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

Summary

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

Results information

Result version number	v1
This version publication date	21 August 2022
First version publication date	21 August 2022

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.

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

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 screend 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 sfatey analysis set (N=78) including two drop-out patients, who withdraw study participation after joining the study and who nevertheless received study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
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			

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

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

Hypophosphatemia subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 4	5 / 37 (13.51%) 5	
Hypovolemia subjects affected / exposed occurrences (all)	2 / 41 (4.88%) 2	1 / 37 (2.70%) 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 ß-HCG in the urine or determination of ß-HCG in the serum (the determination of ß-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	Amendment 06 Substantial Amendment changes of the protocol 1.4 to 1.5 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported