Official Protocol Title:	A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants
NCT number:	NCT03351608
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Title Page

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Protocol Title: A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants

Protocol Number: 089-01

Compound Number: MK-8616

Sponsor Name and Legal Registered Address:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND NUMBER: [68029]

EudraCT NUMBER: [2017-000692-92]

Approval Date: 18-Aug-2017

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

Protocol Amendment Summary of Changes

Amendment 01

Overall Rationale for the Amendment:

To clarify the safety endpoints of treatment-emergent bradycardia and provide information regarding the criteria for stopping the trial.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 5.4.1.2 Safety Endpoints	Clarification of safety endpoint: Treatment-emergent relative bradycardia	The definition of treatment-emergent relative bradycardia was added to align with regulatory requirements.
Section 5.4 Scientific Rationale for Study Design; Section 5.4.1.2 Safety Endpoints; Section 10.7 Interim Analyses	Addition of text regarding trial stopping criteria	The eDMC charter will contain the details of the stopping criteria.
Section 10.2 Responsibility for Analyses/ In-House Blinding	Added text to explain the role of the unblinded statistician and programmer	Clarification provided for role of the unblinded statistician and programmer
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

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1. Synopsis

Protocol Title:

A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants

Short Title:

PK, safety and efficacy of sugammadex in children 2 to <17 years of age

Objectives/Hypotheses and Endpoints:

For male/female participants between the ages of 2 to <17 years administered a NMBA (rocuronium or vecuronium) for either moderate or deep block:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate neuromuscular blockade (NMB) or deep NMB (Part A).	• Pharmacokinetic parameters: Area under the plasma concentration-time curve (AUC), clearance (CL), apparent volume of distribution (V_z), maximum plasma concentration (C_{max}), and half-life ($t_{1/2}$)
• Objective: To evaluate the safety and tolerability of sugammadex (data will be pooled across Part A and Part B of the study).	• Number of participants experiencing adverse events.
• Objective: To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B). • Hypothesis: Sugammadex is superior to neostigmine in reversing moderate NMB as measured by time to recovery to a train-of-four (TOF) ratio of ≥0.9.	• Time to recovery to a TOF ratio of ≥0.9.
Secondary	
• Objective: To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	• Time to recovery to a TOF ratio of ≥0.8. • Time to recovery to a TOF ratio of ≥0.7.

Overall Design:

Trial Phase	Phase 4
Clinical Indication	Reversal of neuromuscular blockade (NMB)
Population	Pediatric participants aged 2 to <17 years who have received rocuronium or vecuronium for either moderate or deep block.
Trial Type	Interventional
Type of Design	Randomized, multi-site, parallel design, active comparator controlled
Type of Control	Active control without placebo
Trial Blinding	Double-blind
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 4 years from the time the first participant signs the informed consent/assent until the last participant's last study-related phone call or visit.

Number of Participants:

Approximately 238 participants will be enrolled.

Treatment Groups and Duration:

Treatment Groups	**Treatment groups:** Part A: • Moderate block and reversal with sugammadex 2 mg/kg; or • Deep block and reversal with sugammadex 4 mg/kg Part B: • Moderate block and reversal with sugammadex 2 mg/kg; or • Moderate block and reversal with neostigmine 50 mcg/kg; or • Deep block and reversal with sugammadex 4 mg/kg

Duration of Participation	Each participant will participate in the trial for approximately 28 days from the time the participant (or parent/legally acceptable representative) signs the informed consent form through the final contact. After a screening period of up to 14 days, each participant will receive a single bolus dose of assigned study treatment. After the end of treatment, each participant will undergo a post-treatment safety visit between 4 and 36 hours after administration of study drug. A follow-up contact (phone call or visit) with the participant (and/or parent/legally acceptable representative) will take place at approximately 14 days post-treatment.

A list of abbreviations used in this document can be found in Appendix 1.

2. Schedule of Activities (SoA)

Trial Period	Screening	Treatment	Follow-up		Notes
Visit Number/Title	**1/Screening**	**2/Peri-anesthetic period**	**3/Post-anesthetic period**	**4/Follow-up contact**	**Visit 1 (Screening) and Visit 2 may occur on the same day** **Follow-up contact may occur via telephone or visit dependent upon hospitalization status**
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**-14 to -1 Days**	**±0 days**	**See Notes**	**+2 days**	**Visit 3 should occur between 4 and 36 hours after administration of study treatment**
Administrative Procedures					
Informed Consent/Assent	X				
Participant Identification Card	X				
Screening Number Assignment	X				
Medical History	X				
Inclusion/Exclusion Criteria	X	X			Visit 2: Inclusion/exclusion criteria will be reviewed for any changes from screening (Visit 1)
Prior/Concomitant Medication Review	X	X	X	X	
Treatment Assignment or Randomization		X			If needed to aid drug preparation, treatment assignment may be performed in IRT the day before Visit 2. See Sections 9.1.7 and 9.1.8.
Administration of NMBA		X			
Administration of Study Treatment		X			For any given participant, the person who administers the study treatment and the person who performs the blinded safety assessments must be different qualified individuals.

Trial Period	Screening	Treatment	Follow-up		Notes
Visit Number/Title	**1/Screening**	**2/Peri-anesthetic period**	**3/Post-anesthetic period**	**4/Follow-up contact**	**Visit 1 (Screening) and Visit 2 may occur on the same day** **Follow-up contact may occur via telephone or visit dependent upon hospitalization status**
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**-14 to -1 Days**	**±0 days**	**See Notes**	**+2 days**	**Visit 3 should occur between 4 and 36 hours after administration of study treatment**
Efficacy Procedures					
Neuromuscular Monitoring		X			Conducted using TOF-Watch® SX device.
Safety Procedures					
Full Physical Examination	X				
Targeted Physical Examination			X		To be collected by the blinded safety assessor.
Vital Signs (heart rate, blood pressure, temperature, respiratory rate, oxygen saturation)	X	X	X		For Visit 2, scheduled vitals are to be performed prior to administration of NMBA; prior to administration of study treatment; and 2, 5, 10 and 30 minutes after study treatment.
Height	X				
Weight	X	X			
Continuous ECG Monitoring		X			To occur at least 5 minutes before, during, and for 30 minutes following administration of study treatment.

Trial Period	Screening	Treatment	Follow-up		Notes
Visit Number/Title	**1/Screening**	**2/Peri-anesthetic period**	**3/Post-anesthetic period**	**4/Follow-up contact**	**Visit 1 (Screening) and Visit 2 may occur on the same day** **Follow-up contact may occur via telephone or visit dependent upon hospitalization status**
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**-14 to -1 Days**	**±0 days**	**See Notes**	**+2 days**	**Visit 3 should occur between 4 and 36 hours after administration of study treatment**
Urine Pregnancy Test, Serum β-hCG, as applicable	X	X			Urine or serum β-hCG test is required prior to surgery (or other clinical situation that requires administration of NMBA) in any young woman with onset of menarche. Serum β-hCG pregnancy test is required only if urine is positive, unless local requirements require otherwise. If Visit 1 (Screening) and Visit 2 occur on the same day, then the pregnancy test does not need to be repeated.
Hematology		X	X		Laboratory samples will be sent to a central laboratory for analysis. Visit 2: Samples need not be drawn if local lab results are available within 14 days of randomization. Visit 3: Samples need not be drawn if local lab results are (or will be) available within 24 hours after administration of study treatment.
Chemistry		X	X		Laboratory samples will be sent to a central laboratory for analysis. Visit 2: Samples need not be drawn if local lab results are available within 14 days of randomization. Visit 3: Samples need not be drawn if local lab results are (or will be) available within 24 hours after administration of study treatment.

Trial Period	Screening	Treatment	Follow-up		Notes
Visit Number/Title	**1/Screening**	**2/Peri-anesthetic period**	**3/Post-anesthetic period**	**4/Follow-up contact**	**Visit 1 (Screening) and Visit 2 may occur on the same day** **Follow-up contact may occur via telephone or visit dependent upon hospitalization status**
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**-14 to -1 Days**	**±0 days**	**See Notes**	**+2 days**	**Visit 3 should occur between 4 and 36 hours after administration of study treatment**
eGFR	X				Performed only for participants with history of renal impairment, eGFR to be calculated with revised Schwartz estimate using serum creatinine at Visit 1 (Screening).
AE/SAE/ECI Review	X	X	X	X	Visit 3 only: Must be performed by blinded safety assessor.
Adverse Device Events Monitoring		X			TOF-Watch® SX device
Pharmacokinetics					
PK Sampling		X	X		For PK, 5 to 6 samples will be drawn at approximately the following time points: 2, 15, 30, 60 minutes; 5, 10 hours after study treatment administration. (See Section 9.6 for details) PK is required for Part A of the study only.
Abbreviations: AE = adverse event, β-hCG = β-human chorionic gonadotropin, ECI = event of clinical interest, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, NMBA = neuromuscular blocking agent, SAE = serious adverse event, SCr = serum creatinine, TOF = train-of-four					

3. Introduction

3.1 Study Rationale

Sugammadex sodium, herein referred to as sugammadex, has been demonstrated to be safe and effective in reversing rocuronium and vecuronium induced neuromuscular blockade (NMB) in adults; however, clinical trial data in children is limited. The current trial aims to demonstrate that sugammadex is generally safe and effective for reversing both moderate and deep block after rocuronium or vecuronium induced NMB in children and adolescents.

Part A of this trial will evaluate the pharmacokinetic (PK) parameters of the 2 mg/kg and 4mg/kg doses of sugammadex in children and adolescents. The PK data that is generated from Part A will be evaluated to ensure that the doses intended to be administered in Part B (2mg/kg and 4 mg/kg) demonstrate similar exposures to the approved doses in adults. Although limited, the pediatric data from a previous PK study [Trial 19.4.306 (P034)] [Plaud, B., et al 2009] provide preliminary evidence that the intended doses will exhibit comparable exposures in the pediatric age groups when compared to adults.

3.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-8616.

3.2.1 Pharmaceutical and Therapeutic Background

Neuromuscular blockade is an important component of many surgical and medical procedures, as it provides muscle relaxation and reduces patient movement. In current anesthesia practice, reversal agents of NMB are often administered at the end of the procedure to aid the recovery of muscle function and prevent residual NMB after the procedure. Prior to the availability of sugammadex, all clinically used reversal agents (eg, neostigmine, edrophonium) were acetylcholinesterase inhibitors. These agents achieved reversal of NMB, but at the cost of multiple side effects due to their nonselective potentiation of cholinergic neurotransmission. Moreover, these agents are only able to reverse NMB at a moderate level of block, in which neuromuscular transmission is partially recovered, which limits their utility.

Sugammadex is a modified gamma-cyclodextrin administered at the end of surgical procedures to reverse paralysis induced by the steroidal neuromuscular blocking agents (NMBAs) rocuronium and vecuronium. Sugammadex accomplishes this reversal of NMB through formation of high affinity sugammadex:NMBA complexes. Given the very high binding affinity and low dissociation rate of the complex, the bound NMBAs can no longer act at the neuromuscular junction, thereby restoring muscle function. The complex is then renally eliminated. Since this mechanism of action does not involve direct interaction with cholinergic systems, it circumvents undesired side effects associated with acetylcholinesterase inhibitors. Furthermore, sugammadex does not require the presence of neuromuscular activity before administration, and is therefore effective in reversal of both moderate and deep levels of NMB.

Sugammadex, as well as the complex of sugammadex and rocuronium or vecuronium, is cleared almost entirely via the kidney. In adults, there are no dose adjustments required for mild or

moderate renal impairment. The use of sugammadex in severe renal impairment is not recommended.

Sugammadex has been extensively studied in 58 clinical trials with a total of 5999 exposures to intravenous (IV) sugammadex in 4453 unique individuals, establishing a well-characterized safety and efficacy profile in adults. Additionally, sugammadex is currently approved in more than 83 countries and marketed in more than 50 countries, with an estimated >30 million exposures worldwide at the time of authoring this document.

In the pediatric population, sugammadex was studied in a randomized placebo-controlled trial [Trial 19.4.306 (P034)] [Plaud, B., et al 2009] that evaluated reversal of rocuronium-induced moderate NMB (n=64). The trial evaluated children and adolescents across 3 age categories: infants (28 days to 23 months inclusive [n=8]); children (2 to 11 years inclusive [n=26]); adolescents (12 to 17 years inclusive [n=30]). The PK, efficacy, and safety results were generally consistent with the adult profile. No data on the use of sugammadex in neonates is available.

3.2.2 Pre-clinical and Clinical Trials

Refer to the IB for information on the pre-clinical and clinical development of sugammadex.

In addition, there are 2 other clinical trials planned to be conducted in an adult population:

1) A safety trial with adult participants who are categorized as American Society of Anesthesiologists (ASA) Class 3 or 4.

2) A safety and efficacy trial with adult participants who are morbidly obese.

3.3 Benefit/Risk Assessment

The Sponsor considers that the currently approved adult doses are appropriate for assessment to provide the optimal benefit/risk ratio in this trial, based on the adult Phase 3 trials, subsequent post marketing data, and the pediatric information collected to date in prior sugammadex trials.

Sugammadex has a positive benefit-risk profile and is well tolerated in the approved indications as described in the Investigator's Brochure. It has specifically been shown to be superior (faster recovery as well as effective in a higher proportion of treated participants) to both placebo and neostigmine for reversal of moderate and deep NMB. Reversal of deep NMB is a unique benefit of sugammadex compared to other current treatments, which can only reverse moderate block. From a risk perspective, sugammadex has been shown to be generally safe and well tolerated. The use of sugammadex at recommended doses is associated with a low risk of residual NMB or recurrence of NMB compared with current treatment.

Additional details regarding specific benefits and risks for participants in this clinical trial may be found in the accompanying IB and informed consent documents.

4. Objectives/Hypotheses and Endpoints

For male/female participants between the ages of 2 to <17 years administered a NMBA for either moderate or deep block (rocuronium or vecuronium):

Objective/Hypothesis	Endpoint
Primary	
• Objective: To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	• Pharmacokinetic parameters: AUC, CL, V_z, C_{max}, and $t_{1/2}$.
• Objective: To evaluate safety and tolerability of sugammadex (data will be pooled across Part A and Part B of the study).	• Number of participants experiencing adverse events.
• Objective: To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B). • Hypothesis: Sugammadex is superior to neostigmine in reversing moderate neuromuscular blockade as measured by time to recovery to a train-of-four (TOF) ratio of ≥0.9.	• Time to recovery to a TOF ratio of ≥0.9.
Secondary	
• Objective: To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	• Time to recovery to a TOF ratio of ≥0.8. • Time to recovery to a TOF ratio of ≥0.7.
Tertiary/Exploratory	
• Objective: To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	• Time to extubation: Interval from administration of reversal agent to removal of the endotracheal tube. • Time to OR discharge • Time to PACU discharge • Time to hospital discharge • Incidence of delayed recovery

5. Study Design

5.1 Overall Design

This is a randomized, active comparator-controlled, parallel group, multi-site, double-blinded trial of sugammadex in pediatric participants from 2 to <17 years of age for the reversal of NMB.

The design of the trial consists of a two-part structure (Part A and Part B). The purpose of the trial is to first identify the doses of sugammadex that will produce similar exposure in the 2 to <17 year old age group when compared to systemic exposure noted in adults following administration of the 2 mg/kg and 4 mg/kg doses (lead-in cohort Part A), followed by the assessment of safety and efficacy parameters (Part B). Once Part A of the study is complete, an interim analysis (IA) will be performed (prior to the commencement of enrollment in Part B) to evaluate PK and safety data. PK and safety data will be reviewed by a standing internal Data Monitoring Committee (siDMC) and safety data will be reviewed by an external Data Monitoring Committee (eDMC). Details are provided in Section 10.7.

All participants will receive a single dose of sugammadex or neostigmine to reverse NMB. Potential trial participants will have a planned non-emergent surgical procedure or clinical situation that requires moderate or deep NMB.

The sample size of the study is in alignment with the minimum number of participants required to obtain the relevant safety information for each level of NMB as specified by the Sponsor's commitments under the Pediatric Research Equity Act (PREA).

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

5.1.1 Study Diagram

The Study Diagram and Study Treatment Randomization are depicted in Figure 1 and Figure 2.

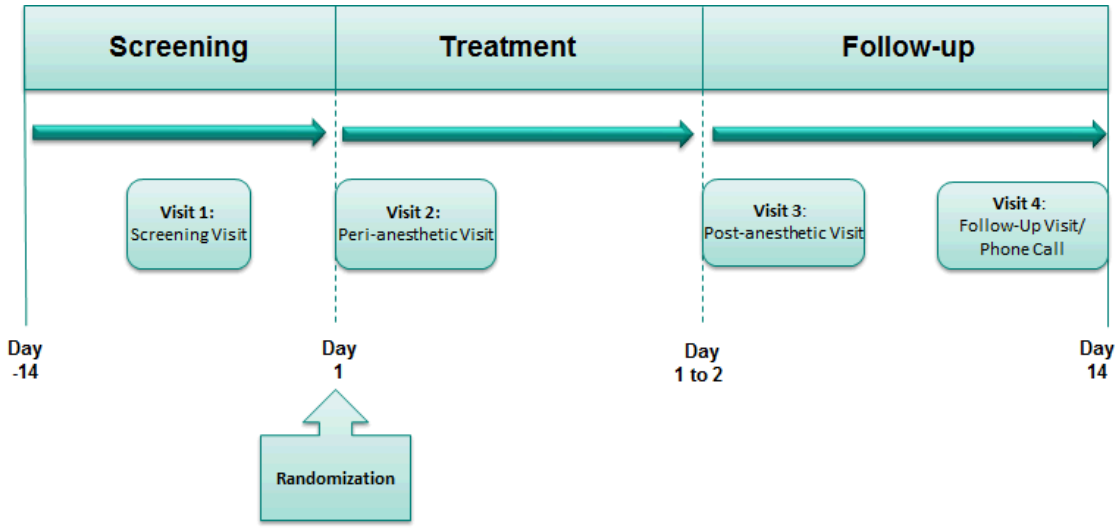

Figure 1 Study Diagram

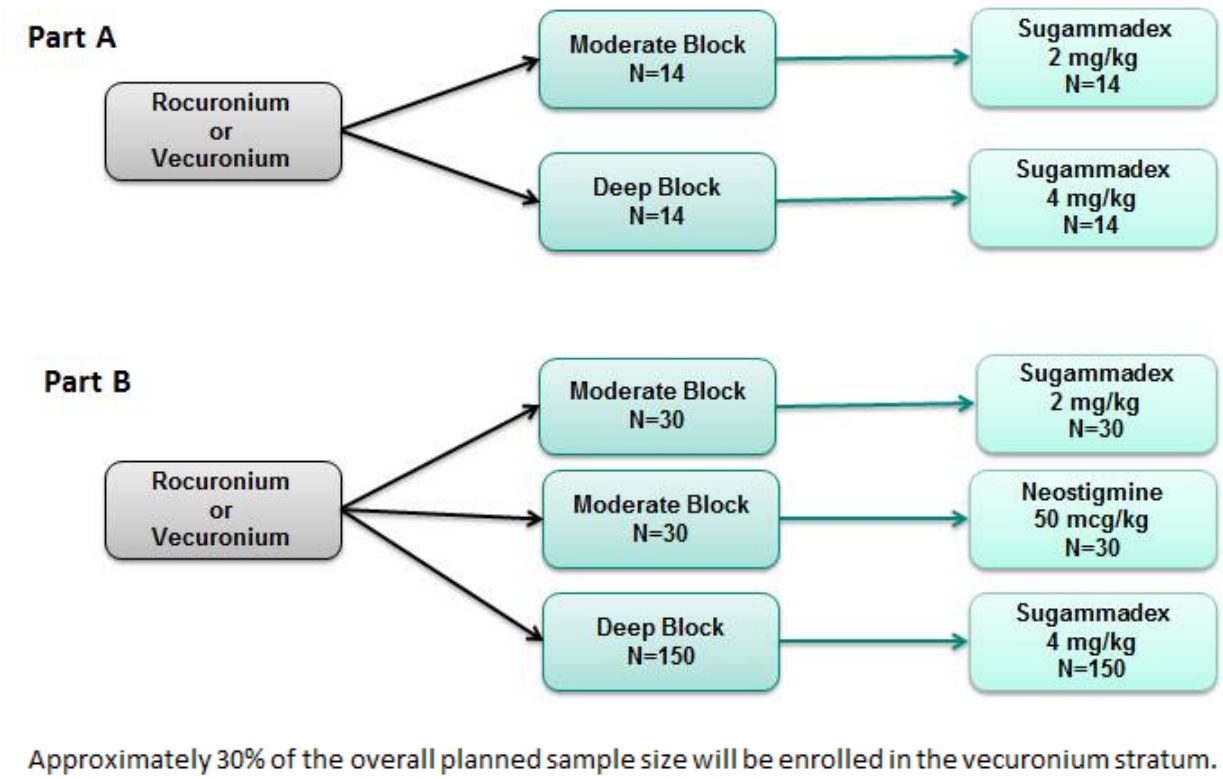

Figure 2 Study Treatment Randomization

5.2 Number of Participants

Approximately 238 participants will be enrolled in this study.

5.3 Beginning and End of Study Definition

The overall trial begins when the first participant signs the informed consent/assent form. The overall trial ends when the last participant completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the participant is unable to be contacted by the investigator).

5.3.1 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5.4 Scientific Rationale for Study Design

In accordance with the Sponsor's commitments under the PREA, pharmacokinetic, safety, and efficacy data will be collected in a two-part structure (Part A and Part B). The study will contain a lead-in cohort where PK parameters and safety will be assessed (Part A), before proceeding to the safety and efficacy portion of the protocol (Part B).

Part A:

Part A is a randomized, double-blinded, multi-site study evaluating PK, safety, and tolerability of sugammadex when used for reversal of NMB. The PK data that is collected in Part A will be used to accurately characterize the PK parameters in pediatric patients of 2 to <17 years of age, and identify the pediatric dose that will provide similar exposure to adults. Based on the known PK characteristics of sugammadex in children and adolescents, the 2 mg/kg and 4 mg/kg doses of sugammadex (for reversal of moderate and deep block, respectively) are predicted to achieve similar exposures to that of adults. However, if PK results of the interim analysis (IA) from Part A of the study are inconsistent with those previously established in pediatrics and/or adults, then Part A and the subsequent IA will be repeated with modified doses until comparable doses are obtained. Details regarding the planned IA are described in Section 10.7.

Study enrollment will be paused after the completion of Part A to allow for review of the IA results by the siDMC and the eDMC. (Details are provided in Section 10.7 and Appendix 3). Once the appropriate doses are confirmed for moderate and deep block, then Part B will commence.

Part B:

Part B is a randomized, double-blinded, active-comparator controlled, multi-site study evaluating the safety and efficacy of sugammadex for reversal of moderate or deep NMB in pediatric participants.

To ensure that adequate safety data is obtained in the relevant age groups, Part B will enroll at least 40% of participants into the 2 to <6 year old age cohort. Enrollment into the 12 to <17 cohort will be capped at approximately 30%.

For the entire pediatric program, including this study, the eDMC will also review accruing data on the protocol-specified ECI's of anaphylaxis and clinically relevant bradycardia. Overall program-wide stopping criteria are in effect for these two ECI's. The detailed criteria are described in the eDMC charter.

The dosing for each depth of block in this study will be based on the results from Part A. The currently predicted doses for Part B include sugammadex 2 mg/kg for moderate block and 4 mg/kg for deep block. While fluctuations in depth of block are expected as matter of course to accommodate the needs of surgical procedures, additional doses of NMBA should be administered as clinically necessary for the duration of the surgery to target maintenance at the assigned depth of block. For participants randomized to the moderate block arms of Part B, either sugammadex 2 mg/kg or neostigmine 50 mcg/kg (up to 5mg maximum dose) will be given after the last dose of administered NMBA and within 2 minutes of detection of reappearance of second twitch (T2) with a lower limit of train of four (TOF) count 1 and upper limit of TOF count of 4. For participants randomized to the deep block arm of Part B, sugammadex 4 mg/kg

will be given after the last dose of administered NMBA and within 2 minutes of detection of 1 to 2 post-tetanic counts (PTC) with a range of 1-5 PTC at a TOF count of 0.

Quantitative monitoring will be performed using acceleromyography (eg, TOF-Watch® SX). The time to recovery to a TOF ratio of ≥0.9 will be the primary efficacy endpoint, consistent with the endpoint approach used in prior studies of sugammadex.

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

The primary efficacy endpoint for the study is the time to recovery of NMB from the administration of study medication to a TOF ratio of ≥0.9. During recovery of neuromuscular transmission after blockade from an NMBA, the TOF ratio rises from zero during deep NMB back to approximately 1.0 at total recovery. Research demonstrates that at TOF ratios of < 0.9, individuals are at potential risk for impaired pharyngeal function with associated risk of aspiration, and hypoxic ventilatory responses are impaired at TOF ratios of <0.7 [Eriksson, L. I., et al 1993]. Conversely, recovery to a TOF ratio of 0.9 has been shown to correlate with essentially complete clinical recovery from the effects of NMB. [Eriksson, L. I. 1999]

5.4.1.2 Safety Endpoints

A primary objective of this study is an overall assessment of safety and tolerability of sugammadex in pediatric participants (2 to <17 years of age).

To ensure timely reporting and comprehensive data collection regarding events of clinical interest (ECI), the following types of events are pre-specified as ECIs:

- Hypersensitivity and/or anaphylaxis (defined by Sampson et al.) [Sampson, H. A., et al 2005]: Adjudication of potential hypersensitivity and/or anaphylaxis events will be conducted by an independent external Adjudication Committee.
- Clinically relevant bradycardia, defined as any bradycardia event necessitating intervention, as determined by investigator judgment.

In addition, the incidence of any treatment-emergent bradycardia or treatment-emergent relative bradycardia after administration of study treatment will be assessed in this study. Continuous electrocardiogram (ECG) monitoring will be performed, beginning at least 5 minutes before and for at least 30 minutes after administration of study treatment to facilitate assessment of treatment-emergent bradycardia.

- **Treatment-emergent relative bradycardia** is defined as a heart rate that has decreased 20% or greater as compared to the participant's pre-dose baseline heart rate value, sustained for at least 30 seconds, [Butterworth, J. F., et al 2013] and occurring after the administration of study treatment.
- **Treatment-emergent bradycardia** is defined as a heart rate generally below the 1st percentile for age that has also decreased 20% or greater as compared to the participant's pre-dose baseline heart rate value, sustained for at least 30 seconds, [Butterworth, J. F., et al 2013] and occurring after the administration of study treatment. Refer to Appendix 6: Bradycardia Definition by Age Range.

Information regarding residual NMB, recurrence of NMB, and adverse respiratory events (eg, hypercapnia, dyspnea, hypoxia, and distress) will be collected via standard adverse event (AE) reporting.

Standard safety assessments (ie, physical examination, laboratory assessments, and vital signs including heart rate and blood pressure) will be recorded at specified time points (refer to Section 2).

5.4.1.3 Pharmacokinetic Endpoints

Pharmacokinetic sparse sampling will be conducted (Part A) to estimate model-based clearance and total exposure of sugammadex. Each participant is to provide at least 5 samples. Pharmacokinetic endpoints include AUC, C_{max}, CL, V_z, and $t_{1/2}$. Details are provided in Section 9.6.

The final decision as to which plasma samples will be assayed will be made by the Sponsor's Department of Pharmacokinetics, Pharmacodynamics, and Drug Metabolism and the Clinical Director.

Information regarding the collection and shipping of plasma samples will be provided in the administrative binder.

5.4.1.4 Pharmacodynamic Endpoints

There are no pharmacodynamic endpoints that will be collected in the current trial.

5.4.2 Rationale for the Use of Comparator

In the case of moderate NMB reversal, neostigmine is the most frequently used acetylcholinesterase inhibitor and is therefore the comparator for the moderate block arm of this trial. Neostigmine and glycopyrrolate (or neostigmine and atropine) will be administered intravenously according to current prescribing information. Where glycopyrrolate is not readily available or in situations where glycopyrrolate is contraindicated, atropine may be used. For the purposes of this study, any reference to the administration of neostigmine herein or in other study documents should be understood as a reference to the administration of neostigmine and glycopyrrolate, or neostigmine and atropine unless otherwise stated. The selected dose of 50 mcg/kg (up to a maximum of 5 mg total dose) for neostigmine is within the range of recommended dosing for children and adolescents, is consistent with prior sugammadex trials, and provides a standardized comparison to the sugammadex arm.

Based on a 50 mcg/kg dose of neostigmine, the following doses of glycopyrrolate and atropine are suggested:

- Glycopyrrolate: 10mcg/kg (or a neostigmine:glycopyrrolate dose ratio of 5:1)
- Atropine: 20 mcg/kg (or a neostigmine:atropine dose ratio of 2.5:1)

Because sugammadex is the only reversal agent indicated for reversal of deep NMB, no comparator is available for study in the setting of deep NMB in this trial.

5.5 Justification for Dose

Based on the available data from the sugammadex clinical trial program, no additional efficacy benefits are expected from higher doses than those recommended for adults (2 and 4 mg/kg, for reversal of moderate and deep NMB respectively). The use of lower doses in children is also unlikely to offer tangible benefits for patients; and based on trial data in adults, the use of doses lower than recommended (ie, <2 mg/kg) may lead to an increased risk of recurrence of NMB after initial reversal. This study aims to provide evidence that the weight-based dosing approach established for sugammadex use in adults is also applicable for pediatric patients; thereby reducing the risk of pediatric patients being administered either supratherapeutic or inadequate doses.

Depending on the depth of NMB (moderate or deep), a sugammadex dose of either 2 or 4 mg/kg will be administered to reverse NMB. Sugammadex will be administered as a single IV bolus dose, in accordance with prescribing information, which states to administer a dose of 2 mg/kg sugammadex if neuromuscular recovery has occurred up to at least the reappearance of T2 following the last dose of administered NMBA (ie, moderate blockade); or to administer a dose of 4 mg/kg sugammadex if neuromuscular recovery has reached at least 1 to 2 PTCs following the last administered dose of NMBA (ie, deep block).

6. Study Population

Male/Female participants between the ages of 2 and <17 years who will be administered NMBA for either moderate or deep block will be enrolled in this trial.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Must be categorized as ASA Physical Status Class 1, 2, or 3, as determined by the investigator.
2. Have a planned non-emergent surgical procedure or clinical situation (eg, intubation) that requires moderate or deep NMB with either rocuronium or vecuronium.
3. Have a planned surgical procedure or clinical situation that would allow objective neuromuscular monitoring techniques to be applied with access to the arm for neuromuscular transmission monitoring.

Demographics

4. Age between 2 to <17 years at Visit 2.
5. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
   OR

b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 7 days after the last dose of study treatment.

Informed Consent/Assent

6. The participant (and/or legally acceptable representative, if applicable) provides written informed consent/assent for the trial.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has any clinically significant condition or situation (eg, anatomical malformation that complicates intubation) other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
2. Has a neuromuscular disorder that may affect NMB and/or trial assessments.
3. Is dialysis-dependent or has (or is suspected of having) severe renal insufficiency (defined as estimated glomerular filtration rate (eGFR) <30 ml/min; using revised Schwartz estimate as method of calculation).
4. Has or is suspected of having a family or personal history of malignant hyperthermia.
5. Has or is suspected of having an allergy to study treatments or its/their excipients, to opioids/opiates, muscle relaxants or their excipients, or other medication(s) used during general anesthesia.
6. Has received or is planned to receive toremifene and/or fusidic acid via IV administration within 24 hours before or within 24 hours after administration of study treatment.
7. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment (see Appendix 5). If the urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

8. Use of medication expected to interfere with study treatments given in this trial, as per prescribing information. Refer to Section 7.7.

Prior/Concurrent Clinical Study Experience

9. Has been previously treated with sugammadex or has participated in a sugammadex clinical trial.
10. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days of signing the informed consent/assent for this current trial.

Other Exclusions

11. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

6.3 Lifestyle Restrictions

There are no lifestyle restrictions that are required for study participation.

6.3.1 Meals and Dietary Restrictions

There are no dietary restrictions required for this study.

6.3.2 Caffeine, Alcohol, and Tobacco

There are no restrictions on caffeine, alcohol, and tobacco for this study.

6.3.3 Activity

There are no activity restrictions for study participation.

6.4 Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

Recruitment will continue until the needed number of evaluable PK participants is obtained for each age cohort.

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1 Treatments Administered

The study treatments to be used in this trial are outlined below in Table 1.

Table 1 Study Treatments

Study Treatment Name:	Sugammadex MK-8616	Neostigmine methylsulfate	Glycopyrrolate	Atropine sulfate
Dosage Formulation:	Solution for injection	Solution for injection	Solution for injection	Solution for injection
Unit Dose Strength(s):	100mg/ml	0.5mg/ml	0.2mg/ml	0.4mg/ml
Dosage Level(s):	2mg/kg or 4mg/kg	50mcg/kg	5 to 15 mcg/kg	10 to 30 mcg/kg
Route of Administration:	Intravenous	Intravenous	Intravenous	Intravenous
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Use:	Investigational	Comparator	Required to be used with comparator	Required to be used with comparator

All supplies indicated in Table 1 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.8 for details regarding administration of the study treatment.

In the current study, neostigmine and glycopyrrolate (or neostigmine and atropine) will be used according to the applicable labeling, and administration of neostigmine, as in usual practice, will be accompanied by administration of glycopyrrolate (or atropine), used to counter the anticipated muscarinic effects of neostigmine. Where glycopyrrolate is not readily available, atropine may be used.

For the purposes of this study, any reference to the administration of neostigmine herein or in other study documents should be understood as a reference to the administration of neostigmine and glycopyrrolate or neostigmine and atropine, unless otherwise stated. Note that the target dose of neostigmine will be administered over 10 seconds; titration to effect is not allowed.

7.1.1 Medical Devices

- Instructions for medical device use are provided in the TOF-Watch® SX Neuromuscular Transmission Monitoring Guidelines (provided separately).

- Device events, adverse device events and medical device incidents, including those resulting from malfunctions of the device must be detected, documented, and reported by the investigator throughout the study. Refer to Section 9.3.8 for details.

7.2 Dose Modification (Escalation/Titration/Other)

This section is not applicable to the study.

7.3 Method of Treatment Assignment

Treatment randomization will occur centrally using interactive response technology (IRT). Participants will be allocated to 1 treatment group as indicated in Figure 2.

Participants in Part A of the study will be assigned randomly in a 1:1 ratio to the following treatment arms:

- Moderate block and reversal with sugammadex 2 mg/kg; or
- Deep block and reversal with sugammadex 4 mg/kg

Participants in Part B of the study will be assigned randomly in a 1:1:5 ratio to the following treatment arms:

- Moderate block and reversal with sugammadex 2 mg/kg; or
- Moderate block and reversal with neostigmine 50 mcg/kg; or
- Deep block and reversal with sugammadex 4 mg/kg

7.3.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Age:

   Participants will be enrolled into the following age cohorts: 12 to <17 years; 6 to <12 years; 2 to <6 years.

   For Part B: To ensure that adequate safety data is obtained in the relevant age groups, Part B will target approximately 40% of participants into the 2 to <6 year old age cohort. Enrollment into the 12 to <17 cohort will be capped at approximately 30%.

   Overall, participants in Part B of the study will be assigned randomly in a 1:1:5 ratio to three treatment arms. However, to ensure that adequate safety database sample sizes are reached within each age group, the allocation ratios will vary slightly by age:

   - 1:1:4 ratio for the 12 to <17 year age cohort
   - 1:1:5 ratio for the 6 to <12 year age cohort
   - 1:1:6 ratio for the 2 to <6 year age cohort

2. Neuromuscular blocking agent:

   - Rocuronium

- Vecuronium
    - Note: Approximately 30% of the overall planned sample size will be enrolled in the vecuronium stratum.

7.4 Blinding

Study Treatment:

With the exception of designated individuals (eg, unblinded Clinical Research Associates), all Sponsor study team personnel will be blinded to study treatment assignments. Refer to Section 10.2 for details.

The site **pharmacist (or delegate)** will be **unblinded** to study treatment assignments in order to prepare study treatment. Study treatment will be provided to site staff in the operating room (OR) (anesthesiologist) in masked syringe(s) to ensure that the contents of the syringe will not be revealed.

Site Personnel Roles:

The **anesthesiologist** (or comparable professionally qualified individual, such as certified nurse anesthetist), and other OR staff will be blinded to the reversal agent in the moderate block arms. While sugammadex for the deep block arm will be provided to the OR (anesthesiologist) in masked syringe(s), OR staff aware of the depth of block will know the study treatment as there is no approved comparator for reversal of deep block.

The **blinded safety assessor** (**BSA)** will be an appropriately qualified health care professional (eg, a licensed physician, nurse practitioner, physician assistant, or certified registered nurse anesthetist [or comparable professional qualification in countries outside of the United States]) with training and experience in anesthesia or post-anesthesia care.

- The **BSA** for any given individual participant will be blinded to:
    - Study treatment assignment
    - The depth of NMB
    - Drug preparation records
- The **BSA** for any given individual participant will:
    - Not be present during the operation and will not administer study treatment
    - Complete the post-anesthetic safety visit (Visit 3)
    - Complete the causality assessment for all AEs, including any perioperative AEs. Note: if the BSA is not a physician, a blinded causality assessor who is a physician (MD, DO) will be responsible for completing the causality assessment for all AEs.
    - Be required to sign a statement confirming that the blind was maintained as to treatment group and relevant records
- Of note, a **BSA** may, for any other participant, fill other study roles as appropriate for their qualifications.

The anesthesiologist performing trial-related procedures during surgery (or other clinical situation requiring NMBA) and the BSA, must be 2 separate individuals and their roles and responsibilities must not overlap for any given individual participant. Given the complexity of maintaining the blind of the BSA for any given individual participant, any inadvertent unblinding of the BSA will be documented.

See Section 9.1.10 for a description of the method of unblinding a participant during the trial, should such action be warranted.

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

The rationale for selection of doses to be used in this trial is provided in Section 5.5. Specific calculations or evaluations which may be required to be performed in order to administer the proper dose to each participant are outlined in the Study Operations Manual.

7.5.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

7.6 Treatment Compliance

Treatment compliance will be based on the actual dosage of study treatment assigned and the actual dose administered by the investigator.

Any dosage that deviates more than 10% from the planned dosage will be considered a medication error. No statistical tests will be performed with respect to treatment compliance.

7.7 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication specifically prohibited during the trial, the investigator should discuss this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant in the trial requires the mutual agreement of the investigator, the Sponsor, and the participant.

Rocuronium or vecuronium are concomitant medications to be used per label as adjunct to general anesthesia. Besides rocuronium or vecuronium, a participant must not be administered any other NMBA during the trial, including:

- Other steroidal NMBAs, such as pancuronium
- Nonsteroidal NMBAs such as succinylcholine or benzylisoquinolinium compound (eg, cisatracurium)*
- Toremifene or fusidic acid use within 24 hours before or within 24 hours after study treatment administration is prohibited.

  *Except in the circumstance that renewed muscle relaxation is needed after administration of study treatment, in which case a non-steroidal NMBA should be administered.

7.7.1 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

7.8 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

7.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind participants and to unmask study treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IRT) should be used in order to unblind participants and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 9.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

8. Discontinuation/Withdrawal Criteria

8.1 Withdrawal from the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will not receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 9.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 8.2.

8.2 Lost to Follow Up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, phone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood drawn from each participant over the duration of the study will not exceed 6.5 mL.

According to current standards, the maximum blood volume collected from each participant should be based on weight and should generally not exceed 1% of total blood volume on a single day (or 3% of total blood volume [2.4 mL blood per kg of body weight] during a given 4-week trial period), unless appropriate justification is documented by the investigator. [EMEA/CPMP 2008] [Food and Drug Administration (CDER) 2014] In this trial, the maximum volume of blood drawn on any single day is 4 mL; this is within approximately 1% of total blood volume even for

eligible participants in this study whose weight falls within the lower ranges of the World Health Organization growth chart (ie, 2-year old girls in the 3rd percentile of growth).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. Refer to Appendix 7 for approximate blood volumes collected by trial visit.

9.1 Administrative and General Procedures

9.1.1 Informed Consent/Assent

The investigator or qualified designee must obtain documented consent, and assent if applicable, from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to the participant's status during the trial (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent/assent is in place.

9.1.1.1 General Informed Consent/Assent

Consent/assent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent/assent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent/assent form should be given to the participant before participation in the trial.

The initial informed consent/assent form, any subsequent revised written informed consent/assent form and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent/assent form or addendum to the original consent/assent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent/assent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements. The assent, as applicable will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Visit 1 and Visit 2 by the investigator or qualified designee to ensure that the participant qualifies for the trial.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will

provide the participant with a Participant Identification Card immediately after the participant provides written informed consent/assent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

9.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. In addition to the evaluation of a participant's medical history in terms of trial eligibility, all medical conditions since birth (including obstetrical history) will be documented on the appropriate electronic case report form (eCRF). The surgical procedure and medical indication for surgery (or other clinical situation that requires administration of NMBA) must be recorded in the Sponsor database.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the participant within 30 days before starting the trial.

9.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication taken by the participant during the trial. Refer to Section 7.7 for additional information on use of concomitant medications. Rocuronium or vecuronium, are concomitant medications to be used per label as adjunct to general anesthesia.

9.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to treatment randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details regarding the screening visit requirements (screening/rescreening) are provided in Section 9.11.1.

9.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

Treatment randomization in IRT may occur on the same day, or one day in advance of, the participant's scheduled procedure. Sites should contact the Sponsor if a participant's procedure is postponed for more than one day from the date of treatment randomization in IRT (eg, surgery postponed due to illness). Trial status of participants in these situations will be handled on a case by case basis in consultation with the Sponsor.

9.1.8 Treatment Administration

Administration of study treatment will be performed by the investigator or qualified designee.

Trial Treatment should begin within 1 day of treatment randomization.

9.1.8.1 Administration of Neuromuscular Blocking Agents

Rocuronium or vecuronium will be dosed as indicated as adjunct to general anesthesia, per prescribing information, for intubation purposes and maintenance of NMB by re-dosing or continuous infusion.

Neuromuscular block should be maintained within the assigned depth of block to ensure that the participant is at target depth of block at time of reversal. Fluctuations in depth of block are expected as matter of course to accommodate of the needs of surgical procedures, however additional doses of NMBA should be administered as clinically necessary for the duration of the surgery (or other clinical situation that requires administration of NMBA) to target maintenance at the assigned depth of block. Only one NMBA should be used for the entire duration of surgery (or other clinical situation that requires administration of NMBA), including the intubation dose. The NMBA used during surgery (or procedure) should be the NMBA noted in the IRT.

9.1.8.2 Timing of Dose Administration

Sugammadex or neostigmine is to be administered as a single bolus injection within 10 seconds, into a fast running existing IV line (per product label), on the day of surgery (or other clinical situation that requires administration of NMBA). After administration, site staff should perform a visual inspection of the line to ensure that study treatment was fully administered.

For participants randomized to moderate block, either sugammadex 2 mg/kg or neostigmine 50 mcg/kg (up to 5mg maximum dose) will be given after the last dose of administered NMBA and within 2 minutes of detection of reappearance of T2 with a lower limit of train of four (TOF) count 1 and upper limit of TOF count of 4.

For participants randomized to deep block, sugammadex 4mg/kg will be given after the last dose of administered NMBA and within 2 minutes of detection of a target of 1 to 2 PTC with a range of 1 to 5 PTC at a TOF count of 0.

9.1.9 Withdrawal/Discontinuation

Once a participant receives study treatment at Visit 2, all applicable procedures at subsequent visits should be performed as per Trial SoA - Section 2.

Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events.

9.1.10 Participant Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a participant and the dosage administered in case of emergency eg, the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's treatment assignment, the investigator or delegate must enter the intensity of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Additionally, the investigator must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IRT should be used for emergency unblinding in the event that this is required for participant safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the participant. Every effort should be made not to unblind the participant unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective participant's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

9.1.11 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- TOF-Watch® SX device and accessories: Details for device calibration and proper use can be found in supplemental documentation (Neuromuscular Transmission Monitoring Guidelines) provided separately.
- Vital sign monitors: Alarm signals should be calibrated to the appropriate range according to the participant's age category.
- ECG equipment: This equipment should be calibrated per manufacturer specifications and/or local guidelines/processes.

9.2 Efficacy Assessments

9.2.1 Neuromuscular Monitoring

Details for NMTM training and site personnel qualification, set-up, calibration, data collection, etc. are provided in the Neuromuscular Transmission Monitoring Guidelines provided separately.

Neuromuscular monitoring will be performed using a TOF-Watch SX®, which will be provided to participating sites with all required accessories and components. After induction of anesthesia, neuromuscular monitoring will start before the administration of NMBA. Neuromuscular monitoring should remain ongoing until the participant reaches the endpoint of TOF ≥0.9, or for at least 30 minutes following administration of study drug. In instances where a return to TOF ≥ 0.9 fails to occur within 30 minutes, a decision to discontinue TOF monitoring and extubate the participant on clinical grounds is to be based on investigator judgment taking into account participant's medical requirements.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (SAE), as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE and other reportable safety event reports can be found in Appendix 4.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

9.3.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of treatment allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to the sponsor or designee within the timeframes as indicated in Table 2.

Table 2 Reporting Time Periods and Timeframes for Adverse Events and Other Reportable Safety Events

Type of Event		Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-Specified Follow-up Period	Reporting Time Period: After the Protocol Specified Follow-up Period		Timeframe to Report Event and Follow-up Information to SPONSOR:
Serious Adverse Event (SAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome.)		Within 24 hours of learning of event
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required		Per data entry guidelines
Overdose		Report if: - receiving placebo run-in or other run-in medication	Report all	Not required		Within 5 days of learning of event
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required		Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required		Within 5 days of learning of event
Cancer		Report if: - due to intervention - causes exclusion	Report all	Not required		Within 5 days of learning of event
Pregnancy/Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE and other reportable safety events including pregnancy and exposure during breastfeeding, ECI, Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.2). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable to the study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the trial are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole,

blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. Hypersensitivity or anaphylaxis
    a. **Hypersensitivity:** The term hypersensitivity describes objectively reproducible symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by normal persons.
    b. **Anaphylaxis:** The term anaphylaxis is an umbrella term for a serious, life-threatening generalized or systemic hypersensitivity reaction that is rapid in onset. For the purpose of this study, all potential cases of anaphylaxis (as defined by Sampson et al.) [Sampson, H. A., et al 2005] will be adjudicated.
3. Clinically relevant bradycardia, defined as any bradycardia event necessitating intervention, as determined by investigator judgment.

Refer to the ECI Guidance document (or equivalent) for reporting the ECIs of hypersensitivity or anaphylaxis, and clinically relevant bradycardia.

9.3.8 Assessing and Recording Patient/Device Events

Device and/or patient events include all untoward events related to the use of the TOF-Watch® SX device. Device events include any malfunction or deterioration in the characteristics and/or performance of the device, as well as any inadequacy in the labeling or the instructions for use, that led to or could have led to an untoward event for the user or any person. Patient events are adverse events experienced by the participant caused by or suspected to be caused by the TOF-Watch® SX.

All device or patient events that occur after allocation/randomization must be reported by the investigator (initial and follow-up) if they cause the participant to be excluded from the trial, or

are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of allocation/randomization through 14 days following cessation of treatment, all device or patient events (initial and follow-up) must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for events not meeting serious criteria, whether or not related to the Sponsor's product must be reported within 5 calendar days of learning of event to the Sponsor. The reporting timeframe for events meeting any serious criteria is described in section 9.3.1. The investigator will make every attempt to follow all non-serious device or patient events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

During the course of the trial, a participant may provide feedback related to the TOF-Watch® SX. This "customer feedback" is defined as a report that does not allege a product quality complaint or defect and has no relevant safety information/untoward event associated with it (e.g., goodwill or courtesy replacement, consumer preference or suggestion, remark which may suggest an improvement in the functionality or quality of the TOF-Watch® SX. All reports of customer feedback must be reported to the Sponsor within 14 calendar days of awareness. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

9.3.8.1 Device Incidents

An incident is any malfunction or deterioration in the characteristics and/or performance of the device (TOF-Watch® SX), as well as any inadequacy in the labeling or the instructions for use that, directly or indirectly, led to or could have led to, the death of a participant or user, or of other persons, or to a serious deterioration in their state of health.

A serious deterioration in the state of health can include:

- Life-threatening illness, even if temporary in nature;
- Permanent impairment of a body function or permanent damage to a body structure;
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within instructions for use;
- Fetal distress, fetal death or any congenital abnormalities or birth defects;
- Condition necessitating medical or surgical intervention, including hospitalization or prolongation or existing hospitalization to prevent one of the above;
- Cases that are considered medically significant.

For the time period beginning at allocation/randomization, any incident, including follow up to an incident, including death due to any cause, that occurs to any participant must be reported within 24 hours to the Sponsor if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any incident, or follow-up to an incident, whether or not related to the device, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any incident considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified above also must be reported immediately to the Sponsor.

All participants involved with incidents must be followed up for outcome.

9.3.8.2 Regulatory Reporting Requirements for Device Events and Incidents

Device Events and Incidents will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

9.4 Treatment of Overdose

In this trial, an overdose of sugammadex is considered a dose ≥ 2 times the intended dose to which the participant was randomized.

In this trial, an overdose of neostigmine is any dose greater than 5.0 mg as indicated in the labeling of neostigmine. An overdose of glycopyrrolate is considered a dose of greater than 2.0 mg. An overdose of atropine is considered a dose of greater than 0.5 mg for participants up to age 11 years, and a dose of 1 mg for ages 12 to <17 years.

9.5 Safety

Details regarding specific safety procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn over the course of the trial, including approximate blood volumes drawn by visit and by sample type per participant can be found in Section 9.

Planned time points for all safety assessments are provided in the SoA.

9.5.1 Physical Examinations

A complete physical examination will be conducted, per institutional standard.

The principal investigator or licensed clinician (ie, physician, physician's assistant, or nurse practitioner) will perform a full physical examination of the following organ systems at screening (Visit 1):

- Head, eyes, ears, nose, and throat
- Neck
- Respiratory system
- Cardiovascular system
- Abdomen

- Skin and extremities
- Neurological system, including mental status, motor strength, muscle tone, and reflexes.

Any medical conditions found during the full physical exam will be recorded in the Sponsor database.

A second physical examination (targeted physical exam) will be performed at the post-anesthetic visit (Visit 3) by the BSA. At a minimum, the following organ systems will be assessed in the targeted physical exam:

- Respiratory system
- Cardiovascular system
- Neurological system, including mental status, motor strength, muscle tone, and reflexes.

Additional organ systems may be assessed at the discretion of the BSA. Any clinically significant change from the initial physical examination will be recorded in the Sponsor database.

9.5.2 Height and Weight

Height (cm) and weight (kg) will be measured and recorded. Measurements should be recorded to the nearest unit. Body weight will be obtained using a standardized digital scale without shoes and with heavy clothing (eg, jacket or coat) removed.

9.5.3 Vital Signs

Heart rate, blood pressure, respiratory rate, oxygen saturation, and core body temperature will be obtained, at the following time points:

- Screening visit (Visit 1)
- Prior to administration of NMBA
- After the final dose of NMBA is administered, prior to administration of study treatment
- At 2, 5, 10, and 30 minutes following administration of study treatment (refer to Table 3 for vital sign assessment windows)
- Post-anesthetic visit (Visit 3)

Blood pressure and heart rate measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The same method for heart rate and blood pressure (eg, manual or automated) should be used for all measurements for each individual participant, unless the clinical situation dictates otherwise.

Core body temperature must be measured; axillary or skin temperature measurements are unacceptable for core body temperature assessment, another method must be used. The investigator will maintain a record of the participant's core body temperature during NMTM (the target core temperature is ≥ 35ºC [95ºF]).

Table 3 Assessment Windows for Vital Signs Following Administration of Study Treatment

Time Point of Assessment for Vital Signs	Assessment Window*
2 minutes	(1, 3) minutes
5 minutes	(3, 7) minutes
10 minutes	(8, 12) minutes
30 minutes	(25, 35) minutes
*upper and lower limits are inclusive.	

9.5.4 Electrocardiogram

During the peri-anesthetic visit (Visit 2), continuous ECG monitoring will occur at least 5 minutes before, during, and for 30 minutes after administration of study treatment.

9.5.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

9.6 Pharmacokinetics

Pharmacokinetic samples are required for Part A of the study only; 5 to 6 samples will be drawn at the following time points:

- At 2, 15, 30, and 60 minutes following administration of sugammadex
- At 4 to 6 hours following administration of sugammadex

- At 10 to 12 hours following administration of sugammadex*

*Note: depending on length of hospital stay, the 10 to 12 hour sample may not be drawn. However, if the participant remains hospitalized, then all attempts should be made to obtain the 10 to 12 hour sample.

Pharmacokinetic sampling windows are not provided because the PK samples will be analyzed using actual time. However, every effort should be made to adhere to the time points specified above.

9.6.1 Blood Collection for Plasma Sugammadex

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

For all participants, PK blood samples are to be drawn from a separate IV line other than the site used for study treatment administration. If the separate site is in the same limb, the second site must be distal to the site into which study treatment was administered. However, if available, a multi-lumen IV, peripherally inserted central catheter, or central venous catheter may be used to both administer study treatment and also draw PK blood samples, provided a different lumen is used and with adequate flushing (per standard hospital procedure) to ensure patency of the access line. Arterial access sites will not be suitable for drawing PK blood samples for this study.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

Future Biomedical Research Samples will not be collected in this study.

9.9 Biomarkers

Biomarkers are not evaluated in this study.

9.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Hospital length of stay (including duration by wards [eg, OR, PACU])

9.11 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.11.1 Screening (Visit 1)

Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1 and Section 6.2. If needed, a participant may repeat screening once; any additional rescreening will require consultation with the Sponsor.

9.11.2 Peri-anesthetic Visit (Visit 2)

The peri-anesthetic period begins when the participant is randomized and continues throughout the surgical period, ending just prior to 4 hours post-surgery (or other clinical situation that requires administration of NMBA).

Study staff will confirm that the participant still meets inclusion/exclusion criteria (eg, negative pregnancy test), review prior/concomitant medications, record the participant's weight per SoA, and then randomize the participant using IRT.

The pharmacist will prepare study treatment according to the Drug Preparation Manual.

An IV cannula for the administration of anesthetic drugs, NMBA, and study treatment will be inserted. A second IV cannula will be inserted into another vein (Refer to Section 9.6.1 for details) to allow collection of blood samples for safety and PK analysis at predefined time points.

Anesthesia will be induced and maintained according to the needs of the participant. Note: All medications, time of dose administration, and actual doses given to the participant are required to be recorded throughout the peri-anesthetic visit and transferred to Sponsor database.

At stable anesthesia, and before administration of the NMBA, the TOF-Watch® SX and accessories will be affixed to the participant's arm according to the Neuromuscular Transmission Monitoring Guidelines. Neuromuscular monitoring will continue until recovery of the TOF ratio ≥0.9. If a TOF ratio ≥0.9 is not reached, then monitoring should continue a minimum of 30 minutes after the administration of study treatment. Refer to Section 9.2.1 for details.

Rocuronium or vecuronium will be administered; only 1 NMBA (either rocuronium or vecuronium per Investigator choice) should be used for the entire duration of surgery (or other clinical situation that requires administration of NMBA). The NMBA used during surgery (or procedure) will be the NMBA noted in the IRT. Additional doses of NMBA will be administered as clinically necessary, as determined by the Primary Investigator or designee, for the duration of the surgery to maintain assigned depth of block. Refer to Section 9.1.8, for details on the administration of NMBA and timing of dose administration.

Vital signs will be recorded per protocol. Blood samples for laboratory safety analyses and PK evaluation will be collected per protocol (refer to Section 2).

9.11.3 Post-anesthetic Visit (Visit 3)

Between at least 4 hours following study treatment administration and up to a maximum of 36 hours after study treatment administration, the BSA will conduct Visit 3. Refer to Section 2 for more information.

The drug preparation records, depth of neuromuscular block, study treatment given, and TOF-Watch® SX traces will be sequestered from the BSA for any participant assessed by that given BSA.

For any given individual participant, the BSA will be required to sign a statement confirming that the blind was maintained. Given the complexity of maintaining the blind of the BSA for any given individual participant, any inadvertent unblinding of the BSA will be documented.

9.11.4 Follow-up Contact (Visit 4)

Approximately 14 days post-study treatment administration, the participant/ participant's legally acceptable representative will be contacted by designated site personnel by telephone (or in person if the participant is still in the hospital). New and ongoing AEs and concomitant medication(s) should be assessed and reported in the database.

10. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental statistical analysis plan and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

10.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 10.2 through Section 10.12.

Study Design Overview	A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants
Treatment Assignment	In Part A, participants will be randomized to 2 doses of sugammadex in a 1:1 ratio with NMBA and age as stratification factors: • 2 mg/kg sugammadex for moderate NMB and reversal • 4 mg/kg sugammadex for deep NMB and reversal In Part B, participants will be randomized to the following treatment groups in a 1:1:5 ratio (overall) with NMBA and age as stratification factors: • 2 mg/kg sugammadex for moderate NMB and reversal • 50 mcg/kg neostigmine for moderate NMB and reversal • 4 mg/kg sugammadex for deep NMB and reversal
Analysis Populations	**Pharmacokinetic:** Pharmacokinetic (PK) Set **Safety**: All Participants as Treated (APaT) **Efficacy**: All Participants Treated (APT)

Primary Endpoint(s)	**Pharmacokinetic**: Area under the plasma concentration-time curve (AUC), clearance (CL), volume of distribution (V_z), maximum plasma concentration (C_{max}), and half-life ($t_{1/2}$) **Safety**: Adverse event (AE) reporting, laboratory and vital sign assessments. **Efficacy**: The time to recovery to a train-of-four (TOF) ratio of ≥0.9
Secondary Endpoints	The time to recovery to a TOF ratio of ≥0.8 The time to recovery to a TOF ratio of ≥0.7
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	**Pharmacokinetic**: Separately for each PK parameter, individual values of CL, AUC, C_{max}, and V_z, will be natural log-transformed and evaluated with a fixed effects model containing terms dose and age group. At each dose, 95% CIs of geometric means for each parameter will be provided. Descriptive summary statistics will be provided for PK parameters including AUC, C_{max}, dnAUC, dnC_{max}, CL, V_z and $t_{1/2}$. **Efficacy**: The efficacy hypothesis will be evaluated within Part B by comparing sugammadex to neostigmine in the setting of moderate block using log-transformed time-to-recovery values via Analysis of Variance (ANOVA), adjusting for neuromuscular blocking agent (NMBA) and age.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with NMBA and age group as stratification factors.
Interim Analyses	One interim analysis (IA) will be performed in this study to evaluate PK and safety data. PK and safety data will be reviewed by a standing internal Data Monitoring Committee (siDMC) and safety data will be reviewed by an external Data Monitoring Committee (eDMC). This interim analysis is summarized below. Details are provided in Section 10.7. • Timing: When Part A has been completed, prior to the commencement of enrollment of Part B. • Testing: IA will evaluate PK and safety data. No formal efficacy analyses are planned.
Multiplicity	No multiplicity adjustment is planned as there is a single comparison of sugammadex versus neostigmine in the setting of moderate block using 1 endpoint in the primary efficacy hypothesis.
Sample Size and Power	The planned sample size is 238 participants, based on minimum safety database requirement. There will be 30 participants per treatment arm (sugammadex and neostigmine) in the setting of moderate block for efficacy analysis. For time to recovery to TOF ≥0.9, the trial has >99% power to demonstrate that sugammadex 2mg/kg is superior to neostigmine at an overall two-sided 5% alpha-level.

10.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. The pharmacokinetic analyses and summaries described in Section 10.6.3 are the responsibility of Pharmacokinetics, Pharmacodynamics and Drug Metabolism – Quantitative Pharmacology and Pharmacometrics department of the Sponsor and Early Clinical Development Statistics – Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study under in-house blinding procedures. With the exception of designated Sponsor personnel (e.g., unblinded Clinical Research Associates [CRAs], and other designated individuals as required), all other Sponsor study team personnel will be blinded to study medication assignment. Separate functional unblinding for PK will be conducted in support of PK evaluations. A small team as specified in a separate unblinding memo will be unblinded for the purpose of preparing the PK analyses for Part A. An unblinded statistician and programmer will prepare the safety analyses in support of the eDMC (and siDMC for IA only).

The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in the IRT.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.

10.4 Analysis Endpoints

Efficacy, safety and PK endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

10.4.1 Efficacy Endpoints

The primary efficacy endpoint is time to recovery to a TOF ratio of ≥0.9. Please see Section 5.4.1.1 for a description of the efficacy endpoints.

10.4.2 Safety Endpoints

Safety will be assessed through descriptive statistics within the All Participants as Treated (APaT) population. Safety assessments will include AEs, laboratory evaluations, and physical exams including vital signs. Adverse events of clinical interest for this protocol include clinically relevant bradycardia, hypersensitivity, and anaphylaxis. Please see Section 5.4.1.2 for a description of safety endpoints.

The primary approach to the summary of AEs will include all events that occur up to 7 days post administration of study medication. A supplemental summary of all AEs occurring up to 14 days post administration of study medication will also be included. Finally, for the cardiac endpoints of clinically relevant bradycardia and treatment emergent bradycardia, an analysis of events

occurring within the 1st 30 minutes after study medication administration will be conducted, as this is the time period during which continuous ECG monitoring will be conducted per protocol.

10.4.3 Pharmacokinetic Endpoints

Pharmacokinetic endpoints include AUC, CL, V_z, C_{max}, and $t_{1/2}$. Please see Section 5.4.1.3 for a description of PK endpoints.

10.4.4 Derivations of Efficacy/Pharmacokinetics Endpoints

For imputation of missing times for calculations of summary statistics from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio of ≥0.7, ≥0.8 and ≥0.9, a "worst" case scenario for sugammadex and a "best" case scenario for neostigmine will be applied, consistent with the approach used throughout the sugammadex program. The following procedure will be used:

If the time from the start of administration of study drug to recovery of the TOF ratio ≥0.9 is missing, there are 3 cases of particular importance for imputation purposes:

1. Time to TOF ratio ≥0.8 is available:
    a. Sugammadex group: First, for all participants randomized to receive sugammadex and with times to recovery of the TOF ratio ≥0.8 and ≥0.9 available, the difference between these 2 recovery times will be calculated. Next, the 95th percentile (P95) of these differences will be added to the time to recovery of the TOF ratio ≥0.8 of the participants with missing times to recovery of the TOF ratio ≥0.9. This will be used as the imputed missing time to recovery of the TOF ratio ≥0.9.
    b. Neostigmine group: Same as for the sugammadex group, but now only participants randomized to receive neostigmine will be used, and the 5th percentile (P5) of the differences in time to recovery of the TOF ratio of ≥0.8 and ≥0.9 will be calculated.
2. Time to TOF ratio ≥0.7 is available, but the time to TOF ratio ≥0.8 is missing:
    a. Sugammadex group: First, for all participants randomized to sugammadex and with times to recovery of the TOF ratio ≥0.7 and ≥0.9 available, the difference in time between these 2 recovery times will be calculated. Next, the P95 of these differences will be added to the time to recovery of the TOF ratio ≥0.7. This will be used as imputation of the missing time to recovery of the TOF ratio ≥0.9.
    b. Neostigmine group: Same as for sugammadex group, but now only participants randomized to receive neostigmine will be used and the P5 of the differences in time to recovery of the TOF ratio ≥0.7 and ≥0.9 will be calculated.
3. Times to TOF ratio ≥0.7 and ≥0.8 are both missing:
    a. Sugammadex group: The P95 of the time to recovery in all participants randomized to sugammadex with an observed recovery time of the TOF ratio ≥0.9 will be imputed.
    b. Neostigmine group: The P5 of the time to recovery in all participants randomized to receive neostigmine with an observed recovery time of the TOF ratio ≥0.9 will be imputed.

A corresponding procedure will be followed for imputation of missing times from the start of administration of study drug to recovery of the TOF ratio ≥0.8 (secondary efficacy variable). For imputation of missing times, P95 (sugammadex) or P5 (neostigmine) of the differences in time between recovery of the T4/T1 ratio ≥0.7 and ≥0.8 will be used.

For imputation of missing times from the start of administration of study drug to recovery of the TOF ratio ≥0.7 (secondary efficacy variable), the P95 observed time for the participants randomized to the sugammadex group will be imputed. For participants randomized to the neostigmine group the P5 observed time will be imputed. Imputation of missing times of the primary and secondary efficacy variables, however, should always result in a non-descending sequence of times to recovery of the TOF ratios of ≥ 0.7, ≥0.8, and ≥0.9.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Populations

The All Participants Treated (APT) population will serve as the primary population for the analysis of efficacy data in this study. The APT population consists of all randomized participants who receive at least 1 dose of study treatment.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the APT population. Details on the approach to handling missing data are provided in Section 10.4.4.

10.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants from both Part A and Part B who received a dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment will be included in the treatment group corresponding to the study treatment actually received.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 10.6.

10.5.3 PK Analysis Populations

In Part A, evaluable PK population for PK data analysis is defined as all participants with 5 to 6 time points approximately at 2 minutes, 15 minutes, 30 minutes, 60 minutes, 4 to 6 hours, and 10 to 12 hours (10 to 12 hour sample is optional; refer to Section 9.6) after study treatment, with 14 participants per dose level in Part A. For descriptive summaries of sugammadex, the population includes all participants with at least 1 measurable PK sample.

10.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Section 10.6.1 and Section 10.6.2 respectively. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

10.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental statistical analysis plan.

The primary efficacy endpoint is the time to recovery, defined as a TOF ratio (ie, T4/T1 ratio) ≥0.9. A formal test for efficacy in the comparison of sugammadex to neostigmine in the setting of moderate block will be conducted with data from Part B. Deep block data will not contribute to the primary efficacy analysis. Log-transformed time to recovery values will be analyzed by analysis of variance (ANOVA), adjusting for NMBA and age.

Additionally, supportive analyses will include a stratified log-rank test (adjusting for age group and NMBA) as well as a Kaplan-Meier curve for time to recovery to a TOF ratio of ≥0.9. The same set of analyses planned for the primary endpoint will be included for the secondary endpoints of times to recovery to a TOF ratio ≥0.8 and TOF ratio ≥0.7.

In addition, summary statistics and a Kaplan-Meier curve will be provided for sugammadex 2 mg/kg and 4 mg/kg from both Part A and Part B. Table 4 summarizes the key efficacy analyses comparing sugammadex to neostigmine in the setting of moderate NMB.

Table 4 Analysis Strategy for Key Efficacy Variables Comparing Sugammadex to Neostigmine in the Setting of Moderate NMB

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoints				
Time to Recovery to TOF ≥0.9	P	Analysis of Variance[a]	APT	Explicit Imputation[b]
	S	Stratified Log-Rank Test, Kaplan Meier Curves	APT	Censored[c]
Secondary Endpoints				
Time to Recovery to TOF ≥0.8	P	Analysis of Variance[a]	APT	Explicit Imputation[b]
	S	Stratified Log-Rank Test, Kaplan Meier Curves	APT	Censored[c]
Time to Recovery to TOF ≥0.7	P	Analysis of Variance[a]	APT	Explicit Imputation[b]
	S	Stratified Log-Rank Test, Kaplan Meier Curves	APT	Censored[c]

[a] Analysis of Variance includes terms for age and NMBA.

[b] Imputation approach described in Section 10.4.4.

[c] Censored at the last time point from TOF observation period.

Abbreviations: APT = All Participants Included, NMBA = neuromuscular blocking agent, P = primary, S = supportive, TOF = train-of-four

10.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

The analyses of safety results will follow a tiered approach (Table 5), and will be performed with data pooled across Part A and Part B. Comparisons between groups will be the 2 pairwise comparisons of the 2 mg/kg and 4 mg/kg sugammadex arms versus neostigmine. The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory or vital signs that are not pre-specified as Tier 1 endpoints will be classified

as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include 0 when treatment groups each have less than 4 events and thus, would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and predefined limits of change.

Continuous measures such as changes from baseline in laboratory and vital sign parameters that are not pre-specified as Tier 1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, clinically-relevant bradycardia, hypersensitivity, and anaphylaxis are considered Tier 1 events. In addition, treatment-emergent bradycardia and the broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with NMBA and age group as stratification factors. For the purposes of this analysis, treatment emergent bradycardia is defined as a heart rate generally below the 1st percentile of age that has also decreased 20% or greater as compared to the participant's pre-dose baseline heart rate value, sustained for at least 30 seconds, [Butterworth, J. F., et al 2013] and occurring after the administration of study treatment. Refer to Appendix 6: Bradycardia Definition by Age Range.

Table 5 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Clinically-relevant bradycardia	X	X	X
	Hypersensitivity (adjudicated)	X	X	X
	Anaphylaxis (adjudicated)	X	X	X
Tier 2	Treatment-emergent bradycardia		X	X
	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs[b] (incidence ≥4 participants in 1 of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs[b] (incidence <4 participants in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X
	Decreased heart rate			X

[a] Adverse Experience references refer to both Clinical and Laboratory AEs.

[b] Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

Abbreviations: AE = adverse event, CI = confidence interval, PDLC = pre-defined limit of change, SOC = system organ class, X = results will be provided.

10.6.3 Statistical Methods for Pharmacokinetics Analyses

For Part A, separately for each PK parameter, individual values of CL, AUC, C_{max}, and V_z, will be natural log-transformed and evaluated with a fixed effects model containing terms dose and age group (2 to <6 years, 6 to <17 years). Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). At each dose, ninety-five percent (95%) CIs for the least squares means for each age group will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% CIs will yield estimates for the population geometric means and 95% confidence intervals about the geometric means on the original scale at each dose level.

At each dose, plots with individual values, geometric means and corresponding 95% CIs will be provided for all PK parameters by age group.

For each dose, individual values will be listed for each PK parameter and the following descriptive statistics will be calculated for all plasma PK parameters (AUC, C_{max}, dose-normalized (dn) AUC, dnC_{max}, CL, V_z, and $t_{1/2}$) for MK-8616 by age group. Sample size (N), arithmetic mean (AM), standard deviation (SD), arithmetic coefficient of variation (ACV), median (Med), minimum (Min), maximum (Max), geometric mean (GM), and geometric CV (GCV) will be provided for all PK parameters by age group.

Additionally, the data from the previous pediatric studies may be pooled with the current study data and the pediatric data will be reclassified into the following age categories: (2 to <6 years, 6 to <12 years, and 12 to <17 years for each dose. The above described fixed effect model containing terms dose and age group (2 to <6 years, 6 to <12 years, and 6 to <17 years) will be used to estimate the geometric means and corresponding 95% confidence intervals for each age group by dose. Also summary statistics for the PK parameters will be provided for these age groups by dose. Also, at each dose, plots with individual values, geometric means and corresponding 95% confidence intervals will be provided for all PK parameters by age group.

A separate population PK analysis utilizing all the pediatric data from Part A, historic pediatric, and/or adult may be performed to characterize the PK in pediatric population.

The appropriate dose in different groups of pediatric participants will be determined following the evaluation of the safety, efficacy, and PK exposures.

10.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

10.6.4.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs by Part A, Part B, and Part A and Part B combined. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, sex, race), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analyses

One formal IA is planned for this trial, to occur after the completion of Part A, including evaluation of PK and safety results. Study enrollment will be paused for review of the IA results by the siDMC and the eDMC (Details are provided in Appendix 3). The eDMC will serve as the primary reviewer of the safety results of the IA and the siDMC will review the PK and safety results of the IA and make recommendations related to the acceptability of doses for this population.

If PK results of IA from Part A of the study are inconsistent with those previous established in pediatrics and/or adults, then Part A and the subsequent IA will be repeated with modified doses until comparable doses are obtained.

Beyond the formal IA described above, the eDMC will also review the safety data periodically throughout the study. Additionally, selected ECIs (e.g., anaphylaxis and clinically-relevant bradycardia) will be monitored by the eDMC; program-wide (i.e., including all data across the pediatric trials) stopping criteria related to these ECIs are described in the eDMC charter.

If the study is stopped early for safety, the final CSR will comprise all available data up to and including the close-out visits, which includes the data used to draw the conclusion in the decisive IA plus the remaining data obtained afterwards (from additional visits and close-out visits). This approach to include all available information is in line with the ICH E9 guideline, the intent-to-treat principle and the Committee for Medicinal Products for Human Use (CHMP) guideline on adaptive designs.

Details of blinding are described in Section 10.2.

10.8 Multiplicity

No corrections for multiplicity are planned for this study as there is a single comparison of sugammadex versus neostigmine in the setting of moderate block using 1 endpoint in the primary efficacy hypothesis.

10.9 Sample Size and Power Calculations

The sample size of the study is in alignment with the number of participants required to obtain the relevant safety information for each level of block, as specified by the Sponsor's commitments under the PREA. A 1:1 randomization ratio will be used for sugammadex 2 mg/kg and 4 mg/kg in the enrollment of 28 participants (14 in each treatment) in Part A, and an overall 1:1:5 randomization ratio will be used for sugammadex 2 mg/kg, neostigmine, and sugammadex 4 mg/kg in the enrollment of approximately 210 participants in Part B (30 on sugammadex 2 mg/kg, 30 on neostigmine 50mcg/kg, 150 on sugammadex 4 mg/kg). The study will enroll approximately 44 participants on sugammadex in moderate block, 164 participants on sugammadex in deep block, and 30 participants on neostigmine in moderate block.

10.9.1 Sample Size and Power Calculations for Efficacy Analyses

Power calculations are based on the primary efficacy hypothesis, a comparison of 2 mg/kg of sugammadex versus neostigmine for moderate block. The database for recovery times in adults is extensive, while objective information in pediatric participants is sparse. Given this, as well as the fact that the limited information that has been obtained in pediatrics to date supports an assumption of similarity of efficacy and tolerability in those patients as compared to the adult population, the approach used for underlying assumptions in this trial is based primarily on the adult data. From the Integrated Summary of Efficacy performed in 2012, summary statistics (in minutes) for the time to recovery to a TOF ratio of ≥0.9 for sugammadex 2 mg/kg and neostigmine 50 mcg/kg for moderate block with rocuronium are noted below in Table 6.

Table 6 Time (in min) to Recovery to a TOF Ratio of ≥0.9 for Sugammadex 2 mg/kg and Neostigmine 50 mcg/kg for Moderate Block with Rocuronium

	Sugammadex 2 mg/kg	Neostigmine 50mcg/kg
Mean (SD)	2.2 (1.3)	14.6 (14.5)
Median	1.7	9.7
Geometric Mean	1.9	10.6
Min, Max	0.6, 12.0	2.5, 106.9

Comparisons will be conducted via ANOVA on the log scale, which assumes that the data in the original scale are lognormal (and thus the log-transformed data are normally distributed). Power estimates for detecting various differences between sugammadex and neostigmine in moderate block are obtained using a 2-sided α of 0.05 for a 2-sample t-test on log-transformed time to recovery to a TOF ratio of ≥0.9, are summarized in Table 7. These assumptions are judged to be

appropriately conservative, especially with respect to the sugammadex arm, given the limited experience in assessing the efficacy in pediatric participants.

Table 7 Power Estimates for Detecting Various Differences Between Sugammadex and Neostigmine in Moderate Block

Sugammadex Mean (SD)	Neostigmine Mean (SD)	Mean Difference	Power[a]
3 (3)	13 (15)	10	>99%
5 (4)	13 (15)	8	92%
6 (6)	13 (15)	7	81%
[a] Based on N=27 for each treatment group to allow for 10% participants with non-evaluable data; 2-sided, 5%-level 2-sample t-test			

10.9.2 Sample Size and Power Calculations for Safety Analyses

The probability of observing at least one Tier 1 AE (such as adjudicated hypersensitivity) in this study depends on the number of participants treated and the underlying percentage of participants with an AE in the study population. If the underlying incidence of a Tier 1 AE is 1% (ie, 1 of every 100 participants receiving the drug), there is a 35.7% chance of observing at least 1 AE among 44 participants in the 2 mg/kg sugammadex treatment group, and a 80.8% chance of observing at least 1 AE among 164 participants in the 4mg/kg sugammadex treatment group.

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of participants with a Tier 1 AE given various hypothetical observed number of participants with a Tier 1 AE within the sugammadex groups are provided in Table 8. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

Table 8 Estimate of Incidence of a Tier 1 Adverse Event and 95% Upper Confidence Bound Based on Hypothetical Number of Participants with a Tier 1 Adverse Event Among 44 (2mg/kg) and 164 (4mg/kg) Participants in the Sugammadex Group

Number of Participants in Sugammadex Group	Hypothetical Number of Participants With a Tier 1 Adverse Event	Estimate of Incidence	95% Upper Confidence Bound[a]
44 (Sugammadex 2mg/kg)	0	0.0%	8.0%
	1	2.3%	12.0%
	3	6.8%	18.7%
	5	11.4%	24.6%
164 (Sugammadex 4mg/kg)	0	0.0%	2.2%
	3	1.8%	5.3%
	9	5.5%	10.2%
	15	9.1%	14.6%

[a] Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

Table 9 summarizes the percentage point differences between the sugammadex and neostigmine groups for a variety of hypothetical underlying incidences of a Tier 1 AE. These calculations assume 44 participants in the sugammadex group and 30 participants in the neostigmine group and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C.P. 1990]; no multiplicity adjustments were made.

Table 9 Differences in Incidence in a Tier 1 Adverse Event between the Sugammadex and Neostigmine Groups (Assuming Two-Sided 5% alpha level with 44 Participants in Sugammadex Group and 30 Participants in Neostigmine Group)

Incidence of Adverse Event		Risk Difference	
Sugammadex (%)	Neostigmine (%)	Percentage Points	95% CI[a]
2.3%	3.3%	1.0	(-14.6%, 8.9%)
6.8%	13.3%	6.5	(-23.8%, 7.4%)

Incidences presented here are hypothetical and do not represent actual adverse experiences in either group.

[a] Based on an asymptotic method (Farrington and Manning (1990)).

10.9.3 Sample Size and Power Calculations for Pharmacokinetic Analyses

A sample size of 6 in each age group has approximately 91% power that 95% confidence interval of the geometric mean of CL (Vz) in this age group will be within 60% and 140% of the geometric mean estimates of the clearance of MK-8616. A between-subject standard deviation of 0.23 in log scale for CL (Vz) that was obtained from previous studies was used for these calculations. This calculation is based on the pediatric guidance proposed by Wang et al [Wang, Y., et al 2012].

10.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% confidence interval) for the primary efficacy endpoint will be estimated and plotted within each category of each subgroup based on the primary efficacy analysis model (ANOVA) in the setting of moderate block. The following are examples of classification variables:

- Age group (2 to <6, 6 to <12, 12 to <17 years)
- Neuromuscular blocking agent (rocuronium or vecuronium)
- Sex (female, male)
- Race (white, other)
- Region (United States, Ex-United States)

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

In addition, a summary of safety parameters will be provided for each category of the following classification variables:

- Depth of block (moderate, deep)
- Age group (2 to <6, 6 to <12, 12 to <17 years)
- Neuromuscular blocking agent (rocuronium or vecuronium)
- Sex (female, male)
- Race (white, other)
- Region (United States, Ex-United States)

Subgroup analyses/summaries will only be performed for those classification variables with ≥10% participants in each subgroup.

10.11 Compliance (Medication Adherence)

Compliance with dosage (in mg/kg) will be assessed based on the actual dosage (mg) of study treatment administered and the reported body weight, per dosing occasion. Any dosage that

differs by more than 10% from the planned dosage will be listed. No statistical tests will be performed with respect to treatment compliance.

10.12 Extent of Exposure

The extent of exposure to study drug will be summarized in a table presenting per treatment group the number of participants who were randomized and received the study drug (ie, were treated). If information on actual dose of study treatment is available, summary statistics will be provided on the actual dose of study treatment received (mg/kg).

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12. Appendices

12.1 Appendix 1: Abbreviations and Trademarks

Term	Definition
AE	adverse event
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
AUC	area under the plasma concentration-time curve
APaT	All Participants As Treated
APT	All Participants Treated
BSA	blinded safety assessor
CAC	Clinical Adjudication Committee
CL	clearance
C_{max}	maximum plasma concentration
CRF	case report form
CSR	clinical study report
CTFG	Clinical Trial Facilitation Group
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
eDMC	External Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormonal replacement therapy
IA	interim analysis

Term	Definition
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
NMAC	Neuromuscular Adjudication Committee
NMB	neuromuscular blockade
NMBA	neuromuscular blocking agent
NSAE	non-serious adverse event
OR	operating room
PACU	Post-anesthesia care unit
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
PTC	post-tetanic count
SAC	Scientific Advisory Committee
SAE	serious adverse event
SoA	Schedule of Activities
$t_{1/2}$	half-life
T_1, T_2, T_3, T_4	first (T_1),second (T_2), third (T_3), or fourth (T_4) twitch in response to TOF stimulation
T_4/T_1 ratio	TOF ratio: Ratio of the height of T_4 over the height of T_1 in the recording of the response to TOF stimulation. Ratio expressed in decimals (eg, 0.7 or 0.8 or 0.9)
TOF	train-of-four stimulation
V_z	apparent volume of distribution
WOCBP	woman of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the central laboratory. Laboratory samples will be sent to a central laboratory for analysis unless local labs that satisfy the protocol requirements are already available.
- Peri-anesthetic period (Visit 2): Samples need not be drawn if local lab results are available within 14 days of randomization.
- Post-anesthetic period (Visit 3): Samples need not be drawn if local lab results are (or will be) available within 24 hours of randomization.
- If local laboratory results are used, the results and normal ranges must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry[a]	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Total Protein
	Creatinine	Sodium	ALT/SGPT	Alkaline phosphatase
	Glucose[b]			
Other Screening Tests	Urine Pregnancy Test, Serum β-hCG, as applicable: Urine or serum β-hCG test is required prior to surgery (or other clinical situation that requires administration of NMBA) in any young woman with onset of menarche. Serum β-hCG pregnancy test is required only if urine is positive, unless local requirements require otherwise			

[a] For participants with history of renal impairment only: SCr will be required for Screening (Visit 1), to calculate eGFR (using revised Schwartz estimate).

[b] Fasting or non-fasting glucose values are acceptable.

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic-pyruvic transaminase, AST/SGOT = aspartate aminotransferase/serum glutamic-oxaloacetic transaminase, β-hCG = β-human chorionic gonadotropin, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, RBC = red blood cell, SCr = serum creatinine, WBC = white blood cell

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participant safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine participant preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Participant Protection

A. IRB/IEC review

All clinical trials will be reviewed and approved by an independent IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/IEC prior to implementation, except that changes required urgently to protect participant safety and well-being may be enacted in anticipation of IRB/IEC approval. For each site, the IRB/IEC and Merck will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Participants are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Participants are enrolled only after providing informed consent for participation. Participants may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research participant by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for participant referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/IEC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/IEC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Committees Structure

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

A standing internal Data Monitoring Committee (siDMC) consisting of internal Sponsor personnel, unblinded to treatment groups for the purposes of reviewing analyses, will be responsible for reviewing the results of the interim analysis of Part A.

The siDMC will generally serve in an advisory role and specifically communicate recommendations to the sugammadex development team to continue the study as originally planned or to amend the study to modify the dose of sugammadex. The siDMC will operate independently of the external Clinical Adjudication and Neuromuscular Monitoring Adjudication Committees. Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

Neuromuscular Monitoring Adjudication Committee

Independent vendor personnel will review all TOF traces to assess overall data quality and acceptability of investigative site TOF-operator's interpretation of the efficacy variables and adherence to Neuromuscular Transmission Monitoring Guidelines. In instances where there is no resolution between the vendor and site personnel regarding the interpretation of trace output,

traces or data points will be reviewed by members of an independent Neuromuscular Monitoring Adjudication Committee (NMAC).

The NMAC will assess trace data objectively, independently, and without knowledge of the participant's treatment or condition. The NMAC will provide the final decision by either confirming the acceptability of the investigative site TOF-operator's interpretation or providing a separate interpretation to be used as part of the efficacy analysis.

Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 10 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

This external committee of independent consultants will assess the following events:

1) Hypersensitivity
2) Anaphylaxis

The BSA and/or Principal Investigator will identify events to be adjudicated based on their AE monitoring of their participants. In addition, the Sponsor will periodically review the blinded clinical database in order to identify events that may meet criteria for adjudication.

All personnel involved in the adjudication process will remain blinded to study treatment allocation throughout the trial.

Publication Policy

The results of this study may be published or presented at scientific meetings. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the sponsor, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by

calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in this appendix under the Merck Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

The Investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection, and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

The sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the sponsor for human use in this study.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer or progression of existing cancer.

Events NOT Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. • Refer to section 9.3.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect • in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events reported

Additional Events which require reporting

• In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.
  ● Is a cancer;
  ● Is associated with an overdose.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will record all relevant AE/SAE information on the Adverse Event case report forms/worksheets at each examination. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page. • There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. (for pediatric trials, awareness of symptoms, but easily tolerated)
  - Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. (for pediatric trials, definitely acting like something is wrong)
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric trials, extremely distressed or unable to do usual activities).

Assessment of Causality

- Did the Sponsor's product cause the adverse event?
  - The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
    - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this trial?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship: There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

- No, there is not a reasonable possibility of Sponsor's product relationship: Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

• The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  • Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information for reporting time requirements
• The site will enter the SAE data into the electronic system as soon as it becomes available.
• After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE Reporting to the Sponsor via Paper CRF
• If the electronic data collection tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

12.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table 11 consistently and correctly during the protocol-defined time frame in Section 6.1.

Table 11 Contraceptive Methods

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception[b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception[b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant[b, c] ● Intrauterine hormone-releasing system (IUS)[b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly). b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

12.6 Appendix 6: Bradycardia Definition by Age Range

Age Range	Heart Rate[a] (beats per minute)	Median Heart Rate (1^{st}- 99^{th} percentile)
2 to <3 years	<80	110 (76 – 142)
3 to <4 years	<70	104 (70 – 136)
4 to <6 years	<65	98 (65 – 131)
6 years and older	<60[b]	N/A[c]

[a] Heart rates were rounded to the more conservative value (Adapted from Fleming, 2011) [Fleming, S., et al 2011]

[b] A heart rate of 60 bpm was selected for the 6 years and older age range; this is consistent with typical practice for adult and pediatric patients.

[c] Median heart rate for participants in the age range of 6 years and older varies by age group and is not presented in detail here.

12.7 Appendix 7: Approximate Blood Volumes Collected by Trial Visit

	Screening Visit 1	Peri-anesthetic visit Visit 2	Post anesthetic visit Visit 3
Blood Parameter	Approximate Blood Volume (mL)		
Hematology		1	1
Serum/Plasma Chemistry		0.5	0.5
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]	0.5		
PK for sugammadex[b]		2.5	0.5
Expected Total (mL)	0.5	4	2

[a] For female participants of child bearing potential only. Sample taken only if the urine pregnancy test is positive at Visit 1.

[b] Required only for Part A of the study.

Abbreviations: β-hCG = β-human chorionic gonadotropin, PK = pharmacokinetic