



Clinical trial results:

A Randomized, Single-blind, Propofol-controlled Phase III Study Evaluating the Efficacy and Safety 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	2014-004565-24
Trial protocol	DE BE NL
Global end of trial date	07 March 2016

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017

Trial information

Trial identification

Sponsor protocol code	CNS7056-011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02523859
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 Deutschland GmbH, +49 (0)24144530, info@paion.com
Scientific contact	Clinical trial information, PAION Deutschland 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	03 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2016
Global end of trial reached?	Yes
Global end of trial date	07 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Randomized, single-blind trial to compare remimazolam and propofol in general anesthesia. Optional use of remimazolam for follow-up sedation on the Intensive Care Unit (ICU) up to a total administration time of 24 hours. Main objectives: efficacy in terms of successful sedation and safety in terms of hemodynamic stability defined as amount of norepinephrine administered during induction and maintenance.

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 the participating countries and the European Union. Conduct of the study was approved by appropriately constituted Independent Ethics Committees in the participating countries.

Background therapy:

Major non-emergency cardiac surgery, i.e. surgery assumed to require more than 2 hours of maintenance of general anesthesia and the use of extracorporeal circulation.
Fentanyl/sufentanil/remifentanyl 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 propofol which is the standard intravenously given sedative-hypnotic agent for general anesthesia in cardiac surgery

Actual start date of recruitment	10 August 2015
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	France: 4
Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	9
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 1 site in France and 5 sites in Germany. Eligible patients were scheduled for non-emergency cardiac surgery, i.e. surgery probably requiring >2 hours maintenance of general anesthesia & extracorporeal circulation, including bypass(es), valve replacement(s), and associated procedures, and on-pump minimal invasive surgery.

Pre-assignment

Screening details:

A total of 28 patients were screened. Three patients were not eligible so 25 patients were randomized. Of these 25 randomized patients, 2 patients stopped the study prior to the start of the study medication. The reasons were a protocol deviation and an unscheduled shift of the surgery.

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?	Yes
Arm title	Remimazolam

Arm description:

Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed

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. Intravenous administration per syringe pump.

Arm title	Propofol
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Arm description:

Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.

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: Bolus administered manually at 1.0 - 2.5 mg/kg slowly over approximately 1 minute. Alternatively, the use of a target-controlled infusion (TCI) system was allowed in clinics where TCI was standard. Propofol for maintenance: 3.0 - 9.0 mg/kg/hr via syringe driver as needed or TCI with target concentrations between 2 and 10 microgram/mL.

Number of subjects in period 1	Remimazolam	Propofol
Started	18	5
Completed	18	5

Period 2

Period 2 title	Start of induction to end of Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Remimazolam

Arm description:

Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed

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. Intravenous administration per syringe pump.

Arm title	Propofol
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Arm description:

Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.

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: Bolus administered manually at 1.0 - 2.5 mg/kg slowly over approximately 1 minute. Alternatively, the use of a target-controlled infusion system was allowed in clinics where target-controlled infusion (TCI) was standard. Propofol for maintenance: 3.0 - 9.0 mg/kg/hr via syringe driver as needed or TCI with target concentrations between 2 and 10 microgram/mL.

Number of subjects in period 2	Remimazolam	Propofol
Started	18	5
Completed	18	5

Baseline characteristics

Reporting groups

Reporting group title	Remimazolam
Reporting group description:	
Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed	
Reporting group title	Propofol
Reporting group description:	
Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.	

Reporting group values	Remimazolam	Propofol	Total
Number of subjects	18	5	23
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	0	9
From 65-84 years	9	5	14
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	63.9	70.2	-
standard deviation	± 12.47	± 6.57	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	5	23
Planned surgical procedure			
Units: Subjects			
Bypass(es) only	7	2	9
Valve replacement(s) only	7	2	9
Other and combined procedures	4	1	5
Duration of administration of study medication			
Time from start of administration of study medication to end of administration of study medication			
Units: Minutes			
arithmetic mean	385	381.5	-
standard deviation	± 126.97	± 98.07	-

Subject analysis sets

Subject analysis set title	mITT Remimazolam
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients who were randomized to remimazolam and who received any amount of remimazolam	
Subject analysis set title	mITT Propofol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients randomized to propofol and having received any amount of propofol	
Subject analysis set title	Safety Set Remimazolam
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients exposed to any amount of remimazolam

Subject analysis set title	Safety Set Propofol
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients exposed to any amount of propofol

Reporting group values	mITT Remimazolam	mITT Propofol	Safety Set Remimazolam
Number of subjects	18	5	18
Age categorical Units: Subjects			
Adults (18-64 years)	9	0	9
From 65-84 years	9	5	9
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	63.9	70.2	63.9
standard deviation	± 12.47	± 6.57	± 12.47
Gender categorical Units: Subjects			
Female	0	0	0
Male	18	5	18
Planned surgical procedure Units: Subjects			
Bypass(es) only	7	2	
Valve replacement(s) only	7	2	
Other and combined procedures	4	1	
Duration of administration of study medication			
Time from start of administration of study medication to end of administration of study medication			
Units: Minutes			
arithmetic mean	385	381.5	385
standard deviation	± 126.97	± 98.07	± 126.97

Reporting group values	Safety Set Propofol		
Number of subjects	5		
Age categorical Units: Subjects			
Adults (18-64 years)	0		
From 65-84 years	5		
Age continuous			
Mean age at baseline			
Units: years			
arithmetic mean	70.2		
standard deviation	± 6.57		
Gender categorical Units: Subjects			
Female	0		
Male	5		

Planned surgical procedure			
Units: Subjects			
Bypass(es) only			
Valve replacement(s) only			
Other and combined procedures			
Duration of administration of study medication			
Time from start of administration of study medication to end of administration of study medication			
Units: Minutes			
arithmetic mean	381.5		
standard deviation	± 98.07		

End points

End points reporting groups

Reporting group title	Remimazolam
Reporting group description: Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed	
Reporting group title	Propofol
Reporting group description: Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.	
Reporting group title	Remimazolam
Reporting group description: Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed	
Reporting group title	Propofol
Reporting group description: Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.	
Subject analysis set title	mITT Remimazolam
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients who were randomized to remimazolam and who received any amount of remimazolam	
Subject analysis set title	mITT Propofol
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: All patients randomized to propofol and having received any amount of propofol	
Subject analysis set title	Safety Set Remimazolam
Subject analysis set type	Safety analysis
Subject analysis set description: All patients exposed to any amount of remimazolam	
Subject analysis set title	Safety Set Propofol
Subject analysis set type	Safety analysis
Subject analysis set description: All patients exposed to any amount of propofol	

Primary: Successful sedation

End point title	Successful sedation ^[1]
End point description: Sedation was successful if Narcotrend index was 60 or less during at least 85% of the maintenance time and if no rescue sedative medication was administered	
End point type	Primary
End point timeframe: From arrival at operation room or time when anesthesiologist permitted surgical team to start until completion of last skin suture	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Justification: Due to small numbers of subjects in each treatment group, no formal statistical analysis was performed.

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Patients				
Success	14	4		
No success	4	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Norepinephrine administered

End point title	Norepinephrine administered
End point description: Amount of norepinephrine administered between start of study medication and completion of last skin suture per body weight and time	
End point type	Secondary
End point timeframe: From start of study medication until completion of last skin suture	

End point values	Safety Set Remimazolam	Safety Set Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16 ^[2]	4 ^[3]		
Units: ng/kg/min				
arithmetic mean (standard deviation)	628.8 (± 477.49)	1453.6 (± 1160.37)		

Notes:

[2] - 16 subjects with norepinephrine used

[3] - 4 subjects with norepinephrine used

Statistical analyses

No statistical analyses for this end point

Secondary: Use of Rescue Medication

End point title	Use of Rescue Medication
End point description: Use of rescue sedative medication in addition to remimazolam or propofol, respectively, to achieve appropriate level of sedation	
End point type	Secondary
End point timeframe: From start of study medication until completion of last skin suture	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Patients				
Rescue sedative medication used	2	0		
Rescue sedative medication not used	16	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to loss of consciousness

End point title	Time to loss of consciousness
End point description: Loss of consciousness was when the Modified Observer's Assessment of Alertness and Sedation Scale (MOAA/S) was at 1 or below for the first time	
End point type	Secondary
End point timeframe: From start of study medication until loss of consciousness	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Seconds				
median (confidence interval 95%)	135 (89 to 161)	79 (42 to 419)		

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 from start of remimazolam or propofol, respectively, until the endotracheal intubation was completed	
End point type	Secondary
End point timeframe: Time from start of study medication until intubation completed	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Seconds				
median (confidence interval 95%)	385.5 (328 to 470)	322 (277 to 590)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to extubation

End point title	Time to extubation
End point description: Time from stop of remimazolam or propofol, respectively, until patient was extubated	
End point type	Secondary
End point timeframe: Time from stop of study medication until extubation	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Minutes				
median (confidence interval 95%)	37.5 (15 to 61)	37 (2 to 200)		

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: Time from start of remimazolam or propofol, respectively, until discharge from hospital where cardiac surgery was performed, regardless whether patient was referred to another hospital or went home	
End point type	Secondary
End point timeframe: Time from start of study medication until discharge from hospital	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: days				
median (confidence interval 95%)	8 (8 to 9)	9 (7 to 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maintenance time with Narcotrend index 60 or less

End point title	Maintenance time with Narcotrend index 60 or less
End point description: Maintenance time with Narcotrend index at 60 or below expressed as percentage of entire time of maintenance of general anesthesia	
End point type	Secondary
End point timeframe: From start of maintenance until last skin suture completed	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: percent				
arithmetic mean (standard deviation)	87.16 (± 21.836)	90.24 (± 3.858)		

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of remifentanil administered

End point title	Amount of remifentanil administered
End point description: Total amount of remifentanil administered per body weight. Calculated only for patients without use of TCI.	
End point type	Secondary
End point timeframe: Amount of opioids administered, remifentanil	

End point values	mITT Remimazolam	mITT Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	4		
Units: microgram /kilogram				
arithmetic mean (standard deviation)	86.89 (± 26.68)	92.89 (± 29.127)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fall in mean arterial blood pressure by more than 30%

End point title	Fall in mean arterial blood pressure by more than 30%
End point description: Mean arterial blood pressure as measured by the PiCCO (Pulse Contour Cardiac Output) system decreasing by at least 30% from baseline. Measurable only in patients with PiCCO data available.	
End point type	Secondary
End point timeframe: From baseline at induction until end of PiCCO recording	

End point values	Safety Set Remimazolam	Safety Set Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14 ^[4]	3 ^[5]		
Units: Patients				
number (not applicable)				
Decrease by 30%	1	0		
No decrease by 30%	13	3		

Notes:

[4] - 14 patients with PiCCO data available

[5] - 3 patients with PiCCO data available

Statistical analyses

No statistical analyses for this end point

Secondary: Heart rate at induction below 50 bpm over at least 1 minute

End point title	Heart rate at induction below 50 bpm over at least 1 minute
End point description: Heart rate below 50 beats per minute (bpm) over at least 1 minute during induction. Calculated only for patients with PiCCO data recording available.	
End point type	Secondary
End point timeframe: During induction	

End point values	Safety Set Remimazolam	Safety Set Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15 ^[6]	3 ^[7]		
Units: Patients				
Heart rate below 50 bpm over 1 min or more	0	0		
Heart rate not below 50 bpm over 1 min or more	15	3		

Notes:

[6] - 15 patients with PiCCO data available

[7] - 3 patients with PiCCO data available

Statistical analyses

No statistical analyses for this end point

Secondary: Delirium

End point title	Delirium
End point description:	
Delirium reported as adverse event and/or as result of the Confusion Assessment Method - Intensive Care Unit (CAM-ICU) and/or a result of the Nursing Delirium Screening Scale (Nu-DESC)	
End point type	Secondary
End point timeframe:	
From start of study medication until discharge from hospital	

End point values	Safety Set Remimazolam	Safety Set Propofol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	18	5		
Units: Patients				
Delirium	6	0		
No delirium	12	5		

Statistical analyses

No statistical analyses for this end point

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 study medication

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Safety Set Remimazolam
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Reporting group description:

Remimazolam for sedation during induction, maintenance, and recovery, and for ICU sedation as needed

Reporting group title	Safety Set Propofol
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Reporting group description:

Propofol for induction, maintenance, and recovery, and during ICU sedation as needed.

Serious adverse events	Safety Set Remimazolam	Safety Set Propofol	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative renal failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			

subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety Set Remimazolam	Safety Set Propofol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 18 (94.44%)	4 / 5 (80.00%)	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Haemorrhage			
subjects affected / exposed	2 / 18 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)	2 / 5 (40.00%)	
occurrences (all)	1	2	
Hypertensive crisis			

subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Hypotension subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Chills subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Hangover subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Injection site haemorrhage subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Oedema subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Pyrexia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion subjects affected / exposed occurrences (all)	9 / 18 (50.00%) 9	2 / 5 (40.00%) 2	
Pneumothorax			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Pulmonary congestion subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Respiratory disorder subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Respiratory failure subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Delirium subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Hallucination subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Sleep disorder subjects affected / exposed occurrences (all)	8 / 18 (44.44%) 8	1 / 5 (20.00%) 1	
Investigations Blood phosphorus decreased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Body temperature increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Enterococcus test positive subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Inflammatory marker increased			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Urine output decreased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Injury, poisoning and procedural complications			
Anaemia postoperative subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Anaesthetic complication neurological subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Delayed recovery from anaesthesia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Procedural nausea subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 5 (40.00%) 2	
Procedural vomiting subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	2 / 5 (40.00%) 2	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	7 / 18 (38.89%) 7	2 / 5 (40.00%) 2	
Atrial flutter subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Atrial thrombosis subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Bradycardia			

subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Cardiac failure chronic subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Nervous system disorders Disturbance in attention subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Dizziness subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 5 (0.00%) 0	
Haemorrhagic anaemia subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Leukocytosis subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Nausea			

subjects affected / exposed occurrences (all)	6 / 18 (33.33%) 6	0 / 5 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3	0 / 5 (0.00%) 0	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 5 (20.00%) 1	
Incontinence subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Oliguria subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	1 / 5 (20.00%) 1	
Renal failure subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	1 / 5 (20.00%) 1	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Infections and infestations Pneumonia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 5 (0.00%) 0	
Metabolism and nutrition disorders Fluid retention			

subjects affected / exposed	2 / 18 (11.11%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Hyperkalaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
Hypocalcaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2015	1. Changes in the list of persons signing the study protocol and laboratories and institutions involved. 2. Definition of start of maintenance phase adapted for sites with no physical transfer of patients between start of study medication and start of surgical procedure. 3. For propofol, induction dose harmonized with approved label of marketed drug product and use via TCI added. 4. Recommended dosing of remimazolam from end of surgery onwards and for ICU sedation harmonized throughout study protocol. 5. Composition of remimazolam formulation in each vial corrected. 6. Opioid use via TCI introduced. 7. Rules on effective birth control modified. 8. Qualification necessary for investigators re-defined. 9. Start of recording for PiCCO® and Narcotrend® harmonized throughout study protocol. 10. Description of how to measure blood pressure and heart rate clarified. 11. Sequence of events during Recovery Phase clarified for Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) for patients on ICU. 12. List of study procedures during Follow-up Phase corrected and clarified. 13. Rules on reporting and follow-up of AEs corrected and clarified. 14. Description of pharmacokinetic sampling corrected. 15. Collection of American Society of Anesthesiologists physical status classification system (ASA classification) added. 16. Time period for patient enrollment and number of sites and countries updated. 17. List of abbreviations, definitions of terms, and protocol tables 3, 4, 5, and 6 adapted and harmonized with protocol text. 18. Protocol Appendix 11 (ASA classification) added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial faced recruitment challenges due to its complex design. Despite intensive efforts to enhance recruitment, the trial was difficult to implement. PAION discontinued the trial to avoid a long and expensive study with the existing design.

Notes: