



Clinical trial results:

An international, multi-center, randomized, controlled trial evaluating the effect of xenon on post-operative delirium in elderly patients undergoing hip fracture surgery.

Summary

EudraCT number	2009-017153-35
Trial protocol	FR DE GB ES IT BE
Global end of trial date	28 October 2014

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	Publication_HIPELD_BJA_2018_120_127-137 (Publication_HIPELD_BJA_2018_120_127-137.pdf)

Trial information

Trial identification

Sponsor protocol code	ALMED-08-C2-020
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01199276
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Air Liquide Santé International
Sponsor organisation address	75, quai d'Orsay, Paris, France, 75007
Public contact	Healthcare Communication, Air Liquide Santé International, fralsi-publiccontact@airliquide.com
Scientific contact	Clinical Development Physician, Air Liquide Santé International, fralsi-ctpublication@airliquide.com

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	24 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 October 2014
Global end of trial reached?	Yes
Global end of trial date	28 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the incidence of Post-Operative Delirium (POD), diagnosed with the Confusion Assessment Method (CAM), in elderly patients undergoing hip fracture surgery under general anaesthesia, with xenon or sevoflurane, for a period of four days post-surgery.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice (GCP) guidelines, the most recent revised version of the Declaration of Helsinki (Seoul, 2008), and the European Directive 2001/20/EC on 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of Good Clinical Practice in the conduct of the clinical trials on medicinal products for human use.

The protocol and subsequent substantial amendments were submitted to the local ethics committee and competent authority for approvals in each participating country.

The enrolment of the patients in the study started in a given participating country only after the written approvals of the corresponding national ethics committee and competent authority.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 90
Country: Number of subjects enrolled	Italy: 31
Worldwide total number of subjects	268
EEA total number of subjects	268

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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	144
85 years and over	124

Subject disposition

Recruitment

Recruitment details:

A total of 268 patients were enrolled (256 randomised and treated, plus 1 not randomised but treated) from 12 centres in 6 countries; 1 in Belgium, 5 in France (5 sites out of the 6 initiated sites), 3 in Germany, 1 in Italy, 1 in Spain and 1 in United Kingdom.

First Patient Enrolled: 22 September 2010

Last Patient Completed: 28 October 2014

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	268
Number of subjects completed	256

Pre-assignment subject non-completion reasons

Reason: Number of subjects	At least one inclusion criterion not fulfilled: 7
Reason: Number of subjects	Technical issues: 2
Reason: Number of subjects	Suspected urinary infection: 1
Reason: Number of subjects	Accidentally used demonstration randomisation env.: 1
Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

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

Blinding implementation details:

There were two teams of physicians:

- Physicians 1 who performed selection of patients and follow-up visits (including Study End visit) were kept blind regarding the natures and doses of all study treatments.

- Physicians 2 who performed the visits including randomisation and surgical procedure under general anaesthesia were unblinded. All information on the study drugs administered was kept confidential by Physicians 2 in separate source documents and specific dedicated Case Report Forms.

Arms

Are arms mutually exclusive?	Yes
Arm title	Xenon - ITT

Arm description:

Xenon 60% (55%-65%)(1 MAC) in oxygen (FiO2 = 0.35-0.45)

ITT – Intent-to-treat, i.e all randomised and treated patients

Arm type	Experimental
Investigational medicinal product name	Xenon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, liquefied
Routes of administration	Inhalation use

Dosage and administration details:

Xenon 60% (55%-65%) (1 MAC) in oxygen (FiO2 = 0.35-0.45)

Arm title	Sevoflurane - ITT
Arm description: sevoflurane 1.1-1.4%(1 MAC) in oxygen (FiO2 = 0.35-0.45) and Medical air ITT – Intent-to-treat, i.e all randomised and treated patients	
Arm type	Active comparator
Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

1.1-1.4% (1 MAC) in oxygen (FiO2 = 0.35-0.45) and medical air

Number of subjects in period 1^[1]	Xenon - ITT	Sevoflurane - ITT
Started	124	132
Completed	109	120
Not completed	15	12
Early discharge	13	6
Adverse event, serious fatal	-	4
Adverse event, non-fatal	1	2
Lost to follow-up	1	-

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: 268 patients signed an informed consent. 256 patients were randomised and treated.

Baseline characteristics

Reporting groups

Reporting group title	Xenon - ITT
Reporting group description: Xenon 60% (55%-65%)(1 MAC) in oxygen (FiO ₂ = 0.35-0.45) ITT – Intent-to-treat, i.e all randomised and treated patients	
Reporting group title	Sevoflurane - ITT
Reporting group description: sevoflurane 1.1-1.4%(1 MAC) in oxygen (FiO ₂ = 0.35-0.45) and Medical air ITT – Intent-to-treat, i.e all randomised and treated patients	

Reporting group values	Xenon - ITT	Sevoflurane - ITT	Total
Number of subjects	124	132	256
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			
arithmetic mean	83.83	84.41	
standard deviation	± 5.13	± 4.55	-
Gender categorical Units: Subjects			
Female	90	103	193
Male	34	29	63
Body Mass Index Units: kg/m ²			
arithmetic mean	23.72	24.19	
standard deviation	± 3.78	± 4.25	-

End points

End points reporting groups

Reporting group title	Xenon - ITT
Reporting group description: Xenon 60% (55%-65%)(1 MAC) in oxygen (FiO2 = 0.35-0.45) ITT – Intent-to-treat, i.e all randomised and treated patients	
Reporting group title	Sevoflurane - ITT
Reporting group description: sevoflurane 1.1-1.4%(1 MAC) in oxygen (FiO2 = 0.35-0.45) and Medical air ITT – Intent-to-treat, i.e all randomised and treated patients	

Primary: Post Operative Delirium diagnosed within four days post-surgery

End point title	Post Operative Delirium diagnosed within four days post-surgery
End point description: Number of patients with Post Operative Delirium (POD) diagnosed with the Confusion Assessment Method within four days post-surgery.	
End point type	Primary
End point timeframe: Four days post-surgery	

End point values	Xenon - ITT	Sevoflurane - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	132		
Units: Patient	12	18		

Statistical analyses

Statistical analysis title	POD diagnosed within 4 days - ITT
Statistical analysis description: POD = Post Operative Delirium ITT – Intent-to-treat, i.e all randomised and treated patients	
Comparison groups	Xenon - ITT v Sevoflurane - ITT
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.325
Method	Chi-squared

Secondary: Post Operative Delirium diagnosed from day 5 post surgery to discharge from hospital

End point title	Post Operative Delirium diagnosed from day 5 post surgery to discharge from hospital
End point description: Number of patients with Post Operative Delirium (POD) diagnosed with the Confusion Assessment Method from day 5 post surgery to discharge from hospital.	
End point type	Secondary
End point timeframe: From day 5 post surgery to discharge from hospital	

End point values	Xenon - ITT	Sevoflurane - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	132		
Units: Patient	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Sequential Organ Failure Assessment from day 1 to day 4 post-surgery

End point title	Sequential Organ Failure Assessment from day 1 to day 4 post-surgery
End point description: Total SOFA (Sequential Organ Failure Assessment) score was obtained as the sum of the 6 SOFA domain subscores (i.e., cardiovascular, respiratory, hepatic, haematological, central nervous system and renal components separately).	
End point type	Secondary
End point timeframe: From day 1 to day 4 post-surgery.	

End point values	Xenon - ITT	Sevoflurane - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124 ^[1]	132 ^[2]		
Units: Unit in a scale				
arithmetic mean (standard deviation)				
Day 1	0.87 (± 0.94)	1.19 (± 1.49)		
Day 2	0.84 (± 1.12)	1.12 (± 1.70)		
Day 3	0.57 (± 0.84)	1.01 (± 1.77)		
Day 4	0.53 (± 0.83)	0.79 (± 1.81)		

Notes:

[1] - Day 1=100; Day 2=96; Day 3=90; Day 4=78

[2] - Day 1=98; Day 2=93; Day 3=85; Day 4=86

Statistical analyses

No statistical analyses for this end point

Secondary: Recovery parameters

End point title	Recovery parameters
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End point description:

Time to open eyes;
Time to react on verbal command;
Time to extubation;
Time to spatial orientation;
Duration of stay in Post-Anaesthesia Care Unit (PACU).
Time calculated in minutes from the end of gas inhalation.

End point type	Secondary
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End point timeframe:

Post general anaesthesia.

End point values	Xenon - ITT	Sevoflurane - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124 ^[3]	132 ^[4]		
Units: minute				
median (inter-quartile range (Q1-Q3))				
1) Time to open eyes	4.0 (2.0 to 8.0)	8.0 (5.0 to 11.0)		
2) Time to react on verbal command	5.0 (3.0 to 9.0)	8.5 (6.0 to 12.0)		
3) Time to extubation	5.4 (3.2 to 9.1)	9.1 (6.0 to 12.7)		
4) Time to spatial orientation	13.0 (6.0 to 21.0)	15.4 (10.0 to 25.8)		
5) Duration of stay in PACU	105 (60 to 145)	112 (75 to 165)		

Notes:

[3] - 1) n=124; 2) n=124; 3) n=124; 4) n=113; 5) n=99

[4] - 1) n=127; 2) n=128; 3) n=131; 4) n=120; 5) n=102

Statistical analyses

No statistical analyses for this end point

Secondary: Vital status at 28 days post-surgery

End point title	Vital status at 28 days post-surgery
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End point description:

Number of patients who died within the 28 days post-surgery

End point type	Secondary
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End point timeframe:

28 days post-surgery

End point values	Xenon - ITT	Sevoflurane - ITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	110		
Units: Patient	0	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events observed from the start of study treatment up to 30 days.

Adverse event reporting additional description:

Participants at risk are the patients from the safety set, i.e. patients treated.

Multiple occurrences of a same adverse event (i.e. same preferred term) for a given patient are counted only once.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Xenon
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Reporting group description:

xenon 60% (55%-65%)(1 MAC) in oxygen (FiO₂ = 0.35-0.45)

Safety population, i.e all treated patients (including one non-randomised patient)

Reporting group title	Sevoflurane
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Reporting group description:

sevoflurane 1.1-1.4%(1 MAC) in oxygen (FiO₂ = 0.35-0.45) and Medical air

Safety population, i.e all treated patients

Serious adverse events	Xenon	Sevoflurane	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 125 (8.00%)	21 / 132 (15.91%)	
number of deaths (all causes)	0	5	
number of deaths resulting from adverse events	0	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device dislocation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombosis in device			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bradypnoea			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 125 (0.00%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 125 (0.80%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cardiac function disturbance postoperative			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site haematoma			
subjects affected / exposed	2 / 125 (1.60%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			

subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 125 (0.80%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 125 (0.80%)	3 / 132 (2.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 125 (1.60%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Anticholinergic syndrome			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 125 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 125 (0.80%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bone abscess			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 125 (0.00%)	4 / 132 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 125 (0.00%)	2 / 132 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 132 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
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	108 / 125 (86.40%)	115 / 132 (87.12%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 125 (4.80%)	9 / 132 (6.82%)	
occurrences (all)	6	9	
Aspartate aminotransferase			

increased			
subjects affected / exposed	10 / 125 (8.00%)	10 / 132 (7.58%)	
occurrences (all)	10	10	
C-reactive protein increased			
subjects affected / exposed	24 / 125 (19.20%)	23 / 132 (17.42%)	
occurrences (all)	24	23	
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 125 (6.40%)	11 / 132 (8.33%)	
occurrences (all)	8	11	
Haemoglobin decreased			
subjects affected / exposed	7 / 125 (5.60%)	8 / 132 (6.06%)	
occurrences (all)	7	8	
Troponin T increased			
subjects affected / exposed	10 / 125 (8.00%)	7 / 132 (5.30%)	
occurrences (all)	10	7	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	10 / 125 (8.00%)	12 / 132 (9.09%)	
occurrences (all)	10	12	
Hypertension			
subjects affected / exposed	16 / 125 (12.80%)	15 / 132 (11.36%)	
occurrences (all)	16	15	
Hypotension			
subjects affected / exposed	32 / 125 (25.60%)	41 / 132 (31.06%)	
occurrences (all)	32	41	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	9 / 125 (7.20%)	4 / 132 (3.03%)	
occurrences (all)	9	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	45 / 125 (36.00%)	57 / 132 (43.18%)	
occurrences (all)	45	57	
Thrombocytopenia			
subjects affected / exposed	3 / 125 (2.40%)	7 / 132 (5.30%)	
occurrences (all)	3	7	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 125 (3.20%)	8 / 132 (6.06%)	
occurrences (all)	4	8	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 125 (7.20%)	10 / 132 (7.58%)	
occurrences (all)	9	10	
Nausea			
subjects affected / exposed	11 / 125 (8.80%)	10 / 132 (7.58%)	
occurrences (all)	11	10	
Retching			
subjects affected / exposed	15 / 125 (12.00%)	11 / 132 (8.33%)	
occurrences (all)	15	11	
Vomiting			
subjects affected / exposed	15 / 125 (12.00%)	14 / 132 (10.61%)	
occurrences (all)	15	14	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	5 / 125 (4.00%)	9 / 132 (6.82%)	
occurrences (all)	5	9	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 125 (5.60%)	5 / 132 (3.79%)	
occurrences (all)	7	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2010	Amendment for France: adjustment of study period, rocuronium allowed as a muscle relaxant
20 May 2010	Amendment for Spain: adjustment of study period, Exclusion criteria added, change of contact detail of Pharmacovigilance department
06 August 2010	Amendment for Italy: adjustment of study period, exclusion criteria added, calculation of SOFA subscore, change of contact detail of Pharmacovigilance department
24 August 2010	Amendment for United Kingdom: PI change in UK, Study period, calculation of SOFA subscore
02 September 2010	Amendment for Germany: to correct the SAE contacts, new PI in UK, Study period, calculation of SOFA subscore
16 March 2011	Amendment for France: 2 new sites in Germany and 3 in France, Troponin T test could be used in place of Troponin I, Calculation of SOFA subscore, updated timelines
10 June 2011	Amendment for Germany: 2 new sites in Germany and 3 in France, Troponin T test could be used in place of Troponin I, updated timelines
05 August 2011	Amendment for Spain: new PI in UK, 2 new sites in Germany and 3 in France, Troponin T test could be used in place of Troponin I, Calculation of SOFA subscore, updated timelines
23 August 2011	Amendment for Italy: new PI in UK, 2 new sites in Germany and 3 in France, Troponin T test could be used in place of Troponin I, updated timelines
25 August 2011	Amendment for United Kingdom: 2 new sites in Germany and 3 in France, Troponin T test could be used in place of Troponin I, updated timelines
10 August 2012	Amendment for France: recruitment extension (Nov 2013), three new sites added, use of blood test results obtained before ICF at hospital's patient admission are allowed, detail of AE definition and reporting of SAE. Use of triplicate ICF
07 January 2013	Amendment for Germany: recruitment extension (Nov 2013), 3 new sites added, detail of AE definition and reporting of SAE, use of blood test results obtained before ICF at hospital's patient admission are allowed, two original ICF to be signed instead of three
10 January 2013	Amendment for United Kingdom: recruitment extension (Nov 2013), two new sites added, detail of AE definition and reporting of SAE, use of blood test results obtained before ICF at hospital's patient admission are allowed
15 January 2013	Amendment for Italy: recruitment extension (Nov 2013), 3 new sites added, detail of AE definition and reporting of SAE, use of blood test results obtained before ICF at hospital's patient admission are allowed
18 January 2013	Amendment for Spain: Recruitment extension (Nov 2013), three new sites added, detail of AE definition and reporting of SAE, use of blood test results obtained before ICF at hospital's patient admission are allowed

30 October 2013	Amendment for United Kingdom: recruitment extension (May 2014), to avoid exams repetition (ECG, MMSE, ...) the use of test results within 24 h before ICF signature are allowed, CAM assessment by physician 1 or trained designee, all investigators can present the study to the patient, clarified that patient data could be transferred outside European Union
05 November 2013	Amendment for Germany and Belgium: recruitment extension (May 2014), to avoid exams repetition (ECG, MMSE, ...) the use of test results within 24 h before ICF signature are allowed, CAM assessment by physician 1 or trained designee, all investigators can present the study to the patient, clarified that patient data could be transferred outside European Union
12 November 2013	Amendment for Italy: recruitment extension (May 2014), to avoid exams repetition (ECG, MMSE, ...) the use of test results within 24 h before ICF signature are allowed, CAM assessment by physician 1 or trained designee, all investigators can present the study to the patient, two original ICF to be signed instead of three
14 November 2013	Amendment for France: recruitment extension (May 2014), to avoid exams repetition (ECG, MMSE, ...) the use of test results within 24 h before ICF signature are allowed, CAM assessment by physician 1 or trained designee, all investigators can present the study to the patient, clarified that patient data could be transferred outside European Union
24 March 2014	Amendment for France, Germany, United Kingdom, Italy and Belgium: recruitment extension (Dec 2014), vital status to be collected 28 days post-surgery, Information letter for patients who signed ICF before clarification that patient data could be transferred outside European Union
16 April 2014	Amendment for Spain: recruitment extension (Dec 2014), to avoid exams repetition (ECG, MMSE, ...) the use of test results within 24 h before ICF signature are allowed, CAM assessment by physician 1 or trained designee, all investigators can present the study to the patient, Vital status to be collected 28 days post-surgery, Information letter for patients who signed ICF without information that patient data could be transferred outside European Union

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29397119>