



## Clinical trial results:

**Xenon as an adjuvant to sevoflurane anaesthesia in children younger than four, undergoing interventional or diagnostic cardiac catheterization: a pilot study.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-002329-20 |
| Trial protocol           | BE             |
| Global end of trial date | 01 April 2016  |

### 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 | SR052015 |
|-----------------------|----------|

#### 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, +32 16344620, christel.huygens@uzleuven.be |
| Scientific contact           | Anesthesia Research, University Hospitals Leuven, +32 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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 23 February 2017 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 01 April 2016    |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 April 2016    |
| Was the trial ended prematurely?                     | Yes              |

Notes:

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**General information about the trial**

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Main objective of the trial:

We hypothesized that the administration of 50-65 % xenon as an adjuvant to general anaesthesia with sevoflurane would result in superior hemodynamic stability when compared to sevoflurane anaesthesia alone.

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 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 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 facilitates reporting of (S)AE's to the principal investigator.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 01 September 2015 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 40 |
| Worldwide total number of subjects   | 40          |
| EEA total number of subjects         | 40          |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 1  |
| Infants and toddlers (28 days-23 months)  | 26 |
| Children (2-11 years)                     | 13 |
| 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 September 2015 to April 2016, 69 children scheduled for elective heart catheterization were screened. A total of 40 were included and randomized to receive general anesthesia either with xenon plus sevoflurane or sevoflurane alone.

### Pre-assignment

Screening details:

A screening failure occurred in 29 patients (16 met exclusion criteria, 7 declined to participate, and 6 had other reasons that excluded them from the participation in the trial).

### 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:

Two investigator types conducted the trial. Investigator I accomplished the enrollment (day prior to intervention) and all postoperative visits and was, similar to the patient and his parents, blinded to treatment allocation. Investigator II performed randomization and the GA and could not be blinded to the treatment due to the kind of intervention (administration and monitoring of either one or two inhalational anesthetics).

### Arms

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

Arm description:

General anesthesia was maintained with 50%-65% xenon (LENOXe™; AirLiquide Santé International, Paris, France) in oxygen (FiO<sub>2</sub> = 0.25-0.4) as an adjuvant to sevoflurane

|  |                   |
|--|-------------------|
| 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

|  |                   |
|--|-------------------|
| 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

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Sevoflurane |
|------------------|-------------|

Arm description:

General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO<sub>2</sub> = 0.25- 0.4).

|          |                   |
|----------|-------------------|
| 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

| <b>Number of subjects in period 1</b> | Xenon | Sevoflurane |
|---------------------------------------|-------|-------------|
| Started                               | 20    | 20          |
| Blinded sample size re-estimation     | 20    | 20          |
| Completed                             | 20    | 20          |

## Baseline characteristics

### Reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Xenon       |
| Reporting group description:   |             |
| General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane |             |
| Reporting group title  | Sevoflurane |
| Reporting group description:   |             |
| General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 0.4).  |             |

| 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       | 1           | 1     |
| Infants and toddlers (28 days-23 months)           | 12      | 14          | 26    |
| Children (2-11 years)                              | 8       | 5           | 13    |
| 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     |
| Age continuous                                     |         |             |       |
| Units: months                                      |         |             |       |
| median   | 18      | 8           |       |
| inter-quartile range (Q1-Q3)                       | 2 to 39 | 3 to 26     | -     |
| Gender categorical                                 |         |             |       |
| Units: Subjects                                    |         |             |       |
| Female   | 11      | 8           | 19    |
| Male   | 9       | 12          | 21    |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Xenon       |
| Reporting group description:   |             |
| General anesthesia was maintained with 50%-65% xenon (LENOXeTM; AirLiquide Santé International, Paris, France) in oxygen (FiO2 = 0.25-0.4) as an adjuvant to sevoflurane |             |
| Reporting group title  | Sevoflurane |
| Reporting group description:   |             |
| General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO2 = 0.25- 0.4).  |             |

### Primary: Intraoperative hemodynamic instability

|  |  |
|--|--|
| End point title  | Intraoperative hemodynamic instability |
| End point description:   |  |
| intraoperative hemodynamic instability, defined by the occurrence of one of following events: (i) a heart rate (HR) change >20% from baseline (not caused by interventional manipulation); (ii) a change in mean arterial blood pressure (MAP) >20% change from baseline (this change has been recently demonstrated to be associated with cerebral desaturations in infants and is frequently used as intervention trigger in pediatric studies); or (iii) the requirement for an hemodynamic intervention performed by investigator II to treat hemodynamic instability as defined above (assessed as the composite of using either vasopressors, inotropes, chronotropes, or fluid boluses). Isolated blood pressure drops >20% from baseline were treated with phenylephrine (2-3 mikrog/kg) and/or a fluid bolus (crystalloid 10 mL/kg), isolated bradycardia with atropine (10-20 mikrog/kg), and the combination of bradycardia with hypotension with ephedrine (50-100 mikrog/kg). |  |
| End point type   | Primary                                |
| End point timeframe:   |  |
| During the administration of IMP/comparator  |  |

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

### Statistical analyses

|   |                     |
|---|---------------------|
| Statistical analysis title              | Primary endpoint    |
| Comparison groups                       | Xenon v Sevoflurane |
| Number of subjects included in analysis | 40                  |
| Analysis specification                  | Pre-specified       |
| Analysis type                           | superiority         |
| P-value                                 | = 1                 |
| Method                                  | Fisher exact        |

**Secondary: Phenylephrine requirements**

|                 |                            |
|-----------------|----------------------------|
| End point title | Phenylephrine requirements |
|-----------------|----------------------------|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During administration of IMP/active comparator

| End point values                      | Xenon           | Sevoflurane       |  |  |
|---------------------------------------|-----------------|-------------------|--|--|
| Subject group type                    | Reporting group | Reporting group   |  |  |
| Number of subjects analysed           | 20              | 20                |  |  |
| Units: mikrogram/kg                   |                 |                   |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 2.49)   | 4.93 (0 to 15.37) |  |  |

**Statistical analyses**

|                            |               |
|----------------------------|---------------|
| Statistical analysis title | Phenylephrine |
|----------------------------|---------------|

|                   |                     |
|-------------------|---------------------|
| Comparison groups | Xenon v Sevoflurane |
|-------------------|---------------------|

|   |    |
|---|----|
| Number of subjects included in analysis | 40 |
|---|----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |        |
|---------|--------|
| P-value | = 0.01 |
|---------|--------|

|        |                         |
|--------|-------------------------|
| Method | Wilcoxon (Mann-Whitney) |
|--------|-------------------------|

**Secondary: Incidence of cerebral desaturation**

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Incidence of cerebral desaturation |
|-----------------|------------------------------------|

End point description:

Incidence of cerebral desaturation, defined as a decrease in rScO<sub>2</sub> of >20% from baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During administration of IMP/active comparator

| End point values            | Xenon           | Sevoflurane     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 20              | 20              |  |  |
| Units: Numbers              | 2               | 10              |  |  |



## Statistical analyses

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Cerebral desaturation left side |
| Comparison groups                       | Xenon v Sevoflurane             |
| Number of subjects included in analysis | 40                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           | superiority                     |
| P-value                                 | = 0.03                          |
| Method                                  | Fisher exact                    |

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | Cerebral desaturation right side |
| Comparison groups                       | Xenon v Sevoflurane              |
| Number of subjects included in analysis | 40                               |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.04                           |
| Method                                  | Fisher exact                     |

## Secondary: Recovery index

|  |                |
|--|----------------|
| End point title                                | Recovery index |
| End point description:                         |                |
| End point type                                 | Secondary      |
| End point timeframe:                           |                |
| During administration of IMP/active comparator |                |

|                                       |                     |                     |  |  |
|---------------------------------------|---------------------|---------------------|--|--|
| <b>End point values</b>               | Xenon               | Sevoflurane         |  |  |
| Subject group type                    | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed           | 20                  | 20                  |  |  |
| Units: /min                           |                     |                     |  |  |
| median (inter-quartile range (Q1-Q3)) | 0.44 (0.39 to 0.69) | 0.27 (0.19 to 0.40) |  |  |

## Statistical analyses

|                                   |                     |
|-----------------------------------|---------------------|
| <b>Statistical analysis title</b> | Recovery index      |
| Comparison groups                 | Xenon v Sevoflurane |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 40                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | < 0.001                 |
| Method                                  | Wilcoxon (Mann-Whitney) |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From enrollment until the first postinterventional day

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Xenon |
|-----------------------|-------|

Reporting group description:

General anesthesia was maintained with 50%-65% xenon (LENOXe™; AirLiquide Santé International, Paris, France) in oxygen (FiO<sub>2</sub> = 0.25-0.4) as an adjuvant to sevoflurane

|                       |             |
|-----------------------|-------------|
| Reporting group title | Sevoflurane |
|-----------------------|-------------|

Reporting group description:

General anesthesia was maintained with sevoflurane (Sevorane; AbbVie, Wavre, Belgium) (FiO<sub>2</sub> = 0.25- 0.4).

| Serious adverse events                            | Xenon          | Sevoflurane    |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 20 (0.00%) | 1 / 20 (5.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Vascular disorders                                |                |                |  |
| Thrombosis  |                |                |  |
| subjects affected / exposed                       | 0 / 20 (0.00%) | 1 / 20 (5.00%) |  |
| 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  | Sevoflurane      |  |
|---|--|------------------|--|
| Total subjects affected by non-serious adverse events |  |                  |  |
| subjects affected / exposed                           | 9 / 20 (45.00%)  | 14 / 20 (70.00%) |  |
| Nervous system disorders                              |  |                  |  |
| Emergence agitation                                   | Additional description: assessed by four-point agitation scale |                  |  |
| subjects affected / exposed                           | 1 / 20 (5.00%)   | 8 / 20 (40.00%)  |  |
| occurrences (all)                                     | 1  | 8                |  |
| Gastrointestinal disorders                            |  |                  |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Postoperative vomiting<br>subjects affected / exposed<br>occurrences (all) | 4 / 20 (20.00%)<br>4 | 2 / 20 (10.00%)<br>2 |  |
|--|----------------------|----------------------|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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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/28872734>