Clinical trial results:
Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery

Summary

EudraCT number	2018-000174-29
Trial protocol	DE BE GB NL FR IT
Global end of trial date	02 April 2020

Results information

Result version number	v1 (current)
This version publication date	22 May 2022
First version publication date	22 May 2022

Trial information

Trial identification

Sponsor protocol code	CNS7056-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03661489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PAION UK Ltd.
Sponsor organisation address	Kew Road 5, Parkshot House, Unit 302, Richmond, United Kingdom, TW9 2 PR
Public contact	Clinical Trial Information, PAION UK Ltd., +49 2414453101, info@paion.com
Scientific contact	Clinical Trial Information, PAION UK Ltd., +49 2414453101, 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	05 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 April 2020
Global end of trial reached?	Yes
Global end of trial date	02 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a confirmatory trial to establish non-inferior efficacy and superior safety of remimazolam compared with propofol for induction and maintenance of general anaesthesia for the purpose of elective surgery in ASA class III/IV patients

Protection of trial subjects:

This trial was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines

Background therapy:

Elective surgical procedure

Evidence for comparator:

The comparator used was propofol which is the standard of care in intravenous general anaesthesia

Actual start date of recruitment	22 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Switzerland: 77
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Netherlands: 46
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Belgium: 52
Country: Number of subjects enrolled	Germany: 154
Worldwide total number of subjects	409
EEA total number of subjects	332

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)	118
From 65 to 84 years	275
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

ASA class III/IV patients undergoing elective surgery with the need for general anaesthesia. Further criteria for inclusion and exclusion were specified in the protocol.

Pre-assignment

Screening details:

After obtaining informed consent, patients were screened between Day -28 to Day -1 prior to the day of the elective surgery

Pre-assignment period milestones

Number of subjects started	409
Number of subjects completed	409

Period 1

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

Blinding implementation details:

Patients were not informed about their assignment to remimazolam or propofol. Investigators were informed about the assignment of each patient to either propofol or remimazolam. The first 2 patients of each trial centre were not assigned to remimazolam or propofol by chance/randomization, but by pre-defined sequence, i.e. 1st patient was assigned to propofol and the 2nd patient assigned to remimazolam. This allowed site teams to learn the study procedures prior to the first use of remimazolam.

Arms

Are arms mutually exclusive?	Yes
Arm title	Propofol

Arm description:

Total intravenous general anaesthesia induced and maintained with the combination of propofol and remifentanil

Arm type	Active comparator
Investigational medicinal product name	Propofol 2% liquid emulsion in 50 mL vials containing 1 g propofol
Investigational medicinal product code	N01AX10
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous administration. 30 mg/kg/h from t= 00 minutes until t = 03 minutes. 10 mg/kg/h from t = 03 minutes until t = 10 minutes. 0. 8 mg/kg/h from t = 10 minutes until t = 20 minutes. 6 mg/kg/h from t = 20 minutes onwards. After t = 20 minutes, titration according to each patient's individual needs was allowed in a range between 4 mg/kg/h an 10 mg/kg/h. Up to 3 boluses of 30 mg/kg/h within 60 minutes were allowed. If the Narcotrend index was below 27 under the lowest allowed dosage of remifentanil, it was allowed to stop the administration of propofol completely.

Arm title	Remimazolam

Arm description:

Total intravenous general anaesthesia induced and maintained with the combination of remimazolam and remifentanil.

Arm type	Experimental
Investigational medicinal product name	Remimazolam
Investigational medicinal product code	N05CD14
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous administration. 6.0 mg/min from t = 00 minutes until t = 03 minutes. 2.5 mg/min from t = 03 minutes until t = 10 minutes. 1.5 mg/min from t = 10 minutes until t = 20 minutes. After t = 20 minutes, titration according to each patient's individual needs was allowed in a range between 0.7 and 2.5 mg/min. Up to 3 bolues of 6 mg/min for 1 minute were allowed within 60 minutes.If the Narcotrend index was below 27 under the lowest allowed dosage of remifentanil, it was allowed to stop the administration of remimazolam completely. Remimazolam was dosed independent from body weight.

Number of subjects in period 1	Propofol	Remimazolam
Started	118	291
Completed	118	288
Not completed	0	3
Immediate re-operation required	-	1
OP cancelled after induction of anaesthesia	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Propofol
Reporting group description:	
Total intravenous general anaesthesia induced and maintained with the combination of propofol and remifentanil	
Reporting group title	Remimazolam
Reporting group description:	
Total intravenous general anaesthesia induced and maintained with the combination of remimazolam and remifentanil.	

Reporting group values	Propofol	Remimazolam	Total
Number of subjects	118	291	409
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	81	118
From 65-84 years	75	200	275
85 years and over	6	10	16
Age continuous			
Units: years			
arithmetic mean	68.13	68.63	
standard deviation	± 10.809	± 10.677	-
Gender categorical			
The gender was not specified for one patient			
Units: Subjects			
Female	34	82	116
Male	84	209	293
ASA class III/IV patients			
Units: Subjects			
ASA III	111	278	389
ASA IV	7	13	20

Subject analysis sets	
Subject analysis set title	Safety Set, Remimazolam, Final Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients at the final analysis who received any amount of remimazolam	
Subject analysis set title	Safety Set, Propofol, Final Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients at the final analysis who received any amount of propofol

Subject analysis set title	Full Analysis Set, Remimazolam, Interim Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients at the interim analysis who were administered remimazolam over 1 minute or longer

Subject analysis set title	Full Analysis Set, Propofol, Interim Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients at the interim analysis who were administered propofol over 1 minute or longer

Subject analysis set title	Per Protocol Set 1, Remimazolam, Interim Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All patients at the interim analysis who were administered remimazolam over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint

Subject analysis set title	Per Protocol Set 1, Propofol, Interim Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All patients at the interim analysis who were administered propofol over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint

Subject analysis set title	Full Analysis Set, Remimazolam, Final Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients at the final analysis who were administered remimazolam over 1 minute or longer

Subject analysis set title	Full Analysis Set, Propofol, Final Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

All patients at the final analysis analysis who were administered propofol over 1 minute or longer

Subject analysis set title	Per Protocol Set 1, Remimazolam, Final Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All patients at the final analysis who were administered remimazolam over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint

Subject analysis set title	Per Protocol Set 1, Propofol, Final Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All patients at the final analysis who were administered propofol over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint.

Subject analysis set title	Full Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set including both treatment groups

Reporting group values	Safety Set, Remimazolam, Final Analysis	Safety Set, Propofol, Final Analysis	Full Analysis Set, Remimazolam, Interim Analysis
Number of subjects	291	118	191
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0

Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	81	37	57
From 65-84 years	200	75	127
85 years and over	10	6	7
Age continuous			
Units: years			
arithmetic mean	68.63	68.13	67.90
standard deviation	± 10.677	± 10.809	± 11.551
Gender categorical			
The gender was not specified for one patient			
Units: Subjects			
Female	82	34	62
Male	209	83	129
ASA class III/IV patients			
Units: Subjects			
ASA III	278	111	180
ASA IV	13	7	11

Reporting group values	Full Analysis Set, Propofol, Interim Analysis	Per Protocol Set 1, Remimazolam, Interim Analysis	Per Protocol Set 1, Propofol, Interim Analysis
Number of subjects	63	165	60
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	46	20
From 65-84 years	38	114	36
85 years and over	4	5	4
Age continuous			
Units: years			
arithmetic mean	67.40		
standard deviation	± 10.495	±	±
Gender categorical			
The gender was not specified for one patient			
Units: Subjects			
Female	15		
Male	48		
ASA class III/IV patients			
Units: Subjects			
ASA III	59	154	56
ASA IV	4	11	4

Reporting group values	Full Analysis Set, Remimazolam, Final	Full Analysis Set, Propofol, Final	Per Protocol Set 1, Remimazolam, Final

	Analysis	Analysis	Analysis
Number of subjects	270	95	235
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	78	30	62
From 65-84 years	183	60	166
85 years and over	9	5	7
Age continuous Units: years			
arithmetic mean	68.32	68.28	69.08
standard deviation	± 10.833	± 10.208	± 10.115
Gender categorical			
The gender was not specified for one patient			
Units: Subjects			
Female	75	25	
Male	195	70	
ASA class III/IV patients Units: Subjects			
ASA III	258	89	
ASA IV	12	6	

Reporting group values	Per Protocol Set 1, Propofol, Final Analysis	Full Safety Set	
Number of subjects	92	409	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	118	
From 65-84 years	58	275	
85 years and over	5	16	
Age continuous Units: years			
arithmetic mean	68.22	68.49	
standard deviation	± 10.268	± 10.705	
Gender categorical			
The gender was not specified for one patient			
Units: Subjects			

Female		292	
Male		116	

ASA class III/IV patients Units: Subjects			
ASA III			
ASA IV			

End points

End points reporting groups

Reporting group title	Propofol
Reporting group description:	
Total intravenous general anaesthesia induced and maintained with the combination of propofol and remifentanil	
Reporting group title	Remimazolam
Reporting group description:	
Total intravenous general anaesthesia induced and maintained with the combination of remimazolam and remifentanil.	
Subject analysis set title	Safety Set, Remimazolam, Final Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients at the final analysis who received any amount of remimazolam	
Subject analysis set title	Safety Set, Propofol, Final Analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients at the final analysis who received any amount of propofol	
Subject analysis set title	Full Analysis Set, Remimazolam, Interim Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients at the interim analysis who were administered remimazolam over 1 minute or longer	
Subject analysis set title	Full Analysis Set, Propofol, Interim Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients at the interim analysis who were administered propofol over 1 minute or longer	
Subject analysis set title	Per Protocol Set 1, Remimazolam, Interim Analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients at the interim analysis who were administered remimazolam over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint	
Subject analysis set title	Per Protocol Set 1, Propofol, Interim Analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients at the interim analysis who were administered propofol over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint	
Subject analysis set title	Full Analysis Set, Remimazolam, Final Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients at the final analysis who were administered remimazolam over 1 minute or longer	
Subject analysis set title	Full Analysis Set, Propofol, Final Analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients at the final analysis analysis who were administered propofol over 1 minute or longer	
Subject analysis set title	Per Protocol Set 1, Remimazolam, Final Analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients at the final analysis who were administered remimazolam over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint	
Subject analysis set title	Per Protocol Set 1, Propofol, Final Analysis
Subject analysis set type	Per protocol

Subject analysis set description:

All patients at the final analysis who were administered propofol over 1 minute or longer and who had no major protocol deviations preventing the accurate evaluation of the primary endpoint.

Subject analysis set title	Full Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety Set including both treatment groups

Primary: The percentage (%) of time of NCI ≤60 during the maintenance phase of the general anaesthesia (GA)

End point title	The percentage (%) of time of NCI ≤60 during the maintenance phase of the general anaesthesia (GA)

End point description:

The primary efficacy endpoint (PEP) was the anaesthetic effect of remimazolam and propofol assessed as percent (%) of time of NCI ≤60 during the maintenance phase of general anaesthesia

End point type	Primary

End point timeframe:

During the maintenance phase of the general anaesthesia defined as the time between the first skin incision and the completion of the last skin suture

End point values	Per Protocol Set 1, Remimazolam, Interim Analysis	Per Protocol Set 1, Propofol, Interim Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	165	60		
Units: Percentage %				
arithmetic mean (standard deviation)	94.6 (± 19.34)	98.9 (± 5.15)		

Statistical analyses

Statistical analysis title	Test for non-inferiority

Statistical analysis description:

non-inferiority margin pre-specified as 10%, t-test

Comparison groups	Per Protocol Set 1, Remimazolam, Interim Analysis v Per Protocol Set 1, Propofol, Interim Analysis
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0003 [2]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	-4.24
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-7.48

Notes:

[1] - Primary confirmatory analysis per definition based on Per Protocol Set 1 at Interim Analysis with missing values over up to 300 seconds imputed by linear regression.
[2] - Non-inferiority of remimazolam to propofol in terms of percent of maintenance time (first skin incision to completion of last skin suture) with Narcotrend index ≤60 was proven.

Secondary: Critical decreases in mean arterial blood pressure (MAP) between start of trial drug and 15 minutes after the first skin incision, Interim Analysis

End point title	Critical decreases in mean arterial blood pressure (MAP) between start of trial drug and 15 minutes after the first skin incision, Interim Analysis

End point description:

Events were defined as: - MAP dropping below 65 mmHg for 1 minute duration - MAP decrease by more than 20% below the calculated (mean) baseline MAP for 1 minute - MAP decrease by more than 30% below the calculated (mean) baseline MAP for 1 minute - Norepinephrine bolues (0.01 mg) or each time interval of 2 minutes of infusion of norepinephrine to maintain MAP equal to or above 65 mmHg. Due to the interdependency of event types 2 and 3 (decrease by 20% and decrease by 30%) and due to progress in the general scientific debate after finalisation of the trial design, a common factor analysis was performed to elaborate on the statistically and clinically meaningful differences between the treatment groups.

End point type	Secondary

End point timeframe:

Start of trial drug (remimazolam or propofol) until 15 minutes after the first skin incision

End point values	Full Analysis Set, Remimazolam, Interim Analysis	Full Analysis Set, Propofol, Interim Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	191	63		
Units: total number of events per patient				
arithmetic mean (standard deviation)	-0.06 (± 0.580)	0.17 (± 0.692)		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test

Statistical analysis description:

The results were found to not follow normal distribution.

Comparison groups	Full Analysis Set, Remimazolam, Interim Analysis v Full Analysis Set, Propofol, Interim Analysis
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0247 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Group-sequential design with 1 interim analysis. Alpha split with prespecified type 1 error rate of 0.0193 at interim analysis and 0.0307 at final analysis.
[4] - P-value above pre-specified alpha error at interim analysis of 0.0193

Secondary: Critical decreases in mean arterial blood pressure (MAP) between start of trial drug and 15 minutes after the first skin incision, Final Analysis

End point title	Critical decreases in mean arterial blood pressure (MAP) between start of trial drug and 15 minutes after the first skin incision, Final Analysis

End point description:

Critical decreases in mean arterial blood pressure (MAP) between start of trial drug (remimazolam or propofol) and 15 minutes after the first skin incision, Final Analysis

End point type	Secondary

End point timeframe:

Between start of trial drug (remimazolam or propofol) and 15 minutes after the first skin incision

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	270	95		
Units: Events				
arithmetic mean (standard deviation)	-0.04 (± 0.529)	0.13 (± 0.584)		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test

Statistical analysis description:

Test for superiority

Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0151 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Actual p-value below pre-specified alpha error of 0.0307

Other pre-specified: Percentage of time of NCI ≤60 and ≥27 during the maintenance phase

End point title	Percentage of time of NCI ≤60 and ≥27 during the maintenance phase

End point description:

Missing Narcotrend Index values up to 300 seconds were imputed by linear regression

End point type	Other pre-specified

End point timeframe:

From first skin incision to last skin suture

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis	Per Protocol Set 1, Remimazolam, Final Analysis	Per Protocol Set 1, Propofol, Final Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	270	95	235	92
Units: percent				
arithmetic mean (standard deviation)	68.4 (± 31.16)	78.0 (± 27.88)	70.1 (± 30.58)	78.1 (± 28.22)

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Propofol, Final Analysis v Full Analysis Set, Remimazolam, Final Analysis
Number of subjects included in analysis	365
Analysis specification	Post-hoc
Analysis type	other[6]
P-value	= 0.0082 [7]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-9.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.7
upper limit	-2.51

Notes:

[6] - Test for difference in means

[7] - The mean time with NCI less than or equal to 60 and greater than or equal to 27 differed between the treatment groups.

Other pre-specified: Percentage of time of NCI <27 during maintenance

End point title	Percentage of time of NCI <27 during maintenance

End point description:

NCI <27 was regarded as generally not desirable, as indicating anaesthesia being too deep, though standards vary between site.

End point type	Other pre-specified

End point timeframe:

Between first skin incision and last skin suture

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis	Per Protocol Set 1, Remimazolam, Final Analysis	Per Protocol Set 1, Propofol, Final Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	270	95	235	92
Units: percent				
arithmetic mean (standard deviation)	24.4 (± 29.28)	21.1 (± 28.12)	25.3 (± 29.52)	21.0 (± 28.46)

Statistical analyses

Statistical analysis title	Test for difference
Statistical analysis description:	
Test for difference in means between both treatment groups	
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	365
Analysis specification	Post-hoc
Analysis type	other[8]
P-value	= 0.3331 [9]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.45
upper limit	10.15

Notes:

[8] - Test for difference in means between both treatment groups

[9] - The means of the treatment groups did not differ from each other.

Other pre-specified: Percentage of patients with NCI ≤60 and ≥27 during 90% of maintenance

End point title	Percentage of patients with NCI ≤60 and ≥27 during 90% of maintenance
End point description:	
End point type	Other pre-specified
End point timeframe:	
Between first skin incision and last skin suture	

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis	Per Protocol Set 1, Remimazolam, Final Analysis	Per Protocol Set 1, Propofol, Final Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	270	95	235	92
Units: Patients	94	54	88	53

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	365
Analysis specification	Post-hoc
Analysis type	other[10]
P-value	= 0.0002 [11]
Method	Chi-squared
Parameter estimate	percentage

Notes:

[10] - Test for difference

[11] - The percentage of patients with NCI ≤ 60 and ≥27 during at least 90% of the maintenance time differed between the treatment groups.

Other pre-specified: Percentage of patients who were administered rescue sedative medication

End point title	Percentage of patients who were administered rescue sedative medication

End point description:

End point type	Other pre-specified

End point timeframe:

Between first skin incision and last skin suture

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis	Per Protocol Set 1, Remimazolam, Final Analysis	Per Protocol Set 1, Propofol, Final Analysis
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	270	95	235	92
Units: Patients	27	1	11	1

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis

Number of subjects included in analysis	365
Analysis specification	Post-hoc
Analysis type	other[12]
P-value	= 0.0009 [13]
Method	Chi-squared
Parameter estimate	percentage

Notes:

[12] - Test for difference

[13] - The treatment groups differed from each other in terms of percentage of patients who received rescue medication during the maintenance period.

Other pre-specified: Intra-operative explicit awareness

End point title	Intra-operative explicit awareness

End point description:

Occurrence of intra-operative awareness emerging from answers to the Brice questionnaire

End point type	Other pre-specified

End point timeframe:

Start of trial drug (remimazolam or propofol) until last skin suture

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	270	95		
Units: Patients	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to loss of consciousness

End point title	Time to loss of consciousness

End point description:

Time from start of trial drug (remimazolam or propofol) until loss of consciousness, defined as Modified Observer Assessment and Sedation Scale = 0

End point type	Other pre-specified

End point timeframe:

Start of trial drug (remimazolam or propofol) until first skin suture

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	268	95		
Units: minutes				
median (confidence interval 95%)	2.5 (2.5 to 2.8)	3.0 (3.0 to 3.2)		

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	363
Analysis specification	Post-hoc
Analysis type	other[14]
P-value	= 0.3523 [15]
Method	Logrank
Parameter estimate	Median

Notes:

[14] - Test for difference in median between treatment groups

[15] - The median time from start of the trial drug (remimazolam or propofol) to loss of consciousness did not differ between the treatment groups.

Other pre-specified: Time to loss of palpebral reflex

End point title	Time to loss of palpebral reflex

End point description:

Median time from start of trial drug (remimazolam or propofol) to loss of palpebral reflex

End point type	Other pre-specified

End point timeframe:

Start of trial drug (remimazolam or propofol) until first skin incision

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	269	95		
Units: minutes				
median (confidence interval 95%)	2.8 (2.7 to 3.0)	3.1 (3.0 to 3.5)		

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis

Number of subjects included in analysis	364
Analysis specification	Post-hoc
Analysis type	other[16]
P-value	= 0.1324 [17]
Method	Logrank
Parameter estimate	Median

Notes:

[16] - Test for difference in median between treatment groups

[17] - The median time from start of the trial drug (remimazolam or propofol) to loss of palpebral reflex did not differ between the treatment groups.

Other pre-specified: Time to first Narcotrend Index 60 or less

End point title	Time to first Narcotrend Index 60 or less

End point description:

Time from start of trial drug (remimazolam or propofol) to first Narcotrend index ≤60

End point type	Other pre-specified

End point timeframe:

Start of trial drug (remimazolam or propofol) to first skin incision

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	269	95		
Units: minutes				
median (confidence interval 95%)	3.2 (2.9 to 3.5)	3.3 (3.1 to 3.5)		

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	364
Analysis specification	Post-hoc
Analysis type	other[18]
P-value	= 0.0553 [19]
Method	Logrank
Parameter estimate	Median

Notes:

[18] - Test for difference in median between treatment groups

[19] - The median time from start of the trial drug (remimazolam or propofol) to the first Narcotrend Index ≤60 did not differ between the treatment groups.

Other pre-specified: Time to extubation

End point title	Time to extubation

End point description:

Time from stop of trial drug (remimazolam or propofol) to successful, completed extubation

End point type	Other pre-specified

End point timeframe:

From stop of trial drug (remimazolam or propofol) to end of follow-up

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	263[20]	95		
Units: minutes				
median (confidence interval 95%)	12 (11 to 13)	11 (10 to 12)		

Notes:

[20] - Some subjects did not qualify due to use other sedatives/anaesthetics during the time of interest

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	358
Analysis specification	Post-hoc
Analysis type	other[21]
P-value	= 0.0076 [22]
Method	Logrank
Parameter estimate	median

Notes:

[21] - Test for difference in median between treatment groups

[22] - The median time from stop of the trial drug (remimazolam or propofol) differed between the treatment groups. The median time from stop of trial drug to end of extubation was 12 minutes in the Remimazolam group and 11 minutes in the Propofol group.

Other pre-specified: Time to response to verbal command

End point title	Time to response to verbal command

End point description:

Time from stop of administration of the trial drug (remimazolam or propofol) to response to verbal command, Modified Observer Assessment of Alertness and Sedation Scale (MOAA/S) ≥ 4

End point type	Other pre-specified

End point timeframe:

From stop of the trial drug (remimazolam or propofol) to end of follow-up

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	257	95		
Units: minutes				
median (confidence interval 95%)	15 (13 to 17)	12 (10 to 13)		

Statistical analyses

Statistical analysis title	Test for difference
Comparison groups	Full Analysis Set, Propofol, Final Analysis v Full Analysis Set, Remimazolam, Final Analysis
Number of subjects included in analysis	352
Analysis specification	Post-hoc
Analysis type	other[23]
P-value	< 0.0001 [24]
Method	Logrank
Parameter estimate	Median

Notes:

[23] - Test for difference in median between treatment groups

[24] - The median time from stop of trial drug (remimazolam or propofol) to response to verbal command differed between the treatment groups.

Other pre-specified: Time to orientation

End point title	Time to orientation

End point description:

Time to orientation to time, place, person and situation

End point type	Other pre-specified

End point timeframe:

From stop of trial drug (remimazolam or propofol) until end of follow-up

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	262	95		
Units: minutes				
median (confidence interval 95%)	54 (47 to 61)	30 (27 to 33)		

Statistical analyses

Statistical analysis title	Test for difference

Statistical analysis description:

Test for difference in median between treatment groups

Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis

Number of subjects included in analysis	357
Analysis specification	Post-hoc
Analysis type	other[25]
P-value	< 0.0001 [26]
Method	Logrank
Parameter estimate	Median

Notes:

[25] - Test for difference in median between treatment groups

[26] - The median time from stop of trial drug (remimazolam or propofol) to orientation differed between the treatment groups.

Other pre-specified: Time to Modified Aldrete Score ≥9

End point title	Time to Modified Aldrete Score ≥9

End point description:

Time from stop of the trial drug (remimazolam or propofol) until the Modified Aldrete Score was 9 or more for the first time

End point type	Other pre-specified

End point timeframe:

Time from stop of trial drug (remimazolam or propofol) until end of follow-up

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	260	95		
Units: minutes				
median (confidence interval 95%)	53 (44 to 58)	37 (28 to 45)		

Statistical analyses

Statistical analysis title	Test for difference

Statistical analysis description:

Test for difference in median between the treatment groups

Comparison groups	Full Analysis Set, Remimazolam, Final Analysis v Full Analysis Set, Propofol, Final Analysis
Number of subjects included in analysis	355
Analysis specification	Post-hoc
Analysis type	other[27]
P-value	= 0.1205 [28]
Method	Logrank
Parameter estimate	Median

Notes:

[27] - Test for difference in median between treatment groups

[28] - The median time from stop of the trial drug (remimazolam or propofol) to Modified Aldrete Score ≥9 did not differ between the treatment groups.

Other pre-specified: Investigator's overall satisfaction with trial drug

End point title	Investigator's overall satisfaction with trial drug

End point description:

Investigator's overall satisfaction with trial drug (remimazolam or propofol) captured as score between 1 and 10 with 1 representing very dissatisfied and 10 representing very satisfied. Success was assumed if the score was 8, 9 or 10.

End point type	Other pre-specified

End point timeframe:

not applicable

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	270	95		
Units: Score 1 to 10				
Success	149	52		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Bradycardia events during induction

End point title	Bradycardia events during induction

End point description:

Events of bradycardia were defined as either heart rate below 45 beats per minute over at at least 1 minute, heart rate decrease by >20% below calculated mean baseline heart rate for at least 1 minute, heart rate decrease by >30% below calculated mean baseline heart rate for at least 1 minute, or injections of atropine or glycopyrrolate.

End point type	Other pre-specified

End point timeframe:

Between start of trial drug (remimazolam or propofol) and 15 minutes after the first skin incision

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	270	95		
Units: mean number of events				
arithmetic mean (standard deviation)	26.00 (± 38.947)	45.95 (± 46.587)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pain on injection

End point title	Pain on injection

End point description:

Pain on injection was measured using a score from 0 to 10 with 0 representing no pain and 10 representing most severe pain imaginable. Pain was regarded as remarkable when the score was 6 or more.

End point type	Other pre-specified

End point timeframe:

Score were to be provided by patient on Day 1, i.e. on the day of the general anaesthesia, after recovery

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	291	118		
Units: Score 0 to 10				
Remarkable pain, score 6 or more	1	30		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Delirium assessed by Nu-DESC

End point title	Delirium assessed by Nu-DESC

End point description:

A Nu-DESC score of 2 or more indicates potential delirium

End point type	Other pre-specified

End point timeframe:

Nu-DESC total score was to be captured on Day 1, during the recovery period of the general anaestheis

End point values	Full Analysis Set, Remimazolam, Final Analysis	Full Analysis Set, Propofol, Final Analysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	291	118		
Units: Patients with score 2 or more	56	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of Screening (Day 28 before the start of trial drug administration) until end of Follow-up (Day 2)

Adverse event reporting additional description:

Any adverse event reported spontaneously by the patient, discovered on physical examination or other assessment procedures (e.g. laboratory testing or scales such as the Nu-DESC) or uncovered as a result of general questioning by the trial staff is recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Safety Analysis Set, Remimazolam

Reporting group description:

All patients who were exposed to any amount of trial drug (remimazolam or propofol), regardless whether assignment to remimazolam or propofol was done by randomization or by pre-defined treatment assignment (first 2 patients of each trial centre, first patient was always assigned to propofol, second patients was always assigned to remimazolam).

Reporting group title	Safety Analysis Set, Propofol

Reporting group description: -

Serious adverse events	Safety Analysis Set, Remimazolam	Safety Analysis Set, Propofol	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 291 (12.37%)	18 / 118 (15.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic cancer metastatic			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 291 (0.34%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 291 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug effect prolonged			
subjects affected / exposed	3 / 291 (1.03%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 291 (0.34%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 291 (0.69%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic artery flow decreased			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Postoperative delirium			

subjects affected / exposed	6 / 291 (2.06%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	6 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site occlusion			
subjects affected / exposed	2 / 291 (0.69%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypertension			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplegia syndrome			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed recovery from anaesthesia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural hypotension			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	3 / 291 (1.03%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 291 (0.69%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anticholinergic syndrome			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Thrombocytopenia			
subjects affected / exposed	3 / 291 (1.03%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 291 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 291 (0.69%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 291 (0.34%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			

subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Peritonitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 291 (2.06%)	4 / 118 (3.39%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 291 (0.00%)	2 / 118 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Analysis Set, Remimazolam	Safety Analysis Set, Propofol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	270 / 291 (92.78%)	114 / 118 (96.61%)	
Investigations			
Oxygen saturation decreased	Additional description: No results available yet		
subjects affected / exposed	28 / 291 (9.62%)	14 / 118 (11.86%)	
occurrences (all)	28	14	
Blood pressure decreased			
subjects affected / exposed	35 / 291 (12.03%)	13 / 118 (11.02%)	
occurrences (all)	296	117	
Mean arterial pressure decreased			

subjects affected / exposed	21 / 291 (7.22%)	7 / 118 (5.93%)	
occurrences (all)	21	7	
Injury, poisoning and procedural complications			
Procedural hypotension			
subjects affected / exposed	22 / 291 (7.56%)	11 / 118 (9.32%)	
occurrences (all)	23	11	
Procedural pain			
subjects affected / exposed	21 / 291 (7.22%)	11 / 118 (9.32%)	
occurrences (all)	22	11	
Procedural nausea			
subjects affected / exposed	20 / 291 (6.87%)	8 / 118 (6.78%)	
occurrences (all)	20	9	
Vascular disorders			
Hypotension			
subjects affected / exposed	156 / 291 (53.61%)	75 / 118 (63.56%)	
occurrences (all)	259	159	
Hypertension			
subjects affected / exposed	24 / 291 (8.25%)	5 / 118 (4.24%)	
occurrences (all)	24	6	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	52 / 291 (17.87%)	33 / 118 (27.97%)	
occurrences (all)	63	36	
General disorders and administration site conditions			
Drug effect prolonged			
subjects affected / exposed	21 / 291 (7.22%)	0 / 118 (0.00%)	
occurrences (all)	21	0	
Pain			
subjects affected / exposed	16 / 291 (5.50%)	5 / 118 (4.24%)	
occurrences (all)	17	5	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	26 / 291 (8.93%)	12 / 118 (10.17%)	
occurrences (all)	26	12	
Vomiting			

subjects affected / exposed	15 / 291 (5.15%)	4 / 118 (3.39%)	
occurrences (all)	16	4	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	21 / 291 (7.22%)	14 / 118 (11.86%)	
occurrences (all)	21	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2018	Clinical trial amendment 1 included the following specific changes: - Addition of atropine for treatment of bradycardia - Replacement of the 3-minute diagnostic interview for Confusion Assessment Method (3D CAM) by the Nursing Delirium Screening Scale (NuDESC) for the assessment of delirium - Addition of contraceptive requirements as per Clinical Trial Facilitation Group - Change of epidural test dose volume - Addition of prone position to Exclusion Criteria - Screening lab samples must have been taken no more than 7 days before start of trial drug (remimazolam or propofol) - Definition of a non-interventional trial and specifics on previous exposure to drugs under investigation - Dose range of remifentanil infusion widened - Norepinephrine bolus dosing regime clarified - Recommendation on goal-directed therapy altered - Remifentanil allowed for post-operative analgesia - Adverse reaction tables added for remimazolam and propofol - Rationale for body weight independent dosing added (remimazolam only) - Detail on rescue medication use updated - A section on remimazolam and propofol contraindications added - Detail on the method of administration of remimazolam added - 20 minutes post-operative remimazolam: an exception to the rule added (i.e. stopping remimazolam to allow for continued use during transfer to post anaesthesia care unit [PACU] if required, for 20 minutes after last skin suture) - Laboratory samples: modified for clarity - Safety reporting: definitions updated - Co-administration of ringer's lactate and remimazolam not allowed - Flowchart updates and corrections included - Troponin added to the set of lab parameters
04 December 2018	- Allergy to lactose of bovine origin was added to the exclusion criteria and contraindications - The NCI corridor to be maintained after reaching an NCI of 60 or less for the first time was changed from between 40 and 60 to between 27 and 60. - A remark was added about the clinical judgement and clinical signs of appropriateness of depth of anaesthesia being relevant in addition to the adherence to the NCI corridor - Instructions on titration of the trial drug (remimazolam or propofol) were amended to avoid changes in dosing that were not necessary. - The dosing schedule for remifentanil was modified from '0.2 ug/kg/min during induction. During maintenance, 0.2 to 0.5 ug/kg/min, for the first 15 minutes after the first skin incision, afterwards 0.05 to 0.5 ug/kg/min' to '0.2 ug/kg/min until intubation. 0.1 to 0.2 ug/kg/min from intubation until 15 minutes after the first skin incision. Afterwards 0.05 to 0.5 ug/kg/min.
24 May 2019	- The end of the Screening Phase was changed from Day-1 to Day 1 prior to arrival at the OR suite. - The Modified Aldrete Score indicating awakening was changed from 10 to 9 or more. - The exclusion criterion regarding drugs that were depressant to the central nervous system was amended to exclude patients with regular use of these drugs.

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/22190555

http://www.ncbi.nlm.nih.gov/pubmed/22253270