



Clinical trial results:

Efficacy and safety of xenon anaesthesia compared to sevoflurane anaesthesia and total intravenous anaesthesia for on-pump coronary artery bypass graft surgery: a randomised, three-arm, single-blind, international study.

Summary

EudraCT number	2010-020677-17
Trial protocol	NL DE
Global end of trial date	05 April 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_CABG_Anesthesiology_2018 (Publication_CABG_Anesthesiology_2018.pdf)

Trial information

Trial identification

Sponsor protocol code	ALMED-09-C3-026
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01294163
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	07 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2014
Global end of trial reached?	Yes
Global end of trial date	05 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of xenon anaesthesia on the postoperative blood level of cardiac troponin _ a predictive marker of medium - and long term clinical outcome after coronary artery bypass graft surgery _ 24 hours after the end of intervention, compared to sevoflurane anaesthesia and total intravenous anaesthesia.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice guidelines, and in keeping with the most recent revised version of the Declaration of Helsinki (Seoul, 2008), and in the European Directive 2001/20/CE 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 substantial amendments were submitted to the local ethics committee and competent authority for approval, in each 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.

There was no formal safety monitoring committee in this study, but for every 80 patients that underwent the surgical procedure, the Sponsor and the Study Chairman reviewed the rates of death by group to ensure that the incidence of death was as expected. A 2-sided 95% exact confidence interval (CI) was calculated for the proportion of deaths in the xenon, sevoflurane and TIVA groups at each review. If the lower range of the 95% CI in the xenon group was greater than the upper range of at least one of the two 2-sided 95% CI is calculated as described above, the trial was to be put on hold and further investigations were to be conducted on the study data to re-assess the benefit-risk ratio of xenon in the context of this study. This criterion was not met at any of the assessments so the trial continued.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2011
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	Netherlands: 36
Country: Number of subjects enrolled	France: 305
Country: Number of subjects enrolled	Germany: 189
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	542
EEA total number of subjects	542

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)	266
From 65 to 84 years	276
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

542 patients were enrolled (492 patients were randomised and treated and 17 pilot patients were treated with Xenon but only analysed for safety) from 17 centres in 4 countries; 8 sites in France, 6 sites in Germany, 1 site in Italy and 2 sites in The Netherlands.

Date of first enrolment: 20 April 2011

Date of last completed: 05 April 2014

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	542
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Number of subjects completed	492
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Pre-assignment subject non-completion reasons

Reason: Number of subjects	Xenon pilot patients only analysed for safety: 17
Reason: Number of subjects	At least 1 Selection/Inclusion criterion not met: 17
Reason: Number of subjects	Investigator not available: 1
Reason: Number of subjects	Technical problem with ventilator: 1
Reason: Number of subjects	Surgical proc. postponed/cancelled/not eligible: 14

Period 1

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

Are arms mutually exclusive?	Yes
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Arm title	Xenon - ITT
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Arm description:

Anesthetic agent before and after cardiopulmonary bypass: xenon

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

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

Maximal inspired concentration of 65%

Arm title	Sevoflurane - ITT
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Arm description:

Anesthetic agent before and after cardiopulmonary bypass: sevoflurane

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

Arm type	Active comparator
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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: Maximal inspired concentration of 1.8%	
Arm title	TIVA - ITT

Arm description:

TIVA = Total intravenous anaesthesia

Anesthetic agent before and after cardiopulmonary bypass: propofol

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

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

Dosage and administration details:

Hourly dose of 2-4 mg/kg

Number of subjects in period 1^[1]	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT
Started	161	165	166
Completed	160	165	163
Not completed	1	0	3
Adverse event, serious fatal	-	-	3
Adverse event, non-fatal	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: 542 patients signed an informed consent. 492 patients were randomised and treated

Baseline characteristics

Reporting groups

Reporting group title	Xenon - ITT
Reporting group description:	
Anesthetic agent before and after cardiopulmonary bypass: xenon ITT – Intent-to-treat, i.e all randomised patients	
Reporting group title	Sevoflurane - ITT
Reporting group description:	
Anesthetic agent before and after cardiopulmonary bypass: sevoflurane ITT – Intent-to-treat, i.e all randomised patients	
Reporting group title	TIVA - ITT
Reporting group description:	
TIVA = Total intravenous anaesthesia Anesthetic agent before and after cardiopulmonary bypass: propofol ITT – Intent-to-treat, i.e all randomised patients	

Reporting group values	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT
Number of subjects	161	165	166
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	64.66	63.86	63.89
standard deviation	± 9.12	± 8.66	± 9.40
Gender categorical			
Units: Subjects			
Female	19	25	20
Male	142	140	146
BMI			
BMI = Body Mass Index			
Units: kg/m ²			
arithmetic mean	27.65	27.21	27.78
standard deviation	± 3.64	± 3.68	± 4.00
Reporting group values	Total		
Number of subjects	492		

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			
standard deviation	-		
Gender categorical Units: Subjects			
Female	64		
Male	428		
BMI			
BMI = Body Mass Index			
Units: kg/m ²			
arithmetic mean			
standard deviation	-		

Subject analysis sets

Subject analysis set title	Xenon - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Xenon and who had no major deviations during the study.	
Subject analysis set title	Sevoflurane - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Sevoflurane and who had no major deviations during the study.	
Subject analysis set title	TIVA - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Propofol and who had no major deviations during the study.	

Reporting group values	Xenon - PP	Sevoflurane - PP	TIVA - PP
Number of subjects	146	151	149
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 64.51 ± 9.35	 63.70 ± 8.82	 63.84 ± 9.37
Gender categorical Units: Subjects			
Female Male	 18 128	 24 127	 17 132
BMI			
BMI = Body Mass Index			
Units: kg/m ² arithmetic mean standard deviation	 27.67 ± 3.69	 27.25 ± 3.75	 27.61 ± 3.91

End points

End points reporting groups

Reporting group title	Xenon - ITT
Reporting group description: Anesthetic agent before and after cardiopulmonary bypass: xenon ITT – Intent-to-treat, i.e all randomised patients	
Reporting group title	Sevoflurane - ITT
Reporting group description: Anesthetic agent before and after cardiopulmonary bypass: sevoflurane ITT – Intent-to-treat, i.e all randomised patients	
Reporting group title	TIVA - ITT
Reporting group description: TIVA = Total intravenous anaesthesia Anesthetic agent before and after cardiopulmonary bypass: propofol ITT – Intent-to-treat, i.e all randomised patients	
Subject analysis set title	Xenon - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Xenon and who had no major deviations during the study.	
Subject analysis set title	Sevoflurane - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Sevoflurane and who had no major deviations during the study.	
Subject analysis set title	TIVA - PP
Subject analysis set type	Per protocol
Subject analysis set description: PP= per protocol Randomised patients who were treated with Propofol and who had no major deviations during the study.	

Primary: Blood level of Troponin I

End point title	Blood level of Troponin I
End point description: Blood level of Troponin I (cTnI) measured by a central laboratory.	
End point type	Primary
End point timeframe: Sampling performed 24 hours after the end of the surgical procedure.	

End point values	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT	Xenon - PP
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	161	165	166	146
Units: ng/ml				
arithmetic mean (standard deviation)	2.33 (± 3.6)	2.66 (± 4.3)	3.40 (± 9.1)	2.12 (± 3.1)

End point values	Sevoflurane - PP	TIVA - PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151	149		
Units: ng/ml				
arithmetic mean (standard deviation)	2.59 (± 4.4)	2.90 (± 4.4)		

Statistical analyses

Statistical analysis title	Non-inferiority cTnI - Xenon and sevoflurane - PP
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Statistical analysis description:

PP = per protocol

The primary comparison was a non-inferiority comparison of the xenon and sevoflurane groups in the PP.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Xenon - PP v Sevoflurane - PP
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.0186
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.11

Notes:

[1] - The xenon group was considered non-inferior to the sevoflurane group if the upper bound of the adjusted two-sided 95% CI for the difference between the two mean log-transformed cTnI concentrations was less than the non-inferiority margin of 0.15ng/ml.

LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Statistical analysis title	Non-inferiority cTnI - Xenon and sevoflurane - ITT
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Statistical analysis description:

Non-inferiority comparison of xenon vs sevoflurane was to be assessed in the ITT only if non-inferiority was demonstrated in the PP.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Xenon - ITT v Sevoflurane - ITT
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	= 0.0136
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[2] - The xenon group was considered non-inferior to the sevoflurane group if the upper bound of the adjusted two-sided 95% CI for the difference between the two mean log-transformed cTnI concentrations was less than the non-inferiority margin of 0.15ng/ml.

LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Statistical analysis title	Superiority cTnI - Xenon and sevoflurane - ITT
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Statistical analysis description:

Superiority analysis was only to be performed if non-inferiority was demonstrated in both ITT and PP Sets.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Xenon - ITT v Sevoflurane - ITT
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.316
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1

Notes:

[3] - LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Statistical analysis title	Superiority cTnI - Xenon and sevoflurane - PP
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Statistical analysis description:

Superiority analysis was only to be performed if non-inferiority was demonstrated in both ITT and PP Sets.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Xenon - PP v Sevoflurane - PP
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.3626
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.11

Notes:

[4] - LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Statistical analysis title	Superiority cTnI - Xenon and TIVA - ITT
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Statistical analysis description:

To check for assay sensitivity, superiority of xenon group over the TIVA group was also assessed.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Xenon - ITT v TIVA - ITT
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.0452
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4142
upper limit	-0.0045

Notes:

[5] - LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Statistical analysis title	Superiority cTnI - Sevoflurane and TIVA - ITT
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Statistical analysis description:

To check for assay sensitivity, superiority of sevoflurane group over the TIVA group was also assessed.

Distribution of cTnI concentrations being skewed with a right-tailed distribution, cTnI were transformed into log values.

Comparison groups	Sevoflurane - ITT v TIVA - ITT
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.3268
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	0.1

Notes:

[6] - LS-mean treatment difference and 95% CI were assessed using ANCOVA with cTnI (log-transformed) as response, treatment group and pre-induction cTnI (log-transformed) as covariates.

Secondary: Other postoperative cardiac damage and prognostic markers: CK-MB Peak Concentration

End point title	Other postoperative cardiac damage and prognostic markers: CK-MB Peak Concentration
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End point description:

The highest CK-MB (creatine kinase-MB fraction) postoperative value observed was derived.

End point type Secondary

End point timeframe:

Between ICU (Intensive Care Unit) admission and 48 hours after the end of the surgical procedure.

End point values	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	161	164	166	
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	18 (10 to 25)	18 (11 to 27)	19 (11 to 30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Other postoperative cardiac damage and prognostic markers: CRP Peak Concentration

End point title Other postoperative cardiac damage and prognostic markers: CRP Peak Concentration

End point description:

The highest CRP (C-reactive protein) postoperative value observed was derived.

End point type Secondary

End point timeframe:

Between ICU (Intensive Care Unit) admission and 48 hours after the end of the surgical procedure

End point values	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	162	166	
Units: mg/L				
median (inter-quartile range (Q1-Q3))	181 (137 to 208)	187 (156 to 229)	195 (159 to 231)	

Statistical analyses

No statistical analyses for this end point

Secondary: Other postoperative cardiac damage and prognostic markers: NT-proBNP Peak Concentration

End point title Other postoperative cardiac damage and prognostic markers: NT-proBNP Peak Concentration

End point description:

The highest NT-proBNP (N-terminal-probrain nautreic protein) postoperative value observed was derived.

End point type

Secondary

End point timeframe:

Between ICU (Intensive Care Unit) admission and 48 hours after the end of the surgical procedure

End point values	Xenon - ITT	Sevoflurane - ITT	TIVA - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	160	163	166	
Units: ng/L				
median (inter-quartile range (Q1-Q3))	1614 (1035 to 2599)	1508 (941 to 2209)	1524 (912 to 2225)	

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.

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	14.0
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Reporting groups

Reporting group title	Xenon Including Pilot Patients
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Reporting group description:

Anesthetic agent before and after cardiopulmonary bypass: xenon

This group is composed of all randomised and treated patients with xenon plus the first included and non randomised patients treated with xenon (xenon pilot patients) in each centre for investigator familiarisation.

Reporting group title	Sevoflurane
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Reporting group description:

Anesthetic agent before and after cardiopulmonary bypass: sevoflurane

Reporting group title	TIVA
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Reporting group description:

Anesthetic agent before and after cardiopulmonary bypass: propofol

Serious adverse events	Xenon Including Pilot Patients	Sevoflurane	TIVA
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 178 (16.85%)	24 / 165 (14.55%)	26 / 166 (15.66%)
number of deaths (all causes)	0	0	3
number of deaths resulting from adverse events	0	0	3
Vascular disorders			
Air embolism			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Deep vein thrombosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			

subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 178 (1.12%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 178 (0.56%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			

subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Bronchial fistula			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 178 (1.12%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 178 (1.12%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Troponin I increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			

subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Operative haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	2 / 178 (1.12%)	4 / 165 (2.42%)	3 / 166 (1.81%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	3 / 166 (1.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical skin tear			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial flutter			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 178 (0.56%)	3 / 165 (1.82%)	2 / 166 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low cardiac output syndrome			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	5 / 178 (2.81%)	4 / 165 (2.42%)	3 / 166 (1.81%)
occurrences causally related to treatment / all	0 / 5	1 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	0 / 178 (0.00%)	2 / 165 (1.21%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 178 (1.12%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pancreatitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic ischaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	2 / 178 (1.12%)	1 / 165 (0.61%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis haemophilus			
subjects affected / exposed	0 / 178 (0.00%)	0 / 165 (0.00%)	1 / 166 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	2 / 166 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 178 (1.12%)	2 / 165 (1.21%)	3 / 166 (1.81%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Postoperative wound infection subjects affected / exposed	2 / 178 (1.12%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	2 / 166 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection subjects affected / exposed	0 / 178 (0.00%)	2 / 165 (1.21%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection subjects affected / exposed	0 / 178 (0.00%)	1 / 165 (0.61%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders Dehydration subjects affected / exposed	1 / 178 (0.56%)	0 / 165 (0.00%)	0 / 166 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Xenon Including Pilot Patients	Sevoflurane	TIVA
Total subjects affected by non-serious adverse events subjects affected / exposed	154 / 178 (86.52%)	139 / 165 (84.24%)	143 / 166 (86.14%)
Investigations	Additional description: Bispectral index considered unexpectedly low for one investigator		
Bispectral index decreased subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	0 / 165 (0.00%) 0	0 / 166 (0.00%) 0
Electrocardiogram ST segment elevation subjects affected / exposed occurrences (all)	18 / 178 (10.11%) 18	22 / 165 (13.33%) 22	13 / 166 (7.83%) 13
Troponin T increased subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	11 / 165 (6.67%) 11	15 / 166 (9.04%) 15
Troponin increased subjects affected / exposed occurrences (all)	10 / 178 (5.62%) 10	13 / 165 (7.88%) 13	11 / 166 (6.63%) 11
Injury, poisoning and procedural complications			
Insomnia subjects affected / exposed occurrences (all)	7 / 178 (3.93%) 7	9 / 165 (5.45%) 9	4 / 166 (2.41%) 4
Post procedural haemorrhage subjects affected / exposed occurrences (all)	12 / 178 (6.74%) 12	12 / 165 (7.27%) 12	10 / 166 (6.02%) 10
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	39 / 178 (21.91%) 39	27 / 165 (16.36%) 27	37 / 166 (22.29%) 37
Hypotension subjects affected / exposed occurrences (all)	55 / 178 (30.90%) 55	63 / 165 (38.18%) 63	55 / 166 (33.13%) 55
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	55 / 178 (30.90%) 55	43 / 165 (26.06%) 43	37 / 166 (22.29%) 37
Bradycardia			

subjects affected / exposed occurrences (all)	12 / 178 (6.74%) 12	9 / 165 (5.45%) 9	13 / 166 (7.83%) 13
Pericardial effusion subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	4 / 165 (2.42%) 4	5 / 166 (3.01%) 5
Tachycardia subjects affected / exposed occurrences (all)	14 / 178 (7.87%) 14	7 / 165 (4.24%) 7	14 / 166 (8.43%) 14
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	29 / 178 (16.29%) 29	33 / 165 (20.00%) 33	30 / 166 (18.07%) 30
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	19 / 178 (10.67%) 19	15 / 165 (9.09%) 15	17 / 166 (10.24%) 17
Pain subjects affected / exposed occurrences (all)	15 / 178 (8.43%) 15	9 / 165 (5.45%) 9	16 / 166 (9.64%) 16
Pyrexia subjects affected / exposed occurrences (all)	13 / 178 (7.30%) 13	20 / 165 (12.12%) 20	6 / 166 (3.61%) 6
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	17 / 178 (9.55%) 17	15 / 165 (9.09%) 15	16 / 166 (9.64%) 16
Nausea subjects affected / exposed occurrences (all)	23 / 178 (12.92%) 23	19 / 165 (11.52%) 19	18 / 166 (10.84%) 18
Vomiting subjects affected / exposed occurrences (all)	17 / 178 (9.55%) 17	9 / 165 (5.45%) 9	13 / 166 (7.83%) 13
Respiratory, thoracic and mediastinal disorders Hypoxia subjects affected / exposed occurrences (all)	14 / 178 (7.87%) 14	15 / 165 (9.09%) 15	14 / 166 (8.43%) 14

Pleural effusion subjects affected / exposed occurrences (all)	10 / 178 (5.62%) 10	8 / 165 (4.85%) 8	10 / 166 (6.02%) 10
Productive cough subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	4 / 165 (2.42%) 4	7 / 166 (4.22%) 7
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	10 / 165 (6.06%) 10	6 / 166 (3.61%) 6
Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all)	19 / 178 (10.67%) 19	17 / 165 (10.30%) 17	15 / 166 (9.04%) 15
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	29 / 178 (16.29%) 29	24 / 165 (14.55%) 24	12 / 166 (7.23%) 12
Hypokalaemia subjects affected / exposed occurrences (all)	11 / 178 (6.18%) 11	10 / 165 (6.06%) 10	6 / 166 (3.61%) 6
Hypovolaemia subjects affected / exposed occurrences (all)	13 / 178 (7.30%) 13	13 / 165 (7.88%) 13	12 / 166 (7.23%) 12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2011	<ul style="list-style-type: none">- Prolongation of inclusion period until March 2013- Change of French coordinator
07 March 2012	<ul style="list-style-type: none">- Change in an eligibility criterion relating to cardioplegia temperature.- Adjustment of the list of biomarkers to detect cardiac necrosis (Troponin and/or CK-MB)- Clarification on AEs to be reported in the clinical setting of cardiac surgery- Change of data collected to report concentrations of xenon and sevoflurane administered.- Update of anaesthetic medications to be administered in case of re-intervention- Update of evaluation of efficacy of the BIS index- Appendix 4: Update of Vaporiser and Felix Dual™ machine settings- Interval of survey of incidence of all deaths reduced from every 160 patients to every 80 patients- Change of national coordinator in Italy
28 February 2013	<p>This amendment is dated from 28/02/2013 to 27/03/2013 according to the countries (France, Germany, Italy, The Netherlands).</p> <ul style="list-style-type: none">- Extension of the inclusion period to March 2014- Number of sites increased to 17 sites and patients to 509

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/28872484>