Clinical trial results:
A Randomized, Single-blind Phase II Study Evaluating the Efficacy, Safety and Pharmacokinetics of Remimazolam in General Anesthesia in Adult Patients Undergoing Cardiac Surgery, Including Follow-up Sedation in the Post-anesthesia Care Unit / Intensive Care Unit

Summary

EudraCT number	2013-001113-32
Trial protocol	DE
Global end of trial date	19 February 2014

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	CNS7056-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01937767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PAION UK Limited
Sponsor organisation address	Unit D1, Brookmount Court, Kirkwood Road, Cambridge, United Kingdom, CB4 2QH
Public contact	Clinical trial information, PAION GmbH, +49 (0)24144530, info@paion.com
Scientific contact	Clinical trial information, PAION GmbH, +49 (0)24144530, info@paion.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	16 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2014
Global end of trial reached?	Yes
Global end of trial date	19 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Randomized, single-blind trial to compare 2 doses of remimazolam against each other and against propofol during induction of general anesthesia and to compare remimazolam with the combination of propofol and sevoflurane during maintenance of general anesthesia. Main objectives: efficacy including dose finding for induction, safety

Protection of trial subjects:

This study was conducted in compliance with the principles of the Declaration of Helsinki and its amendments, the International Conference on Harmonisation (ICH), principles of Good Clinical Practice (GCP), and the applicable regulations in Germany and the European Union.
Conduct of the study was approved by the Ethics Committee at the Medical Faculty of the University of Leipzig, an appropriately constituted Independent Ethics Committee.

Background therapy:

- Major elective cardiac surgery, i.e. surgery assumed to require more than 2 hours of maintenance of general anesthesia and the use of extracorporeal circulation.
- Fentanyl and remifentanil as opioid narcotics and rocuronium bromide as neuro-muscular blocker
- Optionally: further drugs that are used during heart surgery, e.g. catecholamines, heparin

Evidence for comparator:

Remimazolam was compared with the standard regimen for general anesthesia in heart surgery which is the combination of propofol and sevoflurane.

Actual start date of recruitment	29 August 2013
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	Germany: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	49
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at the Heart Center in Leipzig, Germany. Patients were eligible for the study if they were scheduled for major elective cardiac surgery, i.e. surgery assumed to require >2 hours of maintenance of general anesthesia and extracorporeal circulation, including bypass(es), valve replacement(s), and surgery of the aortic arch.

Pre-assignment

Screening details:

A total of 125 patients were screened. 10 patients were not eligible so that 115 patients were randomized. Of these 115 patients, 25 patients stopped the study prior to the start of the study medication, mainly due to rescheduling of the surgery or other organisational reasons. Study medication was administered to 90 patients.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	No
Arm title	Remimazolam 6

Arm description:

Remimazolam 6 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Remimazolam 6 mg/kg/hr for induction, 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery based on the medical condition of each individual patient. Intravenous administration via syringe pump.

Arm title	Remimazolam 12

Arm description:

Remimazolam 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Remimazolam 12 mg/kg/hr for induction, 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery based on the medical condition of each individual patient. Intravenous administration via syringe pump.

Arm title	Remimazolam All

Arm description:

Remimazolam 6 mg/kg/hr or 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.

Arm type	Experimental
Investigational medicinal product name	Remimazolam 6
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Remimazolam 6 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery based on the medical condition of each individual patient. intravenous administration via syringe pump.

Investigational medicinal product name	Remimazolam 12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Remimazolam 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery based on the medical condition of each individual patient. Intravenous administration via syringe pump.

Arm title	Propofol/Sevoflurane

Arm description:

Propofol 2 - 2.5 mg/kg for induction, maintenance with sevoflurane 0.8 - 2.5 MAC until start of extracorporeal circulation, afterwards maintenance with propofol 3 - 12 mg/kg/hr, propofol down titration and stop during recovery.

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

Dosage and administration details:

Propofol for induction: 2.0 - 2.5 mg/kg, manual intravenous administration over approximately 1 minute. Propofol for maintenance: 3 - 12 mg/kg/hr, intravenous administration via syringe pump. Propofol down titration and stop during recovery based on the medical condition of each individual patient, intravenous administration via syringe pump.

Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, solution
Routes of administration	Intrapulmonary use

Dosage and administration details:

Sevoflurane inhalation gas 0.8 -2.5 MAC for maintenance. Administration by inhalation during mechanical ventilation.

Number of subjects in period 1	Remimazolam 6	Remimazolam 12	Remimazolam All
Started	34	28	62
Completed	34	28	62

Number of subjects in period 1	Propofol/Sevoflurane
Started	28
Completed	28

Period 2

Period 2 title	Induction
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Assessor

Blinding implementation details:

Patients were not informed about their treatment allocation. To enable investigators to titrate remimazolam or propofol as effectively and as safely as possible during the induction period, investigators knew about their patients' treatment allocation. An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Remimazolam 6

Arm description:

Remimazolam 6 mg/kg/hr for induction

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/kg/hr for induction, intravenous administration via syringe pump.

Arm title	Remimazolam 12

Arm description:

Remimazolam 12 mg/kg/hr for induction

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

12 mg/kg/hr for induction, intravenous administration via syringe pump.

Arm title	Propofol

Arm description:

Propofol 2.0 - 2.5 mg/kg for induction

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

Dosage and administration details:

Propofol 2.0 - 2.5 mg/kg for induction. Manual intravenous administration over approximately 1 minute.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Number of subjects in period 2	Remimazolam 6	Remimazolam 12	Propofol
Started	34	28	28
Completed	34	28	28

Period 3

Period 3 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Assessor

Blinding implementation details:

Patients were not informed about their treatment allocation. To enable investigators to titrate remimazolam or propofol/sevoflurane as effectively and as safely as possible during the maintenance period, investigators knew about their patients' treatment allocation. An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Arms

Are arms mutually exclusive?	Yes

Arm title	Remimazolam All

Arm description:

Maintenance with remimazolam after induction with remimazolam 6 mg/kg/hr or remimazolam 12 mg/kg/hr

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Remimazolam 1 mg/kg/hr up to 3 mg/kg/hr intravenously administered via syringe pump according to each individual patient's needs.

Arm title	Propofol/Sevoflurane

Arm description:

Maintenance with sevoflurane until start of extracorporeal circulation. From start of extracorporeal circulation onwards maintenance with propofol.

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

Dosage and administration details:

Propofol 3 - 12 mg/kg/hr according to each individual patient's needs. Intravenous administration via syringe pump.

Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, solution
Routes of administration	Intrapulmonary use

Dosage and administration details:

Sevoflurane inhalation gas 0.8 -2.5 MAC according to each individual patient's needs. Administration by inhalation during mechanical ventilation.

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Number of subjects in period 3	Remimazolam All	Propofol/Sevoflurane
Started	62	28
Completed	62	28

Period 4

Period 4 title	Recovery
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[3]
Roles blinded	Subject, Assessor

Blinding implementation details:

Patients were not informed about their treatment allocation. To enable investigators to titrate remimazolam or propofol as effectively and as safely as possible during the recovery period, investigators knew about their patients' treatment allocation. An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Remimazolam All

Arm description:

Down titration and stop of remimazolam

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Downtitration of remimazolam from maintenance dosage according to each individual patient's needs. Intravenous administration via syringe pump.

Arm title	Propofol

Arm description:

Down titration and stop of propofol

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

Dosage and administration details:

Downtitration of propofol from maintenance dosage according to each individual patient's needs. Intravenous administration via syringe pump.

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: An expert assessor who reviewed the Narcotrend data after the end of the general anesthesia was not informed about the patients' treatment allocation.

Number of subjects in period 4	Remimazolam All	Propofol
Started	62	28
Completed	62	28

Period 5

Period 5 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

Patients were not informed about their treatment allocation to avoid bias on patients' statements, e.g. regarding adverse events.

Arms

Are arms mutually exclusive?	Yes
Arm title	Remimazolam All

Arm description:

Study medication-free follow-up

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

No administration of remimazolam during follow-up.

Arm title	Propofol/Sevoflurane

Arm description:

Study medication-free follow-up

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

Dosage and administration details:

No administration of propofol during follow-up.

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:

No administration of sevoflurane during follow-up.

Number of subjects in period 5	Remimazolam All	Propofol/Sevoflurane
Started	62	28
Completed	62	28

Baseline characteristics

Reporting groups	
Reporting group title	Remimazolam 6
Reporting group description:	
Remimazolam 6 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Remimazolam 12
Reporting group description:	
Remimazolam 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Remimazolam All
Reporting group description:	
Remimazolam 6 mg/kg/hr or 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Propofol/Sevoflurane
Reporting group description:	
Propofol 2 - 2.5 mg/kg for induction, maintenance with sevoflurane 0.8 - 2.5 MAC until start of extracorporeal circulation, afterwards maintenance with propofol 3 - 12 mg/kg/hr, propofol down titration and stop during recovery.	

Reporting group values	Remimazolam 6	Remimazolam 12	Remimazolam All
Number of subjects	34	28	62
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60	63.9	61.8
standard deviation	± 11.57	± 11.67	± 11.68
Gender categorical Units: Subjects			
Female	12	5	17
Male	22	23	45
Planned surgical procedure Units: Subjects			
Bypass(es) only	2	3	5
Valve replacement(s) only	9	11	20
Other or combined procedures	23	14	37
Duration of maintenance of anesthesia Units: Minutes			
arithmetic mean	199.14	209.36	203.75
standard deviation	± 52.52	± 54.1	± 53.04

Reporting group values	Propofol/Sevoflurane	Total	
Number of subjects	28	90	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	62.9		
standard deviation	± 10.96	-	
Gender categorical Units: Subjects			
Female	6	23	
Male	22	67	
Planned surgical procedure Units: Subjects			
Bypass(es) only	2	7	
Valve replacement(s) only	19	39	
Other or combined procedures	7	44	
Duration of maintenance of anesthesia Units: Minutes			
arithmetic mean	185.27		
standard deviation	± 44.86	-	

End points

End points reporting groups

Reporting group title	Remimazolam 6
Reporting group description:	
Remimazolam 6 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Remimazolam 12
Reporting group description:	
Remimazolam 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Remimazolam All
Reporting group description:	
Remimazolam 6 mg/kg/hr or 12 mg/kg/hr for induction, remimazolam 1 - 3 mg/kg/hr for maintenance, remimazolam down titration and stop during recovery.	
Reporting group title	Propofol/Sevoflurane
Reporting group description:	
Propofol 2 - 2.5 mg/kg for induction, maintenance with sevoflurane 0.8 - 2.5 MAC until start of extracorporeal circulation, afterwards maintenance with propofol 3 - 12 mg/kg/hr, propofol down titration and stop during recovery.	
Reporting group title	Remimazolam 6
Reporting group description:	
Remimazolam 6 mg/kg/hr for induction	
Reporting group title	Remimazolam 12
Reporting group description:	
Remimazolam 12 mg/kg/hr for induction	
Reporting group title	Propofol
Reporting group description:	
Propofol 2.0 - 2.5 mg/kg for induction	
Reporting group title	Remimazolam All
Reporting group description:	
Maintenance with remimazolam after induction with remimazolam 6 mg/kg/hr or remimazolam 12 mg/kg/hr	
Reporting group title	Propofol/Sevoflurane
Reporting group description:	
Maintenance with sevoflurane until start of extracorporeal circulation. From start of extracorporeal circulation onwards maintenance with propofol.	
Reporting group title	Remimazolam All
Reporting group description:	
Down titration and stop of remimazolam	
Reporting group title	Propofol
Reporting group description:	
Down titration and stop of propofol	
Reporting group title	Remimazolam All
Reporting group description:	
Study medication-free follow-up	
Reporting group title	Propofol/Sevoflurane
Reporting group description:	
Study medication-free follow-up	

Primary: Success of anesthesia

End point title	Success of anesthesia

End point description:

Success defined as no need for another sedative between start of study medication and end of surgical procedure.

End point type	Primary

End point timeframe:

Between start of study medication and end of surgical procedure, defined as time of completion of last skin suture

End point values	Remimazolam All	Propofol/Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	28		
Units: Patients	61	27		

Statistical analyses

Statistical analysis title	CI Remimazolam All vs Propofol/Sevoflurane

Statistical analysis description:

The difference in the success rate between the group of patients on remimazolam and the group of patients on propofol/sevoflurane was assessed by calculating confidence intervals

Comparison groups	Remimazolam All v Propofol/Sevoflurane
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Risk difference (RD)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.61
upper limit	16.16
Variability estimate	Standard error of the mean
Dispersion value	3.855

Secondary: Time to loss of consciousness

End point title	Time to loss of consciousness

End point description:

Loss of consciousness was defined as time by when Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale was found equal or less than 1 for the first time.

End point type	Secondary

End point timeframe:

From start of study medication until loss of consciousness

End point values	Remimazolam 6	Remimazolam 12	Propofol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	28	28	
Units: seconds				
median (confidence interval 95%)	75 (63 to 82)	60.5 (54 to 73)	56 (51 to 65)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time with Narcotrend Index </= 60

End point title	Time with Narcotrend Index </= 60

End point description:

The Narcotrend monitoring system recorded and analyzed the patients' electroencephalogram (EEG). The Narcotrend monitor generated a Narcotrend Index between 100 (fully awake) and 0 (no brain activity) every 5 seconds. During maintenance of general anesthesia, Narcotrend Indices between 50 and 30 were regarded as representing ideal depth of sedation. To allow for minor fluctuations, Narcotrend Indices of 60 and less were regarded as representing appropriate sedation throughout maintenance.

End point type	Secondary

End point timeframe:

General anesthesia, maintenance period

End point values	Remimazolam All	Propofol/Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	28		
Units: Percent				
arithmetic mean (standard deviation)	94.64 (± 5.588)	96.91 (± 2.613)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to extubation

End point title	Time to extubation

End point description:

From arrival at PACU/ICU or first occurrence of normothermia (at least 36 degrees centrigrade), whichever was later, until extubation completed

End point type	Secondary

End point timeframe:
Between completion of last skin suture and discharge from PACU/ICU

End point values	Remimazolam All	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	28		
Units: minute				
median (confidence interval 95%)	145.5 (111 to 170)	97 (83 to 140)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to discharge from hospital

End point title	Time to discharge from hospital

End point description:
Number of days from day of surgery to day of discharge from hospital

End point type	Secondary

End point timeframe:
Date of surgery until discharge from hospital

End point values	Remimazolam All	Propofol/Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	28		
Units: day				
median (confidence interval 95%)	9 (8 to 11)	9.5 (8 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Successful intubation

End point title	Successful intubation

End point description:

End point type	Secondary

End point timeframe:
Between start of study medication and departure from induction room

End point values	Remimazolam 6	Remimazolam 12	Propofol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	28	28	
Units: patients				
Successful	34	28	28	
Not successful	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to intubation completed

End point title	Time to intubation completed

End point description:

Time between start of administration of study drug and intubation completed

End point type	Secondary

End point timeframe:

Between start of study medication and departure from induction room

End point values	Remimazolam 6	Remimazolam 12	Propofol	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	28	28	
Units: seconds				
median (confidence interval 95%)	293 (260 to 328)	284.5 (253 to 323)	286.5 (265 to 301)	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Use of norepinephrine

End point title	Use of norepinephrine

End point description:

Vasopressors were used to treat hemodynamic instability. Norepinephrine was the first-line vasopressor. Low use of norepinephrine was regarded as indicating high hemodynamic stability.

End point type	Post-hoc

End point timeframe:

From start of study medication until end of PiCCO (system of invasive hemodynamic monitoring) recording. PiCCO recording was stopped after end of surgery and before discharge from Post-anesthesia Care Unit / Intensive Care Unit

End point values	Remimazolam All	Propofol/Sevoflurane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[1]	28		
Units: ng/kg/min				
arithmetic mean (standard deviation)	23.676 (± 20.3064)	43.171 (± 38.7774)		

Notes:

[1] - 2 patients did not get any amount of norepinephrine

Statistical analyses

Statistical analysis title	Test for difference in use of norepinephrine

Statistical analysis description:

To investigate whether the use of norepinephrine is lower under remimazolam compared with the use of norepinephrine under the combination of propofol and sevoflurane

Comparison groups	Remimazolam All v Propofol/Sevoflurane
Number of subjects included in analysis	88
Analysis specification	Post-hoc
Analysis type	other[2]
P-value	= 0.0172
Method	t-test, 2-sided

Notes:

[2] - Test for difference

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent until discharge from hospital

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as AEs reported during treatment, i.e. at or after the start of the treatment Administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Safety Population Remimazolam 6 mg

Reporting group description:

All patients who received any amount of study drug and who actually received remimazolam 6 mg/kg/hr for induction. For maintenance, remimazolam 1 - 3 mg/kg/hr was administered. Down titration and stop of remimazolam during recovery.

Reporting group title	Safety Population Remimazolam 12 mg

Reporting group description:

All patients who received any amount of study drug and who actually received remimazolam 12 mg/kg/hr for induction. For maintenance, remimazolam 1 - 3 mg/kg/hr was administered. Down titration and stop of remimazolam during recovery.

Reporting group title	Safety Population Remimazolam All

Reporting group description:

All patients on remimazolam, i.e. patients with induction with remimazolam 6 mg/kg/hr AND patients with induction with remimazolam 12 mg/kg/hr. For maintenance, remimazolam 1 - 3 mg/kg/hr was administered. Down titration and stop of remimazolam during recovery.

Reporting group title	Safety Population Propofol/Sevoflurane

Reporting group description:

All patients who received any amount of study drug and who got propofol for induction. For maintenance, sevoflurane 0.8 - 2.5 MAC was administered until start of extracorporeal circulation. From start of extracorporeal circulation, propofol 3 -12 mg/kg/hr was administered. Down titration and stop of propofol during recovery.

Serious adverse events	Safety Population Remimazolam 6 mg	Safety Population Remimazolam 12 mg	Safety Population Remimazolam All
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 34 (26.47%)	8 / 28 (28.57%)	17 / 62 (27.42%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 34 (0.00%)	1 / 28 (3.57%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve rupture			

subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 34 (0.00%)	1 / 28 (3.57%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block complete			
subjects affected / exposed	0 / 34 (0.00%)	3 / 28 (10.71%)	3 / 62 (4.84%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 34 (0.00%)	1 / 28 (3.57%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial hemorrhage			

subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinoatrial block			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal adhesions			
subjects affected / exposed	0 / 34 (0.00%)	1 / 28 (3.57%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	1 / 34 (2.94%)	1 / 28 (3.57%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	1 / 34 (2.94%)	1 / 28 (3.57%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 34 (5.88%)	0 / 28 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory depression			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient psychosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Wound infection bacterial			
subjects affected / exposed	0 / 34 (0.00%)	0 / 28 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection fungal			
subjects affected / exposed	0 / 34 (0.00%)	1 / 28 (3.57%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	1 / 34 (2.94%)	0 / 28 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety Population Propofol/Sevoflurane		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 28 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac valve rupture			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Postoperative thoracic procedure complication			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrioventricular block complete				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 28 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial hemorrhage				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinoatrial block				

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peritoneal adhesions			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory depression			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient psychosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection bacterial			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection fungal			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Wound infection staphylococcal			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population Remimazolam 6 mg	Safety Population Remimazolam 12 mg	Safety Population Remimazolam All
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 34 (100.00%)	28 / 28 (100.00%)	62 / 62 (100.00%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	3 / 34 (8.82%)	3 / 28 (10.71%)	6 / 62 (9.68%)
occurrences (all)	3	3	6
Bilirubin conjugated increased			
subjects affected / exposed	3 / 34 (8.82%)	2 / 28 (7.14%)	5 / 62 (8.06%)
occurrences (all)	3	2	5
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	18 / 34 (52.94%)	14 / 28 (50.00%)	32 / 62 (51.61%)
occurrences (all)	18	14	32
Procedural nausea			
subjects affected / exposed	18 / 34 (52.94%)	13 / 28 (46.43%)	31 / 62 (50.00%)
occurrences (all)	18	13	31
Vascular disorders			
Haematoma			
subjects affected / exposed	5 / 34 (14.71%)	4 / 28 (14.29%)	9 / 62 (14.52%)
occurrences (all)	5	4	9
Hypertension			
subjects affected / exposed	7 / 34 (20.59%)	9 / 28 (32.14%)	16 / 62 (25.81%)
occurrences (all)	7	9	16
Hypotension			
subjects affected / exposed	4 / 34 (11.76%)	1 / 28 (3.57%)	5 / 62 (8.06%)
occurrences (all)	4	1	5
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	9 / 34 (26.47%)	4 / 28 (14.29%)	13 / 62 (20.97%)
occurrences (all)	9	4	13
Bradycardia			
subjects affected / exposed	5 / 34 (14.71%)	3 / 28 (10.71%)	8 / 62 (12.90%)
occurrences (all)	5	3	8
Pericardial effusion			
subjects affected / exposed	3 / 34 (8.82%)	2 / 28 (7.14%)	5 / 62 (8.06%)
occurrences (all)	3	2	5
Atrioventricular block complete			
subjects affected / exposed	0 / 34 (0.00%)	3 / 28 (10.71%)	3 / 62 (4.84%)
occurrences (all)	0	3	3
General disorders and administration site conditions			
Drug effect prolonged			
subjects affected / exposed	5 / 34 (14.71%)	7 / 28 (25.00%)	12 / 62 (19.35%)
occurrences (all)	5	7	12
Chills			
subjects affected / exposed	5 / 34 (14.71%)	4 / 28 (14.29%)	9 / 62 (14.52%)
occurrences (all)	5	4	9
Oedema			
subjects affected / exposed	4 / 34 (11.76%)	3 / 28 (10.71%)	7 / 62 (11.29%)
occurrences (all)	4	3	7
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	5 / 34 (14.71%)	8 / 28 (28.57%)	13 / 62 (20.97%)
occurrences (all)	5	8	13
Thrombocytopenia			
subjects affected / exposed	4 / 34 (11.76%)	6 / 28 (21.43%)	10 / 62 (16.13%)
occurrences (all)	4	6	10
Coagulopathy			
subjects affected / exposed	3 / 34 (8.82%)	4 / 28 (14.29%)	7 / 62 (11.29%)
occurrences (all)	3	4	7
Leukocytosis			
subjects affected / exposed	3 / 34 (8.82%)	0 / 28 (0.00%)	3 / 62 (4.84%)
occurrences (all)	3	0	3
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	6 / 34 (17.65%)	4 / 28 (14.29%)	10 / 62 (16.13%)
occurrences (all)	6	4	10
Flatulence			
subjects affected / exposed	2 / 34 (5.88%)	1 / 28 (3.57%)	3 / 62 (4.84%)
occurrences (all)	2	1	3
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	28 / 34 (82.35%)	27 / 28 (96.43%)	55 / 62 (88.71%)
occurrences (all)	28	27	55
Cough			
subjects affected / exposed	13 / 34 (38.24%)	6 / 28 (21.43%)	19 / 62 (30.65%)
occurrences (all)	13	6	19
Respiratory failure			
subjects affected / exposed	5 / 34 (14.71%)	7 / 28 (25.00%)	12 / 62 (19.35%)
occurrences (all)	5	7	12
Bronchospasm			
subjects affected / exposed	5 / 34 (14.71%)	4 / 28 (14.29%)	9 / 62 (14.52%)
occurrences (all)	5	4	9
Pneumothorax			
subjects affected / exposed	4 / 34 (11.76%)	3 / 28 (10.71%)	7 / 62 (11.29%)
occurrences (all)	4	3	7
Psychiatric disorders			
Agitation			
subjects affected / exposed	18 / 34 (52.94%)	13 / 28 (46.43%)	31 / 62 (50.00%)
occurrences (all)	18	13	31
Sleep disorder			
subjects affected / exposed	14 / 34 (41.18%)	11 / 28 (39.29%)	25 / 62 (40.32%)
occurrences (all)	14	11	25
Delirium			
subjects affected / exposed	4 / 34 (11.76%)	6 / 28 (21.43%)	10 / 62 (16.13%)
occurrences (all)	4	6	10
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 34 (11.76%)	6 / 28 (21.43%)	10 / 62 (16.13%)
occurrences (all)	4	6	10

Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 34 (2.94%)	3 / 28 (10.71%)	4 / 62 (6.45%)
occurrences (all)	1	3	4
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	12 / 34 (35.29%)	8 / 28 (28.57%)	20 / 62 (32.26%)
occurrences (all)	12	8	20
Hyperglycaemia			
subjects affected / exposed	2 / 34 (5.88%)	5 / 28 (17.86%)	7 / 62 (11.29%)
occurrences (all)	2	5	7

Non-serious adverse events	Safety Population Propofol/Sevoflurane		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Bilirubin conjugated increased			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	12 / 28 (42.86%)		
occurrences (all)	12		
Procedural nausea			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	10		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Hypotension			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	10		
Bradycardia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Pericardial effusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences (all)	1		
Atrioventricular block complete			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
General disorders and administration site conditions			
Drug effect prolonged			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	6		
Chills			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Oedema			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Thrombocytopenia			
subjects affected / exposed	5 / 28 (17.86%)		
occurrences (all)	5		
Coagulopathy			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Leukocytosis			

subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all)	 3 / 28 (10.71%) 3 2 / 28 (7.14%) 2		
Respiratory, thoracic and mediastinal disorders Pleural effusion subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Respiratory failure subjects affected / exposed occurrences (all) Bronchospasm subjects affected / exposed occurrences (all) Pneumothorax subjects affected / exposed occurrences (all)	 23 / 28 (82.14%) 23 3 / 28 (10.71%) 3 4 / 28 (14.29%) 4 4 / 28 (14.29%) 4 2 / 28 (7.14%) 2		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Sleep disorder subjects affected / exposed occurrences (all) Delirium subjects affected / exposed occurrences (all)	 7 / 28 (25.00%) 7 12 / 28 (42.86%) 12 4 / 28 (14.29%) 4		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1		
Metabolism and nutrition disorders Fluid retention subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 28 (14.29%) 4 5 / 28 (17.86%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2013	1.) Remimazolam dosage for maintenance increased from 1 - 2 mg/kg/hr to 1 - 3 mg/kg/hr 2.) post-operative bleedings were to be reported as AEs only if administration of at least one transfusion or at least one unit of products that support blood coagulation was required or if re-surgery was required 3.) cardiac arrhythmias did not need to be reported as AEs if they occurred within 5 minutes before or after cardioplegia that was induced for extracorporeal circulation of if they stopped within 30 seconds 4.) plus further minor corrections and clarifications of the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported