Clinical trial results:
Randomized, Controlled, Parallel-Group, Double-Blind Trial to Compare the Use of Deep or Standard Neuromuscular Blockade in Combination With Low or Standard Insufflation Pressures Using a 2x2 Factorial Design in Patients Undergoing Laparoscopic Cholecystectomy (Protocol No. MK-8616-076-03 also known as SCH 900616, P07982)

Summary

EudraCT number	2012-001886-33
Trial protocol	DE AT FI GB IT
Global end of trial date	29 April 2014

Results information

Result version number	v1
This version publication date	11 May 2016
First version publication date	02 May 2015

Trial information

Trial identification

Sponsor protocol code	MK-8616-076

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01728584
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Registration number: P07982

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 April 2014
Global end of trial reached?	Yes
Global end of trial date	29 April 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Purpose of study is to compare use of deep or standard neuromuscular blockade (NMB) in combination with low or standard insufflation pressure in participants undergoing laparoscopic cholecystectomy. Primary hypothesis is that use of sustained deep NMB improves the surgeon's overall satisfaction with surgical conditions versus standard NMB. Inpatient surgery is performed on Day 1, and participant remains hospitalized for at least 24-48 hours after surgery, with follow-up visit/contact on Day 8. During procedure, surgeon could request modification to randomized treatment conditions ("rescue intervention"), if surgeon considered surgical conditions unacceptable. For participant on standard NMB, preferred rescue intervention was increase of NMB from standard to deep level; second option, if available, was to raise insufflation pressure from low to standard. If the participant was already on deep NMB, preferred option, if available, was to raise insufflation pressure from low to standard.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 November 2012
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	Austria: 43
Country: Number of subjects enrolled	Finland: 11
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	United Kingdom: 13
Worldwide total number of subjects	127
EEA total number of subjects	127

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)	112
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized to 4 arms based on combinations of NMB depth and insufflation pressure level. During procedure, blinded surgeon could request that unblinded anesthetist change the randomized treatment conditions ("rescue intervention"), if surgeon considered surgical conditions to be unacceptable.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Assessor

Blinding implementation details:

The surgeon was blinded to random assignment. The anesthetist controlling the surgical conditions (depth of NMB, insufflation pressure level) was unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard NMB and Standard Insufflation Pressure

Arm description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted Train of Four [TOF] ratio of 10%)/Standard insufflation pressure (starting pressure of 12 mmHg).

Arm type	Experimental
Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	Esmeron® Injection (rocuronium bromide), Zemuron® Injection (rocuronium bromide)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be induced by intravenous (IV) administration of a bolus dose of 0.45 mg/kg rocuronium. NMB will be maintained using rocuronium infusion or additional bolus doses as needed for the management of NMB to the targeted depth according to the assigned treatment condition: Standard NMB - administration of neuromuscular blocking agent (NMBA) titrated to a depth of blockade at a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%); Deep NMB - administration of NMBA titrated to a targeted depth of 1-2 Post Tetanic Counts (PTCs) (range: 1-5 PTC).

Investigational medicinal product name	Carbon dioxide gas
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Intraperitoneal use

Dosage and administration details:

Insufflation (injection) of carbon dioxide will be used to induce pneumoperitoneum, which is presence of air or gas in the abdominal (peritoneal) cavity: Standard insufflation pressure - a starting pressure of 12 mmHg will be used; Low insufflation pressure - a starting pressure of 8 mmHg will be used.

Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	sugammadex sodium injection, SCH 900616, Org 25969, Bridion®
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

NMB will be reversed with IV administration of 2 or 4 mg/kg sugammadex (depending on the depth of NMB) according to the approved label for sugammadex.

Arm title	Standard NMB and Low Insufflation Pressure

Arm description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Low insufflation pressure (starting pressure of 8 mmHg).

Arm type	Experimental
Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	Esmeron® Injection (rocuronium bromide), Zemuron® Injection (rocuronium bromide)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be induced by IV administration of a bolus dose of 0.45 mg/kg rocuronium. NMB will be maintained using rocuronium infusion or additional bolus doses as needed for the management of NMB to the targeted depth according to the assigned treatment condition: Standard NMB - administration of NMBA titrated to a depth of blockade at a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%); Deep NMB - administration of NMBA titrated to a targeted depth of 1-2 PTCs (range: 1-5 PTC).

Investigational medicinal product name	Carbon dioxide gas
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Intraperitoneal use

Dosage and administration details:

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Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	sugammadex sodium injection, SCH 900616, Org 25969, Bridion®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be reversed with IV administration of 2 or 4 mg/kg sugammadex (depending on the depth of NMB) according to the approved label for sugammadex.

Arm title	Deep NMB and Standard Insufflation Pressure

Arm description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Standard insufflation pressure (starting pressure of 12 mmHg).

Arm type	Experimental
Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	Esmeron® Injection (rocuronium bromide), Zemuron® Injection (rocuronium bromide)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be induced by IV administration of a bolus dose of 0.45 mg/kg rocuronium. NMB will be maintained using rocuronium infusion or additional bolus doses as needed for the management of NMB to the targeted depth according to the assigned treatment condition: Standard NMB - administration of

NMBA titrated to a depth of blockade at a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%); Deep NMB - administration of NMBA titrated to a targeted depth of 1-2 PTCs (range: 1-5 PTC).

Investigational medicinal product name	Carbon dioxide gas
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Intraperitoneal use

Dosage and administration details:

Insufflation (injection) of carbon dioxide will be used to induce pneumoperitoneum, which is presence of air or gas in the abdominal (peritoneal) cavity: Standard insufflation pressure - a starting pressure of 12 mmHg will be used; Low insufflation pressure - a starting pressure of 8 mmHg will be used.

Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	sugammadex sodium injection, SCH 900616, Org 25969, Bridion®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be reversed with IV administration of 2 or 4 mg/kg sugammadex (depending on the depth of NMB) according to the approved label for sugammadex.

Arm title	Deep NMB and Low Insufflation Pressure

Arm description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Low insufflation pressure (starting pressure of 8 mmHg).

Arm type	Experimental
Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	Esmeron® Injection (rocuronium bromide), Zemuron® Injection (rocuronium bromide)
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be induced by IV administration of a bolus dose of 0.45 mg/kg rocuronium. NMB will be maintained using rocuronium infusion or additional bolus doses as needed for the management of NMB to the targeted depth according to the assigned treatment condition: Standard NMB - administration of NMBA titrated to a depth of blockade at a targeted TOF ratio of 10% (range: TOF count 2-3 to TOF ratio of 20%); Deep NMB - administration of NMBA titrated to a targeted depth of 1-2 PTCs (range: 1-5 PTC).

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Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Intraperitoneal use

Dosage and administration details:

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Investigational medicinal product name	Sugammadex
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Other name	sugammadex sodium injection, SCH 900616, Org 25969, Bridion®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

NMB will be reversed with IV administration of 2 or 4 mg/kg sugammadex (depending on the depth of NMB) according to the approved label for sugammadex.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: The surgeon, who made ratings of surgical conditions used for primary outcome measures and several other efficacy endpoints, was blinded to random assignment. The anesthetist controlling the surgical conditions was unblinded. A blinded safety assessor evaluated safety parameters, pain scores and analgesic medication use. Appropriate Sponsor personnel were blinded to random assignment.

Number of subjects in period 1	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure
Started	36	30	31
Completed	28	30	30
Not completed	8	0	1
Physician decision	4	-	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-
Other reason (not specified)	1	-	-
Screen failure	1	-	-

Number of subjects in period 1	Deep NMB and Low Insufflation Pressure
Started	30
Completed	29
Not completed	1
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Other reason (not specified)	1
Screen failure	-

Baseline characteristics

Reporting groups	
Reporting group title	Standard NMB and Standard Insufflation Pressure
Reporting group description:	
Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted Train of Four [TOF] ratio of 10%)/Standard insufflation pressure (starting pressure of 12 mmHg).	
Reporting group title	Standard NMB and Low Insufflation Pressure
Reporting group description:	
Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Low insufflation pressure (starting pressure of 8 mmHg).	
Reporting group title	Deep NMB and Standard Insufflation Pressure
Reporting group description:	
Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Standard insufflation pressure (starting pressure of 12 mmHg).	
Reporting group title	Deep NMB and Low Insufflation Pressure
Reporting group description:	
Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Low insufflation pressure (starting pressure of 8 mmHg).	

Reporting group values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure
Number of subjects	36	30	31
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	29	29
From 65-84 years	8	1	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.1	39.1	43.5
standard deviation	± 17.7	± 13.6	± 15.6
Gender categorical Units: Subjects			
Female	15	11	13
Male	21	19	18

Reporting group values	Deep NMB and Low Insufflation Pressure	Total	
Number of subjects	30	127	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	112	
From 65-84 years	4	15	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	46.7		
standard deviation	± 13.8	-	
Gender categorical			
Units: Subjects			
Female	9	48	
Male	21	79	

End points

End points reporting groups

Reporting group title	Standard NMB and Standard Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted Train of Four [TOF] ratio of 10%)/Standard insufflation pressure (starting pressure of 12 mmHg).

Reporting group title	Standard NMB and Low Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Low insufflation pressure (starting pressure of 8 mmHg).

Reporting group title	Deep NMB and Standard Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Standard insufflation pressure (starting pressure of 12 mmHg).

Reporting group title	Deep NMB and Low Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Low insufflation pressure (starting pressure of 8 mmHg).

Subject analysis set title	Standard NMB
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%), whether in combination with Standard or Low insufflation pressure. Therefore, the included arms are Standard NMB/Standard insufflation pressure and Standard NMB/Low insufflation pressure.

Subject analysis set title	Deep NMB
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs), whether in combination with Standard or Low insufflation pressure. Therefore, the included arms are Deep NMB/Standard insufflation pressure and Deep NMB/Low insufflation pressure.

Subject analysis set title	Standard Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Standard insufflation pressure (starting pressure of 12 mmHg), whether in combination with Standard or Deep NMB. Therefore, the included arms are Standard NMB/Standard insufflation pressure and Deep NMB/Standard insufflation pressure.

Subject analysis set title	Low Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Low insufflation pressure (starting pressure of 8 mmHg), whether in combination with Standard or Deep NMB. Therefore, the included arms are Standard NMB/Low insufflation pressure and Deep NMB/Low insufflation pressure.

Subject analysis set title	Standard NMB and Standard Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Standard insufflation pressure (starting pressure of 12 mmHg). Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

Subject analysis set title	Standard NMB and Low Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Low insufflation pressure (starting pressure of 8 mmHg). Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-

intervention condition.

Subject analysis set title	Deep NMB and Standard Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Standard insufflation pressure (starting pressure of 12 mmHg). Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

Subject analysis set title	Deep NMB and Low Insufflation Pressure
Subject analysis set type	Full analysis

Subject analysis set description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Low insufflation pressure (starting pressure of 8 mmHg). Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

Primary: Score on surgeon's assessment of overall satisfaction with the surgical conditions: By depth of NMB (standard, deep) and insufflation pressure (standard, low)

End point title	Score on surgeon's assessment of overall satisfaction with the surgical conditions: By depth of NMB (standard, deep) and insufflation pressure (standard, low)

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (poor, needed intervention) to 10 (excellent): "How satisfied were you overall with the surgical conditions related to anesthesia and pneumoperitoneum during the surgery you just performed?" If at any time the surgeon requests a rescue intervention, the overall assessment of surgical conditions should be rated as 0 (=poor, needed intervention). The surgeon will rate the surgical conditions according to his opinion but if a rescue intervention has been applied, that individual participant will be counted with a score of zero in the analysis. Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Primary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB	Deep NMB	Standard Insufflation Pressure	Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	60	60
Units: score on a scale				
least squares mean (confidence interval 95%)	6.83 (5.97 to 7.69)	7.92 (7.05 to 8.8)	8.89 (8.05 to 9.72)	5.87 (4.96 to 6.77)

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)

Statistical analysis description:

Primary hypothesis – deep NMB improves surgeon’s overall satisfaction with the surgical conditions compared to standard NMB. Analysis of covariance (ANCOVA) model included factors depth of NMB, level of pressure, surgeon and body mass index (BMI).

Comparison groups	Deep NMB v Standard NMB

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	ANCOVA
Parameter estimate	Difference in Least Squares (LS) Means
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	2.04

Statistical analysis title	Comparison by pressure (standard, low)
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Low Insufflation Pressure v Standard Insufflation Pressure
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-3.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	-2.05

Primary: Score on surgeon's assessment of overall satisfaction with the surgical conditions: By treatment arm

End point title	Score on surgeon's assessment of overall satisfaction with the surgical conditions: By treatment arm

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (poor, needed intervention) to 10 (excellent): "How satisfied were you overall with the surgical conditions related to anesthesia and pneumoperitoneum during the surgery you just performed?" If at any time the surgeon requests a rescue intervention, the overall assessment of surgical conditions should be rated as 0 (=poor, needed intervention). The surgeon will rate the surgical conditions according to his opinion but if a rescue intervention has been applied, that individual participant will be counted with a score of zero in the analysis. Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Primary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	30	30	30	30
Units: score on a scale				
least squares mean (confidence interval 95%)	8.65 (7.58 to 9.72)	4.99 (3.88 to 6.11)	9.09 (8.82 to 10.17)	6.69 (5.57 to 7.8)

Statistical analyses

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Standard NMB and Standard Insufflation Pressure v Standard NMB and Low Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Least Squares (LS) Means
Point estimate	3.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	5.02

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Standard NMB and Standard Insufflation Pressure v Deep NMB and Standard Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.91

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Standard NMB and Standard Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	3.36

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Standard NMB and Low Insufflation Pressure v Deep NMB and Standard Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.42
upper limit	-2.78

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Standard NMB and Low Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.01
upper limit	-0.38

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Deep NMB and Standard Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	3.74

Secondary: Participant's overall average pain score in the first 24 hours after administration of sugammadex: By depth of NMB (standard, deep) and insufflation pressure (standard, low)

End point title	Participant's overall average pain score in the first 24 hours after administration of sugammadex: By depth of NMB (standard, deep) and insufflation pressure (standard, low)

End point description:

Participants rated pain at 1, 2, 4, 24 and 48 hours after the administration of sugammadex on day of surgery (Day 1), and daily from Day 3 to Day 8. Pain rating was made using an 11-point scale from 0 (no pain) to 10 (severe pain). Separate ratings were made for overall pain at rest, pain when provoked (e.g., due to participant transition from lying to sitting position) and shoulder pain at rest. The participant’s overall average pain score within 24 hours after sugammadex was the average of all pain assessments (including all 3 pain types assessed) at 1, 2, 4 and 24 hours after sugammadex dose. Population for analysis was randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex, and did not convert to open surgery before NMB and/or pressure. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

End point type	Secondary

End point timeframe:

Up to 24 hours after administration of sugammadex on Day 1

End point values	Standard NMB	Deep NMB	Standard Insufflation Pressure	Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	65	71	49
Units: score on a scale				
least squares mean (confidence interval 95%)	2.48 (2.02 to 2.93)	2.83 (2.39 to 3.28)	2.74 (2.34 to 3.15)	2.57 (2.07 to 3.07)

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)
Statistical analysis description:	
Analysis of variance (ANOVA) model included factors depth of NMB, level of pressure, gender and surgeon.	
Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.148
Method	ANOVA
Parameter estimate	Difference in LS Means
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.84

Statistical analysis title	Comparison by pressure (standard, low)
Statistical analysis description:	
Key secondary hypothesis – low insufflation pressure improves overall average pain score in first 24 hours compared to standard insufflation pressure. ANOVA model included factors depth of NMB, level of pressure, gender and surgeon.	
Comparison groups	Low Insufflation Pressure v Standard Insufflation Pressure
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.494 [1]
Method	ANOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.67
upper limit	0.33

Notes:

[1] - To control for multiple testing, this difference was formally tested only if comparison of surgeon's overall satisfaction with surgical conditions for deep versus standard NMB was significant at the 5% level, with greater satisfaction for deep NMB.

Secondary: Participant's overall average pain score in the first 24 hours after administration of sugammadex: By treatment arm

End point title	Participant's overall average pain score in the first 24 hours after administration of sugammadex: By treatment arm

End point description:

Participants rated pain at 1, 2, 4, 24 and 48 hours after the administration of sugammadex on day of surgery (Day 1), and daily from Day 3 to Day 8. Pain rating was made using an 11-point scale from 0 (no pain) to 10 (severe pain). Separate ratings were made for overall pain at rest, pain when provoked (e.g., due to participant transition from lying to sitting position) and shoulder pain at rest. The participant's overall average pain score within 24 hours after sugammadex was the average of all pain assessments (including all 3 pain types assessed) at 1, 2, 4 and 24 hours after sugammadex dose. Population for analysis was randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex, and did not convert to open surgery before NMB and/or pressure. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

End point type	Secondary

End point timeframe:

Up to 24 hours after administration of sugammadex on Day 1

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	23	39	26
Units: score on a scale				
least squares mean (confidence interval 95%)	2.42 (1.9 to 2.93)	2.62 (1.98 to 3.26)	3.06 (2.56 to 3.57)	2.57 (1.97 to 3.17)

Statistical analyses

Statistical analysis title	Comparison by treatment arm

Statistical analysis description:

ANOVA model included factors treatment group, gender and surgeon.

Comparison groups	Standard NMB and Standard Insufflation Pressure v Standard NMB and Low Insufflation Pressure
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.52

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANOVA model included factors treatment group, gender and surgeon.	
Comparison groups	Standard NMB and Standard Insufflation Pressure v Deep NMB and Standard Insufflation Pressure
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.02

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANOVA model included factors treatment group, gender and surgeon.	
Comparison groups	Standard NMB and Standard Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	0.53

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANOVA model included factors treatment group, gender and surgeon.	
Comparison groups	Standard NMB and Low Insufflation Pressure v Deep NMB and Standard Insufflation Pressure
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	-0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.15
upper limit	0.26

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANOVA model included factors treatment group, gender and surgeon.	
Comparison groups	Standard NMB and Low Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.78

Statistical analysis title	Comparison by treatment arm
Statistical analysis description:	
ANOVA model included factors treatment group, gender and surgeon.	
Comparison groups	Deep NMB and Standard Insufflation Pressure v Deep NMB and Low Insufflation Pressure
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in LS Means
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	1.16

Secondary: Score on surgeon's assessment of overall satisfaction with the visibility of the surgical field: By depth of NMB (standard, deep)

End point title	Score on surgeon's assessment of overall satisfaction with the visibility of the surgical field: By depth of NMB (standard, deep)

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (poor, unacceptable visibility) to 10 (excellent): "How satisfied were you overall with the visual

field during the surgery you just performed?" If at any time the surgeon requests a rescue intervention, the surgeon will rate his overall satisfaction with the visibility of the surgical field according to his opinion, but if a rescue intervention has been applied, that individual patient will be counted with a score of zero in the analysis. Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB	Deep NMB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	60		
Units: score on a scale				
least squares mean (confidence interval 95%)	6.88 (6.02 to 7.75)	7.8 (6.92 to 8.68)		

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)

Statistical analysis description:

ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.

Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063 [2]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	1.87

Notes:

[2] - Not controlled for multiple testing.

Secondary: Score on surgeon's assessment of the overall adequacy of muscle relaxation during surgery: By depth of NMB (standard, deep)

End point title	Score on surgeon's assessment of the overall adequacy of muscle relaxation during surgery: By depth of NMB (standard, deep)

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (poor, unacceptable muscle relaxation, required intervention) to 10 (excellent): "How do you rate the overall adequacy of muscle relaxation during the surgery you just performed?" Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for

laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB	Deep NMB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	60		
Units: score on a scale				
least squares mean (confidence interval 95%)	8.05 (7.56 to 8.54)	8.87 (8.37 to 9.37)		

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)

Statistical analysis description:

ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.

Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004 [3]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.37

Notes:

[3] - Not controlled for multiple testing.

Secondary: Score on surgeon's assessment of the overall adequacy of insufflation pressure during surgery: By depth of NMB (standard, deep)

End point title	Score on surgeon's assessment of the overall adequacy of insufflation pressure during surgery: By depth of NMB (standard, deep)

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (poor, unacceptable insufflation pressure, required intervention) to 10 (excellent): "How do you rate the overall adequacy of insufflation pressure during the surgery you just performed?" Analysis population was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB	Deep NMB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	60		
Units: score on a scale				
least squares mean (confidence interval 95%)	6.73 (6.01 to 7.45)	7.86 (7.12 to 8.59)		

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)

Statistical analysis description:

ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.

Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006 [4]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.92

Notes:

[4] - Not controlled for multiple testing.

Secondary: Number of times participant's movements or increased muscle tone interfered with the surgical conditions during laparoscopy: By depth of NMB (standard, deep)

End point title	Number of times participant's movements or increased muscle tone interfered with the surgical conditions during laparoscopy: By depth of NMB (standard, deep)

End point description:

At the end of the procedure the surgeon responds to the following question: "How many times did patient's movements (coughing, bucking, hiccup) or increased muscle tone (resistance, difficulty to close fasciae or skin) interfere with your surgery?" Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

During surgery, approximate duration of 1-2 hours (Day 1)

End point values	Standard NMB	Deep NMB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	59		
Units: instances of occurrence that interfered				
least squares mean (confidence interval 95%)	0.92 (0.33 to 1.52)	0.32 (-0.29 to 0.92)		

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.073 [5]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	0.06

Notes:

[5] - Not controlled for multiple testing.

Secondary: Score on surgeon's assessment of the effect participant's movements during surgery had on the overall surgical procedure: By depth of NMB (standard, deep)

End point title	Score on surgeon's assessment of the effect participant's movements during surgery had on the overall surgical procedure: By depth of NMB (standard, deep)

End point description:

At the end of the procedure the surgeon responds to the following question, using an 11-point scale from 0 (extremely disruptive) to 10 (not disruptive): "How did the patient movements described above disrupt your surgical performance?" This refers to participant movements during surgery. Population for analysis was randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

End of surgery (Day 1)

End point values	Standard NMB	Deep NMB		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60	60		
Units: score on a scale				
least squares mean (confidence interval 95%)	9.21 (8.72 to 9.7)	9.94 (9.45 to 10.44)		

Statistical analyses

Statistical analysis title	Comparison by NMB (standard, deep)
Statistical analysis description:	
ANCOVA model included factors depth of NMB, level of pressure, surgeon and BMI.	
Comparison groups	Deep NMB v Standard NMB
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.009 [6]
Method	ANCOVA
Parameter estimate	Difference in LS Means
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	1.28

Notes:

[6] - Not controlled for multiple testing.

Secondary: Number of participants with rescue actions performed during surgery in order to improve insufficient surgical conditions: By treatment arm

End point title	Number of participants with rescue actions performed during surgery in order to improve insufficient surgical conditions: By treatment arm

End point description:

During procedure, surgeon could request modification to randomized treatment conditions ("rescue intervention"), if surgeon considered surgical conditions unacceptable. For participant on standard NMB, preferred rescue intervention was increase of NMB from standard to deep level; second option, if available, was to raise insufflation pressure from low to standard. If the participant was already on deep NMB, preferred option, if available, was to raise insufflation pressure from low to standard. The anesthetist recorded any rescue actions performed. This measure presents number of participants: with any rescue action performed, with rescue change in depth of NMB, with rescue change in insufflation pressure level. Analysis included randomized participants with available data who had NMB and pneumoperitoneum for laparoscopic surgery, and did not convert to open surgery before NMB and/or pressure application. Participants were included in the treatment arm to which they were randomized.

End point type	Secondary

End point timeframe:

During surgery, approximate duration of 1-2 hours (Day 1)

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	30	31	30
Units: participants				
Number with rescue action performed	0	7	0	5
Number with rescue change in depth of NMB	0	5	0	0
Number with rescue change in pressure level	0	6	0	5

Statistical analyses

No statistical analyses for this end point

Secondary: Participant's daily assessment of overall pain at rest during post operative period: By treatment arm

End point title	Participant's daily assessment of overall pain at rest during post operative period: By treatment arm

End point description:

Participants rated pain at 1, 2, 4, 24 and 48 hours after the administration of sugammadex on day of surgery (Day 1), and daily (in the morning) from Day 3 to Day 8. Pain rating was made using an 11-point scale from 0 (no pain) to 10 (severe pain). Separate ratings were made for overall pain at rest, pain when provoked (e.g., due to participant transition from lying to sitting position) and shoulder pain at rest. This measure summarizes the assessment of overall pain at rest for the study days following the surgery. Analysis population was randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

End point type	Secondary

End point timeframe:

Days 2 to 8

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	23	40	26
Units: score on a scale				
arithmetic mean (standard deviation)				
24 hours after sugammadex dose (n=29, 22, 38, 25)	1.66 (± 1.45)	2.23 (± 2.09)	2.24 (± 1.62)	2.48 (± 2.2)
48 hours after sugammadex dose (n=27, 22, 33, 23)	1.22 (± 1.45)	1.41 (± 1.68)	1.73 (± 1.53)	1.83 (± 1.64)
Day 3 (N=22, 20, 30, 17)	0.86 (± 0.89)	1.65 (± 1.76)	1.87 (± 1.59)	2 (± 1.84)

Day 4 (N=28, 20, 37, 23)	0.89 (± 1.23)	1.05 (± 1.5)	1.76 (± 1.55)	1.04 (± 1.46)
Day 5 (N=27, 21, 38, 24)	0.89 (± 1.01)	1 (± 1.48)	1.45 (± 1.35)	0.92 (± 1.02)
Day 6 (N=27, 20, 35, 24)	0.56 (± 0.75)	0.85 (± 1.39)	1.31 (± 1.55)	0.75 (± 0.9)
Day 7 (N=27, 21, 34, 22)	0.48 (± 0.64)	0.95 (± 1.43)	1.18 (± 1.57)	0.59 (± 0.85)
Day 8 (N=28, 21, 35, 21)	0.54 (± 0.79)	0.81 (± 1.29)	0.94 (± 1.24)	0.43 (± 0.75)

Statistical analyses

No statistical analyses for this end point

Secondary: Participant's daily assessment of provoked pain during post operative period: By treatment arm

End point title	Participant's daily assessment of provoked pain during post operative period: By treatment arm

End point description:

Participants rated pain at 1, 2, 4, 24 and 48 hours after the administration of sugammadex on day of surgery (Day 1), and daily (in the morning) from Day 3 to Day 8. Pain rating was made using an 11-point scale from 0 (no pain) to 10 (severe pain). Separate ratings were made for overall pain at rest, pain when provoked (e.g., due to participant transition from lying to sitting position) and shoulder pain at rest. This measure summarizes the assessment of provoked pain for the study days following the surgery. Population for analysis included randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

End point type	Secondary

End point timeframe:

Days 2 to 8

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	23	40	26
Units: score on a scale				
arithmetic mean (standard deviation)				
24 hours after sugammadex dose (n=29, 22, 38, 25)	3.38 (± 2.37)	3.27 (± 2.76)	3.68 (± 1.92)	3.76 (± 2.47)
48 hours after sugammadex dose (n=27, 22, 33, 23)	2.67 (± 1.96)	2.14 (± 2.19)	2.94 (± 2.08)	2.91 (± 1.83)
Day 3 (N=22, 20, 30, 17)	2.23 (± 1.51)	2.5 (± 2.33)	2.97 (± 2.11)	3.24 (± 2.11)
Day 4 (N=28, 20, 37, 23)	2.25 (± 1.69)	1.85 (± 1.95)	3.05 (± 2.17)	1.91 (± 1.56)
Day 5 (N=27, 21, 38, 24)	1.93 (± 1.54)	1.9 (± 1.84)	2.58 (± 1.9)	1.71 (± 1.46)
Day 6 (N=27, 20, 35, 24)	1.7 (± 1.59)	1.4 (± 1.82)	2.51 (± 2.06)	1.42 (± 1.28)
Day 7 (N=27, 21, 34, 22)	1.37 (± 1.28)	1.52 (± 1.66)	2.21 (± 2.24)	1.23 (± 1.38)
Day 8 (N=28, 21, 35, 21)	1.21 (± 1.34)	1.38 (± 1.75)	1.91 (± 2.02)	0.81 (± 1.08)

Statistical analyses

No statistical analyses for this end point

Secondary: Participant's daily assessment of shoulder pain during post operative period: By treatment arm

End point title	Participant's daily assessment of shoulder pain during post operative period: By treatment arm

End point description:

Participants rated pain at 1, 2, 4, 24 and 48 hours after the administration of sugammadex on day of surgery (Day 1), and daily (in the morning) from Day 3 to Day 8. Pain rating was made using an 11-point scale from 0 (no pain) to 10 (severe pain). Separate ratings were made for overall pain at rest, pain when provoked (e.g., due to participant transition from lying to sitting position) and shoulder pain at rest. This measure summarizes the assessment of shoulder pain for the study days following the surgery. Population for analysis was randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition

End point type	Secondary

End point timeframe:

Days 2 to 8

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	23	40	26
Units: score on a scale				
arithmetic mean (standard deviation)				
24 hours after sugammadex dose (n=29, 22, 38, 25)	1 (± 1.71)	1.18 (± 2.15)	1.05 (± 1.66)	1.4 (± 2.33)
48 hours after sugammadex dose (n=27, 22, 33, 23)	0.41 (± 0.97)	0.64 (± 1.22)	0.76 (± 1.23)	0.96 (± 2.12)
Day 3 (N=22, 20, 30, 17)	0.18 (± 0.5)	0.8 (± 1.32)	0.67 (± 1.4)	0.88 (± 1.76)
Day 4 (N=28, 20, 37, 23)	0.32 (± 1.09)	0.55 (± 1.23)	0.7 (± 1.6)	0.61 (± 1.27)
Day 5 (N=27, 21, 38, 24)	0 (± 0)	0.43 (± 0.81)	0.68 (± 1.65)	0.25 (± 0.85)
Day 6 (N=27, 20, 35, 24)	0 (± 0)	0.15 (± 0.37)	0.63 (± 1.55)	0.21 (± 0.83)
Day 7 (N=27, 21, 34, 22)	0 (± 0)	0.14 (± 0.48)	0.68 (± 1.63)	0.23 (± 0.69)
Day 8 (N=28, 21, 35, 21)	0.04 (± 0.19)	0.24 (± 0.44)	0.66 (± 1.49)	0.14 (± 0.36)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants using pain/analgesic medication during post operative period: By treatment arm

End point title	Number of participants using pain/analgesic medication during post operative period: By treatment arm

End point description:

Post operative use of pain/analgesic medication by participant through Day 8 was recorded. Population

for analysis was randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

End point type	Secondary

End point timeframe:

Up to Day 8

End point values	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure	Deep NMB and Low Insufflation Pressure
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	23	40	26
Units: participants using pain medication				
Within 3 hours post surgery	31	21	37	24
3 to 24 hours post surgery	26	21	38	24
24 to 48 hours post surgery	26	22	35	23
Between 48 hours and end of Day 5	27	20	29	17
On Day 6, 7 or 8	19	14	25	10

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 8

Adverse event reporting additional description:

Includes randomized participants with available data who had NMB or pneumoperitoneum for laparoscopic surgery, or received sugammadex. Participants were included in arm corresponding to treatment actually received, which in case of rescue intervention was the post-intervention condition.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Standard NMB and Standard Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Standard insufflation pressure (starting pressure of 12 mmHg).

Reporting group title	Standard NMB and Low Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Standard NMB (depth of blockade at a targeted TOF ratio of 10%)/Low insufflation pressure (starting pressure of 8 mmHg).

Reporting group title	Deep NMB and Standard Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Standard insufflation pressure (starting pressure of 12 mmHg).

Reporting group title	Deep NMB and Low Insufflation Pressure

Reporting group description:

Treatment condition for this reporting group is Deep NMB (depth of blockade of 1-2 PTCs)/Low insufflation pressure (starting pressure of 8 mmHg).

Serious adverse events	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 33 (0.00%)	1 / 23 (4.35%)	1 / 40 (2.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	0 / 33 (0.00%)	1 / 23 (4.35%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Necrotising fasciitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Deep NMB and Low Insufflation Pressure		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 26 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Procedural haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Necrotising fasciitis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Standard NMB and Standard Insufflation Pressure	Standard NMB and Low Insufflation Pressure	Deep NMB and Standard Insufflation Pressure
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 33 (93.94%)	23 / 23 (100.00%)	39 / 40 (97.50%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 23 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3
Oxygen saturation decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0

Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	3 / 33 (9.09%)	1 / 23 (4.35%)	4 / 40 (10.00%)
occurrences (all)	3	2	5
Procedural pain			
subjects affected / exposed	28 / 33 (84.85%)	19 / 23 (82.61%)	34 / 40 (85.00%)
occurrences (all)	46	34	63
Procedural vomiting			
subjects affected / exposed	0 / 33 (0.00%)	1 / 23 (4.35%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Wound haemorrhage			
subjects affected / exposed	2 / 33 (6.06%)	4 / 23 (17.39%)	3 / 40 (7.50%)
occurrences (all)	2	4	3
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	2 / 23 (8.70%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 33 (6.06%)	1 / 23 (4.35%)	0 / 40 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	3 / 33 (9.09%)	3 / 23 (13.04%)	3 / 40 (7.50%)
occurrences (all)	3	4	4
Pyrexia			
subjects affected / exposed	4 / 33 (12.12%)	5 / 23 (21.74%)	3 / 40 (7.50%)
occurrences (all)	4	5	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 33 (6.06%)	0 / 23 (0.00%)	1 / 40 (2.50%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 33 (9.09%)	4 / 23 (17.39%)	4 / 40 (10.00%)
occurrences (all)	3	4	5
Abdominal pain upper			

subjects affected / exposed	2 / 33 (6.06%)	1 / 23 (4.35%)	1 / 40 (2.50%)
occurrences (all)	2	2	2
Constipation			
subjects affected / exposed	2 / 33 (6.06%)	1 / 23 (4.35%)	1 / 40 (2.50%)
occurrences (all)	2	1	1
Nausea			
subjects affected / exposed	11 / 33 (33.33%)	3 / 23 (13.04%)	8 / 40 (20.00%)
occurrences (all)	11	3	8
Vomiting			
subjects affected / exposed	5 / 33 (15.15%)	2 / 23 (8.70%)	6 / 40 (15.00%)
occurrences (all)	6	2	6
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 23 (4.35%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	3 / 33 (9.09%)	2 / 23 (8.70%)	0 / 40 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 23 (0.00%)	0 / 40 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	5 / 33 (15.15%)	5 / 23 (21.74%)	8 / 40 (20.00%)
occurrences (all)	5	5	8

Non-serious adverse events	Deep NMB and Low Insufflation Pressure		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Oxygen saturation decreased			

subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Procedural nausea			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	24 / 26 (92.31%)		
occurrences (all)	42		
Procedural vomiting			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	3		
Wound haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	2 / 26 (7.69%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	4 / 26 (15.38%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences (all)	1		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1		
Nausea subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Vomiting subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3		
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2		
Musculoskeletal pain subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2012	Amendment 01: Primary reason for amendment was to revise definition of standard NMB, methodology for administration of rocuronium to maintain NMB and scoring instruction on surgical conditions questionnaire.
10 June 2013	Amendment 02: Primary reason for amendment was to allow prematurely discontinued subjects with missing outcome for the primary and/or key secondary endpoints to be replaced.
06 August 2013	Amendment 03: Primary reason for amendment was to revise two exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported