Clinical trial results:
Xenon for the prevention of postoperative delirium in cardiac surgery: A prospective randomized controlled observer-blinded trial

Summary

EudraCT number	2014-005370-11
Trial protocol	BE
Global end of trial date	12 December 2018

Results information

Result version number	v1 (current)
This version publication date	30 December 2019
First version publication date	30 December 2019

Trial information

Trial identification

Sponsor protocol code	SR12/2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Research Anesthesiology, University Hospitals Leuven, +32 16344270, christel.hugyens@uzleuven.be
Scientific contact	Research Anesthesiology, University Hospitals Leuven, +32 16344270, christel.hugyens@uzleuven.be
Sponsor organisation name	University Hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Anesthesia Research, University Hospitals Leuven, Mrs Cchristel Huygens, University Hospitals Leuven, 0032 16344620, christel.huygens@uzleuven.be
Scientific contact	Anesthesia Research, University Hospitals Leuven, Mrs Cchristel Huygens, University Hospitals Leuven, 0032 16344620, christel.huygens@uzleuven.be

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	28 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2017
Global end of trial reached?	Yes
Global end of trial date	12 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Incidence of postoperative delirium (POD) as assessed by the 3D-CAM or CAM-ICU during the first 5 postoperative day

Protection of trial subjects:

The interventional treatment was administered to patients with standard haemodynamic monitoring in the setting of a fully equipped cardiac operation room. This enabled immediate detection and treatment of adverse events. Xenon inhalation was to be immediately stopped in case that the study patient showed a life-threatening deterioration. Also after leaving the operation room, all patients were closely monitored by the study team for the occurrence of eventual (S)AE's, first on the ICU, later on the normal ward. Moreover, the inclusion of each individual patient into the study was indicated in the electronic hospital information system and hence visible to all physicians and nurses involved in the care of this patient. This facilitates reporting of (S)AE's to the principal investigator.

Background therapy:

Older patients undergoing cardiac surgery have a 40–60% risk of developing postoperative delirium (POD), which is associated with increased morbidity and mortality. In animals, xenon was found to be neuroprotective. Yet, little is known about its neuroprotective effects in humans. We therefore evaluated whether xenon-anaesthesia prevents POD in patients undergoing cardiac surgery.

Evidence for comparator:

The noble gas xenon has neuro- and cardio-protective effects in animal studies and maintains haemodynamics and myocardial contractility better than other anaesthetics. These neuroprotective properties have been confirmed in various in vitro and animal models of traumatic brain injury, neuronal ischaemia, cardiac arrest, intracranial bleeding, and postoperative cognitive dysfunction following cardiopulmonary bypass (CPB). Notably, in patients undergoing off-pump coronary artery bypass surgery, xenon reduced the occurrence of POD, as compared to the routinely used anaesthetic sevoflurane. This study was, however, not designed to address the prophylactic effects of xenon on POD.

Actual start date of recruitment	01 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 190
Worldwide total number of subjects	190
EEA total number of subjects	190

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)	0
From 65 to 84 years	177
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

From November 2015 to December 2017, 258 patients scheduled for on-pump cardiac surgery were screened. In total, 190 patients were included and randomly assigned to the xenon (n = 96) or sevoflurane (n = 94) groups . In all patients, xenon or sevoflurane was stopped and replaced with propofol infusion during the cardiopulmonary bypass period.

Pre-assignment

Screening details:

All patients received the allocated treatment and were eligible for the final analysis of the primary outcome. Screening failure occurred in 68 patients (33 not met inclusion criteria, 20 declined to participate, and 15 had other reasons that excluded them from the participation in the trial).

Period 1

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

Blinding implementation details:

We applied a masked randomization procedure, using closed, sequentially numbered, opaque envelopes that were unsealed upon the patient’s arrival in the operating room. Patients were randomized by computer-generated software. Randomization was stratified by dichotomizing the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) with a cut-off score of 3.Investigator I accomplished the enrollment & all postop assessment & was, similar to the patient,blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Xenon

Arm description:

General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with xenon 40–60% in oxygen,

Arm type	Experimental
Investigational medicinal product name	xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

EEG-titrated administration via inhalation via endotracheal tube,

Arm title	Sevoflurane

Arm description:

General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with sevoflurane 1.0–1.4%.

Arm type	Active comparator
Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

EEG-titrated administration via inhalation via endotracheal tube,

Number of subjects in period 1	Xenon	Sevoflurane
Started	96	94
Completed	96	94

Baseline characteristics

Reporting groups	
Reporting group title	Xenon
Reporting group description:	
General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with xenon 40–60% in oxygen,	
Reporting group title	Sevoflurane
Reporting group description:	
General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with sevoflurane 1.0–1.4%.	

Reporting group values	Xenon	Sevoflurane	Total
Number of subjects	96	94	190
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			
Units: years			
median	76	76	
inter-quartile range (Q1-Q3)	71 to 81	70 to 81	-
Gender categorical			
Units: Subjects			
Female	43	48	91
Male	53	46	99

End points

End points reporting groups

Reporting group title	Xenon
Reporting group description:	
General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with xenon 40–60% in oxygen,	
Reporting group title	Sevoflurane
Reporting group description:	
General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with sevoflurane 1.0–1.4%.	

Primary: Incidence of postoperative delirium

End point title	Incidence of postoperative delirium
End point description:	
The primary endpoint was the POD incidence during the first 5 postoperative days, as determined using the 3D-CAM for non-ventilated patients, or the confusion assessment method adapted for ventilated patients in the ICU (CAM-ICU).Daily POD screening was performed by trained research nurses who were blinded to group allocation.	
End point type	Primary
End point timeframe:	
The first 5 postoperative days.	

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	94		
Units: Incidence of POD, n/N (%)	41	37		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
logistic regression analysis, adjusting for the stratification variable "EuroSCORE II ≤ 3 vs > 3	
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Notes:

[1] - POD incidence was similar between the 2 groups. The odds ratio (95%CI for POD when comparing xenon with sevoflurane=1.18 (0.65; 2.16).After multiple imputation to address the issue of un-evaluable days, the odds ratio was 1.09 (0.59; 2.01), p=0.793.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrollment until the discharge of patient.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Xenon

Reporting group description:

General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with xenon 40–60% in oxygen,

Reporting group title	Sevoflurane

Reporting group description:

General anesthesia was maintained pre- and post-cardiopulmonary bypass (CPB) with sevoflurane 1.0–1.4%.

Serious adverse events	Xenon	Sevoflurane	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 96 (14.58%)	7 / 94 (7.45%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
pericardial tamponade			
subjects affected / exposed	1 / 96 (1.04%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 96 (0.00%)	3 / 94 (3.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	3 / 96 (3.13%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	5 / 96 (5.21%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 96 (3.13%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Xenon	Sevoflurane	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 96 (33.33%)	30 / 94 (31.91%)	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	22 / 96 (22.92%)	17 / 94 (18.09%)	
occurrences (all)	22	17	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 96 (1.04%)	1 / 94 (1.06%)	
occurrences (all)	1	1	
respiratory infection			
subjects affected / exposed	8 / 96 (8.33%)	12 / 94 (12.77%)	
occurrences (all)	8	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported