Clinical trial results:
Ballon aortic valvuloplasty performed without heparin to decrease vascular and bleeding complications of the procedure

Summary

EudraCT number	2012-003391-39
Trial protocol	FR
Global end of trial date	25 October 2016

Results information

Result version number	v1 (current)
This version publication date	13 August 2022
First version publication date	13 August 2022

Trial information

Trial identification

Sponsor protocol code	9026

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01823393
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UH of Montpellier
Sponsor organisation address	Avenue du Doyen Gaston Giraud, Montpellier, France,
Public contact	DRI, Direction de la Recherche et de l'Innovation, 0033 467330924, depotac@chu-montpellier.fr
Scientific contact	DRI, Direction de la Recherche et de l'Innovation, 0033 467330924, depotac@chu-montpellier.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 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2016
Global end of trial reached?	Yes
Global end of trial date	25 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess if the non-use of heparin sodium during balloon aortic valvuloplasty reduces serious complications due to the procedure, by decreasing the rate of vascular and hemorrhagic complications without increasing the risk of ischaemic events.

Protection of trial subjects:

Constitution of an IDMC that provides patient safety and benefit/risk ratio.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 89
Worldwide total number of subjects	89
EEA total number of subjects	89

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)	2
From 65 to 84 years	38
85 years and over	49

Subject disposition

Recruitment

Recruitment details:

The target population will concern all adult patients justifying balloon aortic valvuloplasty, whatever the indication.

Pre-assignment

Screening details:

Adult patient with tight and symptomatic aortic stenosis of degenerative or congenital origin (bicuspid valve)? with an indication for balloon aortic valvuloplasty

Period 1

Period 1 title	OVERALL (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	HEPARIN

Arm description:

injection of unfractionated heparin (50 IU / kg)
Valvuloplasty is performed in a conventional manner, ie with an injection of unfractionated heparin (50 IU / kg) at the start of procedure

Arm type	Experimental
Investigational medicinal product name	HEPARIN
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled injector
Routes of administration	Intravenous use

Dosage and administration details:

La dose d'héparine administrée sera de 50UI/kg en IV directe en début de procédure de la valvuloplastie dès la mise en place du désilet.

Héparine choay 25 000 UI / 5 ml solution injectable intraveineuse (héparine sodique, flacon de 5 ml), fournisseur laboratoire Sanofi-Aventis France.

Arm title	PLACEBO NaCl

Arm description:

without heparin
valvuloplasty is performed without heparin (placebo injection)

Arm type	Placebo
Investigational medicinal product name	NaCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Intravenous use

Dosage and administration details:

La dose d'héparine administrée sera de 50UI/kg en IV directe en début de procédure de la valvuloplastie dès la mise en place du désilet. Un volume équivalent de Chlorure de Sodium 0.9% (NaCl 0.9%) sera injecté aux patients randomisés dans le groupe placebo.

Placebo: Chlorure de Sodium PROAMP 0.9% solution injectable (ampoule de 10 ml), fournisseur laboratoire Aguettant.

Number of subjects in period 1	HEPARIN	PLACEBO NaCl
Started	44	45
Completed	39	43
Not completed	5	2
death	1	-
Lost to follow-up	4	-
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	HEPARIN
Reporting group description:	
injection of unfractionated heparin (50 IU / kg) Valvuloplasty is performed in a conventional manner, ie with an injection of unfractionated heparin (50 IU / kg) at the start of procedure	
Reporting group title	PLACEBO NaCl
Reporting group description:	
without heparin valvuloplasty is performed without heparin (placebo injection)	

Reporting group values	HEPARIN	PLACEBO NaCl	Total
Number of subjects	44	45	89
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)	0	2	2
From 65-84 years	19	19	38
85 years and over	25	24	49
Gender categorical Units: Subjects			
Female	21	27	48
Male	23	18	41

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
exclusion of patients with consent issues and those who did not have valvuloplasty	

Reporting group values	Intention to treat		
Number of subjects	82		
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)	2		
From 65-84 years	36		
85 years and over	44		
Gender categorical Units: Subjects			
Female	45		
Male	37		

End points

End points reporting groups

Reporting group title	HEPARIN
Reporting group description:	
injection of unfractionated heparin (50 IU / kg) Valvuloplasty is performed in a conventional manner, ie with an injection of unfractionated heparin (50 IU / kg) at the start of procedure	
Reporting group title	PLACEBO NaCl
Reporting group description:	
without heparin valvuloplasty is performed without heparin (placebo injection)	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
exclusion of patients with consent issues and those who did not have valvuloplasty	

Primary: occurrence of a serious complication

End point title	occurrence of a serious complication
End point description:	
End point type	Primary
End point timeframe:	
between inclusion/valvuloplasty and end of study	

End point values	HEPARIN	PLACEBO NaCl	Intention to treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39	43	82	
Units: number	6	1	7	

Statistical analyses

Statistical analysis title	primary endpoint via regression logistic
Statistical analysis description:	
Analysis of the primary endpoint adjusted for sex, the presence of diabetes, renal failure and arteriopathy of the lower limbs and the closure system + COPD	
Comparison groups	HEPARIN v PLACEBO NaCl
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.034
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	117.24

Adverse events

Adverse events information

Timeframe for reporting adverse events:

immediately upon knowledge of the adverse event

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	ALL GROUPS

Reporting group description: -

Serious adverse events	ALL GROUPS		
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 89 (39.33%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Haematoma			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Lymphocele			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			

Aortic valve replacement				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Biliary tract operation				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
fatigue				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hyperthermia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	2 / 89 (2.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				

subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Tachypnoea				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Investigations				
Angiogram				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inflammatory marker increased				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Vascular pseudoaneurysm				
subjects affected / exposed	3 / 89 (3.37%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina pectoris				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Bradyarrhythmia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	8 / 89 (8.99%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	1 / 3			
Nervous system disorders				
Aphasia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Brain stem stroke				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Hemiplegia				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ischaemic attack				
subjects affected / exposed	1 / 89 (1.12%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 89 (5.62%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 89 (3.37%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary retention			

subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ALL GROUPS		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 89 (4.49%)		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 89 (4.49%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2013	addition of a co-investigator
10 June 2014	extension of the duration of inclusions.
12 November 2014	temporary suspension of inclusions following a meeting of the CSI
13 January 2015	resumption of inclusions requires the authorizations of the CPP and the ANSM via substantial modification n°4.
12 May 2015	extend the duration of inclusions

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
24 October 2014	This decision by the promoter comes following a meeting of the Independent Monitoring Committee (ISC) which took place on September 24, 2014. Indeed, pending additional information from PR LECLERCQ, coordinating investigator, on the seriousness (or not) of the complications that occurred in some patients (primary endpoint) with regard to the protocol in force, the members of the CSI cannot decide whether or not to continue the research.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35402691