Clinical trial results:
Impact of preoperative midazolam on outcome of elderly patients: a multicenter randomised controlled trial

Summary

EudraCT number	2016-004555-79
Trial protocol	DE
Global end of trial date	24 June 2019

Results information

Result version number	v1 (current)
This version publication date	25 May 2022
First version publication date	25 May 2022

Trial information

Trial identification

Sponsor protocol code	16-115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03052660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	RWTH Aachen University represented by the Rector himself, represented by the Dean of the Medical Faculty
Sponsor organisation address	Pauwelsstraße 30, Aachen, Germany, 52074
Public contact	Center for Translational and Clinical Research Aachen (CTC-A), Uniklinik RWTH Aachen, +49 24180092, ctc-a-spoqs@ukaachen.de
Scientific contact	Center for Translational and Clinical Research Aachen (CTC-A), Uniklinik RWTH Aachen, +49 24180092, ctc-a-spoqs@ukaachen.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	26 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2019
Global end of trial reached?	Yes
Global end of trial date	24 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We aim to assess, if placebo administration compared to preoperative administration of midazolam in elderly patients is different in regard to the global postoperative patient satisfaction.

Protection of trial subjects:

Since Midazolam is a preoperatively, routinely used medication in surgical patients, no specific measures have been necessary to protect trial subjects. Study-specific baseline tests were not expected to have an influence on patients stresslevel.

Background therapy:

Patients have been recruited consecutively during the preoperative anaesthesia consultation in the clinical routine. Anaesthesia has been conducted according to the clinical routine, including the kind of anaesthesia as well as administered drugs. An additional application of benzodiazepines was not desired, but left to the discretion of the attending anaesthetist, who was blinded to the allocation treatment. Surgical procedures were performed according to the patients disease/needs. Pre- and postoperative care, including monitoring of vital signs, administration of medication and doctor's visits, has been conducted following the hospitals standard operating procedures (SOPs).

Evidence for comparator: -

Actual start date of recruitment	17 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 607
Worldwide total number of subjects	607
EEA total number of subjects	607

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)	0
From 65 to 84 years	607
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients have been recruited during the preoperative anaesthesia consultation in the clinical routine. Each participating centre recruited as many patients as possible. Recruitment started 17.10.2017. Site 001 recruited 120, Site 002 40, site 003 33, site 004 48, site 005 26, site 006 34, site 007 88, site 008 81 and site 009 137 patients.

Pre-assignment

Screening details:

All screened patients (including the screening failures and enrolled patients) have been documented in a screening/ enrollment log. The screening number has been coded independently from the randomization number with 3 digits. Of overall 3605 screened patients, 616 patients were enrolled in the trial.

Period 1

Period 1 title	Visit 0
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Midazolam group (Baseline visit)

Arm description:

Patients, meeting all inclusion and none exclusion criteria, will be randomly assigned to either receive 3.75 mg midazolam 30-45 minutes before surgery .

Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

The dosage of 3.75mg midazolam (halved 7.5mg tablet) was chosen according to the recommendation to reduce the dosage for elderly patients, which is described in the SmPC. Furthermore, it complies with the clinical routine in many German hospitals (including the participating centres) to use this reduced dosage in elderly patients. According to the clinical routine, the patients will receive the drug 30-45 minutes before the surgery.

Arm title	Placebo group (Baseline visit)

Arm description:

The patients in the placebo group received a placebo capsule 30-45 minutes before surgery

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Patients, meeting all inclusion and none exclusion criteria, will be randomly assigned to either receive 3.75 mg midazolam or placebo.

Number of subjects in period 1	Midazolam group (Baseline visit)	Placebo group (Baseline visit)
Started	304	303
Completed	304	303

Period 2	
Period 2 title	Visit 1 - surgery day, pre-operative
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Midazolam group (surgery day, pre-operative)

Arm description:

Patients receive 3.75 mg midazolam 30-45 minutes before surgery.

Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

3.75mg midazolam (hard) capsule, oral use

Arm title	Placebo group (surgery day, pre-operative)

Arm description:

Patients receive a placebo capsule 30-45 minutes before surgery.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

placebo (hard) capsule, oral use

Number of subjects in period 2	Midazolam group (surgery day, pre-operative)	Placebo group (surgery day, pre-operative)
Started	304	303
Completed	304	303

Period 3	
Period 3 title	Visit 2 - surgery day intra-operative
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Midazolam group (surgery day intra-operative)
Arm description: No IMP administration	
Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: None	
Arm title	Placebo group (surgery day intra-operative)
Arm description: No placebo administration.	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: None	

Number of subjects in period 3	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)
Started	304	303
Completed	304	303

Period 4	
Period 4 title	Visit 3 - surgery day post-operative
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Midazolam group (surgery day post-operative)

Arm description:

No IMP administration.

Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

None

Arm title	Placebo group (surgery day post-operative)

Arm description:

No placebo administration

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

None

Number of subjects in period 4	Midazolam group (surgery day post-operative)	Placebo group (surgery day post-operative)
Started	304	303
Completed	304	303

Period 5	
Period 5 title	Visit 4 - post-operative day 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Midazolam group (post-operative day 1)

Arm description:

No IMP administration

Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

None

Arm title	Placebo group (post-operative day 1)

Arm description:

No placebo administration.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

None

Number of subjects in period 5	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)
Started	304	303
Completed	304	303

Period 6	
Period 6 title	Visit 5 - post-operative day 30
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Midazolam group (post-operative day 30)

Arm description:
No IMP administration.

Arm type	Experimental
Investigational medicinal product name	Dormicum
Investigational medicinal product code	IMP 1
Other name	Midazolam
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
None

Arm title	Placebo group (post-operative day 30)

Arm description:
No placebo administration.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
None

Number of subjects in period 6	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)
Started	304	303
Completed	304	303

Baseline characteristics

Reporting groups	
Reporting group title	Midazolam group (Baseline visit)
Reporting group description:	
Patients, meeting all inclusion and none exclusion criteria, will be randomly assigned to either receive 3.75 mg midazolam 30-45 minutes before surgery .	
Reporting group title	Placebo group (Baseline visit)
Reporting group description:	
The patients in the placebo group received a placebo capsule 30-45 minutes before surgery	

Reporting group values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)	Total
Number of subjects	304	303	607
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	71.5	72.3	
standard deviation	± 4.37	± 4.43	-
Gender categorical Units: Subjects			
Female	106	124	230
Male	198	179	377
Physical status (ASA) Units: Subjects			
type I	12	11	23
type II	200	198	398
type III	91	92	183
type IV	1	2	3
Smoking status Units: Subjects			
smoker	25	25	50
Ex-smoker	103	109	212
Non-smoker	176	169	345
Medical history - Diabetes Units: Subjects			
yes	62	50	112
no	242	253	495

Medical history - Arterial hypertension Units: Subjects			
yes	198	208	406
no	106	95	201
Medical history - Adipositas Units: Subjects			
yes	168	171	339
no	136	132	268
Medical history - Hypercholesterolemia Units: Subjects			
yes	79	81	160
no	225	222	447
Medical history - Chronic heart disease Units: Subjects			
yes	41	34	75
no	263	269	532
Medical history - Pulmonary disease Units: Subjects			
yes	21	25	46
no	283	278	561
Medical history - Renal disease Units: Subjects			
yes	33	37	70
no	271	266	537
Medical history - Cerebrovascular disease Units: Subjects			
yes	19	18	37
no	285	285	570
Medical history - Malignant disease Units: Subjects			
yes	114	135	249
no	190	168	358
Medical history - previous surgery Units: Subjects			
yes	254	258	512
no	50	45	95
Height Units: cm			
arithmetic mean	171.92	170.54	
standard deviation	± 9.11	± 9.27	-
Body mass index (BMI) Units: kg / cm²			
arithmetic mean	27.195	27.192	
standard deviation	± 4.632	± 4.403	-
Hemoglobin Units: g / dl			
arithmetic mean	13.822	13.665	
standard deviation	± 1.719	± 1.729	-
Haematocrit Units: percentage			

arithmetic mean	40.431	40.106	
standard deviation	± 4.705	± 4.881	-
Albumin			
Units: g / dl			
arithmetic mean	4.354	4.219	
standard deviation	± 0.358	± 0.432	-
Creatinine			
Units: mg / dl			
arithmetic mean	1.062	1.063	
standard deviation	± 0.861	± 0.861	-

End points

End points reporting groups

Reporting group title	Midazolam group (Baseline visit)
Reporting group description:	
Patients, meeting all inclusion and none exclusion criteria, will be randomly assigned to either receive 3.75 mg midazolam 30-45 minutes before surgery .	
Reporting group title	Placebo group (Baseline visit)
Reporting group description:	
The patients in the placebo group received a placebo capsule 30-45 minutes before surgery	
Reporting group title	Midazolam group (surgery day, pre-operative)
Reporting group description:	
Patients receive 3.75 mg midazolam 30-45 minutes before surgery.	
Reporting group title	Placebo group (surgery day, pre-operative)
Reporting group description:	
Patients receive a placebo capsule 30-45 minutes before surgery.	
Reporting group title	Midazolam group (surgery day intra-operative)
Reporting group description:	
No IMP administration	
Reporting group title	Placebo group (surgery day intra-operative)
Reporting group description:	
No placebo administration.	
Reporting group title	Midazolam group (surgery day post-operative)
Reporting group description:	
No IMP administration.	
Reporting group title	Placebo group (surgery day post-operative)
Reporting group description:	
No placebo administration	
Reporting group title	Midazolam group (post-operative day 1)
Reporting group description:	
No IMP administration	
Reporting group title	Placebo group (post-operative day 1)
Reporting group description:	
No placebo administration.	
Reporting group title	Midazolam group (post-operative day 30)
Reporting group description:	
No IMP administration.	
Reporting group title	Placebo group (post-operative day 30)
Reporting group description:	
No placebo administration.	
Subject analysis set title	Men (Midazolam group)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients in the midazolam group with male gender	
Subject analysis set title	Men (Placebo group)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients in the placebo group with male gender.	
Subject analysis set title	Women (Midazolam group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the midazolam group with female gender.

Subject analysis set title	Women (Placebo group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the placebo group with female gender.

Subject analysis set title	Patients without frailty (Midazolam group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the midazolam group without frailty (assessment includes medical history, laboratory values, history of falls, the Mini-Cog and timed "Up & Go" test

Subject analysis set title	Patients without frailty (Placebo group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the placebo group without frailty (assessment includes medical history, laboratory values, history of falls, the Mini-Cog and timed "Up & Go" test

Subject analysis set title	Patients with frailty (Midazolam group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the midazolam group with frailty (assessment includes medical history, laboratory values, history of falls, the Mini-Cog and timed "Up & Go" test

Subject analysis set title	Patients with frailty (Placebo group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the placebo group with frailty (assessment includes medical history, laboratory values, history of falls, the Mini-Cog and timed "Up & Go" test

Subject analysis set title	Patients without anxiety (Midazolam group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the midazolam group without anxiety (APAIS-Score ≤ 12)

Subject analysis set title	Patients without anxiety (Placebo group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the placebo group without anxiety (APAIS-Score ≤ 12)

Subject analysis set title	Patients with anxiety (Midazolam group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the midazolam group with anxiety (APAIS-Score > 12)

Subject analysis set title	Patients with anxiety (Placebo group)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in the placebo group with anxiety (APAIS-Score > 12)

Primary: Global patient satisfaction

End point title	Global patient satisfaction

End point description:

End point type	Primary

End point timeframe:

post-operative day 1

End point values	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)	Men (Midazolam group)	Men (Placebo group)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	304[1]	303[2]	198[3]	179[4]
Units: none				
arithmetic mean (standard deviation)	43.33 (± 9.95)	43.83 (± 10.41)	43.89 (± 10.580)	44.36 (± 10.862)

Notes:

[1] - 3 missing data

[2] - 2 missing data

[3] - 1 missing data

[4] - 2 missing data

End point values	Women (Midazolam group)	Women (Placebo group)	Patients without frailty (Midazolam group)	Patients without frailty (Placebo group)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	106[5]	124	298[6]	298[7]
Units: none				
arithmetic mean (standard deviation)	42.27 (± 8.565)	43.07 (± 9.713)	43.43 (± 9.965)	43.84 (± 10.492)

Notes:

[5] - 2 missing data

[6] - 3 missing data

[7] - 2 missing data

End point values	Patients with frailty (Midazolam group)	Patients with frailty (Placebo group)	Patients without anxiety (Midazolam group)	Patients without anxiety (Placebo group)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	5	258[8]	242[9]
Units: none				
arithmetic mean (standard deviation)	38.53 (± 8.174)	43.33 (± 2.150)	43.67 (± 10.082)	43.61 (± 10.603)

Notes:

[8] - 1 missing data

[9] - 2 missing data

End point values	Patients with anxiety (Midazolam group)	Patients with anxiety (Placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46[10]	61		
Units: none				
arithmetic mean (standard deviation)	41.38 (± 8.963)	44.68 (± 9.633)		

Notes:
[10] - 2 missing data

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Midazolam group (post-operative day 1) v Placebo group (post-operative day 1)
Number of subjects included in analysis	607
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.447
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2
upper limit	1.1

Statistical analysis title	Treatment effect among men
Comparison groups	Men (Midazolam group) v Men (Placebo group)
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.353
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2.3
upper limit	1.6

Statistical analysis title	Treatment effect among women
Comparison groups	Women (Midazolam group) v Women (Placebo group)
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.986

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.5
upper limit	1.6

Statistical analysis title	Treatment effect among patients without frailty
Comparison groups	Patients without frailty (Midazolam group) v Patients without frailty (Placebo group)
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.493
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-2.1
upper limit	1.1

Statistical analysis title	Treatment effect among patients with frailty
Comparison groups	Patients with frailty (Midazolam group) v Patients with frailty (Placebo group)
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-4.541
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-19.2
upper limit	10.2

Statistical analysis title	Treatment effect among patients without anxiety
Comparison groups	Patients without anxiety (Midazolam group) v Patients without anxiety (Placebo group)
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.0326

Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-1.8
upper limit	1.7

Statistical analysis title	Treatment effect among patients with anxiety
Comparison groups	Patients with anxiety (Placebo group) v Patients with anxiety (Midazolam group)
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-3.033
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-6.8
upper limit	0.8

Secondary: Assessment of preoperative anxiety

End point title	Assessment of preoperative anxiety

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	303		
Units: none				
arithmetic mean (standard deviation)	8.339 (± 4.0)	8.802 (± 4.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: IADL score

End point title	IADL score

End point description:

End point type	Secondary

End point timeframe:

Baseline & POD 30

End point values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	303[11]	301[12]	280[13]	276[14]
Units: none				
arithmetic mean (standard deviation)	8.974 (± 2.806)	8.894 (± 2.733)	10.114 (± 4.175)	10.355 (± 4.512)

Notes:

[11] - 1 missing data

[12] - 2 missing data

[13] - 23 missing data

[14] - 25 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: SBT Score

End point title	SBT Score

End point description:

End point type	Secondary

End point timeframe:

Baseline, POD 1 & POD 30

End point values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	304	303	299[15]	296[16]
Units: none				
arithmetic mean (standard deviation)	3.178 (± 3.431)	3.274 (± 3.448)	2.221 (± 3.365)	2.176 (± 3.124)

Notes:

[15] - 5 missing data

[16] - 7 missing data

End point values	Midazolam group (post-operative day	Placebo group (post-operative day 30)		

	30)			
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282[17]	277[18]		
Units: none				
arithmetic mean (standard deviation)	1.734 (± 2.876)	1.845 (± 2.993)		

Notes:

[17] - 22 missing data

[18] - 26 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Confusion Assessment Method CAM

End point title	Confusion Assessment Method CAM

End point description:

End point type	Secondary

End point timeframe:

post-operative day 1

End point values	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	303		
Units: subjects				
positive	1	3		
negative	301	300		
no data	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of well-being - extubation

End point title	Change in perioperative condition of well-being - extubation

End point description:

End point type	Secondary

End point timeframe:

shortly after extubation compared to Baseline

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269[19]	262[20]		
Units: none				
arithmetic mean (standard deviation)	-0.8104 (± 30.75)	-1.7023 (± 31.12)		

Notes:

[19] - 35 missing data

[20] - 41 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of pain - extubation

End point title	Change in perioperative condition of pain - extubation

End point description:

End point type	Secondary

End point timeframe:

directly after extubation compared to Baseline

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	280[21]	277[22]		
Units: none				
arithmetic mean (standard deviation)	-9.139 (± 32.74)	-11.032 (± 30.61)		

Notes:

[21] - 24 missing data

[22] - 26 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of sleeping - POD 1

End point title	Change in perioperative condition of sleeping - POD 1

End point description:

End point type	Secondary

End point timeframe:
post-operative day 1 compared to Baseline

End point values	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[23]	300[24]		
Units: none				
arithmetic mean (standard deviation)	-17.58 (± 35.13)	-15.42 (± 36.05)		

Notes:
[23] - 3 missing data
[24] - 3 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Patient cooperation

End point title	Patient cooperation

End point description:

End point type	Secondary

End point timeframe:
directly before surgery

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299[25]	295[26]		
Units: none				
arithmetic mean (standard deviation)	96.02 (± 14.77)	96.02 (± 13.96)		

Notes:
[25] - 5 missing data
[26] - 8 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Amount of patients with rescue midazolam application

End point title	Amount of patients with rescue midazolam application

End point description:

End point type	Secondary

End point timeframe:
during surgery

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	303		
Units: subjects				
yes	2	0		
no	301	303		
no data	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to extubation

End point title	Time to extubation

End point description:

End point type	Secondary

End point timeframe:
during surgery

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[27]	299[28]		
Units: min				
arithmetic mean (standard deviation)	10.007 (± 6.853)	9.201 (± 6.251)		

Notes:
[27] - 2 missing data
[28] - 4 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: change in EQ 5D-5L

End point title	change in EQ 5D-5L

End point description:

End point type	Secondary

End point timeframe:

Baseline & POD 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281[29]	277[30]		
Units: none				
arithmetic mean (standard deviation)	0.0396 (± 0.2398)	0.0223 (± 0.2435)		

Notes:

[29] - 23 missing data

[30] - 26 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of well-being - surgery

End point title	Change in perioperative condition of well-being - surgery

End point description:

End point type	Secondary

End point timeframe:

after surgery compared to Baseline

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289[31]	285[32]		
Units: none				
arithmetic mean (standard deviation)	-5.734 (± 28.64)	-9.189 (± 28.90)		

Notes:

[31] - 15 missing data

[32] - 18 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of well-being - POD 1

End point title	Change in perioperative condition of well-being - POD 1

End point description:

End point type	Secondary

End point timeframe:

post-operative day 1 compared to Baseline

End point values	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[33]	299[34]		
Units: none				
arithmetic mean (standard deviation)	-0.6279 (± 24.53)	-2.8127 (± 22.82)		

Notes:

[33] - 3 missing data

[34] - 4 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of pain - surgery

End point title	Change in perioperative condition of pain - surgery

End point description:

End point type	Secondary

End point timeframe:

after surgery compared to Baseline

End point values	Midazolam group (surgery day intra-operative)	Placebo group (surgery day intra-operative)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	299[35]	296[36]		
Units: none				
arithmetic mean (standard deviation)	0.1438 (± 34.11)	0.2939 (± 36.18)		

Notes:

[35] - 5 missing data

[36] - 7 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Change in perioperative condition of pain - POD 1

End point title	Change in perioperative condition of pain - POD 1

End point description:

End point type	Secondary

End point timeframe:

post-operative day 1 compared to Baseline

End point values	Midazolam group (post-operative day 1)	Placebo group (post-operative day 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[37]	301[38]		
Units: none				
arithmetic mean (standard deviation)	-3.993 (± 31.67)	-1.166 (± 32.62)		

Notes:

[37] - 3 missing data

[38] - 2 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

post-operative day 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	303		
Units: subjects				
alive	298	295		
dead	0	2		
no data	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury

End point title	new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury

End point description:

End point type	Secondary

End point timeframe:
post-operative day 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304	303		
Units: subjects				
yes	6	10		
no	291	283		
no data	7	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Longer-term outcome after 30 days (new-onset complications)

End point title	Longer-term outcome after 30 days (new-onset complications)

End point description:

End point type	Secondary

End point timeframe:
post-operative day 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	10		
Units: subjects				
cardiac complications	1	5		
pulmonary complications	3	2		
acute stroke	0	2		

acute kidney injury	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay in hospital

End point title	Length of stay in hospital

End point description:

End point type	Secondary

End point timeframe:

post-operative day 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[39]	302[40]		
Units: days				
arithmetic mean (standard deviation)	6.791 (± 5.363)	6.798 (± 5.201)		

Notes:

[39] - 3 missing data

[40] - 1 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Length of stay in Intensive Care Unit

End point title	Length of stay in Intensive Care Unit

End point description:

End point type	Secondary

End point timeframe:

post-operative day 30

End point values	Midazolam group (post-operative day 30)	Placebo group (post-operative day 30)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301[41]	302[42]		
Units: days				
arithmetic mean (standard deviation)	0.1561 (± 1.003)	0.2947 (± 1.911)		

Notes:

[41] - 3 missing data

[42] - 1 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Frailty - Mini-Cog

End point title	Frailty - Mini-Cog

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[43]	300[44]		
Units: points				
arithmetic mean (standard deviation)	3.553 (± 1.447)	3.487 (± 1.460)		

Notes:

[43] - 2 missing data

[44] - 3 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Frailty - Timed up and go test

End point title	Frailty - Timed up and go test

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Midazolam group (Baseline visit)	Placebo group (Baseline visit)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247[45]	258[46]		
Units: sec				
arithmetic mean (standard deviation)	11.530 (± 6.290)	11.671 (± 6.103)		

Notes:

[45] - 57 missing data

[46] - 45 missing data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
30 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	none
Dictionary version	0

Reporting groups	
Reporting group title	Midazolam group
Reporting group description:	
Patients, meeting all inclusion and none exclusion criteria, will be randomly assigned to either receive 3.75 mg midazolam 30-45 minutes before surgery .	
Reporting group title	Placebo group
Reporting group description:	
The patients in the placebo group received a placebo capsule 30-45 minutes before surgery	

Serious adverse events	Midazolam group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 304 (1.97%)	13 / 303 (4.29%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant tumor			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Iatrogenic injury of esophagus and trachea			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iatrogenic ureteral injury			
subjects affected / exposed	1 / 304 (0.33%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-operative bleeding			

subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematoma abdominal wall			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac decompensation			
subjects affected / exposed	1 / 304 (0.33%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Stroke			
subjects affected / exposed	0 / 304 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	2 / 304 (0.66%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Midazolam group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	264 / 304 (86.84%)	251 / 303 (82.84%)	
Injury, poisoning and procedural complications			
Extravasation of colloids			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Vascular disorders			
Bleeding			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Collapse			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Hypothermia			

subjects affected / exposed	7 / 304 (2.30%)	0 / 303 (0.00%)	
occurrences (all)	7	0	
Cardiac disorders			
Arrythmia			
subjects affected / exposed	2 / 304 (0.66%)	3 / 303 (0.99%)	
occurrences (all)	3	5	
Bradycardia			
subjects affected / exposed	62 / 304 (20.39%)	63 / 303 (20.79%)	
occurrences (all)	64	65	
Hypertension			
subjects affected / exposed	34 / 304 (11.18%)	34 / 303 (11.22%)	
occurrences (all)	38	37	
Hypotension			
subjects affected / exposed	229 / 304 (75.33%)	222 / 303 (73.27%)	
occurrences (all)	250	241	
Hypovolaemia			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	7 / 304 (2.30%)	6 / 303 (1.98%)	
occurrences (all)	7	7	
Nervous system disorders			
Agitation			
subjects affected / exposed	0 / 304 (0.00%)	2 / 303 (0.66%)	
occurrences (all)	0	2	
Central anticholinergic syndrome			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
delayed awakening			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Delirium			
subjects affected / exposed	3 / 304 (0.99%)	3 / 303 (0.99%)	
occurrences (all)	3	3	
Drowsiness			

subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	5 / 304 (1.64%)	5 / 303 (1.65%)	
occurrences (all)	5	5	
Numbness occipital right side			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	2	0	
post-operative cognitive dysfunction			
subjects affected / exposed	0 / 304 (0.00%)	2 / 303 (0.66%)	
occurrences (all)	0	2	
post-operative nausea and vomitting			
subjects affected / exposed	17 / 304 (5.59%)	14 / 303 (4.62%)	
occurrences (all)	18	14	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 304 (0.66%)	0 / 303 (0.00%)	
occurrences (all)	2	0	
Hemoglobin drop			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Hypoxemia			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Lymphocele			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Desaturation			
subjects affected / exposed	25 / 304 (8.22%)	21 / 303 (6.93%)	
occurrences (all)	26	24	
General disorders and administration site conditions			
Shivering			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Anaphylaxis			
subjects affected / exposed	2 / 304 (0.66%)	0 / 303 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 304 (0.33%)	0 / 303 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Bronchospasm			
subjects affected / exposed	2 / 304 (0.66%)	0 / 303 (0.00%)	
occurrences (all)	3	0	
Respiratory insufficiency			
subjects affected / exposed	3 / 304 (0.99%)	0 / 303 (0.00%)	
occurrences (all)	3	0	
Thoracic rigidity			
subjects affected / exposed	0 / 304 (0.00%)	1 / 303 (0.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Laryngospasm			
subjects affected / exposed	2 / 304 (0.66%)	1 / 303 (0.33%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2019	change of sponsor name

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported