Clinical trial results:
Triple Modality Functional Magnetic Resonance Lung Imaging in Cystic Fibrosis and Non-CF Bronchiectasis

Summary

EudraCT number	2019-003052-36
Trial protocol	GB
Global end of trial date	31 December 2023

Results information

Result version number	v1 (current)
This version publication date	24 January 2025
First version publication date	24 January 2025

Trial information

Trial identification

Sponsor protocol code	19067

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	University of Nottingham, E-Floor, Yang Fujia Building, Jubilee Campus, Wollaton Road, Nottingham, United Kingdom, NG8 1BB
Public contact	Head of Research Integrity, Governance and Compliance, The University of Nottingham, sponsor@nottingham.ac.uk
Scientific contact	Head of Research Integrity, Governance and Compliance, The University of Nottingham, sponsor@nottingham.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	31 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2023
Global end of trial reached?	Yes
Global end of trial date	31 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the value of novel MRI techniques to image the lungs of people with CF and bronchiectasis. Our main aims are to see how they compare to current measurements of lung function/structure and check that they give us useful information. Overall, we hope to identify the best MRI scanning methods for assessment of these lung diseases and employ those techniques in future clinical trials.

In CF, there is great interest in newer treatments that can improve lung function. At present, we use relatively simple measures such as blowing tests to assess and monitor the efficacy of these therapies. These measurements may not always be sensitive enough to detect changes in the lungs, so newer tests that are more sensitive are required. The lung disease in bronchiectasis is similar to CF and so studying both patient groups will highlight the utility of lung MRI in a broader population.

Following this study, we aim to run a clinical trial that will use our lung MRI scanning expertise.

Protection of trial subjects:

Safety monitoring during hyperpolarised Xe scanning

Background therapy:

None

Evidence for comparator:

Pilot study, no comparators used.

Actual start date of recruitment	01 January 2020
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: 20
Worldwide total number of subjects	20
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Nottingham, UK
Recruitment from Jan1st 2020-Dec 31st 2023

Pre-assignment

Screening details:

After consent, the following were performed:
Relevant past medical history and current medical records
Physical examination
Pregnancy test
St George's Respiratory Questionnaire
CFQ-R QoL questionnaire
Height and weight
Spirometry (post bronchodilator)
Full lung function tests
Blood pressure
Pulse ox. at rest
ECG
Sputum samples

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	HP Xe Imaging

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Hyperpolarised Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

The IMP (hp 129Xe) was administered via inhalation from a Tedlar bag via an inhalation tube in the hpXe arm. The maximum volume of hp 129Xe per scan was 1L for adults. IMP was administered in the cystic fibrosis arm of the study

Arm title	Cystic fibrosis

Arm description: -

Arm type	Proton scan

No investigational medicinal product assigned in this arm

Number of subjects in period 1	HP Xe Imaging	Cystic fibrosis
Started	8	12
Completed	8	12

Period 2	
Period 2 title	Completion of scan
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	HP Xe Imaging

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Hyperpolarised Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

The IMP (hp 129Xe) was administered via inhalation from a Tedlar bag via an inhalation tube in the hpXe arm. The maximum volume of hp 129Xe per scan was 1L for adults. IMP was administered in the cystic fibrosis arm of the study

Arm title	Cystic fibrosis

Arm description: -

Arm type	Proton scan

No investigational medicinal product assigned in this arm

Number of subjects in period 2	HP Xe Imaging	Cystic fibrosis
Started	8	12
Completed	8	12

Baseline characteristics

End points

End points reporting groups

Reporting group title	HP Xe Imaging
Reporting group description: -	
Reporting group title	Cystic fibrosis
Reporting group description: -	
Reporting group title	HP Xe Imaging
Reporting group description: -	
Reporting group title	Cystic fibrosis
Reporting group description: -	

Primary: successful completion of imaging

End point title	successful completion of imaging[1]
End point description: Safety monitoring during Xe scanning	
End point type	Primary
End point timeframe: during MR scanning plus 24 hour follow up	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is a binary outcome variable; all subjects successfully completed imaging.

End point values	HP Xe Imaging	HP Xe Imaging		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[2]	8[3]		
Units: oxygen saturations				
number (not applicable)	8	8		

Notes:

[2] - Oxygen saturation pre-scan

[3] - Oxygen saturation monitored throughout and following scan

Statistical analyses

Statistical analysis title	Xe gas transfer

Statistical analysis description:

The primary outcome of this arm of this study was whether longitudinal change could be measured in xenon gas transfer (RBC:M), lung microstructure (LmD), lung ventilation (VDP) and lung perfusion (PBV, PBF and MTT) across the post Covid cohort. Changes in metrics with time were assessed using mixed-effect linear regression, which were set up using a random intercept model using IBM SPSS Statistics 27 (SPSS, New York, USA). Results were meta analysed as part of a national post-COVID study.

Comparison groups	HP Xe Imaging v HP Xe Imaging
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	> 0.05 [5]
Method	Friedmans with bonferroni correction
Parameter estimate	Mean difference (final values)
Point estimate	2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	7.2
Variability estimate	Standard error of the mean

Notes:

[4] - measure of lung ventilation

[5] - compared with established range in previously studied normal volunteers (not part of this study)

Primary: image quality from proton scans

End point title	image quality from proton scans[6]

End point description:

Abnormal ventilation determined using proton scanning protocol

End point type	Primary

End point timeframe:

during scan

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Satisfactory images were obtained from all subjects to allow further analyses to be undertaken.

End point values	Cystic fibrosis	Cystic fibrosis		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[7]	12[8]		
Units: % abnormal ventilation				
number (not applicable)	12	12		

Notes:

[7] - Pre-scan

[8] - Scan completion

Statistical analyses

Statistical analysis title	VOLVE

Statistical analysis description:

ventilation measured using VOLVE protocol

Comparison groups	Cystic fibrosis v Cystic fibrosis
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	VOLVE
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.54
Variability estimate	Standard error of the mean

Notes:
[9] - VOLVE analysis

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: Jan 1st 2020-Dec 31st 2023	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	hp Xe
Reporting group description: imaging with hp Xe	
Reporting group title	proton imaging
Reporting group description: proton imaging in subjects with cystic fibrosis	

Serious adverse events	hp Xe	proton imaging	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	hp Xe	proton imaging	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 12 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: As this was purely an imaging study no adverse events were seen.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2020	1) Addition of a new cohort of patients (n=20) who have viral-induced lung disease due to previous covid-19 infection or other significant previous respiratory virus infection (e.g. influenza) 2) Aerosol generating procedures (namely: full lung function tests and lung clearance index) have been made optional, given the current covid-19 outbreak 3) The number of measurements performed at each study visit has been redefined as a minimum of one and maximum of four from the following: xenon MRI, oxygen-enhanced MRI, UTE MRI and lung clearance index) 4) Addition of an extra MRI scanning platform - 7 Tesla Philips Achieva MRI scanner (only used for adult participants)
05 May 2021	Addition of one additional calibration 129Xe scan per study visit (using a smaller volume of 129Xe than full dose scans) to help optimise image quality. Total dosing of hyperpolarized xenon now up to 2.1L (from 2L) compared to previous version of protocol. Test dose of non-hyperpolarized xenon only required for 1st study visit and protocol adjusted to reflect this
13 August 2021	1) Use of both natural abundance and isotopically enriched 129Xe for MRI scanning. a. Both the protocol (version 5.1) and investigator brochure (version 2.0) were updated to reflect the use of the two formulations of 129Xe b. The investigator brochure was also updated to accurately reflect manufacturing/batch release processes for both calibration and full doses of hyperpolarized 129Xe. 2) Addition to the protocol of sharing anonymised data with research teams at the University of Sheffield and University of Oxford. 3) Addition of dynamic contrast enhanced (DCE) lung MRI as an optional modality. 4) Altered timing of study visits

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	scanning suspended during Covid pandemic from March 2020-August 2020	03 August 2020

Notes:

Limitations and caveats

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

data analysed then used as part of meta analysis with other centres as part of Xmas study (publication submitted)

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38819593