Clinical trial results:
A study to determine regional lung function in patients with Non-small cell lung cancer (NSCLC) undegoing radiotherapy using hyperpolarised xenon gas MR imaging

Summary

EudraCT number	2011-002028-41
Trial protocol	GB
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2021
First version publication date	09 October 2021

Trial information

Trial identification

Sponsor protocol code	HPX-2011-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02151604
WHO universal trial number (UTN)	-
Other trial identifiers	Ethics Ref: 13/SC/0473, Sponsor's Protocol Code Number: HPX-2011-003

Notes:

Sponsors

Sponsor organisation name	Oxford University Hospitals NHS Foundation Trust
Sponsor organisation address	Garsington Road, Oxford, United Kingdom, OX4 2PG
Public contact	Katie Flight Deputy Head of R&D Governance, Joint Research Office Oxford University Hospitals NHS Foundation Trust, 44 01865 572973, ouh.sponsorship@ouh.nhs.uk
Scientific contact	Katie Flight Deputy Head of R&D Governance, Joint Research Office Oxford University Hospitals NHS Foundation Trust, 44 01865 572973, ouh.sponsorship@ouh.nhs.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	17 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate that hyperpolarized Xe-129 is sensitive to change at midpoint, end of treatment and 3 months following radiotherapy, and thus may be developed as an objective and quantifiable method of functional lung assessment in patients with NSCLC undergoing radiotherapy.

Protection of trial subjects:

Safety reporting protocol in place throughout the trial.

All adverse events observed by the investigator or reported by the patient during and for 24 hours after Xe-129 lung MRI are reported on the case report forms. A member of the research team will contact the participant by telephone 24 hours after completion of hyperpolarized Xe-129 MR imaging to record any AEs that may have occurred after leaving the hospital. These will be clearly documented on the patient CRFs. Thereafter only adverse events where there is a reasonable possibility of a relationship to inhaled xenon (adverse reactions) as judged by the chief investigator, and any adverse event considered by the chief investigator to be of medical interest/ importance are reported. These events will be reported on the case report forms.

It will be left to the investigator's clinical judgment whether or not an AE/ AR is of sufficient severity to require the patient's removal from Xe-129 MRI scanning. A patient may also voluntarily withdraw from study procedures if they tolerate it poorly.

All SAEs (other than those defined in the protocol as not requiring reporting) following Xe-129 lung MRI scanning must be reported on the SAE reporting form to R&D within 24 hours of the Site Study Team becoming aware of the event. R&D will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. It will also be reviewed at the next Trial Safety Group meeting. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed, to R&D. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to R&D.

The Oxford University Hospitals Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively.

Background therapy:

No treatment involved in this study

Evidence for comparator:

Results compared to patients' clinical data, lung function test and chest CT, as in keeping with the standard clincal evaluation of patients receiving radiotherapy therapy to their thorax, and to monitor for the development of radiation pneumonitis and fibrosis.

Actual start date of recruitment	08 April 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: 22
Worldwide total number of subjects	22
EEA total number of subjects	0

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)	6
From 65 to 84 years	15
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients (n=3) were recruited between 08/04/2014 to 20/05/2014 (first recruitment period), then a substantial amendment was made to the study to adjust the study objectives.
More patients (n = 19) were recruited between 06/02/2018 to 19/08/2019 (second recruitment period).
All patients were recruited at the Churchill Hospital, Oxford, UK.

Pre-assignment

Screening details:

Patients were screend by the team amongst those referred to the lung cancer radiation oncology clinic, checking against inclusion and exclusion criteria as specified in the study protocol.

Period 1

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

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Single arm

Arm description:

All patients in this arm were included in the analysis

Arm type	Imaging
Investigational medicinal product name	Hyperpolarised 129-Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Inhalation gas

Arm title	Pre-amendment arm

Arm description:

Before substantial amendment

Arm type	Imaging
Investigational medicinal product name	Hyperpolarised 129-Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Inhalation gas

Number of subjects in period 1	Single arm	Pre-amendment arm
Started	19	3
Completed	14	0
Not completed	5	3
Physician decision	-	3
Lost to follow-up	5	-

Baseline characteristics

Reporting groups

Reporting group title	Second recruitment period

Reporting group description:

19 from the second recruitment period

Reporting group values	Second recruitment period	Total	
Number of subjects	22	22	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
72.10 (12.81)			
Units: years			
median	72.10		
standard deviation	± 12.81	-	
Gender categorical			
Two males, one female			
Units: Subjects			
Female	10	10	
Male	12	12	

Subject analysis sets

Subject analysis set title	Ventilation Change
Subject analysis set type	Full analysis

Subject analysis set description:

Eighteen patients undergoing radiotherapy with expected pulmonary irradiation were recruited for the trial. All patients were previously radiotherapy-naïve. Ten (age: 65.0±15.9, 3:7 = male:female, four with lung, three breast, two oesophageal cancers and one lymphoma) underwent pulmonary function tests (PFTs), chest computed tomography (CT) and HPX-MRI ventilation at 1.5-Tesla, before and on at least one follow-up post-treatment. Images were independently reviewed by two radiologists of 29 and 3 years of specialist experience. Ventilation information was acquired as a summation of the temporal HPX-MRI ventilation signal in the irradiated lung, normalised to the signal in the trachea. Pearson's correlation analysis was performed on the measured ventilation, with CT-derived measurements including airway radius and thickness, and mean attenuation in the irradiated lung, and PFT measurements. A statistical significance level of 5% was used.

Reporting group values	Ventilation Change		
Number of subjects	10		
Age categorical 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			
72.10 (12.81)			
Units: years median standard deviation	 ±		
Gender categorical			
Two males, one female			
Units: Subjects			
Female Male	7 3		

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description:	
All patients in this arm were included in the analysis	
Reporting group title	Pre-amendment arm
Reporting group description:	
Before substantial amendment	
Subject analysis set title	Ventilation Change
Subject analysis set type	Full analysis

Subject analysis set description:

Eighteen patients undergoing radiotherapy with expected pulmonary irradiation were recruited for the trial. All patients were previously radiotherapy-naïve. Ten (age: 65.0±15.9, 3:7 = male:female, four with lung, three breast, two oesophageal cancers and one lymphoma) underwent pulmonary function tests (PFTs), chest computed tomography (CT) and HPX-MRI ventilation at 1.5-Tesla, before and on at least one follow-up post-treatment. Images were independently reviewed by two radiologists of 29 and 3 years of specialist experience. Ventilation information was acquired as a summation of the temporal HPX-MRI ventilation signal in the irradiated lung, normalised to the signal in the trachea. Pearson's correlation analysis was performed on the measured ventilation, with CT-derived measurements including airway radius and thickness, and mean attenuation in the irradiated lung, and PFT measurements. A statistical significance level of 5% was used.

Primary: Ventilation change of hyperpolarised xenon MRI

End point title	Ventilation change of hyperpolarised xenon MRI

End point description:

End point type	Primary

End point timeframe:

Midpoint, end of treatment and 3 months post-treatment completion

End point values	Single arm	Pre-amendment arm	Ventilation Change	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	10[1]	3[2]	10[3]	
Units: Number				
Ventilation change	4	0	4	
Correlation with CT	4	0	4	
Correlation with lung function tests	4	0	4	

Notes:

[1] - 10 with complete lung function test results
(4 - lung ca, 3 breast, 2 oesophagueal, and 1 lymphoma)

[2] - Not analysed

[3] - 10 with complete lung function test results
(4 - lung ca, 3 breast, 2 oesophagueal, and 1 lymphoma)

Attachments (see zip file)	Result figure/RSNA-fig.jpg

Statistical analyses

Statistical analysis title	Pearson's correlation with CT
Statistical analysis description:	
measured ventilation and the ratio of airway thickness to radius (derived from CT)	
Comparison groups	Single arm v Ventilation Change
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.041 [5]
Method	Pearson's correlation analysis
Parameter estimate	Pearson's correlation coefficient
Point estimate	-0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	-0.43

Notes:

[4] - Pearson's correlation analysis was performed on the measured ventilation, with CT-derived measurements - including airway radius and thickness.

[5] - A statistical significance level of 5% was used.

Statistical analysis title	Pearson's correlation with lung function tests

Statistical analysis description:

alveolar volume/VA (R = 0.60, p = 0.037), diffusing capacity for carbon monoxide/TLCO (R = 0.70, p = 0.012), residual volume/RV (R = -0.85, p = 0.032), functional residual capacity/FRC (R = -0.95, p = 0.004) and inspiratory capacity/IC (R = 0.88, p = 0.012).

Comparison groups	Single arm v Ventilation Change
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Pearson's correlation analysis
Parameter estimate	Pearson's correlation coefficient
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from the first scan to 24 hours after the last scan.

Adverse event reporting additional description:

All observed adverse events or reported by the patient during and for 24 hours after Xe-129 lung MRI are reported on the case report forms. A member of the research team will contact the participant by telephone 24 hours after completion of hyperpolarized Xe-129 MR imaging to record any AEs that may have occurred after leaving the hospital

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Study cohort

Reporting group description:

All patients receiving xenon inhalation

Serious adverse events	Study cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (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	Study cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 22 (63.64%)		
Cardiac disorders			
Palpitations	Additional description: Mild, brief and transient		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dizziness			

subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	19		
Euphoric mood	Additional description: Mild, brief and transient		
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Paraesthesia oral	Additional description: Lip, brief and self-limiting		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dysphonia	Additional description: Voice alteration - minor, transient and brief		
subjects affected / exposed	7 / 22 (31.82%)		
occurrences (all)	10		
Throat irritation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Chest discomfort	Additional description: Chest tightness - mild, brief and transient		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Endocrine disorders			
Saliva altered	Additional description: Hypersalivation - brief and transient		
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2017	The number of participants has been reduced to 30 in total. The number of study visits have been reduced to a maximum of five: - Visit 1 – enrolment (compulsory) Visit 2 – Baseline (compulsory) Visit 3 – Half-way through radiotherapy schedule Visit 4 - Final day of radiotherapy treatment Visit 5 – 3-months post-radiotherapy. Participants will be required to complete at least one follow-up visit, the others are optional. Study measures have been reduced: - Ventilation/perfusion nuclear medicine scan is only to be completed at baseline and is optional Exercise tests have been removed from the protocol Clarification of study measures to be completed by patients with and without a diagnosis of lung cancer The study duration has been reduced to nine months to account for the reduced follow-up period The planned trial period has been increased to 5 years The primary objective has been amended to account for the reduced number of study visits/follow-up period. The change in hyperpolarised Xe-129 MRI will now be determined between baseline and time points post-radiotherapy initiation. The inclusion criteria have been amended to include any patient considered for radiotherapy or chemotherapy affecting the lung. The name of the xenon hyperpolariser model and manufacturer (Polarean) has been amended. Clarification that thoracic CT will be performed at the Churchill hospital The maximum total number of xenon inhalations has been reduced to 24 to account for the reduced number of study visits. Clarification of type of Xe-129 MR sequences to be acquired.

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.

Two patients were unable to tolerate xenon at baseline and thus withdrawn.
Five more patients withdrew before the the first follow-up, thus were deemed not ot have completed the trial
Two further patients tolerated xenon at baseline but not at F/U

Notes: