



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 remifentanyl

| | |
|--|--|
| 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 and 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 remifentanyl, 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 remifentanyl.

| | |
|--|----------------------------------|
| 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 boluses 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 remifentanyl, 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 remifentanyl | |
| Reporting group title | Remimazolam |
| Reporting group description: | |
| Total intravenous general anaesthesia induced and maintained with the combination of remimazolam and remifentanyl. | |

| 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 remifentanyl | |
| Reporting group title | Remimazolam |
| Reporting group description: Total intravenous general anaesthesia induced and maintained with the combination of remimazolam and remifentanyl. | |
| 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 boluses (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 (\pm 0.580) | 0.17 (\pm 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 (\pm 0.529) | 0.13 (\pm 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 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 occurrences (all) | 21 / 291 (7.22%) 21 | 7 / 118 (5.93%) 7 | |
| Injury, poisoning and procedural complications | | | |
| Procedural hypotension subjects affected / exposed occurrences (all) | 22 / 291 (7.56%) 23 | 11 / 118 (9.32%) 11 | |
| Procedural pain subjects affected / exposed occurrences (all) | 21 / 291 (7.22%) 22 | 11 / 118 (9.32%) 11 | |
| Procedural nausea subjects affected / exposed occurrences (all) | 20 / 291 (6.87%) 20 | 8 / 118 (6.78%) 9 | |
| Vascular disorders | | | |
| Hypotension subjects affected / exposed occurrences (all) | 156 / 291 (53.61%) 259 | 75 / 118 (63.56%) 159 | |
| Hypertension subjects affected / exposed occurrences (all) | 24 / 291 (8.25%) 24 | 5 / 118 (4.24%) 6 | |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 52 / 291 (17.87%) 63 | 33 / 118 (27.97%) 36 | |
| General disorders and administration site conditions | | | |
| Drug effect prolonged subjects affected / exposed occurrences (all) | 21 / 291 (7.22%) 21 | 0 / 118 (0.00%) 0 | |
| Pain subjects affected / exposed occurrences (all) | 16 / 291 (5.50%) 17 | 5 / 118 (4.24%) 5 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 26 / 291 (8.93%) 26 | 12 / 118 (10.17%) 12 | |
| Vomiting | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 06 July 2018 | <p>Clinical trial amendment 1 included the following specific changes:</p> <ul style="list-style-type: none">- 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 remifentanyl infusion widened- Norepinephrine bolus dosing regime clarified- Recommendation on goal-directed therapy altered- Remifentanyl 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 | <ul style="list-style-type: none">- 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 remifentanyl 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 | <ul style="list-style-type: none">- 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>