



Clinical trial results:

A study to determine regional lung function in patients with Non-small cell lung cancer (NSCLC) undergoing 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 clinical 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 screened 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 | 7 | | |
| Male | 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 oesophageal, and 1 lymphoma)
[2] - Not analysed
[3] - 10 with complete lung function test results
(4 - lung ca, 3 breast, 2 oesophageal, 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

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

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 first follow-up, thus were deemed not to have completed the trial
Two further patients tolerated xenon at baseline but not at F/U

Notes: