung imaging will be proceeding with endoscopic valve lung volume reduction surgery as part of their clinical care. These patients will undergo a different exercise test (six-minute walk test rather than an incremental shuttle walk test), and their follow-up will be at six months post procedure so that data collected will be comparable with other published series. These patients will not take part in follow-up studies and 1 and 2 years, salbutamol or exacerbation components of the follow-up. A recommendation for patients not to eat for 2 hours before CT scanning when contrast is used has been added to the patient information sheet. Dr Najib Rahman will temporarily take over as Chief Investigator and Principal Investigator for this trial from 23rd July 2014 to February 2015.

03 July 2015	SA06, Protocol 08May2015 Simplification of study objectives: Reduction in the number of study visits from 11 to 3. Patients will now undertake the following visits: enrolment, baseline imaging with optional salbutamol element and the longitudinal visit at 1 year or at 6 months (if valve placement patient). Chief Investigator: Dr Najib Rahman will now be the permanent Chief Investigator. Stand-alone study: the Xenon in COPD imaging study will become a stand-alone study and will cease to be a sub-study of the COPD Cohort. Recruitment: this will cease from the COPD Cohort and instead, COPD patients will be recruited from a range of settings including Respiratory out-patient clinics, in-patient wards and pulmonary rehabilitation. The study team have made a video aimed at patients. In the video, a patient is interviewed about their experience of taking part in the trial. Patients will be shown this video if they express an interest in seeing it. The web link to the video has also been put in both patient information sheets. Addition of recruitment posters up in the hospital aimed at patients. Exacerbation-free period: the requirement for patients to be exacerbation free for 4 weeks prior to imaging has been reduced to 2 weeks. Study end date: we would like to extend the end date of the study from 2 years to 3 years after study initiation in order to achieve the primary aims of the amended study. Patient confidentiality: we have updated section 18, "Will my taking part in this study be kept confidential?", in the patient information sheet to ensure it is consistent with the Patient Consent form. Valve placement/surgery patients: a separate Patient Information Sheet and GP letter have been produced which are more relevant to this group of patients. Patient Information Sheet (non-surgery patients) and Patient Consent Form (all patients): amended to reflect the above changes.
27 February 2017	SA07, Protocol 7.0 - Flexibility of visits - Sample size reduced from 100 to 50 - Nuclear medicine scan removed at 1 year - PIS updated accordingly

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/27732160