



## Clinical trial results:

### Xenon as an adjuvant to sevoflurane anaesthesia in children undergoing interventional or diagnostic cardiac catheterization: a randomized controlled clinical trial

#### Summary

EudraCT number	2014-002510-23
Trial protocol	BE
Global end of trial date	12 December 2017

#### Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

#### Trial information

##### Trial identification

Sponsor protocol code	SR062014
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##### 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	Anesthesia research, University Hospitals Leuven, 0032 16344620, christel.huygens@uzleuven.be
Scientific contact	Anesthesia research, 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	08 February 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 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

As a primary study aim we hypothesized that the administration of 50% Xenon as an adjuvant to general anesthesia with sevoflurane is safe and feasible.

Protection of trial subjects:

The interventional treatment was administered to patients with standard haemodynamic monitoring in the setting of a fully equipped cardiac catheterization room. This enabled immediate detection and treatment of adverse events. Xenon inhalation was to be immediately stopped in case that the study patient would show 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 PACU, 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 facilitated reporting of (S)AE's to the principal investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

From November 2014 to November 2016, 40 children aged between 4 and 12 years old were included in this trial and random- ized to receive either xenonaugmented sevoflurane or monosevoflurane for the maintenance of the anesthesia. 22 age and gendermatched healthy and nonhospitalized children underwent the at comparable time intervals.

### Pre-assignment

Screening details:

72 children were assessed for eligibility. A screening failure occurred in 32 children (7 refused, 14 met exclusion criteria, 11 had other reasons for exclusion).

### 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:

Subjects were allocated based on a closed envelope method [1:1 ratio, stratified by age (stratum I: age 47 years; stratum II: 812 years)]. 2 types of investigators conducted the trial. Inves- tigator I accomplished the enrollment on the day before the inter- vention and performed all postoperative visits. He was, as the patient and his parents, blinded to treatment allocation. Investigator II conducted the GA and was necessarily unblinded to the treatment due to the treatment conditions.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Xenon

Arm description:

General anesthesia with 50%65% xenon (LENOXeTM, AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.250.4) as an adjuvant to sevoflurane

Arm type	Experimental
Investigational medicinal product name	Xenon
Investigational medicinal product code	N01AX15
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

50%65% xenon in oxygen (FiO2 = 0.250.4) as an adjuvant to sevoflurane applied via inhalation by means of an endotracheal tube

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 dosing, application via inhalation via endotracheal tube

<b>Arm title</b>	Sevoflurane
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Arm description:

Sevoflurane (Sevorane, AbbVie, Wavre, Belgium) alone (FiO2 = 0.250.4)

Arm type	Active comparator
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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 dosing, application via inhalation via endotracheal tube

<b>Number of subjects in period 1<sup>[1]</sup></b>	Xenon	Sevoflurane
Started	20	20
Completed	20	20

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: We included 62 children in total. 40 of them were randomized to receive general anesthesia. Twentytwo additional healthy children matched for age and gender were included as control group for the neurocognitive assessments but received no treatment, neither with the IMP nor the active comparator.

## Baseline characteristics

### Reporting groups

Reporting group title	Xenon
Reporting group description: General anesthesia with 50%65% xenon (LENOXe™, AirLiquide Santé International, Paris, France) in oxygen (FiO <sub>2</sub> = 0.250.4) as an adjuvant to sevoflurane	
Reporting group title	Sevoflurane
Reporting group description: Sevoflurane (Sevorane, AbbVie, Wavre, Belgium) alone (FiO <sub>2</sub> = 0.250.4)	

Reporting group values	Xenon	Sevoflurane	Total
Number of subjects	20	20	40
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)	20	20	40
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	9	17
Male	12	11	23

## End points

### End points reporting groups

Reporting group title	Xenon
Reporting group description: General anesthesia with 50%65% xenon (LENOXeTM, AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.250.4) as an adjuvant to sevoflurane	
Reporting group title	Sevoflurane
Reporting group description: Sevoflurane (Sevorane, AbbVie, Wavre, Belgium) alone (FiO2 = 0.250.4)	

### Primary: Hemodynamic instability

End point title	Hemodynamic instability
End point description: Incidence of intraoperative hemodynamic adverse events (not caused by obvious interventional manipulation), defined by a > 20% change from baseline for HR or MAP or by the need for fluid boluses, vasopressors, inotropes, or chronotropes.	
End point type	Primary
End point timeframe: During administration of IMP	

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Counts	19	20		

### Statistical analyses

Statistical analysis title	Categorical endpoints
Statistical analysis description: Statistical analysis was performed using SPSS 24 software (SPSS Statistics version 24 for Windows, IBM, Armonk, New York, United states) according to the intention to treat principle. Categorical data are summarized by observed frequencies and percentages and compared using Fisher's exact test.	
Comparison groups	Xenon v Sevoflurane
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	= 1
Method	Fisher exact

### Primary: Anesthetic depth

End point title	Anesthetic depth
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End point description:

End point type	Primary
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End point timeframe:

During administration of IMP

End point values	Xenon	Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Bispectral index				
median (inter-quartile range (Q1-Q3))	48 (42 to 57)	44 (36 to 49)		

## Statistical analyses

Statistical analysis title	Continuous variables
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Statistical analysis description:

Continuous variables are reported using median and interquartile range (IQR) and were compared using the MannWhitney U test.

Comparison groups	Sevoflurane v Xenon
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Continuous variables are reported using median and interquartile range (IQR) and were compared using the MannWhitney U test.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From enrollment (the day before the intervention) until the first post-interventional day.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	Xenon
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Reporting group description:

General anesthesia with 50%65% xenon (LENOXeTM, AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.250.4) as an adjuvant to sevoflurane

Reporting group title	Sevoflurane
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Reporting group description:

Sevoflurane (Sevorane, AbbVie, Wavre, Belgium) alone (FiO2 = 0.250.4)

Serious adverse events	Xenon	Sevoflurane	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Surgical and medical procedures			
Device embolization			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
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	13 / 20 (65.00%)	7 / 20 (35.00%)	
Gastrointestinal disorders			
PONV			
subjects affected / exposed	7 / 20 (35.00%)	6 / 20 (30.00%)	
occurrences (all)	7	6	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2015	20 healthy children will undergo the neuropsychological testing on three consecutive days in order to evaluate the effect of repeated testing.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30004615>

<http://www.ncbi.nlm.nih.gov/pubmed/31287192>