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 Aged Birth to <2 Years
NCT number:	NCT03909165
Document Date:	27-OCT-2022

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 Aged Birth to <2 Years

Protocol Number: 169-02

Compound Number: MK-8616

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	68029
EudraCT	2017-000693-11

Approval Date: 27 October 2022

Sponsor Signatory

Typed Name: Date
Title:

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

Investigator Signatory

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

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 2	27-OCT-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 1	17-MAR-2020	Study endpoint of "time to neuromuscular recovery" moved to primary efficacy endpoint. Study endpoint of "time to extubation" moved to secondary efficacy endpoint. Protocol updated to assist sites with managing participant assignment in the case of delayed or rescheduled surgeries or clinical procedures
Original Protocol	05-FEB-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 10.1.1. Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.3 Schedule of Activities (SoA) 8.3.3 Vital Signs	At Visit 2, after extubation or if decision is made not to extubate and the required 30-minute postdose NMTM is complete, body temperature can be measured according to routine care (eg, axillary/skin thermometer is acceptable).	"Core temperature" is required for assessing the ERA question for core temperature and to ensure accuracy of NMTM. Once the participant is extubated or if the participant will not be extubated and neuromuscular recovery has been monitored for at least 30 minutes after administration of study treatment, core temperature is no longer required and routine body temperature may be obtained.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 5.1 Inclusion Criteria	Section 4.1 second paragraph and inclusion criterion #2: added clarification that "non-emergent" refers to a surgical procedure or clinical situation that is not an acute life-threatening emergency.	Clarification was needed to explain exactly what "non-emergent" refers to.
1.1 Synopsis 4.4 Beginning and End of Study Definition 5.1 Inclusion Criteria 8.1.1 Informed Consent/Assent 8.1.3 Participant Identification Card 8.4.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information 10.1.8 Data Quality Assurance	Changed "written consent/assent" to "documented informed consent/assent"	To align with text updates and legal language updates.

Section # and Name	Description of Change	Brief Rationale
8.3.3 Vital Signs	Changed "must" to "should" in sentence regarding blood pressure measurement method.	Typographical error where blood pressure measurement method should be consistent across visits, but is not a requirement.
8.4.1: Table 4 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events	Event of Clinical Interest (do not require regulatory reporting) – the last column for time frame to report event and follow-up information to Sponsor was listed incorrectly as 5 days and is now changed to 24 hours.	24 hours is the requirement for pediatric study ECI reporting, even if regulatory reporting is not required.
10.4: Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation	Changed this section from "Not Applicable" to the standard text regarding medical device reporting.	This section was inadvertently shown as "Not Applicable" when it should have included standard medical device text, as the study includes a medical device.

Section # and Name	Description of Change	Brief Rationale
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 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 Aged Birth to <2 Years

Short Title: PK, safety, and efficacy of sugammadex in children aged birth to <2 years

Acronym: Not Applicable

Hypotheses, Objectives, and Endpoints:

For male/female participants between the ages of birth to <2 years undergoing a surgery or clinical procedure requiring a neuromuscular blocking agent (rocuronium or vecuronium) for either moderate or deep block:

Primary Objectives	Primary Endpoints
- Objective: To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	- Pharmacokinetic parameters: Area under the plasma concentration-time curve (AUC), clearance (CL), apparent volume of distribution (Vz and Vss), maximum plasma concentration (Cmax), and half-life (t1/2)
- Objective: To evaluate the time to neuromuscular recovery 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 neuromuscular recovery.	- Time to neuromuscular recovery: Interval from administration of reversal agent to time to neuromuscular recovery.
- 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.

Secondary Objectives	Secondary Endpoints
- Objective: To evaluate the time to extubation 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.

Overall Design:

Study Phase	Phase 4
Primary Purpose	Treatment
Indication	Reversal of neuromuscular blockade (NMB)
Population	Pediatric participants aged birth to <2 years undergoing a surgery or clinical procedure requiring an NMBA (rocuronium or vecuronium) for either moderate or deep block.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active control without placebo
Study Blinding	Double-blind
Masking	Participant or Subject Care Provider Investigator Outcomes Assessor Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant's legally acceptable representative provides documented informed consent/assent through the last participant's final contact.

Number of Participants:

Approximately 126 participants will be enrolled.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Treatment Period	Use
Part A-Panel 1	Sugammadex	2 mg/kg	Once	Intravenous	Treatment	Experimental Treatment
Part A-Panel 2	Sugammadex	4 mg/kg	Once	Intravenous	Treatment	Experimental Treatment
Part B	Sugammadex	2 mg/kg	Once	Intravenous	Treatment	Experimental Treatment
	Sugammadex	4 mg/kg	Once	Intravenous	Treatment	Experimental Treatment
	Neostigmine methylsulfate	50 mcg/kg	Once	Intravenous	Treatment	Treatment

kg=kilogram; mcg=microgram; mg=milligram

Total Number: 5

Duration of Participation: Each participant will participate in the study for approximately 28 days from the time the participant's 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 posttreatment safety visit between 4 and 36 hours after administration of study treatment. A follow-up contact (phone call or visit) with the participant's parent/legally acceptable representative will take place at approximately 14 days posttreatment.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1 and Figure 2.

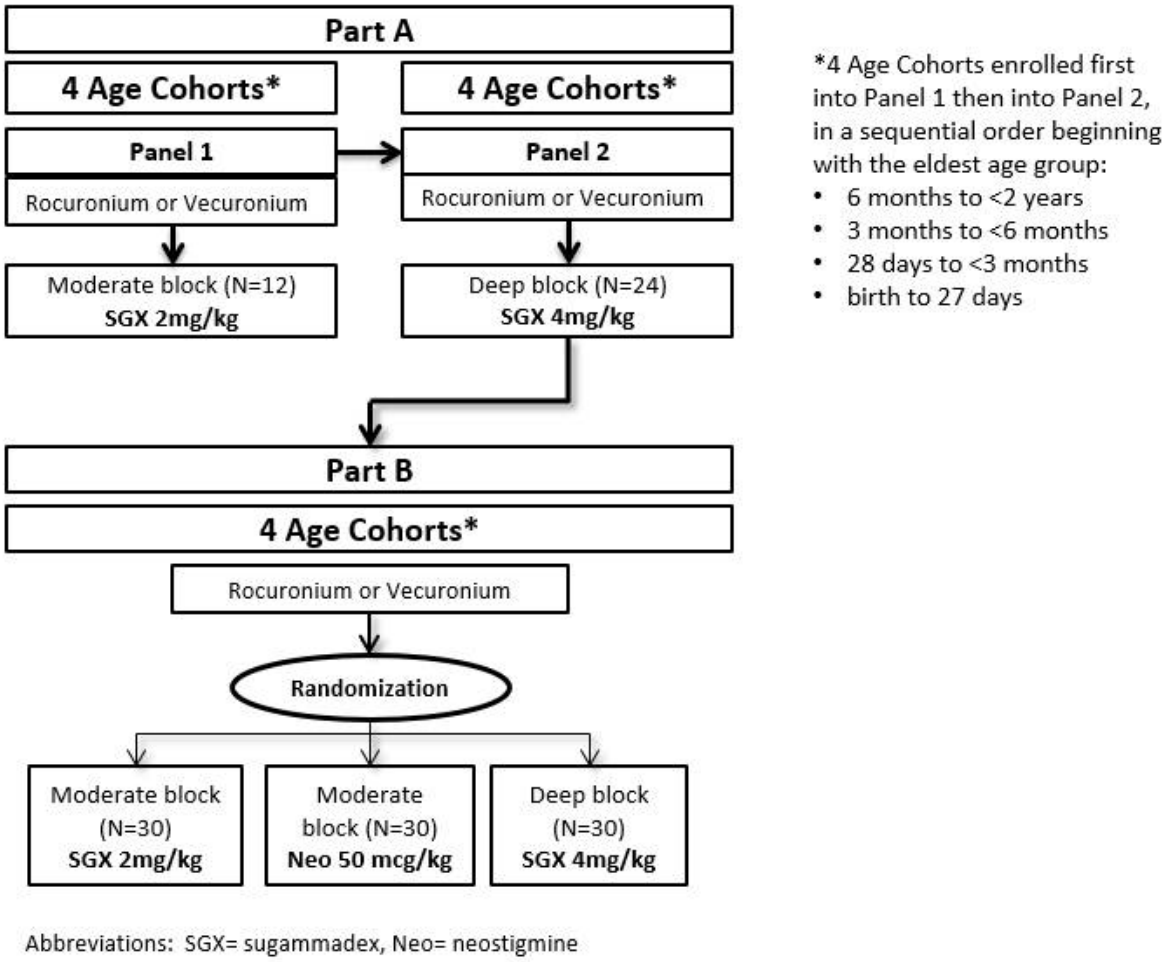

Figure 1 Study Diagram

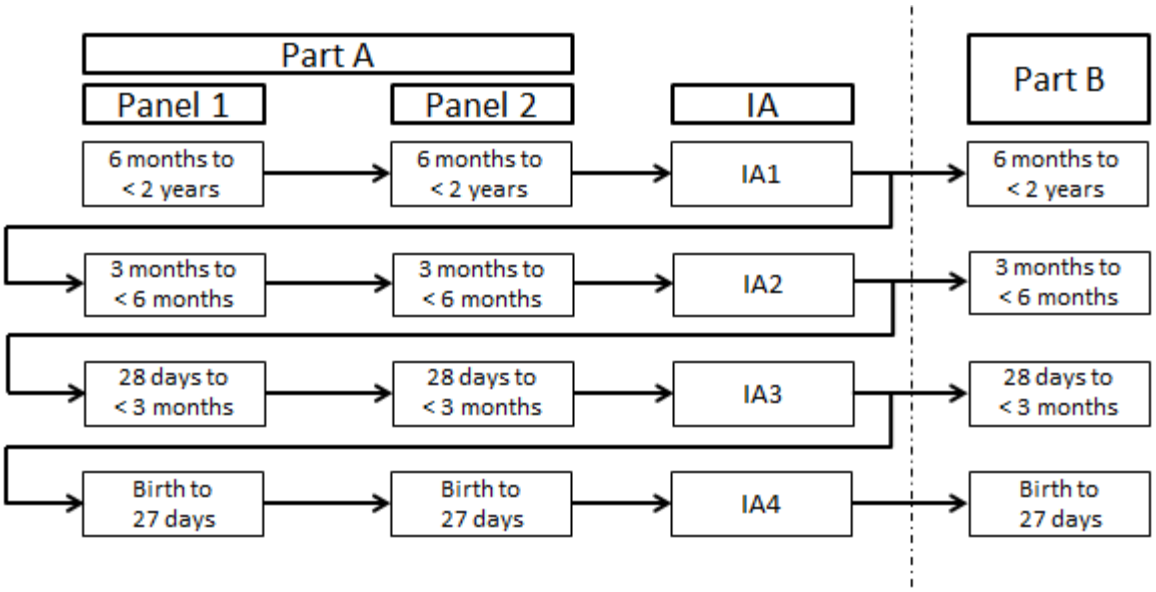

Figure 2 Sequence of Study Enrollment and Timing of Interim Analyses

1.3 Schedule of Activities (SoA)

Study Period	Screening	Treatment	Follow-up		Notes
Visit Number/Title	**Visit 1/Screening**	**Visit 2/Peri-anesthetic period**	**Visit 3/Post-anesthetic period**	**Visit 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 on hospitalization status.
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**Day -14 to Day 1**	**±0 days**	**See Notes**	**+2 days**	Visit 3 should occur between 4 and 36 hours after administration of study treatment.
Administrative Procedures					
Informed Consent	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 8.1.7 and 8.1.8.
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 will be different qualified individuals.

Study Period	**Screening**	**Treatment**	**Follow-up**		**Notes**
Visit Number/Title	**Visit 1/Screening**	**Visit 2/Peri-anesthetic period**	**Visit 3/Post-anesthetic period**	**Visit 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 on hospitalization status.
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**Day -14 to Day 1**	**±0 days**	**See Notes**	**+2 days**	Visit 3 should occur between 4 and 36 hours after administration of study treatment.
Efficacy Procedures					
Extubation Readiness Assessment		X			Assessment performed by OR anesthesiologist or other medically qualified clinician fully trained on the protocol requirements.
Neuromuscular Monitoring		X			NMTM will be performed to assess depth of block. Sites may use a locally available device (TOF-Watch®SX or PNS). See Section 8.2.2.
Safety Procedures					
Full Physical Examination	X				
Targeted Physical Examination			X		To be collected by the blinded safety assessor.

Study Period	**Screening**	**Treatment**	**Follow-up**		**Notes**
Visit Number/Title	**Visit 1/Screening**	**Visit 2/Peri-anesthetic period**	**Visit 3/Post-anesthetic period**	**Visit 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 on hospitalization status.
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**Day -14 to Day 1**	**±0 days**	**See Notes**	**+2 days**	Visit 3 should occur between 4 and 36 hours after administration of study treatment.
Vital Signs (heart rate, blood pressure, temperature, respiratory rate, oxygen saturation)	X	X	X		For Visit 2, collect core body temperature (after extubation or if the participant will not be extubated and neuromuscular recovery has been monitored for at least 30 minutes after administration of study treatment, body temperature can be measured according to routine care); scheduled vitals are to be performed before administration of NMBA; after the final dose of NMBA is administered, before administration of study treatment; and 2, 5, 10, and 30 minutes after study treatment.
Height		X			To be measured before study treatment preparation.
Weight		X			To be measured at the time of randomization and before study treatment preparation. Refer to Section 8.3.2.
Continuous Heart Rate Monitoring (ECG)		X			To occur at least 5 minutes before, during, and for 30 minutes after administration of study treatment.

Study Period	**Screening**	**Treatment**	**Follow-up**		**Notes**
Visit Number/Title	**Visit 1/Screening**	**Visit 2/Peri-anesthetic period**	**Visit 3/Post-anesthetic period**	**Visit 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 on hospitalization status.
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**Day -14 to Day 1**	**±0 days**	**See Notes**	**+2 days**	Visit 3 should occur between 4 and 36 hours after administration of study treatment.
Hematology		X	X		Laboratory samples will be collected and analyzed by the local laboratory. Visit 2: Samples will be drawn before study treatment administration and need not be drawn if other local laboratory results are available within 14 days of randomization. Visit 3: Samples need not be drawn if other local laboratory results are (or will be) available within 36 hours after administration of study treatment.
Chemistry		X	X		Laboratory samples will be collected and analyzed by the local laboratory. Visit 2: Samples will be drawn before study treatment administration and need not be drawn if other local laboratory results are available within 14 days of randomization. Visit 3: Samples need not be drawn if other local laboratory results are (or will be) available within 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 SCr at Visit 1 (Screening).

Study Period	**Screening**	**Treatment**	**Follow-up**		**Notes**
Visit Number/Title	**Visit 1/Screening**	**Visit 2/Peri-anesthetic period**	**Visit 3/Post-anesthetic period**	**Visit 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 on hospitalization status.
Scheduled Day	**Day -1**	**Day 1**	**Day 1 to 2**	**Day 14**	
Scheduling Window Days	**Day -14 to Day 1**	**±0 days**	**See Notes**	**+2 days**	Visit 3 should occur between 4 and 36 hours after administration of study treatment.
AE/SAE/ECI Review	X	X	X	X	Visit 3 only: Must be collected by blinded safety assessor.
Adverse Device Events Monitoring		X	X	X	For sites using TOF-Watch®SX only.
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; 4 to 6, 10 to 12 hours after study treatment administration. (See Section 8.6 for details). PK is required for Part A of the study only.
Abbreviations: AE = adverse event, ECI = event of clinical interest, eGFR = estimated glomerular filtration rate, NMBA = neuromuscular blocking agent, NMTM = neuromuscular transmission monitoring; PK = pharmacokinetics; SAE = serious adverse event, SCr = serum creatinine, TOF = train-of-four.					

2 INTRODUCTION

Note that the terms “study intervention”, “study medication”, and “study treatment” are used interchangeably in this document.

2.1 Study Rationale

Sugammadex sodium, herein referred to as sugammadex, has been demonstrated to be safe and effective in reversing rocuronium and vecuronium induced NMB in adults; however, clinical trial data in children is limited. The current study aims to show that sugammadex is generally safe and effective for reversing both moderate and deep block after rocuronium or vecuronium induced NMB in term neonates and young children.

Part A of this study will evaluate the pharmacokinetic (PK) parameters of the 2 and 4 mg/kg doses of sugammadex in pediatric participants between the age of birth and <2 years. The PK data that is generated from Part A will be evaluated to ensure that the doses intended to be administered in Part B (2 mg/kg and 4 mg/kg) show comparable exposures to the next oldest age cohort or efficacy to the approved doses in adults. The pediatric data from prior studies [Trial 19.4.306 (P034) and P089 Part A PK analysis] [Plaud, B., et al 2009] provide evidence that the intended doses will show comparable exposures or efficacy across the pediatric age groups under study when compared with adults and to older children.

2.2 Background

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

2.2.1 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. Before 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 moderate NMB, a degree of block that requires partial spontaneous recovery of neuromuscular transmission, 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 59 clinical trials with a total of 6149 exposures to intravenous (IV) sugammadex in 4603 unique individuals, establishing a well-characterized safety and efficacy profile in adults. Additionally, sugammadex is currently registered and approved in more than 90 countries, with an estimated 53,490,227 vials sold worldwide as of 30-SEPT-2019.

In the pediatric population, sugammadex was studied in a randomized placebo-controlled study [Trial 19.4.306 (P034)] [Plaud, B., et al 2009] that evaluated reversal of rocuronium-induced moderate NMB (n=64). The study evaluated children and adolescents over 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.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

An ongoing 2-part clinical study (P089) evaluating the PK, safety, and efficacy of sugammadex 2 mg/kg and 4 mg/kg for the reversal of moderate and deep block in pediatric participants 2 to <17 years of age is being conducted; as of 01-FEB-2020, unblinded data is not yet available. However, the PK and efficacy data from Part A of P089 support the doses being evaluated in this study, and the external data monitoring committee's (eDMC's) recommendation was that P089 should continue without modification.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

The Sponsor considers that the currently approved adult doses are appropriate for assessment to provide the optimal benefit/risk ratio in this study, based on the adult Phase 3 studies,

subsequent post marketing data, and the pediatric information collected to date in prior sugammadex studies.

Sugammadex has a positive benefit-risk profile and is well tolerated in the approved indications as described in the IB. 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 with 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 participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

For male/female participants between the ages of birth to <2 years undergoing a surgery or clinical procedure requiring a neuromuscular blocking agent (rocuronium or vecuronium) for either moderate or deep block:

Objectives	Endpoints
Primary	
Objective: To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	Pharmacokinetic parameters: Area under the plasma concentration-time curve (AUC), clearance (CL), apparent volume of distribution (V_z and V_{ss}), maximum plasma concentration (C_{max}), and half-life ($t_{1/2}$)
Objective: To evaluate the time to neuromuscular recovery 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 neuromuscular recovery.	Time to neuromuscular recovery: Interval from administration of reversal agent to time to neuromuscular recovery.
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.

Objectives	Endpoints
Secondary	
Objective: To evaluate the time to extubation 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.
Tertiary/Exploratory	
Objective: To evaluate the time to discharge, incidence of delayed recovery and proportion of participants with neuromuscular recovery after the first 5 minutes of administration of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	Time to OR discharge Time to PACU discharge Time to hospital discharge Incidence of delayed recovery (any observation that is >3 times the geometric mean recovery time of neuromuscular recovery using readiness for extubation assessment) Proportion of participants with neuromuscular recovery after the first 5 minutes of study medication administration

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active comparator-controlled, parallel-group, multisite, double-blinded trial to evaluate the PK, safety, and efficacy of sugammadex in pediatric participants aged birth to <2 years for the reversal of moderate and deep NMB.

The design of this study consists of a 2-part structure (Part A and Part B). Part A will be open-label, while Part B will be double-blinded. Part A will evaluate safety and confirm the doses of sugammadex that will produce comparable exposure in children from birth to <2 years of age when compared with systemic exposure noted in the next oldest age cohort or comparable efficacy to adults after administration of the 2 mg/kg and 4 mg/kg doses. In Part B of this study, the safety and efficacy parameters of sugammadex 2 mg/kg and 4 mg/kg will be assessed. Potential study participants will have a planned non-emergent (not an acute life-threatening emergency) surgical procedure or clinical situation that can be conducted under both moderate and/or deep NMB.

Enrollment into the study will begin with Part A, which is further divided into Panel 1 and Panel 2. First, Panel 1 will evaluate the PK and safety of sugammadex 2 mg/kg in the setting of moderate block; next, Panel 2 will evaluate the PK and safety of sugammadex 4 mg/kg in

the deep block setting. Panels 1 and 2 will run in succession and consecutively within each age cohort (Figure 1).

Participants will be enrolled within 1 of the following 4 age cohorts in a sequential approach (within each Part), beginning with the eldest age cohort. Enrollment within each age cohort will be based on the participant's age at time of treatment allocation (age will be defined as the anniversary date of the participant's actual birthdate):

- 6 months to <2 years
- 3 months to <6 months
- 28 days to <3 months
- Birth to 27 days

Part A:

Part A is a 2-panel, open-label, single-arm, multisite study evaluating PK and safety of sugammadex when used for reversal of NMB. Within Part A, Panel 1 and Panel 2 will run in succession within each age cohort to evaluate the dose of sugammadex appropriate for moderate and deep block, respectively. An interim analysis (IA) of safety and PK data will occur after the completion of each age cohort within Part A (ie, on completion of Panels 1 and 2) before beginning enrollment of the next age cohort and simultaneous initiation of Part B (see Figure 2).

The PK data that is collected in Part A will be used to accurately characterize the PK parameters in pediatric participants aged birth to <2 years, and identify the pediatric dose that will provide comparable exposure to the next oldest age cohort. 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 exposures comparable to that of adults. However, if PK results of an IA from Part A of the study are substantially different with those in the next oldest age cohort, then efficacy data will also be taken into consideration. If the efficacy data are substantially different with those previously established in adults, then Part A and the subsequent IAs may be repeated with modified doses until comparable exposure and/or efficacy are obtained. Details regarding the planned IAs are described in Section 9.7.

Study enrollment will be paused after the completion of each age cohort within Part A to allow for review of the PK data by the Sponsor (and efficacy if PK is substantially different) and safety data by the eDMC (details are provided in Section 9.7 and Appendix 1). Once the appropriate doses are confirmed for moderate and deep block within each age cohort, then Part B will begin for that particular age cohort (as shown in Figure 2).

Part B:

Part B is a randomized, double-blinded, active comparator-controlled, multisite study evaluating the efficacy and safety of sugammadex for reversal of NMB as determined by time to neuromuscular recovery (TTNMR) in the moderate and deep block setting. 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 and medical procedures, additional doses of NMBA should be administered for the duration of the procedure to target maintenance at the assigned depth of block. The active control, neostigmine methylsulfate 50 mcg/kg (up to 5 mg maximum dose), will be used to evaluate TTNMR in comparison with the sugammadex 2 mg/kg treatment arm for moderate 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). The study will target an approximately even distribution of participants across the birth to < 2 years age range, with each age cohort contributing at least 20% to the total study enrollment.

The minimum number of participants required in each age cohort to obtain relevant PK (and efficacy, if PK is substantially different) and safety data in Part A:

- Panel 1 (moderate block and reversal with 2 mg/kg sugammadex): 3 participants/age cohort
- Panel 2 (deep block and reversal with 4 mg/kg sugammadex): 6 participants/age cohort

The minimum number of participants required to obtain relevant efficacy and safety data in each treatment arm of Part B:

- Moderate block and reversal with 2 mg/kg sugammadex: 30 participants
- Moderate block and reversal with 50 mcg/kg neostigmine: 30 participants
- Deep block and reversal with 4 mg/kg sugammadex: 30 participants

The study will consist of 4 visits: screening visit, perianesthetic visit, postanesthetic visit, and a follow-up safety contact.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

In accordance with the Sponsor's commitments under the PREA, PK, safety, and efficacy data will be collected in a 2-part structure (Part A and Part B). The study will contain a lead-in cohort where PK parameters (and efficacy, if PK is substantially different) and safety will be assessed (Part A), before proceeding to the safety and efficacy portion of the protocol (Part B).

Four age cohorts will be enrolled sequentially beginning with the eldest age group. The eldest age group will be enrolled first to ensure that safety data from older age cohorts have been reviewed and confirmed before initiating the study in the younger age cohorts.

For the entire pediatric program, including this study, the eDMC will also review accruing data on the protocol-specified events of clinical interest (ECIs) of anaphylaxis and clinically relevant bradycardia. Overall program-wide stopping criteria are in effect for these 2 ECIs. The detailed criteria are described in the eDMC charter.

This study will allow the use of either awake or deep endotracheal extubation. Published data describes the safety and potential advantages associated with use of deep endotracheal extubation in children and infants less than 2 years old. These results have been summarized in a recent systematic review and meta-analysis, which supported the safety of deep endotracheal extubation as a way to "minimize overall airway complications except airway obstruction" [Koo, C. H., et al 2018]. In addition, for certain clinical circumstances, such as in cardiac catheterization where patients must be recumbent and nonambulatory during recovery, use of deep endotracheal extubation under anesthesia confers advantages during recovery over extubation while awake [Gautam, N. K., et al 2019]. In an observational study conducted in a US children's hospital in pediatric participants undergoing adenotonsillectomy, investigators made the clinical decision to perform deep endotracheal extubation in 66.6 of subjects versus awake extubation in 33.4% of subjects, indicating that deep endotracheal extubation is a common practice in pediatrics. No differences were noted in the incidence of peri-operative respiratory complications between the 2 extubation methods [Baijal, R. G., et al 2015]. To accommodate flexibility and consistency with real world practice, in this study the choice of extubation method will be made based on investigator judgment.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary and secondary efficacy endpoints of this study will evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of NMB.

- Primary endpoint: Time to neuromuscular recovery (TTNMR), defined as the interval from administration of reversal agent to time to neuromuscular recovery.

- Secondary endpoint: Time to extubation, defined as the interval from administration of reversal agent to removal of the endotracheal tube.

The primary endpoint in this study is TTNMR, as it is the most proximal measure available to estimate the time to NMB reversal. In 2 prior pediatric studies evaluating NMBAs in this age group, data collected using quantitative NMTM with the TOF-Watch® SX has shown considerable interpatient variability. In addition, quantitative NMTM involves technical challenges in obtaining and maintaining adequate calibration in the youngest age groups given their small size. Therefore, in this study, recovery endpoint data assessment methods are not limited to quantitative NMTM to TOF ratio ≥0.9. Instead, the endpoint of TTNMR may be assessed by 1 of 4 methods selected by the investigator, based on their judgment of what is technically feasible and clinically appropriate for the participant's procedure. These are inclusive of both clinical signs (head lift or hip flexion) and neuromuscular transmission monitoring (using either a standard PNS or the technically challenging quantitative neuromuscular monitoring to TOF ratio ≥0.9, as stipulated in the ERA).

If clinically necessary, the recovery assessment method may be adjusted during management of the case, based on investigator judgment, as long as TTNMR is established by 1 of the 4 allowable approaches. When a change is made to the assessment method after administration of study medication, the method is to be reflected in the ERA eCRF. For further information, refer to MK-8616 P169 Guidance Document for Extubation Readiness Assessment. To assess for potential bias due to switch in recovery assessment method, a sensitivity analysis will be performed (see Section 9.6.1 for details).

Investigator sites will be trained on the use of their chosen NMTM device to conduct the protocol-required intraoperative monitoring (see Section 8.2.3), as guided by study-specific guidelines. NMTM training will be supportive of neuromuscular recovery data quality, for applicable participants. As flexibility in NMTM assessment method is allowed in this study, it is acknowledged that increased variability in TTNMR data may be observed in comparison to the pivotal studies where quantitative TOF NMTM was exclusively used.

While neuromuscular recovery is a major determinant for extubation readiness in surgeries where NMB is used, it is not the sole factor influencing timing to extubation. Thus, given its clinical relevance, "time to extubation" is the secondary endpoint of this study. The ERA will be used to ensure all clinically relevant elements are evaluated consistently across all sites (neuromuscular recovery, mental status, return of spontaneous ventilation, adequate oxygenation, hemodynamically stabile, and core body temperature; refer to Appendix 10 for details). Either awake or deep endotracheal extubation will be allowed and the investigator will determine which method is the most appropriate for each participant, such as occurs in real world clinical practice. Regardless of extubation method, the ERA will be used to assess and document extubation readiness in all participants, with modification for those undergoing deep endotracheal extubation.

4.2.1.2 Safety Endpoints

The overall assessment of safety and tolerability of sugammadex in pediatric participants between the ages of birth to <2 years is the primary safety objective of this study. The number of participants experiencing AEs will be evaluated as the primary safety endpoint. Safety data will be pooled across Part A and Part B of the study.

To ensure timely reporting and comprehensive data collection regarding ECIs, the following types of events are prespecified as ECIs:

- Hypersensitivity and/or anaphylaxis (as 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 that occurs after administration of study treatment and requires 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. While these outcomes could be reported at any time after study treatment administration, continuous heart rate 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 with the participant's predose 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 first percentile for age that has also decreased 20% or greater as compared to the participant's predose 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 9: Bradycardia Definition by Age Range.

Information regarding residual NMB, recurrence of NMB, and adverse respiratory events (eg, hypercapnia, dyspnea, hypoxia, distress) will be collected via standard AE reporting. Additional clarifying information regarding these events may also be collected.

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).

4.2.1.3 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, V_{ss}, and $t_{1/2}$. Details are provided in Section 8.6.

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.

4.2.1.4 Pharmacodynamic Endpoints

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

4.2.2 Rationale for the Use of Comparator/Placebo

For Part B: The active control, neostigmine methylsulfate 50 mcg/kg (up to 5 mg maximum dose), will be used to evaluate TTNMR in comparison with the sugammadex 2 mg/kg treatment arm for moderate NMB.

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 study. 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 studies, 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: 10 mcg/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 study.

4.3 Justification for Dose

Based on the available data from the sugammadex 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; based on data in adults, sugammadex labeling states that the use of doses lower than recommended (ie, <2 mg/kg) may lead to an increased risk of recurrence of NMB after initial reversal. In light of the well-established safety and efficacy profile and extensive postmarketing experience associated with the approved adult doses, this study aims to confirm that the doses established for sugammadex use in adults show a comparable profile when administered to pediatric patients. This comparability is

initially suggested by the results of the prior pediatric study (19.4.306) and further supported by the results from P089 Part A. Confirmation of dose comparability will provide important information to practitioners for the appropriate use of sugammadex in pediatric patients, thereby minimizing administration of 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 after the last dose of administered rocuronium or vecuronium (ie, moderate block); or to administer a dose of 4 mg/kg sugammadex if neuromuscular recovery has reached at least 1 to 2 post-tetanic counts (PTC) after the last administered dose of NMBA (ie, deep block).

4.4 Beginning and End of Study Definition

The overall trial begins when the first participant's legally acceptable representative provides documented informed consent/assent. The overall trial ends when the last participant's legally acceptable representative completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant's legally acceptable representative is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study 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 study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/Female participants between the ages of birth and <2 years undergoing a procedure requiring an NMBA for either moderate or deep block will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is categorized as ASA Physical Status Class 1, 2, or 3 as determined by the investigator.

2. Has a planned non-emergent (not an acute life-threatening emergency) surgical procedure or clinical situation (eg, intubation) that requires moderate or deep NMB with either rocuronium or vecuronium.

3. Has a surgical procedure or clinical situation that would allow neuromuscular monitoring techniques to be applied for neuromuscular transmission monitoring.

Demographics

4. Is male or female, between birth and <2 years of age at Visit 2.

Informed Consent/Assent

5. The participant's legally acceptable representative for the study participant provides documented informed consent/assent for the trial.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is a preterm infant or neonate <36 weeks gestational age at birth.

2. Has any clinically significant condition or situation (eg, anatomical malformation that complicates intubation) other than the condition requiring the use of NMBA that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.

3. Has a neuromuscular disorder that may affect NMB and/or trial assessments.

4. 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).

5. Has or is suspected of having a family or personal history of malignant hyperthermia.

6. 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.

7. Is expected to require mechanical ventilation after the procedure.

8. 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.

Prior/Concomitant Therapy

9. Use of medication expected to interfere with study treatments given in this trial, as per prescribing information. 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). (Except in the circumstance that renewed muscle relaxation is needed after administration of study treatment, in which case a nonsteroidal NMBA should be administered)

Prior/Concurrent Clinical Study Experience

10. Has been previously treated with sugammadex or has participated in a sugammadex clinical trial within 30 days of providing documented informed consent/assent for this current trial.

11. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days of providing documented informed consent/assent for this current trial

Other Exclusions

12. Is or has an immediate family member (eg, parent/legal guardian, or sibling) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

There are no lifestyle restrictions required for study participation.

5.3.1 Meals and Dietary Restrictions

There are no dietary restrictions required for this study.

5.3.2 Activity Restrictions

There are no activity restrictions for study participation.

5.4 Screen Failures

Screen failures are defined as participants whose legally acceptable representative provides consent to participate in the clinical study but are not subsequently enrolled/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.

5.5 Participant Replacement Strategy

A participant who withdraws from the study will not be replaced. (see Section 7.2 for additional information regarding participants that withdraw from the study).

For Part A, recruitment will continue until the number of participants with evaluable PK samples is obtained for each age cohort.

For Part B, recruitment will continue until at least the minimum number of treated participants for each age cohort is obtained (refer to Table 2 in Section 6.3.2).

6 STUDY INTERVENTION

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.

Clinical supplies (study intervention[s] provided by the Sponsor) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/	Use	IMP/ NIMP	Sourcing
Sugammadex MK-8616	Experimental	Sugammadex MK-8616	Drug	Solution for injection	100 mg/ml	2 mg/kg or 4 mg/kg	IV Injection	Once	Experimental	IMP	Provided centrally by the Sponsor
Neostigmine methylsulfate	Active Comparator	Neostigmine methylsulfate	Drug	Solution for injection	0.5 mg/ml	50 mcg/kg	IV Injection	Once	Experimental	IMP	Provided centrally by the Sponsor
Glycopyrrolate	Other	Glycopyrrolate	Drug	Solution for injection	0.2 mg/ml	5 to 15 mcg/kg	IV Injection	Once	Experimental	IMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee
Atropine sulfate	Other	Atropine sulfate	Drug	Solution for injection	0.5 mg/ml	10 to 30 mcg/kg	IV Injection	Once	Experimental	IMP	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.
Other Arm Type: Required to be used with active comparator.
Glycopyrrolate may be labeled as Glycopyrronium Bromide depending on source and will be used interchangeably in this study
Unit Dose Strength concentration/presentation may vary based on market availability for glycopyrrolate and/or atropine sulfate

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

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.

6.1.1 Medical Devices

For any site using the TOF-Watch®SX: 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 8.4.8 for details.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study 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 study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) 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 interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation/randomization will occur centrally using IRT. Participants will be allocated to 1 treatment group.

Participants in Part A will be assigned the following treatment regimen:

- Panel 1: Moderate block and reversal with sugammadex 2 mg/kg
- Panel 2: Deep block and reversal with sugammadex 4 mg/kg

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

- 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

6.3.2 Stratification

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

1. Age: Four age cohorts will be enrolled sequentially, beginning with the eldest age group: 6 months to <2 years; 3 months to <6 months; 28 days to <3 months; Birth to 27 days.

   Safety data from older age cohorts will be reviewed before initiating the study in the younger age cohorts. To ensure that approximately even age distributions are met, this study will target a minimum of approximately 20% of participants within each age cohort.

   Part A enrollment:

   - Part A- Panel 1 will enroll a minimum of 3 participants with evaluable PK in each age cohort.
   - Part -A- Panel 2 will enroll a minimum of 6 participants with evaluable PK in each age cohort.

   Part B enrollment:

Table 2 Number of Participants Required for Part B (Minimum/Maximum Enrollment)

Age Group	Minimum Enrolled and Treated to meet 20% (20% *N=90 (total sample size)	Recommended Max Enrollment Cap
Part B		
6 months to <2 years	18	26
3 months to <6 months	18	26
28 days to <3 months	18	26
Birth to 27 days	18	18
Part B Total	**72**	**96**

2. Neuromuscular blocking agent:

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

6.3.3 Blinding

Study Treatment

With the exception of designated individuals (eg, unblinded Clinical Research Associates, etc.), Sponsor study team personnel will be blinded to study treatment assignments and depth of block in Part B. Refer to Section 9.2 for details.

The site **pharmacist (or delegate)** will be **unblinded** to study treatment assignments to prepare study treatment. Study treatment will be provided to site staff in the operating room (OR) (anesthesiologist) in a masked syringe 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 during Part B. While sugammadex for the deep block arm will be provided to the OR (anesthesiologist) in a masked syringe, 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 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)

NOTE: Vital signs may be administered by appropriate staff; however, the BSA should review the vital signs to determine if findings are clinically significant and report any related adverse events.

- 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, but may not fulfill any roles that would grant them access to Inform™.

The anesthesiologist performing study-related procedures 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 8.1.10 for a description of the method of unblinding a participant during the trial, should such action be warranted.

6.4 Study Intervention 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.

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding 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 on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination:

1. 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 study, including:

    - Other steroidal NMBAs, such as pancuronium

- Nonsteroidal NMBAs such as succinylcholine or benzylisoquinolinium compound (eg, cisatracurium) (except in the circumstance that renewed muscle relaxation is needed after administration of study treatment, in which case a nonsteroidal NMBA should be administered)

2. Toremifene or fusidic acid use within 24 hours before or within 24 hours after study treatment administration is prohibited.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

This section is not applicable to the study.

6.7 Intervention After the End of the Study

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

6.8 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. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). 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 8.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the trial, should such action be warranted.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Not applicable.

7.2 Participant 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 8.1.9. 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 7.3.

7.3 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's legally acceptable representative and reschedule the missed visit. If the participant's legally acceptable representative is contacted, the participant's legally acceptable representative 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's legally acceptable representative at each missed visit (eg, telephone calls and/or a certified letter to the participant's legally acceptable representative 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.

8 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.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- 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.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent, and assent if applicable, be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The blood volume required for each PK sample is 0.5 mL, which is the minimum amount needed for an accurate evaluation of the sample.

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 during a given 4-week study period (unless appropriate justification is documented by the investigator). [EMEA/CPMP 2008] [Food and Drug Administration (CDER) 2014]

The total volume drawn is within an allowable amount of 3% of total blood volume (2.4 mL blood per kg of body weight), even for the smallest neonates allowed in this study.

While larger volumes may be collected per local laboratory policies for laboratory testing in older children, no more than 3% of the total blood volume should be drawn during the course of this study.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent/Assent

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

8.1.1.1 General Informed Consent/Assent

Consent/assent must be documented 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 informed consent/assent form should be given to the participant's legally acceptable representative before participation in the study.

The initial informed consent/assent form, any subsequent revised 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's 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 study. 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 legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent 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/IEC requirements, applicable laws and regulations and Sponsor requirements.

8.1.2 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 study.

8.1.3 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's legally acceptable representative provides documented 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.

8.1.4 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 study eligibility, all active medical conditions since birth will be documented on the appropriate electronic case report form (eCRF). The surgical procedure and medical indication for the procedure must be recorded in the Sponsor database.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 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 study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication taken by the participant during the study. Refer to Section 6.5 for additional information on use of concomitant medications. Rocuronium or vecuronium are concomitant medications to be used per label as adjunct to general anesthesia.

8.1.6 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 allocation. Each participant will be assigned a screening number. Refer to Section 8.1.7 if surgery is delayed for more than one day. 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 on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will receive a treatment/randomization number; participants will be randomly allocated in Part B of the study. 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 reassigned to another participant.

After a participant is screened and randomized, unexpected events such as a delay in the surgery or the clinical procedure may occur that prevent administration of study treatment and lead to discontinuation. In these situations, it may be permissible, after consultation with the Sponsor, for the participant to be reassigned to a new allocation number if the original one is no longer appropriate due to either enrollment closure or participant's age. A consultation with the Sponsor will be required. Depending on the time that has elapsed since the participant's initial visit, the Sponsor may require that some of the screening assessments be repeated before randomization.

Treatment allocation 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 allocation in IRT (eg, procedure 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.

8.1.8 Study Intervention Administration

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

Study treatment should begin within 1 day of treatment randomization.

8.1.8.1 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 redosing or continuous infusion.

NMB should be maintained within the assigned depth of block for the entire duration of the procedure 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 the needs of surgical procedures. Only one NMBA should be used for the entire duration of the procedure, including the intubation dose (if NMBA is used for intubation). The NMBA used during the procedure should be the NMBA noted in the IRT.

8.1.8.2 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 the procedure. 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, sugammadex 2 mg/kg or neostigmine 50 mcg/kg (up to 5 mg maximum dose) will be given after the last dose of administered NMBA and within 2 minutes of detection of reappearance of T2.

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

8.1.9 Discontinuation and Withdrawal

Once a participant receives study treatment at Visit 2, all applicable procedures at subsequent visits should be performed as per Study SoA in Section 1.3.

During the procedure and before administration of study medication, if the participant is no longer planned to be extubated, then study medication should not be administered and the participant should be discontinued from the study. Additional information regarding these situations should be collected and communicated to the clinical team.

Any adverse events, which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, 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 intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

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.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Additionally, the investigator or medically qualified designee 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 study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.11 Calibration of Equipment

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

8.2 Efficacy Assessments

8.2.1 Monitoring Time to Neuromuscular Recovery

The methods used to confirm the TTNMR are outlined by item #1 of the ERA (Appendix 10). In all circumstances, the investigator must select 1 of the 4 methods of assessment of TTNMR assessment that is appropriate for the participant and method of extubation:

1) able to sustain head lift against resistance for at least 5 seconds,
2) able to sustain hip flexion against resistance for at least 5 seconds,
3) 4 twitches without fade (or, for neonates, 4 twitches comparable to pre-op baseline) observed in response to TOF via NMTM device, or
4) TOF ratio ≥0.9 observed on objective NMTN.

If clinically necessary, the recovery assessment method may be adjusted midprocedure, based on investigator judgment, as long as it is by 1 of the above 4 approaches. When the adjustment is made after administration of study medication, then the method should be reflected in the ERA eCRF. For participants undergoing deep endotracheal extubation, neuromuscular recovery must be assessed by either 4 twitches without fade (or, for neonates, 4 twitches comparable to pre-op baseline) observed in response to TOF via NMTM device or TOF ratio ≥0.9 observed on objective neuromuscular transmission monitoring. Neuromuscular recovery is expected to be achieved before extubation; in addition, if the participant will not be extubated, all efforts should be made to monitor for neuromuscular recovery every minute for at least 30 minutes after administration of study treatment. For further information, refer to MK-8616 P169 Guidance Document for Extubation Readiness Assessment.

8.2.2 Monitoring Time to Extubation

Monitoring of time to extubation will be achieved using the Extubation Readiness Assessment (Appendix 10). The OR anesthesiologist or other medically qualified clinician fully trained on the protocol requirements will be responsible for assessing extubation readiness beginning about 1 minute after study treatment administration and reassessing every 60 seconds until time of extubation readiness is achieved. Beginning 30 minutes after study treatment administration, readiness for extubation must be assessed at least every 5 minutes until time of extubation readiness is achieved.

Extubation readiness should be assessed until either the removal of the endotracheal tube or the clinical decision is made that the participant will not be extubated after the procedure as planned. (Refer to Section 8.1.9.) Refer to MK-8616 P169 Guidance Document for Extubation Readiness Assessment for further information.

8.2.3 Neuromuscular Monitoring

Neuromuscular monitoring will be performed to maintain the target depth of block throughout the surgical procedure and to ensure appropriate timing of dose administration of

study medication. Neuromuscular monitoring will be performed using a locally available NMTM device (eg, TOF-Watch®SX or PNS). Refer to Section 8.1.8.1 and Section 8.1.8.2 for details regarding the administration of neuromuscular blocking agents and timing of dose administration. Depth of block must be assessed and recorded at depth appropriate intervals to ensure appropriate timing of dose administration. Refer to MK-8616 P169 Neuromuscular Transmission Monitoring Guidelines for further information regarding neuromuscular monitoring procedures and requirements.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

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 examination will be recorded in the Sponsor database.

A second physical examination (targeted physical examination) 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 examination:

- 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.

8.3.2 Height and Weight

Height (cm) and weight (kg) will be measured and recorded at Visit 2 before study treatment preparation. If randomization occurs on the day before the procedure, then weight will be collected at the time of randomization to permit study treatment preparation. 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. Refer to Section 8.1.7 if surgery is delayed more than one day.

8.3.3 Vital Signs

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

- Screening visit (Visit 1)
- Before administration of NMBA
- After the final dose of NMBA is administered, before administration of study treatment
- At 2, 5, 10, and 30 minutes after 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 blood pressure (eg, manual or automated, position, and location) should be used for all measurements for each individual participant as clinically appropriate.

Core body temperature must be measured at Visit 2. Axillary or skin temperature measurements are unacceptable for core body temperature assessment; therefore, another

method must be used. However, after extubation or if the participant will not be extubated and neuromuscular recovery has been monitored for at least 30 minutes after administration of study treatment, body temperature can be measured according to routine care (eg, axillary/skin measurements are acceptable). The investigator or delegate will maintain a record of the participant's core body temperature during NMTM (the target core temperature is ≥35 ºC [95 ºF]).

Table 3 Assessment Windows for Vital Signs Following Study Treatment Administration

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

8.3.4 Electrocardiograms

During the perianesthetic visit (Visit 2), continuous heart rate monitoring will occur at least 5 minutes before, during, and for 30 minutes after administration of study treatment to facilitate assessment of treatment-emergent bradycardia, treatment-emergent relative bradycardia, and clinically relevant bradycardia (according to definitions in Section 4.2.1.2).

8.3.5 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 or medically qualified designee (consistent with local requirements) 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 that 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 nonprotocol-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 intervention, 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.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or 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 3.

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 and any designees are responsible for detecting, 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 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 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 participant’s legally acceptable representative provides documented informed consent but before intervention 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 study, 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 intervention 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 related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs 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 intervention 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 time frames as indicated in Table 4.

Table 4 Reporting Time Periods and Time Frames 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**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious 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
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
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (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 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

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

8.4.3 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 AEs, SAEs, and other reportable safety events, events of clinical interest (ECIs), 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 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 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 intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

This section is not applicable to the study.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

This section is not applicable to the study.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study 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 study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

2. Hypersensitivity and/or anaphylaxis:

Adjudication of potential hypersensitivity and/or anaphylaxis events will be conducted by an independent external Adjudication Committee.

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. Refer to the ECI Guidance document (or equivalent) for more information.

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 that occurs after administration of study treatment and requires 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.

8.4.8 Device Events, Patient Events, and Medical Device Incidents (Including Malfunctions)

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device events, patient events, and medical device incidents including malfunctions that occur during the study with such devices.

Device and/or patient events include all untoward events related to the use of the TOF-Watch®SX device.

8.4.8.1 Prompt Reporting of Medical Device Incidents to Sponsor

Medical device incidents will be reported to the Sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

8.4.8.2 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 AEs experienced by the participant caused by or suspected to be caused by the TOF-Watch®SX device.

For the time period before allocation/randomization through 14 days after 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 AE CRF/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 8.4.1. The investigator will make every attempt to follow all nonserious 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 study, 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 (eg, 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).

8.4.8.3 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 before treatment allocation/randomization through 14 days after 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 the time period specified above also must be reported immediately to the Sponsor.

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

8.4.8.4 Regulatory Reporting Requirements for Medical Device Incidents

The investigator will within 24 hours report all medical device incidents occurring with any medical device as defined in the study protocol in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.5 Treatment of Overdose

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

In this study, an overdose of neostigmine is any single dose greater than 5.0 mg as indicated in the labeling of neostigmine. An overdose of glycopyrrolate is considered a single dose of greater than 2.0 mg. An overdose of atropine is considered a single dose of greater than 0.5 mg.

8.6 Pharmacokinetics

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

- 4 samples: At 2, 15, 30, and 60 minutes after administration of sugammadex
- 1 sample: At 4 to 6 hours after administration of sugammadex
- 1 sample: 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.

8.6.1 Blood Collection for Plasma MK-8616

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 multilumen 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. If venous access is not feasible, then collection from an arterial site will be considered acceptable for drawing PK blood samples for this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.10 Health Economics 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])

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 8 – Study Assessments and Procedures.

8.11.1 Screening (Visit 1)

Potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 and Section 5.2. If needed, a participant may repeat screening once; any additional rescreening will require consultation with the Sponsor. Depending on the time that has elapsed since the participant's initial visit, the Sponsor may require that some of the screening assessments be repeated before randomization.

8.11.2 Peri-anesthetic Visit (Visit 2)

The peri-anesthetic period begins when the participant is assigned a treatment allocation/randomization number and continues throughout the surgical period, ending just before 4 hours post procedure. Refer to Section 8.1.7 for situations such as a delay in surgery.

Study staff will confirm that the participant still meets inclusion/exclusion criteria, review prior/concomitant medications, record the participant's height and weight per the SoA (Section 1.3).

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 8.6.1 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.

Rocuronium or vecuronium will be administered; only 1 NMBA (either rocuronium or vecuronium) should be used for the entire duration of the procedure. The NMBA used during

the procedure will be the NMBA noted in the IRT. Additional doses of NMBA will be administered as clinically required to maintain depth of block for the entire duration of the procedure, as determined by the Primary Investigator or designee. Refer to Section 8.1.8, 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 1.3).

Extubation readiness will be assessed per protocol by the OR anesthesiologist or other qualified clinician.

8.11.3 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 1.3 and Section 6.3.3 for more information.

The drug preparation records, depth of neuromuscular block, and study treatment given 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.

8.11.4 Follow-up Contact (Visit 4)

Approximately 14 days post-study treatment administration, the 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.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but before 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 nonconfirmatory analyses made after the protocol has been finalized, but before final database lock, will be documented in a supplemental statistical analysis plan (SAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

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 Aged Birth to <2 Years
Treatment Assignment	In Part A, participants will be sequentially enrolled to 2 doses of sugammadex within each age cohort (6 months to <2 years; 3 months to <6 months; 28 days to <3 months; birth to 27 days) with NMBA (Rocuronium and Vecuronium) as a stratification factor. 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 with a 1:1:1 ratio with NMBA (Rocuronium and Vecuronium) and age cohort (6 months to <2 years; 3 months to <6 months; 28 days to <3 months; birth to 27 days) as stratification factors: Sugammadex 2 mg/kg and Moderate NMB Neostigmine and Moderate NMB Sugammadex 4 mg/kg and Deep NMB
Analysis Populations	**Pharmacokinetic (Part A):** Pharmacokinetic (PK) set. **Safety (Part A and Part B)**: All Participants as Treated (APaT) **Efficacy (Part B)**: All Participants Treated (APT)
Primary Endpoint(s)	**Pharmacokinetic (Part A)**: AUC, C_{max}, CL, V_z, V_{ss}, and $t_{1/2}$ **Safety (Part A and Part B)**: AE reporting, vital sign assessments **Efficacy (Part B)**: TTNMR
Key Secondary Endpoints	Time to extubation (Part B)
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	**Pharmacokinetic**: Individual values will be listed for each PK parameter and descriptive statistics will be calculated for all plasma PK parameters (ie, AUC, CL, C_{max}, V_z, V_{ss} , and $t_{1/2}$) by dose. **Efficacy**: The primary efficacy analysis is Cox Proportional Hazards model comparing sugammadex and neostigmine in the setting of moderate block (adjusting for age, stratified by NMBA) with TTNMR censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
Statistical Methods for Key Safety Analyses	p-values (Tier 1 only) and 95% CIs (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 (1985) with NMBA and age group as stratification factors.
Interim Analyses	In Part A, 4 IAs will be performed in this study. Each IA will include the evaluation of the PK data by an internal group of the Sponsor and the evaluation of the safety data by an eDMC. If PK results of an IA from Part A of the study are substantially different with those in the next oldest age cohort, then efficacy data will also be taken into consideration. If the efficacy data are substantially different with those previously established in adults, then Part A and the subsequent IAs may be repeated with modified doses until comparable exposure and/or efficacy are obtained. The timing of each IA is after the completion of the older age cohort, before the commencement of enrollment of the next younger age cohort.
Multiplicity	No multiplicity adjustment is needed.

Sample Size and Power	The planned sample size is 126 participants. There will be 30 participants per treatment arm (sugammadex and neostigmine) in the setting of moderate block for efficacy analysis. For TTNMR, the study has >99% power to show that sugammadex 2 mg/kg is superior to neostigmine at an overall 2-sided 5% alpha level under the assumption that mean and standard deviation are 3 and 2 for sugammadex 2 mg/kg and 13 and 15 for neostigmine.

9.2 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 PK analyses and summaries described in Section 8.6 are the responsibility of PK, Pharmacodynamics and Drug Metabolism – Quantitative Pharmacology and Pharmacometrics department of the Sponsor and Early Clinical Development Statistics – Clinical Biostatistics of the Sponsor.

Part A will be conducted as an open-label study, while Part B will be conducted as a double-blind study under in-house blinding procedures. With the exception of designated unblinded Sponsor personnel (eg, unblinded Clinical Research Associates [CRAs], and other designated individuals as required), all other Sponsor study team personnel will be blinded to study treatment assignment in Part B. An internal unblinded statistician and programmer will prepare the safety analyses in support of the eDMC as needed. Part B data will remain blinded until final database lock.

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.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 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.

9.4.1 Efficacy Endpoints

The primary efficacy endpoint is TTNMR. The secondary efficacy endpoint is time to extubation. Please see Section 4.2.1.1 for a description of the efficacy endpoints.

9.4.2 Safety Endpoints

Safety will be assessed through descriptive statistics within the APaT population. Safety assessments will include AEs, laboratory evaluations, and physical exams including vital signs. AEs of clinical interest for this protocol include clinically relevant bradycardia, hypersensitivity, and anaphylaxis. Please see Section 4.2.1.2 for a description of safety measures.

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 (clinically relevant bradycardia and treatment-emergent bradycardia), an analysis of events occurring within the first 30 minutes after study medication administration will be conducted, as this is the time period during which continuous heart rate monitoring will be conducted per protocol.

9.4.3 Pharmacokinetic Endpoints

The PK endpoints include AUC, CL, C_{max}, V_z, V_{ss}, and $t_{1/2}$. Please see Section 4.2.1.3 for a description of PK endpoints.

9.4.4 Derivations of Efficacy Endpoints

The primary efficacy endpoint, TTNMR, is defined as the interval from administration of reversal agent to TTNMR (refer to Section 4.2.1). The secondary efficacy endpoint, time to extubation, is defined as the interval from administration of reversal agent to removal of the endotracheal tube. It is a relevant measure of neuromuscular recovery. TTNMR will be censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved. Also, time to extubation will be censored at the time of last assessment of extubation readiness if extubation readiness is not achieved.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The 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 one 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 9.6.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled/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 are given incorrect study treatment will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained after at least one 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 9.6.

9.5.3 PK Analysis Populations

In Part A, the evaluable PK population for the PK data analysis is defined as all participants with at least 5 samples at the time points of approximately 2 minutes, 15 minutes, 30 minutes, 60 minutes, and 4 to 6 hours (with an additional optional time point of 10 to 12 hours; refer to Section 8.6) after study treatment, with 6 participants per age group in Part A. For descriptive summaries of sugammadex, the population includes all participants with at least one measurable PK sample.

9.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Section 9.6.1 and Section 9.6.2, respectively. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. 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. All statistical tests will be conducted at the α=0.05 (2-sided) level.

9.6.1 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 SAP.

The primary efficacy endpoint is the TTNMR and the secondary efficacy endpoint is the time to extubation. 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. TTNMR and time to extubation will be analyzed by a Cox PH model, adjusting age (continuous) and stratified by NMBA (rocuronium and vecuronium). In addition, the Cox PH model for time to extubation will include a covariate of endotracheal extubation type (deep and not deep). A sensitivity analysis will be performed for TTNMR including participants with neuromuscular recovery assessment using TOF/PNS devices only.

Additionally, supportive analyses will include a stratified log-rank test (adjusting for age cohort and NMBA) as well as a Kaplan-Meier (KM) curve for TTNMR and time to

extubation. If a model does not converge for analysis of a particular endpoint, the stratified log-rank test will be stratified by age cohort only.

For both the primary and supportive analyses, TTNMR will be censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved, and time to extubation will be censored at the time of last assessment of extubation readiness if extubation readiness is not achieved. In addition, descriptive statistics including geometric means, medians, and 95% confidence intervals, as well as a KM curve will be provided for the primary and secondary efficacy endpoints for sugammadex 2 mg/kg and sugammadex 4 mg/kg from both Part A and Part B (combined) and neostigmine from Part B. Table 5 summarizes the key efficacy analyses comparing sugammadex to neostigmine in the setting of moderate NMB.

Table 5 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 Neuromuscular Recovery	P	Cox Proportional Hazards Model[a]	APT	Censored[b]
	S	Stratified Log-rank Test[c], Kaplan-Meier Curves	APT	Censored[b]
Secondary Endpoints				
Time to Extubation	P	Cox Proportional Hazards Model[d]	APT	Censored[e]
	S	Stratified Log-rank Test[c], Kaplan-Meier Curves	APT	Censored[e]

[a] Cox Proportional Hazards model includes terms for age and stratified by NMBA.
[b] Censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
[c] Stratified by age cohort and NMBA.
[d] Cox Proportional Hazards model includes terms for age and extubation type, stratified by NMBA.
[e] Censored at the time of last assessment of extubation readiness if extubation readiness is not achieved.

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

9.6.2 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 6) and will be performed pooled across Part A and Part B (and across age cohorts). 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% CIs 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% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. In addition, the 2 pairwise (between-group) comparisons will also be performed for Tier 1 safety endpoints using just Part B data.

AEs (specific terms as well as system organ class terms) and predefined limits of change in laboratory or vital signs that are not prespecified 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 show 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% CI 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% CIs may be provided without adjustment for multiplicity, the CIs 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 prespecified as Tier-2 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 will be considered Tier 1 events. In addition, treatment-emergent bradycardia, the broad clinical and laboratory AE categories consisting of the percentage of participants with any AE, a drug-related AE, an SAE, an AE that 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% CIs (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 cohort as stratification factors.

Table 6 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
	AE (specific or SOCs) or PDLCs[b] (incidence ≥4 participants in one of the treatment groups)		X	X
Tier 3	AEs (specific or SOCs), or PDLCs[b] (incidence <4 participants in all of the treatment groups)			X
	Change from baseline results (laboratory test results, vital signs)			X
	Treatment-emergent relative bradycardia			X

[a] Adverse events references refer to both clinical and laboratory AEs.
[b] Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier-2 endpoints.
Abbreviations: AE = adverse event; CI = confidence interval; PDLC = Predefined Limit of Change; SOC = System Organ Class; X = results will be provided.

9.6.3 Statistical Methods for Pharmacokinetics Analyses

Separately for each PK parameter, individual values of CL, AUC, C_{max}, V_{ss}, and V_z, will be natural log-transformed and evaluated with a fixed effects model containing fixed terms, dose, and age cohort (6 months to <2 years; 3 months to <6 months; 28 days to <3 months; birth to 27 days) and an interaction term, dose by age cohort. (Note: if the variability in PK parameters is markedly different in the age groups then the analysis will be performed separately for each age cohort with a fixed effects model containing dose as a fixed term). Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects (DDFM=KR). At each dose, 95% CIs for the least-squares means for each age cohort 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 GMs and 95% CIs about the GMs on the original scale at each dose level.

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

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, CL, C_{max}, V_z, V_{ss}, $t_{1/2,}$ and other PK parameters as appropriate) for MK-8616 by age cohort. Sample size (N), arithmetic mean (AM), standard deviation (SD), arithmetic coefficient of variation (ACV), median (Med), minimum (Min), maximum (Max), GM, and geometric CV (GCV) will be provided for all PK parameters by age cohort.

For exploratory purposes, summary statistics for additional PK parameters not listed here may be evaluated.

A separate population PK analysis utilizing all the pediatric data from the current study, 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 after the evaluation of the safety, efficacy, and PK exposures.

9.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

9.6.4.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed for APT using 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.

9.7 Interim Analyses

Four IAs are planned for this study, including evaluation of PK and safety results. To ensure that the safety data from older age cohorts has been reviewed by the eDMC (details are provided in Appendix 1) before initiating the study in the younger age cohorts, beginning with the eldest age cohort, the IA for each age cohort will occur before the enrollment of the next younger age cohort. The eDMC will serve as the primary reviewer of the safety results of each IA and will make recommendations as to whether to continue the study as planned.

The PK results will be reviewed by an internal group of the Sponsor. If PK results of an IA from Part A of the study are substantially different with those in the next oldest age cohort, then efficacy data will also be taken into consideration. If the efficacy data are substantially different with those previously established in adults, then Part A and the subsequent IAs may be repeated with modified doses until comparable exposure and/or efficacy are obtained.

Beyond the formal IAs described above, the eDMC will also review the safety data periodically throughout the study. Additionally, selected ECIs (eg, hypersensitivity,

anaphylaxis, and clinically relevant bradycardia) will be monitored by the eDMC; program-wide (ie, including all data across the pediatric studies) 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 ITT principle, and the CHMP guideline on adaptive designs.

Details of blinding are described in Section 9.2.

9.8 Multiplicity

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

9.9 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 1:1:1 randomization ratio will be used for sugammadex 2 mg/kg, neostigmine, and sugammadex 4 mg/kg in the enrollment of approximately 90 participants in Part B (30 in each treatment group). Along with 12 participants on sugammadex 2 mg/kg and 24 participants on sugammadex 4 mg/kg in Part A, the study will enroll approximately 42 participants on sugammadex in moderate block, 54 participants on sugammadex in deep block, and 30 participants on neostigmine in moderate block.

9.9.1 Sample Size and Power for Efficacy Analyses

Power calculations are based on the primary 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 participants as compared with the adult population, the approach used for underlying assumptions in this study 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 for moderate block with rocuronium are noted below in Table 7.

Table 7 Time (in Minutes) to Recovery to a TOF Ratio of ≥0.9 for Sugammadex 2 mg/kg and Neostigmine for Moderate Block with Rocuronium

	Sugammadex 2 mg/kg	**Neostigmine**
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

SD = standard deviation; TOF = train-of-four.

TTNMR is correlated with time to recovery to a TOF ratio of ≥0.9 in adults; however, TTNMR in this study is expected to be more variable than time to recovery to a TOF ratio of ≥0.9 as 4 different methods will be allowed to determine neuromuscular recovery. In addition, as clinical signs require the participant to be awake, TTNMR in these participants may be longer. Therefore, the assumptions for power calculations will be made appropriately conservative compared with the summary statistics listed in the table above. Power estimates for detecting various differences with respect to TTNMR between sugammadex and neostigmine in moderate block are obtained based on a Cox PH model using a 2-sided, 5%-level test, and are summarized in Table 8.

Table 8 Power Estimates for Detecting Various Differences in Time to Neuromuscular Recovery (in Minutes) Between Sugammadex and Neostigmine in Moderate Block

Sugammadex Mean (SD)	**Neostigmine Mean (SD)**	**Hazard Ratio**	**Power[a]**
3 (2)	13 (15)	6.96	>99%
5 (3)	13 (15)	3.39	97%
6 (4)	13 (15)	2.55	85%

SD = standard deviation

[a] Based on N=27 for each treatment group to allow for 10% participants not treated with study medication using Cox PH model; 2-sided, 5%-level Chi-Square Test;

Data are simulated based on log-normal distribution.

9.9.2 Sample Size and Power 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 hypersensitivity is, eg, 1% (1 of every 100 participants receiving the study treatment), there is a 34.4% chance of observing at least 1 AE among 42 participants in the 2 mg/kg

sugammadex treatment group, and a 41.9% chance of observing at least 1 AE among 54 participants in the 4 mg/kg sugammadex treatment group.

The estimate of the upper bound of the 95% CI for the underlying percentage of participants with a Tier 1 AE within the sugammadex groups are provided in Table 9. These calculations are based on the exact binomial method proposed by Clopper and Pearson [Clopper, C. J. 1934].

Table 9 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 42 (2 mg/kg) and 54 (4 mg/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]
42 (Sugammadex 2 mg/kg)	0	0.0%	8.4%
	1	2.4%	12.6%
	3	7.1%	19.5%
	5	11.9%	25.6%
54 (Sugammadex 4 mg/kg)	0	0.0%	6.6%
	1	1.9%	9.9%
	3	5.6%	15.4%
	5	9.3%	20.3%

[a] Based on the 2-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

Table 10 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 42 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 10 Differences in Incidence in a Tier 1 Adverse Event Between the Sugammadex and Neostigmine Groups (Assuming 2-sided 5% Alpha Level With 42 Participants in Sugammadex Group and 30 Participants in Neostigmine Group)

Incidence of Adverse Event		Risk Difference	
Sugammadex (%)	Neostigmine (%)	Percentage Points	95% CI[a]
2.4%	3.3%	1.1	(-14.5%, 9.5%)
7.1%	13.3%	6.2	(-23.5%, 8.2%)

CI = confidence interval

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

Incidences presented here are hypothetical and do not represent actual AEs in either group

9.9.3 Sample Size and Power for Pharmacokinetic Analyses

A sample size of 6 in each age group has approximately 91% likelihood that the 95% CI of the GM of CL in that particular age group will be within 60% and 140% of the GM estimates of the clearance of MK-8616. A between-subject SD of 0.23 in log scale for CL that was obtained from previous studies was used for these calculations. These calculations are also applicable to V_z. This calculation is based on the pediatric guidance proposed by Wang et al. [Wang, Y., et al 2012].

9.9.4 Sample Size and Power for Efficacy Data Comparison with Adults (for Dose Selection)

If PK results of an IA from Part A of the study are substantially different with those in the next oldest age cohort, comparison of efficacy data with those from adults will also be taken into consideration. The efficacy data comparison will be made between TTNMR in each age cohort of Part A and TOF ratio of ≥0.9 in adults. In each of the age cohorts, participants in both Panels will be pooled since the difference in time to recovery to a TOF ratio of ≥0.9 between moderate and deep block is clinically insignificant in adults.

From the Integrated Summary of Efficacy performed in 2012, GM and its 95% CI for the time to recovery to a TOF ratio of ≥0.9 for sugammadex 2 mg/kg is 1.9 (1.8, 2.0). TTNMR is similar to time to recovery to a TOF ratio of ≥0.9; however, TTNMR in pediatrics is expected to be slightly longer and more variable than time to recovery to a TOF ratio of ≥0.9 as 4 different methods of assessments will be used, 2 of which require an awake and cooperative participant. Thus, we assume the TTNMR (in seconds) in pediatrics follows a log-normal distribution with mean and SD of 5.7 and 2.0 (the corresponding GM is 5 minutes). With a sample size of 9 participants there is 85% probability that the estimated GM in pediatrics is <10 minutes under the above assumptions.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a 95% CI) for the primary and

secondary efficacy endpoints will be estimated and plotted within each subgroup of each classification variable below based on the primary efficacy analysis model (Cox PH) in the setting of moderate block (age or NMBA will not be in the model for subgroup analysis of that classification variable). The following are the classification variables:

- Age cohort (6 months to <2 years, 3 months to <6 months, 28 days to <3 months, Birth to 27 days)
- Neuromuscular blocking agent (rocuronium or vecuronium)
- Sex (female, male)
- Race (white, other)
- Region (US, Ex-US)

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

In addition, a summary of Tier 1 safety parameters will be provided for each subgroup of the following classification variables:

- Depth of block (moderate, deep)
- Age cohort (6 months to <2 years, 3 months to <6 months, 28 days to <3 months, Birth to 27 days)
- Neuromuscular blocking agent (rocuronium or vecuronium)
- Sex (female, male)
- Race (white, other)
- Region (US, Ex-US)

Subgroup analyses/summaries will only be performed for those classification variables with at least 5 participants in each subgroup.

9.11 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.

9.12 Extent of Exposure

The extent of exposure to study treatment will be summarized in a table presenting per treatment group the number of participants who were randomized and received the study treatment (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).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

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

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD 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.

MSD does not pay for participant referrals. However, MSD 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 MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD 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.

V. Investigator Commitment

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

10.1.2 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.

10.1.3 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 that 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.

10.1.3.1 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 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 study 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.

10.1.3.2 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 study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF 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 study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the study.

10.1.4.2 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 -Interim Analysis) and recommend to the EOC whether the study 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 study 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.

10.1.4.3 Clinical Adjudication Committee (CAC)

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 9, as well as evaluating the presence of confounding factors.

AE of hypersensitivity

Events of anaphylaxis

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

10.1.5 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.

10.1.6 Compliance with Study 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD

entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study 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 study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

10.1.8 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.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study 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 any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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 participants' legally acceptable representatives' documented informed consent, 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.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 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 study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be collected and analyzed by the local laboratory.
- Perianesthetic period (Visit 2): Samples will be drawn before study treatment administration and need not be drawn if local laboratory results are available within 14 days of randomization.
- Post-anesthetic period (Visit 3): Samples need not be drawn if local laboratory results are (or will be) available within 36 hours after administration of study treatment.
- The results and normal ranges of protocol-required safety laboratory assessments from local laboratories must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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 11 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes (% or numeric), if locally available	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry[a]	BUN or urea per local regulations	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]			

Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic-pyruvic transaminase, AST/SGOT = aspartate aminotransferase/serum glutamic-oxaloacetic transaminase, 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.

[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 nonfasting glucose values are acceptable.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- 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 intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), 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, 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 intervention 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 intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, 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 8.4.6 for protocol-specific exceptions.

10.3.2 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.

An 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 an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant'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) that 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 1 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.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs 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

10.3.4 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 AE CRFs/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 studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, 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 used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 AE 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 AE:

- **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 studies 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 study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - 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 study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND 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 IRB/IEC.

- **Consistency with study intervention 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 1 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.

10.3.5 Reporting of AEs, SAEs, 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 8.4.1 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 EDC 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 EDC 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 Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC 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 Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol, that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Customer Feedback - A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark which may suggest an improvement in the functionality or quality of a medical device or device-like features of a drug delivery system).

Device Events - 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.

Device Incident - 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, 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.

Malfunction - The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device - Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Participant Events - AEs experienced by the participant caused by or suspected to be caused by the medical device.

PQC - Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by external customers. This includes potential device malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

Refer to Section 8.4.8.

Assessing Causality

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

- The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Not applicable.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
APaT	All participants as treated
APT	All participants treated
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BSA	Blinded safety assessor
CAC	Clinical Adjudication Committee
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
Cox PH	Cox Proportional Hazards
CRF	Case report form
CSR	Clinical study report
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
ERA	Extubation readiness assessment
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
GM	Geometric mean
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intention-to-treat
IV	Intravenous
IVD	In vitro diagnostic
KM	Kaplan-Meier (curve)

Term	Definition
NMB	Neuromuscular blockade
NMBA	Neuromuscular blocking agent
NMTM	Neuromuscular transmission monitoring
NSAE	Nonserious adverse event
OR	Operating room
PACU	Post-anesthesia care unit
PK	Pharmacokinetic
PNS	Peripheral nerve stimulator
PREA	Pediatric Research Equity Act
PTC	Post-tetanic count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SLAB	Supplemental laboratory
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
TTNMR	Time to Neuromuscular Recovery
V_z	Apparent volume of distribution
V_{ss}	Apparent volume of distribution at steady state

10.9 Appendix 9: Bradycardia Definition by Age Range

Age Range	Heart Rate[a] (beats per minute)	Median Heart Rate (1st- 99th percentile)
0 to 3 months	<110	143 (107-181)
3 to 6 months	<105	140 (104-175)
6 to 12 months	<95	128-134 (93-168)
12 to 24 months	<85	116-123 (82-156)

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

10.10 Appendix 10: Extubation Readiness Assessment

EXTUBATION READINESS ASSESSMENT (PEDIATRIC)

Instructions: ALL core questions (Bolded Yes/No) must be answered. For the supporting data elements, assess and document any/all that apply. Refer to MK8616 P169 Guidance Document for Extubation Readiness Assessment for further details.

1) Neuromuscular Recovery [ ] Yes [ ] No

- Able to sustain head lift against resistance for at least 5 seconds
- Able to sustain hip flexion against resistance for at least 5 seconds
- 4 twitches without fade (or, for neonates, 4 twitches comparable to pre-op baseline) observed in response to TOF via NMTM device*
- TOF ratio ≥0.9 observed on objective neuromuscular transmission monitoring*

*If deep endotracheal extubation is performed, then neuromuscular recovery must be assessed by 4 twitches without fade (or, for neonates, 4 twitches comparable to pre-op baseline) observed in response to TOF via NMTM device or TOF ratio ≥0.9 observed on objective neuromuscular transmission monitoring

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2) Mental Status appropriate for extubation [ ] Yes [ ] No

- Awake
- Eye opening
- Purposeful movements

Note: If deep endotracheal extubation is performed, mental status at the time of extubation should be confirmed to be appropriate. The core question should be answered as “yes” with the supporting data to be “other – extubation at deep sedation”.

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3) Return of Spontaneous ventilation [ ] Yes [ ] No

- Spontaneous ventilation with clinically adequate tidal volume and regular respiratory rate as per individual's age and weight
- Spontaneous ventilation and no evidence of increased work of breathing (eg, no tracheal tug, no nasal flaring, no use of accessory muscles)
- End tidal CO2 <50mm Hg

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4) Adequate Oxygenation [ ] Yes [ ] No

- SpO2 >92%
- SpO2 <92%, but within 5% points of pre-operative baseline

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5) Hemodynamically stable [ ] Yes [ ] No

- Systolic and diastolic blood pressure at or above acceptable minimum for age
- Systolic and diastolic blood pressure within 30% of baseline post-induction levels
- Heart rate at or above acceptable minimum for age
- Heart rate within 30% of baseline post-induction levels

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6) Core Body Temperature at least 35 degrees Celsius [ ] Yes [ ] No

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