Clinical trial results:
Xenon as an adjuvant to propofol anaesthesia in patients undergoing off-pump coronary artery bypass graft surgery: a randomized controlled trial

Summary

EudraCT number	2013-000485-11
Trial protocol	BE
Global end of trial date	01 December 2014

Results information

Result version number	v1 (current)
This version publication date	22 December 2019
First version publication date	22 December 2019

Trial information

Trial identification

Sponsor protocol code	SR022013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01948765
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University hospitals Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Anesthesia Research, University Hospitals of the KU Leuven, 0032 16344620, christel.huygens@uzleuven.be
Scientific contact	Anesthesia Research, University Hospitals of the KU 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	01 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2014
Global end of trial reached?	Yes
Global end of trial date	01 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to assess whether the administration of xenon as an adjuvant to propofol anesthesia is superior to anesthesia with propofol alone in patients undergoing off-pump coronary artery bypass surgery.

Protection of trial subjects:

The interventional treatment was administered to patients under advanced hemodynamic monitoring in the setting of a fully equipped cardiac surgical operating room. This enables immediate detection and treatment of adverse events. Xenon inhalation was immediately stopped in case that the study patient shows a life-threatening deterioration. After leaving the operation room, all patients were closely monitored by the study team for the occurrence of eventual adverse or serious adverse events (S) AE's during the whole postoperative period until hospital discharge. 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. Finally, suspected unexpected serious adverse reactions were reported by the principal investigator to the federal health authorities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	0
Adults (18-64 years)	18
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After obtaining written informed consent, 50 patients scheduled for elective OPCAB surgery were enrolled in this prospective, single-centre, randomized, single-blinded controlled trial.
Patients assessed for eligibility; (n = 86)
Patients did not meet inclusion criteria; (n = 25)
Patients decline to participate; (n= 11)

Pre-assignment

Screening details:

Eighty-six patients planned for elective coronary artery surgery in off-pump technique were screened from June 2013 to February 2014. A total of 50 patients were allocated randomly to receive either propofol-TCI alone (n = 25) or xenon 30%+propofol-TCI (n = 25). All patients received the allocated intervention, and no patient was lost to follow-up.

Period 1

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

Blinding implementation details:

Randomization was performed using a software-generated allocation sequence (QuickCalcs; GraphPad Software, La Jolla, CA). To avoid selection bias, we used a masked randomization process in which group assignments were hidden in closed, consecutively numbered envelopes that were only opened on arrival of the participant into the operation room. Two separate and independent investigators performed the study. Investigator I performed enrolment and the assessment of postoperative outcomes.

Arms

Are arms mutually exclusive?	Yes
Arm title	Xenon+propofol

Arm description:

30%Xenon with Propofol-TCI (n = 25).

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:

30% xenon bases on EEG monitoring and clinical and hemodynamic signs.

Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion in pre-filled syringe
Routes of administration	Intravenous drip use , Intravenous bolus use

Dosage and administration details:

Propofol target-controlled infusion; doses were adjusted based on EEG-monitoring

Arm title	Propofol alone

Arm description:

propofol-TCI (n = 25)

Arm type	Active comparator
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intravenous drip use , Intravenous bolus use

Dosage and administration details:

propofol target-controlled infusion titrated based on EEG-monitoring and clinical signs of light anaesthesia (n = 25)

Number of subjects in period 1	Xenon+propofol	Propofol alone
Started	25	25
Completed	25	25

Baseline characteristics

Reporting groups	
Reporting group title	Xenon+propofol
Reporting group description: 30%Xenon with Propofol-TCI (n = 25).	
Reporting group title	Propofol alone
Reporting group description: propofol-TCI (n = 25)	

Reporting group values	Xenon+propofol	Propofol alone	Total
Number of subjects	25	25	50
Age categorical Units: Subjects			
Adults (18-64 years)	8	10	18
From 65-84 years	17	15	32
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	68	66	
standard deviation	± 9	± 7	-
Gender categorical Units: Subjects			
Female	2	3	5
Male	23	22	45

End points

End points reporting groups

Reporting group title	Xenon+propofol
Reporting group description: 30%Xenon with Propofol-TCI (n = 25).	
Reporting group title	Propofol alone
Reporting group description: propofol-TCI (n = 25)	

Primary: norepinephrine doses

End point title	norepinephrine doses
End point description: The primary outcome was intraoperative hemodynamic stability, which was quantified with the doses of norepinephrine required intraoperatively to accomplish the predefined hemodynamic targets (MAP > 70 mmHg).	
End point type	Primary
End point timeframe: Start of anaesthesia induction to end surgery (Intraoperatively)	

End point values	Xenon+propofol	Propofol alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: µg/kg/min				
median (inter-quartile range (Q1-Q3))	0.01 (0.006 to 0.02)	0.04 (0.02 to 0.06)		

Statistical analyses

Statistical analysis title	Primary outcome
Statistical analysis description: This trial was designed to demonstrate that the application of 30% xenon in addition to general anaesthesia with a TCI of propofol results in superior hemodynamics when compared to equipotent general anaesthesia with propofol alone.	
Comparison groups	Xenon+propofol v Propofol alone
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Confidence interval	
level	95 %

Secondary: Anesthesia depth (BIS)

End point title	Anesthesia depth (BIS)

End point description:

Depth of anaesthesia as assessed by the bispectral index (BIS) monitoring

End point type	Secondary

End point timeframe:

Intraoperative

End point values	Xenon+propofol	Propofol alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: value				
arithmetic mean (standard deviation)	36 (± 5)	35 (± 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Postoperatve delirium

End point title	Postoperatve delirium

End point description:

End point type	Secondary

End point timeframe:

In the first 5 postoperative days.

End point values	Xenon+propofol	Propofol alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: n (%)	7	2		

Statistical analyses

Statistical analysis title	Postoperative delirium
Comparison groups	Propofol alone v Xenon+propofol
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 [1]
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Notes:

[1] - The incidence of postoperative delirium (pod) was similar between the groups; POD, n (%)= xenon-propofol 7 (28%) vs propofol alone 2 (8%); p = 0.138

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From enrollment until patient's discharge.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23
Reporting groups	
Reporting group title	Xenon+propofol
Reporting group description: 30%Xenon with Propofol-TCI (n = 25).	
Reporting group title	Propofol alone
Reporting group description: propofol-TCI (n = 25)	

Serious adverse events	Xenon+propofol	Propofol alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ventricular arrhythmia	Additional description: In-hospital (postoperatively) ventricular fibrillation/tachycardia		
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CVA	Additional description: Postoperative cerebrovascular accident		
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	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+propofol	Propofol alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 25 (36.00%)	9 / 25 (36.00%)	
Cardiac disorders			
Arrhythmia supraventricular	Additional description: Postoperative atrial fibrillation		
subjects affected / exposed	4 / 25 (16.00%)	5 / 25 (20.00%)	
occurrences (all)	4	5	
Angina pectoris			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Pericarditis			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Infections and infestations			
Wound infection	Additional description: Surgical wound infection		
subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	
occurrences (all)	3	0	

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