Clinical trial results:
A Phase 4 Randomized, Active-Comparator Controlled Clinical Trial to Study the Safety of Sugammadex (MK-8616) for the Reversal of Neuromuscular Blockade Induced by Either Rocuronium Bromide or Vecuronium Bromide in American Society of Anesthesiologists (ASA) Class 3 or 4 Subjects

Summary

EudraCT number	2017-000187-15
Trial protocol	AT DK
Global end of trial date	04 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 September 2020
First version publication date	10 September 2020

Trial information

Trial identification

Sponsor protocol code	8616-145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03346057
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-8616-145

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	04 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2019
Global end of trial reached?	Yes
Global end of trial date	04 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to evaluate the safety of sugammadex for the reversal of neuromuscular blockade (NMB) induced by neuromuscular blockade agents (NMBA) rocuronium or vecuronium in adult American Society of Anesthesiologists (ASA) Physical Status Class 3 and 4 participants. The primary objectives of the study are to characterize the incidence of treatment emergent sinus bradycardia, treatment emergent sinus tachycardia, or other treatment emergent cardiac arrhythmias after administration of sugammadex and to evaluate the general safety of sugammadex in a population of ASA Class 3 and 4 participants in a surgical setting

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	20 December 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	Austria: 52
Country: Number of subjects enrolled	Denmark: 38
Country: Number of subjects enrolled	Germany: 114
Country: Number of subjects enrolled	United States: 140
Worldwide total number of subjects	344
EEA total number of subjects	204

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	218
85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Male and female participants with a body mass index (BMI) of <40 kg/m2, of American Society of Anesthesiologists (ASA) Class 3 or 4, and a planned surgical procedure requiring Neuromuscular Blockade (NMB) with either rocuronium or vecuronium were recruited.

Pre-assignment

Screening details:

Of 344 participants randomized to the study, 331 received at least one dose of study treatment (All Treated Population) and were evaluable for all safety analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sugammadex 2 mg/kg

Arm description:

Sugammadex 2 mg/kg administered as a single intravenous (IV) dose

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616, Bridion
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Following administration of NMBA (Rocuronium or Vecuronium) to achieve moderate NMB, participants received a single i.v. bolus of Sugammadex 2 mg/kg for reversal of moderate NMB. Moderate block is a level of NMB in which peripheral nerve stimulation elicits one to four muscle twitches.

Investigational medicinal product name	Vecuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Vecuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Rocuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Arm title	Sugammadex 4 mg/kg

Arm description:

Sugammadex 4 mg/kg administered as a single IV dose

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616, Bridion
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Following administration of NMBA (Rocuronium or Vecuronium) to achieve deep NMB, participants received a single i.v. bolus of Sugammadex 4 mg/kg for reversal of deep NMB. Deep block is a level of NMB in which peripheral nerve stimulation elicits no muscle twitches and high-frequency muscle stimulation elicits minimal levels of muscle contraction.

Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Rocuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Investigational medicinal product name	Vecuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Vecuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Arm title	Sugammadex 16 mg/kg

Arm description:

Sugammadex 16 mg/kg administered as a single IV dose

Arm type	Experimental
Investigational medicinal product name	Sugammadex
Investigational medicinal product code	
Other name	MK-8616, Bridion
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Following administration of NMBA (Rocuronium) to achieve deep NMB, participants received a single i.v. bolus of Sugammadex 16 mg/kg for reversal of deep NMB. Deep block is a level of NMB in which peripheral nerve stimulation elicits no muscle twitches and high-frequency muscle stimulation elicits minimal levels of muscle contraction.

Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Rocuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Arm title	Neostigmine + Glycopyrrolate

Arm description:

Neostigmine 50 µg/kg (up to 5 mg maximum dose) plus glycopyrrolate 10 µg/kg (up to 1 mg maximum dose) administered as a single IV dose

Arm type	Active comparator
Investigational medicinal product name	Neostigmine + Glycopyrrolate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Following administration of NMBA (Rocuronium or Vecuronium) to achieve moderate NMB, participants received a single i.v. bolus of Neostigmine (50 µg/kg; 5 mg maximum) and Glycopyrrolate (10 µg/kg; 1 mg maximum) for reversal of moderate NMB. Moderate block is a level of NMB in which peripheral nerve stimulation elicits one to four muscle twitches.

Investigational medicinal product name	Vecuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Vecuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Investigational medicinal product name	Rocuronium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

To achieve NMB, participants received steroidal NMBA Rocuronium Bromide administered via IV infusion and dosed according to participant body weight. NMBAs were concomitant medications used per label and at Investigator's discretion as an adjunct to general anesthesia.

Number of subjects in period 1	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg
Started	111	112	68
Treated	105	107	68
Completed	104	104	67
Not completed	7	8	1
Adverse event, serious fatal	1	2	-
Physician decision	3	2	-
Consent withdrawn by subject	1	-	-
Renal Insufficiency - Not Treated	1	-	-
Randomization Mistake - Not Treated	1	1	-
Lost to follow-up	-	2	1
Ineligible For Study - Not Treated	-	1	-

Number of subjects in period 1	Neostigmine + Glycopyrrolate

Started	53
Treated	51
Completed	51
Not completed	2
Adverse event, serious fatal	-
Physician decision	2
Consent withdrawn by subject	-
Renal Insufficiency - Not Treated	-
Randomization Mistake - Not Treated	-
Lost to follow-up	-
Ineligible For Study - Not Treated	-

Baseline characteristics

Reporting groups	
Reporting group title	Sugammadex 2 mg/kg
Reporting group description:	
Sugammadex 2 mg/kg administered as a single intravenous (IV) dose	
Reporting group title	Sugammadex 4 mg/kg
Reporting group description:	
Sugammadex 4 mg/kg administered as a single IV dose	
Reporting group title	Sugammadex 16 mg/kg
Reporting group description:	
Sugammadex 16 mg/kg administered as a single IV dose	
Reporting group title	Neostigmine + Glycopyrrolate
Reporting group description:	
Neostigmine 50 µg/kg (up to 5 mg maximum dose) plus glycopyrrolate 10 µg/kg (up to 1 mg maximum dose) administered as a single IV dose	

Reporting group values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg
Number of subjects	111	112	68
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	69.5	67.8	69.4
standard deviation	± 10.7	± 12.1	± 10.0
Sex: Female, Male Units:			
Female	50	41	29
Male	61	71	39
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	2	0	0
Black or African American	3	9	2
White	106	103	66
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	6	0
Not Hispanic or Latino	109	105	67
Unknown or Not Reported	0	1	1
Participant Stratifications Units: Subjects			
Rocuronium, ASA Class 3	50	49	51
Rocuronium, ASA Class 4	15	18	17
Vecuronium, ASA Class 3	29	31	0
Vecuronium, ASA Class 4	11	11	0
Missing	6	3	0

Reporting group values	Neostigmine + Glycopyrrolate	Total	
Number of subjects	53	344	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous Units: Years			
arithmetic mean	66.6		
standard deviation	± 10.9	-	
Sex: Female, Male Units:			
Female	15	135	
Male	38	209	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	2	
Black or African American	3	17	
White	50	325	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	10	
Not Hispanic or Latino	51	332	
Unknown or Not Reported	0	2	
Participant Stratifications			

Units: Subjects			
Rocuronium, ASA Class 3	25	175	
Rocuronium, ASA Class 4	8	58	
Vecuronium, ASA Class 3	14	74	
Vecuronium, ASA Class 4	5	27	
Missing	1	10	

End points

End points reporting groups

Reporting group title	Sugammadex 2 mg/kg
Reporting group description:	
Sugammadex 2 mg/kg administered as a single intravenous (IV) dose	
Reporting group title	Sugammadex 4 mg/kg
Reporting group description:	
Sugammadex 4 mg/kg administered as a single IV dose	
Reporting group title	Sugammadex 16 mg/kg
Reporting group description:	
Sugammadex 16 mg/kg administered as a single IV dose	
Reporting group title	Neostigmine + Glycopyrrolate
Reporting group description:	
Neostigmine 50 µg/kg (up to 5 mg maximum dose) plus glycopyrrolate 10 µg/kg (up to 1 mg maximum dose) administered as a single IV dose	

Primary: Percentage of Participants With Treatment-Emergent Sinus Bradycardia Events

End point title	Percentage of Participants With Treatment-Emergent Sinus Bradycardia Events
End point description:	
The percentage of participants experiencing treatment-emergent sinus bradycardia events was identified with continuous electrocardiogram (ECG) monitoring. Treatment-emergent sinus bradycardia defined as a heart rate <60 beats per minute (bpm) that has also decreased more than 20% compared to participant baseline heart rate value, sustained for at least 1 minute after administration of study intervention. Treatment-emergent sinus bradycardia events may or may not have been considered an adverse event (AE), as determined by investigator judgment. All randomized participants who received at least one dose of study intervention were analyzed.	
End point type	Primary
End point timeframe:	
Up to approximately 35 minutes post-administration	

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of participants				
number (not applicable)	1.0	1.9	7.4	7.8

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by neuromuscular blocking agent (NMBA) and American Society of Anesthesiologists (ASA) class was used to provide estimated between-treatment difference, 95%

confidence interval, and p-value

Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.5
upper limit	-0.8

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.058
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3
upper limit	0.2

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.73
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	8.6

Primary: Percentage of Participants With Treatment-Emergent Sinus Tachycardia Events

End point title	Percentage of Participants With Treatment-Emergent Sinus Tachycardia Events

End point description:

The percentage of participants experiencing treatment-emergent sinus tachycardia events was identified with continuous ECG monitoring. Treatment-emergent sinus tachycardia is defined as a heart rate ≥100 bpm that has also increased more than 20% compared to participant baseline heart rate value, sustained for at least 1 minute after administration of study intervention. Treatment-emergent sinus tachycardia events may or may not have been considered an AE, as determined by investigator judgment. All randomized participants who received at least one dose of study intervention were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 35 minutes post-administration

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of participants				
number (not applicable)	6.7	9.3	8.8	21.6

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-14.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.8
upper limit	-4

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value	
Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.036
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.1
upper limit	-0.8

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value	
Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.158
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.6
upper limit	3.6

Primary: Percentage of Participants With Other Treatment-Emergent Cardiac Arrhythmia Events

End point title	Percentage of Participants With Other Treatment-Emergent

	Cardiac Arrhythmia Events

End point description:

The percentage of participants experiencing other treatment-emergent cardiac arrhythmia events was identified with continuous ECG monitoring. Other treatment-emergent cardiac arrhythmias were defined as new or worsening arrhythmias (e.g., atrial fibrillation, atrial tachycardia, ventricular fibrillation, or ventricular tachyarrhythmia), sustained for at least 1 minute after administration of study intervention. Worsening arrhythmia events may or may not have been considered an AE, as determined by investigator judgment. All randomized participants who received at least one dose of study intervention were analyzed.

End point type	Primary

End point timeframe:

Up to approximately 35 minutes post-administration

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of participants				
number (not applicable)	1.0	0.0	1.5	2.0

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.637
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.4
upper limit	4

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.134
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	1.5

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference, 95% confidence interval, and p-value

Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.577
Method	Stratified Miettinen & Nurminen method
Parameter estimate	Estimated Difference in percentage
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	5.8

Primary: Percentage of Participants Experiencing an Adverse Event (AE) Up To 7 Days After Administration of Study Intervention

End point title	Percentage of Participants Experiencing an Adverse Event (AE) Up To 7 Days After Administration of Study Intervention

End point description:

As per the protocol primary analysis, the percentage of participants experiencing an AE up to 7 days after administration of study intervention was reported. An AE was defined as any untoward medical occurrence in a participant which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition that was temporally associated with the use of the Sponsor’s product was also an AE. All randomized participants who received at least one dose of study intervention were analyzed.

End point type	Primary

End point timeframe:

Up to 7 days

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of participants				
number (not applicable)	94.3	88.8	92.6	88.2

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval	
Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	18.5

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval	
Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	13.1

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval

Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	17.7

Primary: Percentage of Participants Experiencing a Serious Adverse Event (SAE) Up To 7 Days After Administration of Study Intervention

End point title	Percentage of Participants Experiencing a Serious Adverse Event (SAE) Up To 7 Days After Administration of Study Intervention

End point description:

As per the protocol primary analysis, the percentage of participants experiencing an SAE up to 7 days after administration of study intervention was reported. An SAE was an adverse event that: resulted in death; was life threatening; resulted in persistent or significant disability or incapacity; resulted in or prolonged an existing inpatient hospitalization; was a congenital anomaly or birth defect; was an other important medical event, was a cancer; or was associated with an overdose. All randomized participants who received at least one dose of study intervention were analyzed.

End point type	Primary

End point timeframe:

Up to 7 days

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of Participants				
number (not applicable)	11.4	7.5	10.3	5.9

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval

Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	14.3

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval	
Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	9.3

Statistical analysis title	Estimated Difference in percentage of participants
Statistical analysis description:	
Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval	
Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.1
upper limit	12.7

Primary: Percentage of Participants Experiencing an Event of Clinical Interest (ECI)

Up To 7 Days After Administration of Study Intervention

End point title	Percentage of Participants Experiencing an Event of Clinical Interest (ECI) Up To 7 Days After Administration of Study Intervention

End point description:

As per the protocol primary analysis, the percentage of participants experiencing an ECI up to 7 days after administration of study intervention was reported. ECIs were a discrete set of both AEs and SAEs, specifically designated as such for the trial. For the purposes of this investigation, ECIs included 1) drug-induced liver injury; 2) clinically-relevant arrhythmias, inclusive of bradycardia and tachycardia defined as events necessitating intervention, as determined by investigator judgment; and 3) instances of hypersensitivity and/or anaphylaxis adjudicated by an external expert Adjudication Committee. All randomized participants who received at least one dose of study intervention were analyzed. A participant could have experienced more than one type of ECI.

End point type	Primary

End point timeframe:

Up to 7 days

End point values	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg	Neostigmine + Glycopyrrolate
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	105	107	68	51
Units: Percentage of participants				
number (not applicable)				
With one or more ECIs	1.9	5.6	7.4	3.9
Adjudicated Hypersensitivity	0.0	0.0	0.0	0.0
Adjudicated Anaphylaxis	0.0	0.0	0.0	0.0
Clinically Relevant Bradycardia	0.0	2.8	0.0	2.0
Clinically Relevant Tachycardia	1.9	1.9	5.9	0.0
Other Clinically Relevant Cardiac Arrhythmia	0.0	0.9	1.5	2.0
Drug Induced Liver Injury	0.0	0.0	0.0	0.0

Statistical analyses

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

The percentage of participants experiencing one or more ECIs was compared between the Sugammadex 2 mg/kg arm and the Neostigmine plus Glycopyrrolate arm. Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval

Comparison groups	Sugammadex 2 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	-2.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	3.8

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

The percentage of participants experiencing one or more ECIs was compared between the Sugammadex 4 mg/kg arm and the Neostigmine plus Glycopyrrolate arm. Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval

Comparison groups	Sugammadex 4 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.1
upper limit	8.4

Statistical analysis title	Estimated Difference in percentage of participants

Statistical analysis description:

The percentage of participants experiencing one or more ECIs was compared between the Sugammadex 16 mg/kg arm and the Neostigmine plus Glycopyrrolate arm. Miettinen & Nurminen method stratified by NMBA and ASA was used to provide estimated between-treatment difference and 95% confidence interval

Comparison groups	Sugammadex 16 mg/kg v Neostigmine + Glycopyrrolate
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Estimated Difference in percentage
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	11.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 21 days.

Adverse event reporting additional description:

All-Cause Mortality reported for all randomized participants (N = 344: Sugammadex 2 mg/kg: n = 111, Sugammadex 4 mg/kg: n = 112, Sugammadex 16 mg/kg: n = 68, and Neostigmine + Glycopyrrolate: n = 53). Serious AEs and Other AEs were reported for all randomized participants who received at least 1 dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Sugammadex 2 mg/kg

Reporting group description:

Sugammadex 2 mg/kg administered as a single intravenous (IV) dose

Reporting group title	Sugammadex 4 mg/kg

Reporting group description:

Sugammadex 4 mg/kg administered as a single intravenous (IV) dose

Reporting group title	Sugammadex 16 mg/kg

Reporting group description:

Sugammadex 16 mg/kg administered as a single intravenous (IV) dose

Reporting group title	Neostigmine + Glycopyrrolate

Reporting group description:

Neostigmine 50 µg/kg (up to 5 mg maximum dose) plus glycopyrrolate 10 µg/kg (up to 1 mg maximum dose) administered as a single IV dose

Serious adverse events	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 105 (15.24%)	12 / 107 (11.21%)	9 / 68 (13.24%)
number of deaths (all causes)	1	2	0
number of deaths resulting from adverse events	0	0	0
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	2 / 105 (1.90%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic leak			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Fascial rupture			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma necrosis			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incision site pain			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Postoperative delirium			
subjects affected / exposed	1 / 105 (0.95%)	1 / 107 (0.93%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Postoperative ileus			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	0 / 68 (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
Procedural pain			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Vascular graft occlusion			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocele			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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

Cardiac arrest			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Tachycardia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	0 / 68 (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
Dehiscence			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hernia			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	2 / 105 (1.90%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	0 / 68 (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
Vomiting			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Dyspnoea			

subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Pneumonia aspiration			
subjects affected / exposed	2 / 105 (1.90%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 105 (0.95%)	1 / 107 (0.93%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous emphysema			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 105 (0.00%)	2 / 107 (1.87%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder haemorrhage			

subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder abscess			
subjects affected / exposed	0 / 105 (0.00%)	0 / 107 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	1 / 105 (0.95%)	0 / 107 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Purulent discharge			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 105 (0.00%)	1 / 107 (0.93%)	0 / 68 (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

Serious adverse events	Neostigmine + Glycopyrrolate		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 51 (7.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
C-reactive protein increased			

subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Abdominal wound dehiscence				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Accidental overdose				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anastomotic leak				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fascial rupture				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stoma necrosis				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incision site pain				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haematoma				

subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative delirium				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative ileus				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural pain				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention postoperative				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular graft occlusion				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphocele				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				

Acute myocardial infarction			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions				
Catheter site haemorrhage				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehiscence				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hernia				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Ileus				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 51 (1.96%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 51 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subcutaneous emphysema			

subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gallbladder abscess			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural infection			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Purulent discharge			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sugammadex 2 mg/kg	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	89 / 105 (84.76%)	89 / 107 (83.18%)	60 / 68 (88.24%)
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	25 / 105 (23.81%)	31 / 107 (28.97%)	19 / 68 (27.94%)
occurrences (all)	26	31	19
Postoperative hypertension			
subjects affected / exposed	1 / 105 (0.95%)	3 / 107 (2.80%)	4 / 68 (5.88%)
occurrences (all)	1	3	4
Procedural nausea			
subjects affected / exposed	4 / 105 (3.81%)	2 / 107 (1.87%)	5 / 68 (7.35%)
occurrences (all)	4	2	5
Procedural pain			
subjects affected / exposed	58 / 105 (55.24%)	56 / 107 (52.34%)	31 / 68 (45.59%)
occurrences (all)	66	67	38
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 105 (5.71%)	6 / 107 (5.61%)	1 / 68 (1.47%)
occurrences (all)	8	6	1
Hypotension			
subjects affected / exposed	6 / 105 (5.71%)	8 / 107 (7.48%)	5 / 68 (7.35%)
occurrences (all)	6	8	6
Cardiac disorders			
Bradycardia			
subjects affected / exposed	4 / 105 (3.81%)	4 / 107 (3.74%)	1 / 68 (1.47%)
occurrences (all)	4	4	1
Sinus tachycardia			
subjects affected / exposed	2 / 105 (1.90%)	3 / 107 (2.80%)	5 / 68 (7.35%)
occurrences (all)	2	3	5

Tachycardia			
subjects affected / exposed	5 / 105 (4.76%)	8 / 107 (7.48%)	3 / 68 (4.41%)
occurrences (all)	5	8	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 105 (2.86%)	5 / 107 (4.67%)	2 / 68 (2.94%)
occurrences (all)	4	5	2
Hypoaesthesia			
subjects affected / exposed	3 / 105 (2.86%)	3 / 107 (2.80%)	2 / 68 (2.94%)
occurrences (all)	3	3	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 105 (1.90%)	6 / 107 (5.61%)	2 / 68 (2.94%)
occurrences (all)	2	6	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 105 (6.67%)	7 / 107 (6.54%)	6 / 68 (8.82%)
occurrences (all)	7	7	6
Diarrhoea			
subjects affected / exposed	2 / 105 (1.90%)	6 / 107 (5.61%)	0 / 68 (0.00%)
occurrences (all)	2	6	0
Nausea			
subjects affected / exposed	17 / 105 (16.19%)	19 / 107 (17.76%)	13 / 68 (19.12%)
occurrences (all)	18	20	14
Vomiting			
subjects affected / exposed	4 / 105 (3.81%)	6 / 107 (5.61%)	3 / 68 (4.41%)
occurrences (all)	4	6	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 105 (1.90%)	2 / 107 (1.87%)	0 / 68 (0.00%)
occurrences (all)	2	2	0
Hypoxia			
subjects affected / exposed	4 / 105 (3.81%)	4 / 107 (3.74%)	4 / 68 (5.88%)
occurrences (all)	6	4	4
Psychiatric disorders			

Insomnia			
subjects affected / exposed	3 / 105 (2.86%)	8 / 107 (7.48%)	4 / 68 (5.88%)
occurrences (all)	3	8	4
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 105 (5.71%)	3 / 107 (2.80%)	4 / 68 (5.88%)
occurrences (all)	6	3	4

Non-serious adverse events	Neostigmine + Glycopyrrolate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 51 (80.39%)		
Injury, poisoning and procedural complications			
Incision site pain			
subjects affected / exposed	9 / 51 (17.65%)		
occurrences (all)	9		
Postoperative hypertension			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Procedural nausea			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	27 / 51 (52.94%)		
occurrences (all)	31		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Sinus tachycardia			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	5		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 51 (7.84%)		
occurrences (all)	4		
Hypoaesthesia			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	7 / 51 (13.73%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	2 / 51 (3.92%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 51 (5.88%)		
occurrences (all)	3		
Hypoxia			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences (all)	0		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 51 (3.92%) 2		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 51 (1.96%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2018	The major change in amendment 1 was to provide flexibility to trial sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported