Clinical trial results:
Assessment of Osteoblastic Activity With 18F-Fluoride in Aortic Bioprosthesis Structural Valve Dysfunction (SVD)

Summary

EudraCT number	2016-002886-77
Trial protocol	FR
Global end of trial date	03 May 2019

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	RC16_0137

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03015818
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Nantes
Sponsor organisation address	5 allée de l'île Gloriette , Nantes, France, 44000
Public contact	Direction de la Recherche, CHU de Nantes, 0033 2 40 08 49 84, soizic.boinet@chu-nantes.fr
Scientific contact	Direction de la Recherche, CHU de Nantes, 0240084984 2 40 08 49 84, soizic.boinet@chu-nantes.fr

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	22 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 May 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate in patients with severe aortic bioprosthesis degeneration the existence of an active calcification phenomenon in the bioprosthetic tissue by 18F-NaF PET

Protection of trial subjects:

PET slots are dedicated to research to allow patients who agree to participate in the study to have the PET scan on the same day as the routine care visit for their bioprosthesis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 January 2017
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	France: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	5
From 65 to 84 years	16
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

25 patients were included.
4 out of 25 patients did not undergo FNA PET, so the study population is 21 patients

Pre-assignment

Screening details:

The study population consisted of patients operated who underwent aortic valve replacement, isolated or associated with another surgical procedure with the installation of a biological valve of animal origin and with echographic signs of severe or moderate degeneration of this biological valve.

Period 1

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

Arms

Arm title	18F-NaF PET-CT

Arm description:

Patients underwent 18F-NaF PET/CT (125 MBq), 18F-FDG PET/CT and thoracic CT to evaluate bioprosthesis calcified plaque burden. Radi-otracer uptake on bioprostheses was analyzed both qualitatively and quantitatively by measuring the blood-pool-corrected standardized up-take value (target-to-background ratio (TBR)).

Arm type	Experimental
Investigational medicinal product name	18F-NaF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Radiopharmaceutical precursor
Routes of administration	Intravenous use

Dosage and administration details:

18F-NaF is administered once in the study, as a single direct IV dose of 125 MBq. There is no dose adjustment.

Number of subjects in period 1	18F-NaF PET-CT
Started	25
Completed	21
Not completed	4
Protocol deviation	4

Baseline characteristics

Reporting groups

Reporting group title	essais global (overall period)

Reporting group description: -

Reporting group values	essais global (overall period)	Total	
Number of subjects	25	25	
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)	5	5	
From 65-84 years	16	16	
85 years and over	4	4	
Age continuous Units: years			
median	76.5		
standard deviation	± 10.3	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	20	20	

Subject analysis sets

Subject analysis set title	analysis of the study population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The analyses of the primary and secondary endpoints are performed on an intention-to-treat basis. Data from all included patients are used for the statistical analysis

Reporting group values	analysis of the study population		
Number of subjects	21		
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)	4		
From 65-84 years	14		
85 years and over	3		
Age continuous			
Units: years			
median	76.5		
standard deviation	± 10.3		
Gender categorical			
Units: Subjects			
Female	4		
Male	17		

End points

End points reporting groups

Reporting group title	18F-NaF PET-CT

Reporting group description:

Patients underwent 18F-NaF PET/CT (125 MBq), 18F-FDG PET/CT and thoracic CT to evaluate bioprosthesis calcified plaque burden. Radi-otracer uptake on bioprostheses was analyzed both qualitatively and quantitatively by measuring the blood-pool-corrected standardized up-take value (target-to-background ratio (TBR)).

Subject analysis set title	analysis of the study population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The analyses of the primary and secondary endpoints are performed on an intention-to-treat basis. Data from all included patients are used for the statistical analysis

Primary: Evaluation of the 18F-NaF binding rate on the valve bioprosthesis

End point title	Evaluation of the 18F-NaF binding rate on the valve bioprosthesis

End point description:

The intensity of 18F-NaF binding to the valve bioprosthesis is assessed by the tissue to blood pool ratio (TBR).
Patients are separated into two groups according to echocardiographic data moderate degeneration (functional area ≥ 0.8 and ≤ 1.2 cm²) or severe degeneration (functional area < 0.8 cm²) and the 18F-NaF TBR will be compared between compared between the two groups.

End point type	Primary

End point timeframe:

The day of the 18F-NaF PET scan

End point values	18F-NaF PET-CT	analysis of the study population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21[1]	21		
Units: ratio	21	21		

Notes:

[1] - The population studied for FNA PET is 21 patients (4 of 25 patients did not perform FNA PET)

Statistical analyses

Statistical analysis title	Comparison of ultrasound characteristics

Statistical analysis description:

All statistical analyses will be descriptive. Patients will be separated into two groups according to their functional surface measured on ultrasound: moderate degeneration (functional surface ≥ 0.8 and ≤ 1.2 cm²) or severe degeneration (functional surface < 0.8 cm²). This obtained variable is analysed as a binary qualitative criterion. The ratio of valve uptake to blood background (TBR) of 18F-NaF is analysed as a quantitative variable. A Mann-Whitney test will be used to compare the 2 groups.

Comparison groups	18F-NaF PET-CT v analysis of the study population

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 5
Method	Mann- Whitney

Notes:

[2] - descriptive

Secondary: association of an inflammatory process by 18F-FDG PET in severe forms of SVD

End point title	association of an inflammatory process by 18F-FDG PET in severe forms of SVD

End point description:

comparison of 18F-FDG RBT between the two groups defined in the primary endpoint

End point type	Secondary

End point timeframe:

6 months

End point values	18F-NaF PET-CT	analysis of the study population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: NK	21	21		

Statistical analyses

Statistical analysis title	comparison of TBRs

Statistical analysis description:

A comparison of 18F-NaF and 18F-FDG TBRs respectively is performed between leaky and stenosing forms of SVD. stenosing forms of SVD

Comparison groups	18F-NaF PET-CT v analysis of the study population
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 5
Method	Mann- Whitney

Secondary: Respective correlations between the valvular TBR of 18F-NaF and 18F-FDG and ultrasound parameters

End point title	Respective correlations between the valvular TBR of 18F-NaF and 18F-FDG and ultrasound parameters

End point description:

End point type	Secondary

End point timeframe:

M6

End point values	18F-NaF PET-CT	analysis of the study population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	21	21		
Units: NK	21	21		

Statistical analyses

Statistical analysis title	calculation of respective correlations

Statistical analysis description:

Calculation of the respective correlations between the 18F-NaF and 18F-FDG valve TBR and the following ultrasound parameters: aortic leak grade, maximum trans-prosthetic velocity, mean trans-prosthetic pressure gradient, indexed and non-indexed body surface area of the valve, visual ultrasound scores of degeneration, thickening, restriction and calcification of the valve leaflets.

Comparison groups	18F-NaF PET-CT v analysis of the study population
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 5
Method	Chi-squared

Notes:

[3] - descriptive

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From D0 to M6	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21
Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 21 (9.52%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiogenic shock			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2018	Extension of the inclusion period by 6 months
07 November 2018	The MS2 amendment concerns: an extension of the inclusion period by one year and an increase in the number of subjects to 40 patients in total. The patient information letter and consent form have been modified to comply with the General Data Protection Regulation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported