



Clinical trial results: Lormetazepam versus Midazolam used as sedatives for critically ill patients.

Summary

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|--------------------------|----------------|
| EudraCT number | 2012-000188-25 |
| Trial protocol | DE |
| Global end of trial date | 12 March 2020 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 28 September 2022 |
| First version publication date | 21 August 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set correction of a transmission error: Serious adverse event Urinary stasis grade 2 was not related to the study drug "midazolam" |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | LoveMi |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02022592 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Charité - Universitätsmedizin Berlin |
| Sponsor organisation address | Augustenburger Platz 1, Berlin, Germany, 13353 |
| Public contact | Univ.-Prof. Dr. C. Spies, Charité - Universitätsmedizin Berlin, +49 30450551102, claudia.spies@charite.de |
| Scientific contact | Univ.-Prof. Dr. C. Spies, Charité - Universitätsmedizin Berlin, +49 30450551 102, claudia.spies@charite.de |

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 | 02 June 2022 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

"Controllability of sedation"; this is defined as the percentage share of measures where the actual depth of sedation (measured with the Richmond Agitation and Sedation Scale) (RASS)) matches the target depths of sedation. The individual sedation target is defined by the attending physician.

Protection of trial subjects:

The study was conducted at the University Hospital wards. Incidence of adverse events which start after the application of the study drug were evaluated for five days after last last dose.

Background therapy:

Surgical and intensive care unit patients received standard of care in the university hospital

Evidence for comparator:

Every patient enrolled in the study was in need of sedation, thus a placebo could not be considered as a control and an active comparator was needed. Intravenous midazolam is the standard treatment for longer-term sedation in intensive-care unit patients. It is licensed in this population, regarded as standard of care, and recommended by treatment guidelines.

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|---|---------------------|
| Actual start date of recruitment | 17 July 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Scientific research |
| Long term follow-up duration | 3 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 78 |
| Worldwide total number of subjects | 78 |
| EEA total number of subjects | 78 |

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) | 34 |
| From 65 to 84 years | 44 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study group: 17.07.2014 - 11.12.2019 (Last study patient in)

Pre-assignment

Screening details:

n= 3432 patients were screened,

n= 3348 screening failure (1. n= 44 refused participation; 2. n= 3232 did not meet inclusion criteria, 3. n= 72 other)

n= 84 were included n=8 patients drop-out criteria occurred after inclusion, reasons: 1. n=2 refused study participation but received study drug; 2. n=5 no indication, 3. n=1 died

Period 1

| | |
|------------------------------|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

All role members were unblinded after database closure.

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Lormetazepam |

Arm description:

SEDALAM® 2 mg/10 ml, Lormetazepam® glas ampoules with 10 ml sterile solution, EV substance code: SUB08588MIG; ATC Code N05CD06, MA number: 74788.00.00, Concentration unit: 0.2mg/ml
Mode of administration: Intravenous use; Test product was a 50 ml syringe containing 10 mg Lormetazepam

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lormetazepam |
| Investigational medicinal product code | N05CD06 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

According to protocol v1.1:

Specify total dose: 14 d day

Dosis of bolus: Lormetazepam 1.25 ml (0.25 mg), continuous dose: 2.8 ml/h (0.56 mg/h)

According to protocol V1.2 (Amendment 02):

Specify total dose: 14 d day

Dosis of bolus: Lormetazepam 1.2 ml (2.4 mg), continuous dose: 2.8 ml/h (0.56 mg/h)

According to protocol V1.3 (Amendment 03):

Specify total dose: 2 d day

Dosis of bolus: Lormetazepam 1.2 ml (2.4 mg), continuous dose is calculated from the requirement of the individual dose finding phase lasting two hours.

| | |
|-----------|-----------|
| Arm title | Midazolam |
|-----------|-----------|

Arm description:

Midazolam 100 mg/50 ml; EV substance code: SUB08950MIG; ATC Code N05CD06, Concentration unit: 2mg/ml; Mode of administration: Intravenous use

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|-----------------------|
| Investigational medicinal product name | Midazolam |
| Investigational medicinal product code | N05CD08 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Infusion |

Dosage and administration details:

According to protocol v1.1 :

Midazolam ratiopharm; MA number 54705.01.00; specify total dose: 14 d day

Dosis of bolus: 1.25 ml (2.5 mg), continuous dose: 2.8 ml/h (0.56 mg/h)

According to protocol V1.2 (Amendment 02):

Midazolam hameln; MA number 47046.01.00; specify total dose: 14 d day

Dosis of bolus: midazolam hameln 1.2 ml (2.4 mg), continuous dose midazolam hameln: 2.8 ml/h (0.56 mg/h)

According to protocol V1.3 (Amendment 03):

Midazolam hameln; MA number 47046.01.00, specify total dose: 2 d day

Dosis of bolus: 1.2 ml (2.4 mg), continuous dose is calculated from the requirement of the individual dose finding phase lasting two hours.

| Number of subjects in period 1 | Lormetazepam | Midazolam |
|---------------------------------------|--------------|-----------|
| Started | 41 | 37 |
| Completed | 40 | 36 |
| Not completed | 1 | 1 |
| Consent withdrawn by subject | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | overall trial (overall period) |
|-----------------------|--------------------------------|

Reporting group description:

The intention-to-treat population includes 40 patients in the lormetazepam group and 36 patients in the midazolam group. 2 dropout-patients refused participation after study inclusion, but received study medication (1 dropout received lormetazepam and 1 dropout received midazolam).

| Reporting group values | overall trial (overall period) | Total | |
|---------------------------------------|--------------------------------|-------|--|
| Number of subjects | 78 | 78 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 34 | 34 | |
| From 65-84 years | 44 | 44 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 21 | 21 | |
| Male | 57 | 57 | |

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Lormetazepam |
|-----------------------|--------------|

Reporting group description:

SEDALAM® 2 mg/10 ml, Lormetazepam® glas ampoules with 10 ml sterile solution, EV substance code: SUB08588MIG; ATC Code N05CD06, MA number: 74788.00.00, Concentration unit: 0.2mg/ml
Mode of administration: Intravenous use; Test product was a 50 ml syringe containing 10 mg Lormetazepam

| | |
|-----------------------|-----------|
| Reporting group title | Midazolam |
|-----------------------|-----------|

Reporting group description:

Midazolam 100 mg/50 ml; EV substance code: SUB08950MIG; ATC Code N05CD06, Concentration unit: 2mg/ml; Mode of administration: Intravenous use

Primary: Controllability of sedation

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|-----------------|-----------------------------|
| End point title | Controllability of sedation |
|-----------------|-----------------------------|

End point description:

Controllability of sedation is defined as the percentage share of measures where the actual depth of sedation (measured with the Richmond Agitation and Sedation Scale) (RASS)) matches the target depths of sedation. The individual sedation target is defined by the attending physician. It will be measured during administration of study drug until 2 hours after its termination. The study drug was administered in patients with the indication for sedation at the beginning of a Richmond Agitation-Sedation Scale (RASS) difference +/-1.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

The study drug was administered in patients at a maximum of 14 days (protocol 1.1 and 1.2)/48 hours (protocol 1.3, 1.4, 1.5).

| End point values | Lormetazepam | Midazolam | | |
|---------------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 40 | 36 | | |
| Units: Decimal number | | | | |
| median (inter-quartile range (Q1-Q3)) | 0.5 (0.34 to 0.63) | 0.42 (0.25 to 0.59) | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Primary endpoint |
| Comparison groups | Lormetazepam v Midazolam |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1524 |
| Method | Wilcoxon (Mann-Whitney) |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients were screened for adverse events within five days after the end of the study treatment.

Adverse event reporting additional description:

Adverse events had to be documented and reported in the safety analysis set (N=78) including two drop-out patients, who withdrew study participation after joining the study and who nevertheless received study medication.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

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|--------------------|----|
| Dictionary version | 25 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Lormetazepam |
|-----------------------|--------------|

Reporting group description:

40 study patients and 1 Drop-Out who received Lormetazepam. Mortality was evaluated until study day 100.

| | |
|-----------------------|-----------|
| Reporting group title | Midazolam |
|-----------------------|-----------|

Reporting group description:

36 study patients and 1 Drop-Out who received midazolam. Mortality was documented until study day 100.

| Serious adverse events | Lormetazepam | Midazolam | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 41 (34.15%) | 10 / 37 (27.03%) | |
| number of deaths (all causes) | 9 | 3 | |
| number of deaths resulting from adverse events | 4 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Breathing depression | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drowsiness and prolonged sedation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Administration of expired study medication | | | |

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|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon perforation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dislocation of the pacemaker | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Acute bleeding with hemorrhagic shock | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hemorrhagic shock | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Circulatory failure | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac disorders | | | |
| Tachyarrhythmia absoluta | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 3 / 37 (8.11%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Hemodynamic relevant bradycard atrial fibrillation | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoidal bleeding | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Worsening of anasarca | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| On spec. hypersensitivity to Gelafundin | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusions | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue emphysema | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Urinary stasis grade 2 | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle weakness | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 2 / 37 (5.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |

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

| Non-serious adverse events | Lormetazepam | Midazolam | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 41 (100.00%) | 37 / 37 (100.00%) | |
| Investigations | | | |
| Rise in the serum alanine aminotransferase | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 2 / 37 (5.41%) | |
| occurrences (all) | 3 | 2 | |
| Rise in the alkaline phosphatase | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 0 / 37 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rise in the gamma-glutamyltransferase | | | |
| subjects affected / exposed | 11 / 41 (26.83%) | 9 / 37 (24.32%) | |
| occurrences (all) | 11 | 9 | |
| Rise in the C-reactive protein | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 4 / 37 (10.81%) | |
| occurrences (all) | 7 | 4 | |
| Rise in the aspartate transaminase | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 41 (4.88%) | 6 / 37 (16.22%) | |
| occurrences (all) | 2 | 6 | |
| Rise in the urea | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 1 / 37 (2.70%) | |
| occurrences (all) | 3 | 1 | |
| Rise in the creatine Kinase MB Isoenzyme (CK-MB) | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 3 / 37 (8.11%) | |
| occurrences (all) | 1 | 3 | |
| Rise in the creatinin kinase | | | |
| subjects affected / exposed | 7 / 41 (17.07%) | 8 / 37 (21.62%) | |
| occurrences (all) | 7 | 8 | |
| Rise in the lactate | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 3 / 37 (8.11%) | |
| occurrences (all) | 2 | 3 | |
| Rise in the myoglobin | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Neutrophilia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 0 / 37 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Rise in the activated partial thromboplastin time | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Rise in the transaminases | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 1 / 37 (2.70%) | |
| occurrences (all) | 5 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Inadequate awakening | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Prolonged sedation | | | |
| subjects affected / exposed | 5 / 41 (12.20%) | 4 / 37 (10.81%) | |
| occurrences (all) | 5 | 4 | |
| Cardiac disorders | | | |

| | | | |
|--|------------------------|----------------------|--|
| Pericardial effusion subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 2 / 37 (5.41%) 2 | |
| General disorders and administration site conditions | | | |
| Edema subjects affected / exposed occurrences (all) | 11 / 41 (26.83%) 11 | 8 / 37 (21.62%) 8 | |
| Pain subjects affected / exposed occurrences (all) | 12 / 41 (29.27%) 12 | 9 / 37 (24.32%) 9 | |
| Shivering subjects affected / exposed occurrences (all) | 5 / 41 (12.20%) 5 | 4 / 37 (10.81%) 4 | |
| Heavy sweating subjects affected / exposed occurrences (all) | 0 / 41 (0.00%) 0 | 3 / 37 (8.11%) 3 | |
| Fever subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | 2 / 37 (5.41%) 2 | |
| Blood and lymphatic system disorders | | | |
| Anemia subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 3 / 37 (8.11%) 3 | |
| Gastrointestinal disorders | | | |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 37 (2.70%) 1 | |
| Obstipation subjects affected / exposed occurrences (all) | 4 / 41 (9.76%) 4 | 1 / 37 (2.70%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 5 / 37 (13.51%) 5 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 19 / 41 (46.34%) 19 | 9 / 37 (24.32%) 9 | |
| Pulmonary congestion subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 37 (2.70%) 1 | |
| Heavy secretion subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 1 / 37 (2.70%) 1 | |
| Hyperventilation subjects affected / exposed occurrences (all) | 1 / 41 (2.44%) 1 | 2 / 37 (5.41%) 2 | |
| Hepatobiliary disorders Hyperbilirubinemia subjects affected / exposed occurrences (all) | 7 / 41 (17.07%) 7 | 3 / 37 (8.11%) 3 | |
| Psychiatric disorders Subsyndromal delirium subjects affected / exposed occurrences (all) | 30 / 41 (73.17%) 30 | 22 / 37 (59.46%) 22 | |
| Anxiety subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 2 / 37 (5.41%) 2 | |
| Hallucinations subjects affected / exposed occurrences (all) | 2 / 41 (4.88%) 2 | 3 / 37 (8.11%) 3 | |
| Agitation subjects affected / exposed occurrences (all) | 8 / 41 (19.51%) 8 | 8 / 37 (21.62%) 8 | |
| Renal and urinary disorders Oliguria subjects affected / exposed occurrences (all) | 3 / 41 (7.32%) 3 | 1 / 37 (2.70%) 1 | |
| Polyuria subjects affected / exposed occurrences (all) | 6 / 41 (14.63%) 6 | 2 / 37 (5.41%) 2 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Hypophosphatemia | | | |
| subjects affected / exposed | 4 / 41 (9.76%) | 5 / 37 (13.51%) | |
| occurrences (all) | 4 | 5 | |
| Hypovolemia | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 29 November 2013 | 29.11.2013 Amendment 01: changes of the protocol 1.0 to 1.1 within the ethical applications, submitted to the local authority again as substantial Amendment 01 |
| 18 June 2015 | Amendment 02: Substantial Amendment changes of the protocol 1.1 to 1.2: Registration of Dr. med. Björn Weiß as representative of Professor Spies; the additional inclusion of surgical consenting patients; updated Summary of product characteristics (SMPC) for Sedalam (03/2014) and Midazolam – hameln (02/2014) instead of midazolam-ratiopharm, which will not be produced anymore. |
| 13 January 2017 | Amendment 03 Substantial Amendment changes of the protocol 1.2 to 1.3 The registration of Dr. med. Tim-Philipp Simon as representative of Univ.- Prof. Marx in the trial center Aachen and a new trial center UKGM Gießen; the premature end of the intervention phase after 3 days, a new titration scheme, a duration for the safety documentation adapted to the shortened intervention phase, a new exclusion criterion "diagnosed intolerance to propofol/propofol infusion syndrome in the medical history" and specification of the exclusion criterion "known pregnancy or positive pregnancy test (detection of β -HCG in the urine or determination of β -HCG in the serum (the determination of β -HCG in the serum must be carried out in anuric patients))" a new secondary end point "pain threshold measurement", updated Summary of product characteristics (SMPC) for Sedalam (04/2016), and adjusted trial schedule (planned end of the clinical trial at 03/2020). |
| 08 September 2017 | Amendment 04 Substantial Amendment changes of the protocol 1.3 to 1.4 The changes concern the registration of a new representative of the principle investigator (Ms. Simone Lindau) at the trial site Frankfurt. Furthermore, the schematic representation of the flow rate dosage of the investigational medicinal product in tabular form in the investigational plan and in the documents instructions for handling the investigational medicinal product doctor/pharmacy was adjusted. The inclusion procedure for surgical patients and the independent physician procedure were also described in more detail in the V1.4 study plan. The Summary of product characteristics information of Midazolam-hameln (01/2015) was updated. |
| 26 October 2017 | Amendment 05 The substantial Amendment changes concern the registration of a new representative of the principle investigator at the trial site Gießen Dr. med. Christian Koch. |

| | |
|-------------------|---|
| 21 September 2018 | <p>Amendment 06 Substantial Amendment changes of the protocol 1.4 to 1.5</p> <p>The changes include the registration of an additional new deputy of the principle investigator Dr. Alexander Schiemann at trial site (1) Charité and a new principle investigator (Simone Lindau) and representative (Prof. Dr. med. Patrick Meybohm) at trial site 3 Frankfurt; additional patient information for patients who are able to consent in the intensive care unit, additional information according to the General data protection regulation (GDPR) for patients/caregivers/authorized patients by additional sheet: the Summary of product characteristics (SMPC) from Sedalam (01/2017) has been updated, the recruitment time has been increased, MicroRNA should additionally be determined at the trial site (1) Charité, additional Inclusion and exclusion criteria were defined.</p> |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported