Clinical trial results:
Prediction of Recurrent Events with 18F-Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction - the PREFFIR study

Summary

EudraCT number	2014-004021-41
Trial protocol	GB
Global end of trial date	20 May 2022

Results information

Result version number	v1 (current)
This version publication date	09 December 2023
First version publication date	09 December 2023

Trial information

Trial identification

Sponsor protocol code	15-SS-0059

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02278211
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Edinburgh &NHs Lothian
Sponsor organisation address	Old College, South Bridge, Edinburgh, United Kingdom, EH8 9YL
Public contact	Professor David Newby, University of Edinburgh, +44 0131 242 6515 , d.e.newby@ed.ac.uk
Scientific contact	Professor David Newby, University of Edinburgh, +44 0131 242 6515 , d.e.newby@ed.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	20 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2022
Global end of trial reached?	Yes
Global end of trial date	20 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether coronary 18F-fluoride uptake is associated with major adverse cardiac events in patients with multi-vessel coronary artery disease and recent myocardial infarction.

Protection of trial subjects:

The study was overseen by the Edinburgh Clinical Trials Unit and an independent trial steering committee. The study was performed under a clinical trial authorization from the Medicines and Healthcare products Regulatory Agency, with approval from the South East Scotland Research Ethics Committee in accordance with the Declaration of Helsinki24 and
with the written informed consent of each participant.

Background therapy:

The study population consisted of patients aged 50 years or older with a recent (within 21 days) type 1 MI and multivessel coronary artery disease shown on invasive coronary angiography, defined as at least 2 major epicardial vessels with either more than 50% luminal stenosis or previous coronary revascularization(percutaneous coronary intervention or coronary artery bypass graft surgery).

Evidence for comparator:

No Comparator

Actual start date of recruitment	28 September 2015
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: 694
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Australia: 5
Worldwide total number of subjects	704
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)	393
From 65 to 84 years	305
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This was an international, multicenter, prospective longitudinal cohort study conducted in 9 centres across 4 countries between September 2015 and February 2020.

Pre-assignment

Screening details:

Among 2684 patients screened, 995 were eligible, a total of 712 participants were recruited and attended for baseline 18Fsodium fluoride PET and CT scans. Of these, 6 participants received the radiotracer but were unable to complete the scan, and 2 patients were scanned but image reconstruction could not be completed. The study population was 704.

Period 1

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

Arms

Arm title	Overall Trial

Arm description:

This was a cohort study, not a randomised trial.

Arm type	Overall Trial
Investigational medicinal product name	[18F] Sodium Fluoride
Investigational medicinal product code	18FNaF
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

250 MBq

Number of subjects in period 1	Overall Trial
Started	704
Completed	704

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Analysis Population	

Reporting group values	Overall Trial	Total	
Number of subjects	704	704	
Age categorical			
Age Categorical			
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)	393	393	
From 65-84 years	305	305	
85 years and over	6	6	
Age continuous			
Units: years			
arithmetic mean	63.8		
standard deviation	± 8.2	-	
Gender categorical			
Units: Subjects			
Female	103	103	
Male	601	601	

Subject analysis sets	
Subject analysis set title	Analysis Population Overall
Subject analysis set type	Full analysis
Subject analysis set description:	
All Patients analysed	
Subject analysis set title	Low coronary atherosclerotic plaque activity
Subject analysis set type	Full analysis
Subject analysis set description:	
Low coronary atherosclerotic plaque activity was defined as coronary microcalcification activity [CMA] of 0.	
Subject analysis set title	High coronary atherosclerotic plaque activity
Subject analysis set type	Full analysis
Subject analysis set description:	
High coronary atherosclerotic plaque activity was defined as a coronary microcalcification activity (CMA) greater than 0.	

Reporting group values	Analysis Population Overall	Low coronary atherosclerotic plaque activity	High coronary atherosclerotic plaque activity
Number of subjects	704	283	421
Age categorical			
Age Categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	393	189	204
From 65-84 years	305	93	212
85 years and over	6	1	5
Age continuous			
Units: years			
arithmetic mean	63.8	61.8	65.1
standard deviation	± 8.2	± 7.4	± 8.4
Gender categorical			
Units: Subjects			
Female	103	61	42
Male	601	222	379

End points

End points reporting groups

Reporting group title	Overall Trial
Reporting group description:	
This was a cohort study, not a randomised trial.	
Subject analysis set title	Analysis Population Overall
Subject analysis set type	Full analysis
Subject analysis set description:	
All Patients analysed	
Subject analysis set title	Low coronary atherosclerotic plaque activity
Subject analysis set type	Full analysis
Subject analysis set description:	
Low coronary atherosclerotic plaque activity was defined as coronary microcalcification activity [CMA] of 0.	
Subject analysis set title	High coronary atherosclerotic plaque activity
Subject analysis set type	Full analysis
Subject analysis set description:	
High coronary atherosclerotic plaque activity was defined as a coronary microcalcification activity (CMA) greater than 0.	

Primary: Primary Endpoint

End point title	Primary Endpoint
End point description:	
Primary outcome of cardiac death, non-fatal recurrent myocardial infarction, or unscheduled (late) coronary revascularisation for patients in analysis population	
End point type	Primary
End point timeframe:	
Participants were followed up by site investigators until the last recruited patient had completed their 2-year follow-up visit.	

End point values	Overall Trial	Low coronary atherosclerotic plaque activity	High coronary atherosclerotic plaque activity	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	704	283	421	
Units: Number				
Yes	141	51	90	

Statistical analyses

Statistical analysis title	Hazard ratio for primary outcome
Statistical analysis description:	
Time to event analysis, Cox regression.	
Comparison groups	Low coronary atherosclerotic plaque activity v High coronary atherosclerotic plaque activity

Number of subjects included in analysis	704
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.76

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events within 48 hours of baseline visit

Adverse event reporting additional description:

Performance of PET and coronary CT angiography was associated with 15 adverse events, which were predominantly
iodinated contrast reactions. Two events were graded as serious: palpitation and β-blocker–induced bradycardia

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Overall Trial

Reporting group description:

Site Investigator Reported Adverse Events. The total number of subjects exposed to IMP is 712. The denominator is 712, not 704. Eight subjects had IMP but didn't progress into the study.

Serious adverse events	Overall Trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 704 (0.28%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Beta-blocker induced bradycardia	Additional description: Admitted with Heart failure to CCU, exacerbated by beta blocker.		
alternative dictionary used: MedDRA 21			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 704 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations	Additional description: Subject admitted to hospital with palpitations following caffeine intake.		
alternative dictionary used: MedDRA 21			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 704 (0.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Overall Trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 704 (1.85%)		
Surgical and medical procedures			
Venous cannula issue			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 704 (0.71%)		
occurrences (all)	5		
Immune system disorders			
Contrast reaction			
alternative assessment type: Systematic			
subjects affected / exposed	8 / 704 (1.14%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2019	IB updated to include a stand-alone RSI section
14 April 2020	Update to the primary and secondary endpoints. Removal of PREFFIR-TIME 6 week timepoint from protocol. Protocol window on 1 yr and subsequent annual reviews amended from -/+2weeks to -2/+26 weeks. Protocol window on 2 year visits amended from -/+2 weeks to 0 to +52 weeks. Protocol wording updated to allow 2 year CTCA scan to be performed on a separate date from other 2 year assessments if it is not possible for the scan to be performed on the same date. Data protection wording updated to reflect sponsor's approved wording. Typographical errors corrected throughout protocol. Data management section added to the protocol to reflect the Sponsor's current protocol template.

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.

There was a lower event rate in the study population despite recruiting patients with MI and multivessel disease. There was a low inclusion of women . We did not undertake end point adjudication because there was strict blinding of study imaging.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37379010