# CLINICAL REVIEW

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| **Application Type** | NDA Supplement |
| **Application Number** | NDA 022225 Supplement 0008 |
| **Priority or Standard** | Standard |
| **Submit Date** | August 26, 2020 |
| **Received Date** | August 26, 2020 |
| **PDUFA Goal Date** | June 26, 2021 |
| **Division/Office** | Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP) |
| **Reviewer Name** | Susan Yost, MD |
| **Review Completion Date** | June 16, 2021 |
| **Established/Proper Name** | Sugammadex |
| **Trade Name** | Bridion® |
| **Applicant** | Merck & Company |
| **Dosage Form** | Bridion® 2mL single dose vial containing 200mg sugammadex/2 mL or Bridion® 5 mL single dose vial containing 500 mg sugammadex/5 mL for intravenous infusion |
| **Applicant Proposed Dosing Regimen** | Bridion® dosing for pediatric patients ages 2 to <17 years is based on actual body weight.<br>4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation.<br>2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation |
| **Applicant Proposed Indication/Population** | For the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in pediatric patients ages 2 years to < 17 years |
| **Recommendation on Regulatory Action** | *Approval* |
| **Recommended Indication/Population** | For the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in pediatric patients ages 2 years to <17 years. |

**Table of Contents**

**Table of Tables**

**Table of Figures**

## Glossary

| | |
|---|---|
| AC | advisory committee |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug Application |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |

| | |
|---|---|
| NMB | neuromuscular blockade |
| NMBA | neuromuscular blocking agent |
| NME | new molecular entity |
| NMTM | neuromuscular transmission monitoring |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PACU | Post Anesthesia Care Unit |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information or package insert |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |
| TOF | train-of-four |

# 1. Executive Summary

## 1.1. Product Introduction

Bridion®, referred to as sugammadex in this review, contains sugammadex sodium, a modified gamma-cyclodextrin. Sugammadex forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium. The most commonly used neuromuscular reversal agent, neostigmine, is an anticholinesterase that is typically co-administered with an anticholinergic agent, e.g., atropine or glycopyrrolate. The coadministration of an anticholinergic with neostigmine is required to manage the cholinergic effects of neostigmine, e.g., bradycardia. The advantage of sugammadex over neostigmine is that sugammadex has a rapid onset and fully reverses deeper neuromuscular blockade.

Sugammadex is labeled for three dosages, based on depth of neuromuscular blockade:

- 2 mg/kg for reversal of a (b) (4) neuromuscular blockade (spontaneous recovery has reached the reappearance of the second twitch in response to train-of-four (TOF) stimulation)
- 4 mg/kg for reversal of a (b) (4) neuromuscular blockade (spontaneous recovery has reached 1 or 2 post tetanic counts (PTC) and there are no twitch responses to TOF stimulation)
- For reversal of rocuronium only: 16 mg/kg, if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of rocuronium.

At the time of approval four postmarketing requirements were issued:

> 3003-1- A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old
>
> 3003-2- Conduct a postmarketing study to analyze the demographic characteristics, concomitant medication use, and comorbid conditions in patients who do not respond to sugammadex
>
> 3003-3- Conduct a postmarketing clinical trial comparing sugammadex to

> placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in American Society of Anesthesiologists Class 3 and 4 patients
> 3003-4- Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in patients with morbid obesity, specifically whether to dose by actual vs. ideal body weight.

On April 19, 2018, the Applicant was released from PMR 300-1. At the same time, the following two pertinent PMRs were issued to replace PMR 3003-1:

> 3003-5: A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages 2 to less than 17 years old
>
> 3003-6: A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to less than 2 years old
>
> 3003-7: A multicenter, single-arm, open-label trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION 16 mg/kg injection to simulate reversal of neuromuscular blockade induced by rapid-sequence dose of rocuronium in pediatric patients ages birth to less than 17 years old.

On July 11, 2018, the Agency determined that studying the 16 mg/kg dose of sugammadex was not ethical or feasible in pediatric subjects. The Applicant was released from PMR 3003-7. Typographical errors were found in the milestone dates for PMRs 3003-5 and 3003-6. Therefore, the following PMRs were reissued to replace PMR's 3003-5 and 3003-6:

> 3003-8: A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages 2 to less than 17 years old
>
> 3003-9: A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or

vecuronium must be conducted in pediatric patients ages birth to less than 2 years old

On August 26, 2020, the Applicant submitted Supplement 008, with the results of Study P089 conducted to satisfy PMR 3003-8 and to extend the indication of sugammadex to children from 2 to less than 17 years of age.

## 1.2. Benefit-Risk Assessment

Prior to this submission, data on the use of sugammadex in the pediatric population was limited. Pediatric patients may be particularly sensitive to bradycardia, a known side effect of sugammadex. The Agency determined that identifying a safe dose of sugammadex for this population was necessary and then determining if a difference in safety and efficacy was noted in various age groups. Administration of too small of a sugammadex dose may result in incomplete neuromuscular blockade reversal or recurarization. Administration of too large a dose may result in an increased incidence of adverse events such as bradycardia and anaphylaxis and hypersensitivity.

Study P089, a Phase 4, double-blinded, randomized, active comparator-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of sugammadex for reversal of neuromuscular blockade in pediatric patients (P089MK8616) was conducted to fulfill the requirements of PMR 3003-8.

Part A of the study was conducted to determine the pharmacokinetics of sugammadex in three age cohorts, 2 to less than 6 years old, 6 to less than 12 years old and 12 to less than 16 years old. The results would determine the doses to be used in Part B of the study. Although the 2 to 6 years old age group was found to have an AUC and $C_{max}$ approximately 40% lower than the older age groups, efficacy was determined to be acceptable. Therefore, the doses used in Part B were the same as the currently recommended adult doses, sugammadex 2 mg/kg for reversal of (b) (4) neuromuscular blockade and sugammadex 4 mg/kg for reversal of (b) (4) neuromuscular blockade.

The results of Study P089 demonstrated that in pediatric patients age 2 to less than 17 years old, sugammadex 2 mg/kg reduced the time to recovery of train-of-four when compared to neostigmine when used to reverse moderate neuromuscular blockade. The difference in the geometric mean times to a train of four ratio of ≥0.9 for sugammadex 2 mg/kg compared to neostigmine was statistically significant with a p-value < 0.0001

There were no adjudicated anaphylaxis or hypersensitivity events. There were few events of clinically relevant bradycardia in general, but overall, there were fewer events of treatment

emergent and treatment emergent relative bradycardia in the sugammadex treatment groups compared to the neostigmine treatment group. No pattern was noted across the age group cohorts.

I recommend approval of Supplement 008 to NDA 022225 and thus fulfillment of PMR 3003-8.

### 1.3. Patient Experience Data

Patient experience data was not submitted as part of this application.

## 2. Therapeutic Context

### 2.1. Analysis of Condition

Neuromuscular blocking agents (NMBA) are frequently used in anesthesia to facilitate intubation of the trachea and muscle relaxation for surgical procedures. The aminosteroid agents, rocuronium bromide and vecuronium bromide are two commonly used intermediate-acting (lasting 20-35minutes) neuromuscular blocking agents or muscle relaxants. These agents work, as do all nondepolarizing neuromuscular blocking agents, by binding noncovalently and competitively at the nicotinic acetylcholine receptor at the neuromuscular junction. Neuromuscular transmission stops when 80-90% of the receptors are blocked. A neuromuscular blockade reversal agent is required when there is incomplete recovery from neuromuscular blockade via metabolic pathways or a need for urgent recovery of muscle function. The ideal reversal agent would have a rapid onset, no residual neuromuscular blockade, and no risk of recurarization in the post anesthesia care unit (PACU)

### 2.2. Analysis of Current Treatment Options

Two anticholinesterase (antagonist) products, pyridostigmine (NDA 017398) and neostigmine (NDA 204078) are currently marketed as reversal agents for the neuromuscular blocking effects of all available nondepolarizing muscle relaxants. In the United States, neostigmine is the most commonly used reversal agent for neuromuscular blockade. It is preferred in clinical practice over pyridostigmine because of the onset of action is within one minute with a full effect at 10 minutes compared to pyridostigmine onset of 15 to 30 minutes. An anticholinergic agent, e.g., atropine or glycopyrrolate, is usually co-administered with the anticholinesterase to counter

the cholinergic effects of these agents.

Bridion® (sugammadex), is the third agent currently marketed, but is only available for the reversal of the aminosteroid, nondepolarizing muscle relaxants, rocuronium bromide and vecuronium bromide. Sugammadex is a substituted gamma-cyclodextrin, with a novel mechanism of action. It forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to the nicotinic cholinergic receptors at the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Sugammadex was approved December 15, 2015. At the time of approval, four post marketing requirements were issued including post marketing requirement 3003-1; "A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old". The following table outlines the regulatory history of the pediatric aspect of the of the sugammadex drug development program following approval; and the evolution of PMR 3003-1, revised to PMR 3003-8, and NDA 022225 supplement 008.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

**Table 1: Summary of Regulatory Events for NDA 022225, Supplement 008, Following Approval of NDA**

| ***Date*** | ***Event*** |
|---|---|
| December 15, 2015 | Bridion® (sugammadex) was approved with postmarketing requirement 3003-1-*A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old.* |
| July 1 2016 | Proposed Pediatric Study Request received. The study sbumitted requested:<br>• Obtain written request<br>• Satisfiy required PMR 3003-1 |
| January 13, 2017 | Revised Written Request submitted, proposed changes included:<br>• Conduct two-part studies to include a pharmacokinetic component as welll as efficacy and safety at 3 doses of sugammadex; 2 mg/kg, 4 mg/kg and 16 mg/kg |

| ***Date*** | ***Event*** |
|---|---|
| May 24, 2017 | Amended Written Request (reqyested January 13, 2017) |
| April 19, 2018 | The Applicant was released from PMR 3003-1; three PMRs were issued to replace PMR 3003-1:<br>3003-5: *A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages.*<br>*2 to less than 17 years old.*<br>3003-6: *A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to less than 2 years old.*<br>3003-7 *A multicenter, single-arm, open-label trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION 16 mg/kg injection to simulate reversal of neuromuscular blockade induced by rapid-sequence dose of rocuronium in pediatric patients ages birth to less than 17 years old.* |
| July 6, 2018 | Division determined that studying the 16 mg/kg dose of sugammadex was not feasable or ethical in pediatric subjects |
| July 11, 2018 | Division issued a PMR Relaease and Reissue letter notifying the Applicant they no longer needed to study the sugammadex 16 mg/kg dose in pediatric subjects.Therefore, the Applicant was released from PMR 3003-7. Typopgraphical errors were made in the mlestone dates included in the April 18, 2019 letter regarding PMRs 3003-5 and 3003-6. The following two PMRs were issued :<br>3003-8: *A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages 2 to less than 17 years old.*<br>3003-9: *A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to less than 2 years old.* |
| October 19, 2018 | Revised Written Request with revisions to align the Written request with the agreed upon PREA studies (including P089) |

| ***Date*** | ***Event*** |
|---|---|
| January 11, 2019 | Applicant submitted Part A of Protocol P089 for Division review. The PK profile for the 2 mg/kg and 4 mg/kg doses in the 2 to 6 year old cohort did not match the PK profile for the adults. |
| February 19, 2019 | An Advice Letter was sent stating that the Applicant must increase the dose to establish adequate PK matching in the 2 to 6 year old cohort. |
| April 9, 2019 | The Applicant responded to the Agency's comments regarding dose increase stating efficacy results in the age group were acceptable and requested modifying the PWR to reflect recovery time comparability to be included in the benefit-risk assessment of the adequacy of existing dosing. Th Division detemined this to be an acceptable approach. |
| July 17, 2019 | The Applicant submitted an amendment to the PWR (Jauanry 22, 2019) reflecting the changes to the interim prhamacokinetic and safety analysis for Part A of Study P089 |
| August 26, 2020 | PMR 3003-8, NDA Supplement 008 submission for review with the completed Study P089, for Section 8 of the label for pediatric patients. |

Source: Reviewer Generated

On December 4, 2020, The Applicant submitted a 120-day Safety Update for review.

### 3.3. Foreign Regulatory Actions and Marketing History

Sugammadex was approved in the European Union July 25, 2008. In the European Union and Great Britain, sugammadex is recommended for routine reversal of rocuronium-induced blockade at the reappearance of T2 (b) (4) in children and adolescents (2-17 years). The recommended dose is 2 mg/kg.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

Dr. Christian Shenouda inspected Site 6, a single investigator site, March 23-29, 2021

Gregory Hammer, MD
Site #6
Department of Anesthesia,
Stanford University Medical Center
300 Pasteur Drive
Stanford, CA 94305

The site was chosen for inspection using a risk-based approach. This included number of enrolled subjects, site efficiency, protocol deviations, and prior inspection history.

During his inspection, Dr. Shenouda found two patients where the primary efficacy endpoints (TOF ratio ≥0.9) could not be verified because an imputation method was used to determine times. Both patients were randomized to the Part A, sugammadex 4 mg/kg group. In one patient, the TOF-Watch SX Monitor malfunctioned, there were no TOF readings for this subject. The value of the time to TOF ration >0.9 was imputed as per the Applicant's protocol. The second subject, the data did not show that a TOF ratio of 0.9 was achieved. The Applicant stated that the time to both TOF ratio of 0.7 and 0.8 were available in the in the source record. The time to TOF of 0.9 was imputed per protocol.

Dr. Shenouda concluded that the Protocol appeared to have been conducted adequately and the data generated appears acceptable in support of the indication. I concur as the data imputation was performed according to protocol.

## 4.2. Product Quality

No studies were submitted for this NDA supplement.

## 4.3. Clinical Microbiology

Sugammadex is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

## 4.4. Nonclinical Pharmacology/Toxicology

There was no information submitted for this NDA supplement.

## 4.5. Clinical Pharmacology

In adults, sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus. The elimination half-life ($t_{1/2}$) of sugammadex is about 2 hours in adult anesthetized patients.

Part A is a was a randomized, double -blinded, multi-site evaluating PK, safety, and tolerability of sugammadex when used for reversal of NMB. The PK data that was collected in Part A were used to identify the doses of sugammadex tested in Part B.

Dr. Srikanth Nallani summarized in his review the results of the pharmacology review of Part A.

Because the sugammadex dosing is based on bodyweight, it is not necessary to alter dosing regimen of sugammadex in pediatric patients 2 – 17 years of age.

Pharmacokinetic parameters from Study P089 after single-dose administration of 2 or 4 mg/kg sugammadex in pediatric patients 2 to <17 years of age are shown in Table 1. Patients were enrolled into 3 age groups and intravenous doses of 2 or 4 mg/kg sugammadex were administered for reversal of moderate or deep neuromuscular blockade, respectively. Sugammadex exposure (AUC0-inf and Cmax) increased in a dose-dependent, linear manner following administration of 2 and 4 mg/kg across patients 2 to <17 years of age. Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant.

For further discussion of PK characteristics in the three age groups, refer to Dr. Nallani's review.

Table 1: Geometric Mean (% GCV) Pharmacokinetic Parameters in Pediatric Participants After Single-Dose Administration of Sugammadex.

| Age Group (years) | Dose (mg/kg) | Pharmacokinetic Parameters | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $AUC_{0\text{-}inf}$ (h*µg/mL) | $C_{max}$ (µg/mL) | CL (L/hr) | wnCL ((L/hr)/kg) | Vss (L) | wnVss (L) | t1/2 (hr) |
| 2 to <6 | 2 | 14.1 (19.4) | 17.5 (33.1) | 2.30 (21.4) | 0.142 (19.4) | 3.58 (21.3) | 0.221 (22.5) | 1.23 (17.4) |
| | 4 | 26.9 (18.5) | 47.1 (22.1) | 2.26 (29.4) | 0.149 (18.5) | 3.10 (27.7) | 0.204 (7.95) | 1.23 (25.2) |
| 6 to <12 | 2 | 18.8 (27.4) | 32.2 (15.6) | 3.58 (26.2) | 0.107 (27.4) | 5.16 (31.4) | 0.154 (6.27) | 1.29 (25.1) |
| | 4 | 38.2 (73.0) | 51.6 (69.2) | 3.43 (105) | 0.105 (73.0) | 6.24 (73.9) | 0.190 (38.4) | 1.66 (32.5) |
| 12 to <17 | 2 | 27.6 (58.0) | 41.3 (85.8) | 4.68 (52.5) | 0.0726 (58.0) | 7.20 (32.8) | 0.112 (38.7) | 1.49 (23.2) |
| | 4 | 49.2 (20.1) | 61.9 (13.5) | 5.69 (24.1) | 0.0812 (20.1) | 9.88 (27.7) | 0.141 (17.4) | 1.49 (19.2) |

$AUC_{0\text{-}inf}$=area under the concentration-time curve from time zero to infinity; CL=clearance; $C_{max}$=maximum concentration; GCV=geometric coefficient of variation; t1/2=half-life; Vss=apparent volume of distribution at steady state; wnCL=weight-normalized clearance; wnVss=weight normalized apparent volume of distribution at steady state.

Dr. Nallani also confirmed that the molar excess for the for patients 2 to <6 for sugammadex 4mg/kg was consistently >4. From his review:

For the single participant 2 to <6 years of age administered sugammadex 4 mg/kg, a molar excess of 9.88 was estimated. These results confirm the molar excess of sugammadex versus rocuronium being consistently >4 in the different age categories at the initial 2-minute timepoint for both 2- and 4-mg/kg doses. At later timepoints through 60-minutes post-dose, this molar excess is maintained at a level >2 for the 2-mg/kg dose and >4 for the 4-mg/kg dose in all included age categories. Overall, sugammadex doses of 2 and 4 mg/kg can be assumed to

provide a minimum molar excess of >2 and continue to ensure encapsulation of NMBA, reducing the risk of recurrence of NMB.

Based on the information from the PK studies from Part A, the dosing for Part B was determined to be sugammadex 2 mg/kg and 4 mg/kg as previously designated in the protocol.

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

**Table 2: Clinical Study Supporting NDA Supplement 008**

| *Study Identity* | *Study Design* | *Regimen and Route* | *Primary Study Endpoints* | *No. of Patients Dosed* | *Study Population* | *No. and Location of Centers* |
|---|---|---|---|---|---|---|
| P089MK8616 | Two part, randomized, double-blind, active-comparator, parallel group,multisite | **Part A:** Sugammadex 2 or 4 mg/kg, IV dosed by actual body, single dose, perianesthetic period<br>**Part B**: Sugammadex 2 or 4 mg/kg or neostimine 50 mg/kg with glycopyrrolate 5 to 15 mcg/kg or atropine sulfate 10 to 20 mcg/kg IV, dosed by actual body weight, single dose, perianesthetic period. | **Pharmacokinetics**<br>**Part A only**<br>-Describe the pharmacokinetic parameters of sugammadex in pediatric patients (AUC,CL, $V_z$, $C_{max}$,, $t_{½}$)<br>**Safety**<br>**Part A and Part B**<br>- Safety and tolerability of sugammadex by evaluating number of participants esperiencing adverse events<br>**Efficacy**<br>**Part B Only**<br>-Assessment of sugammadex compared to neostigmine using time to recover to TOF ratio of ≥0.9 | Sugammadex 2 mg/kg<br>2 to < 6 years = 22<br>6 to < 12 years = 15<br>12 to < 17 years = 14<br><br>Sugammadex 4 mg/kg<br>2 to < 6 years = 80<br>6 to < 12 years = 64<br>12 to < 17 years = 47<br><br>Neostigmine + (Glycopyrrolate or Atropine)<br>2 to < 6 years = 12<br>6 to < 12 years = 13<br>12 to < 17 years = 9 | Pediatric patients between the ages of 2 and <17 years, ASA Class 1, 2 or 3, undergoing a planned, nonemergent surgical procedure or clinical situation requiring neuromuscular block with rocuronium or vecuronium | 26 sites total<br>18 European Sites<br>Austria: 1<br>Belgium: 2<br>Denmark:1<br>Finland:1<br>Germany: 5<br>Spain: 4<br>Turkey: 4<br>8 Sites in the United States |

Source: Reviewer generated

## 5.2. Review Strategy

The following sources of information were included for review of the postmarketing pediatric requirement efficacy supplemental application.

**Study Performed by Merck Sharp & Dohme**
The applicant conducted one study to fulfil the postmarketing requirement 3003-8, Phase 4

Study P089MK8616 (P089). This review will focus on the efficacy and safety information provided from this two-part, adequate, and well controllled study (Part B only). The final determination of Section 8 of the sugammadex label for the pediatric patient, ages 2 to <17 years, for safety and dose administration, will be based the data analysis outcome for this study.

There are no other sources of information provided, Study P089 will be the only study reviewed for final labeling determinination.

# 6. Review of Relevant Individual Trials Used to Support Efficacy

## 6.1. A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled, Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex for Reversal of Neuromuscular Blockade in Pediatric Participants (P089MK8616)

### 6.1.1. Study Design

**Overview and Objective**

The purpose of the study was to evaluate the PK, safety, and efficacy for reversal of moderate and deep neuromuscular block induced by vecuronium or rocuronium in pediatric patients age 2 years to <17 years. The data were collected in a two-part structure, Part A and Part B. All patients were administered sugammadex based on actual body weight.

The Study objectives (verbatim) were as follows:

- Primary objectives:
  - To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).
  - To evaluate the safety and tolerability of sugammadex (data will be pooled across Part A and Part B of the study).
  - To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).
    - Time to recovery to a TOF ratio of ≥0.9. (endpoint)
- Secondary objectives:
  - To evaluate the efficacy of sugammadex in comparison to neostigmine for reversal of moderate NMB (Part B)
    - Time to recovery to a TOF ratio of ≥0.8 (endpoint)

- Time to recovery to a TOF ratio of ≥0.7 (endpoint)

- Exploratory Objectives
  - To evaluate the efficacy of sugammadex to neostigmine for the reversal of moderate NMB (Part B).

**Trial Design**

Study P089 was a Phase 4, randomized, double blind, active-comparator, multicenter, two-part study to evaluate the efficacy, safety, and pharmacokinetics of sugammadex administered for the reversal of neuromuscular blockade, induced by vecuronium or rocuronium, in pediatric patients ages 2 years old to less than 17 years old. The patients were divided into three age groups for the study.

- 2 years old to < 6 years old
- 6 years old to < 12 years old
- 12 years old to < 17 years old

The study design consisted of two parts, Part A and B. Part A is a was a randomized, double - blinded, multi-site evaluating PK, safety, and tolerability of sugammadex when used for reversal of NMB. The PK data that was collected in Part A were used to identify the doses of sugammadex tested in Part B. Following completion of Part A, an interim analysis was performed before proceeding with Part B. Part B was a randomized, double-blinded, active comparator controlled, multicenter study, conducted to further evaluate the safety and efficacy sugammadex for reversal of moderate or deep NMB in pediatric patients.

Part A – Patients were randomized within each age group in a 1:1 ratio within each age group as follows:

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

- Part B – Patients were randomized in an approximate 1:1:5 ratio within each age group as follows:
  - Moderate block and reversal with 2 mg/kg of sugammadex
  - Moderate block and reversal with neostigmine 50 mcg/kg (to a max dose of 1 mg) + glycopyrrolate or atropine sulfate
  - Deep block and reversal with 4 mg/kg of sugammadex

The doses of sugammadex were defined by the target train of four using a peripheral nerve stimulator (PNS).

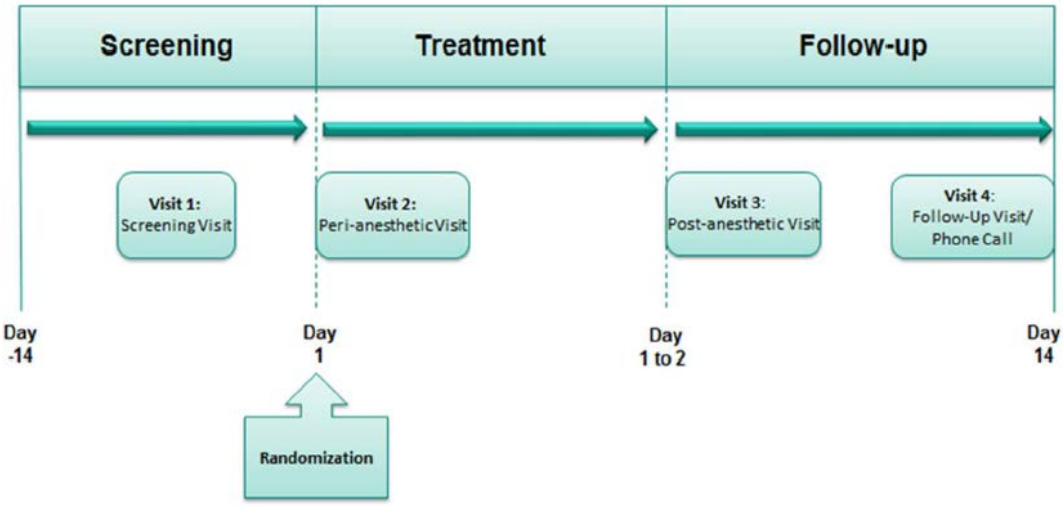
- The moderate neuromuscular blockade group was administered sugammadex 2 mg/kg

after the last dose of neuromuscular blocking agent (NMBA) and within two minutes of detection of T2, the second twitch on the train-of-four with a lower limit of train of four (TOF) count 1 and upper limit of TOF count of 4 OR

- The active comparator group, neostigmine 50 mcg/kg (up to 5mg maximum dose) + atropine or glycopyrrolate was administered after the last dose of NMBA and within 2 minutes of detection of reappearance of second twitch (T2) with a lower limit of train of four (TOF) count 1 and upper limit of TOF count of 4
- The deep neuromuscular blockade group was administered sugammadex 4 mg/kg after the last dose of NMBA and within 2 minutes of detection of 1 to 2 post-tetanic counts (PTC) with a range of 1-5 PTC at a TOF count of 0

Patients were screened up to 14 days prior to the scheduled surgery date. Screening and surgery were allowed on the same day; however, urine or serum β-hCG test results, if applicable, were required prior to surgery. If screening and surgery occurred on the same day, the pregnancy test did not need to be repeated. Hematology and chemistry samples were drawn on the day of surgery (Day 1) unless local lab results were available within 24 hours after administration. The general treatment plan is shown in the diagram below.

**Figure 1: Treatment Plan for Study P-089**




Source: Applicants Submission: August 26, 2020 CSR p 28

On Day 1 of the study, patients were administered a neuromuscular blocking agent intraoperatively as per stratification, either vecuronium or rocuronium. Following the last dose of administered NMBA, patients were administered the predetermined, assigned study drug. As per protocol, patients were not allowed any other neuromuscular blocking agents.

*Trial Location*

This study was conducted in 18 European sites and 8 sites within the United states. All studies

were conducted in compliance with the International Conference on Harmonization (ICH)E6 and 21 CFR 312.120.

*Choice of Control Group*
As discussed in section 2.2, neostigmine is the most frequently used anticholinesterase inhibitor for neuromuscular blockade reversal in the practice of anesthesia. Therefore, it serves as an appropriated comparator for evaluating the effectiveness of sugammadex in the reversal of moderate neuromuscular blockade. However, neostigmine is not indicated for reversal of deep neuromuscular blockade. Sugammadex is the only reversal agent indicated for reversal of deep neuromuscular blockade. Therefore, the active comparator was only dosed once there was a return of TOF, as described for reversal of moderate neuromuscular blockade.

Due to the cholinergic activity of neostigmine, it is usually administered with an anticholinergic. With a neostigmine dose of 50 mcg/kg, one of the following was administered:

- 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)

*Key Inclusion Criteria*
1. Male/female participants between the ages of 2 and <17 years at Visit 2
2. Categorized as ASA physical status Class 1, 2, or 3, as determined by the investigator
3. Had a planned nonemergent surgical procedure or clinical situation (e.g., intubation) that required moderate or deep NMB with either rocuronium or vecuronium
4. Had a planned surgical procedure or clinical situation that would allow objective neuromuscular monitoring techniques to be applied with access to the arm for neuromuscular transmission monitoring

*Key Exclusion Criteria (verbatim)*
1. Had any clinically significant condition or situation (e.g., anatomical malformation that complicates intubation) other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial
2. Had a neuromuscular disorder that could have affected NMB and/or trial assessments
3. Dialysis-dependent or had (or was suspected of having) severe renal insufficiency.
4. Had or was suspected of having a family or personal history of malignant hyperthermia
5. Had received or was planned to receive toremifene and/or fusidic acid via IV administration within 24 hours before or within 24 hours after administration of study treatment

*Dose Selection*
Sugammadex dosing was based on the findings of the original clinical trials for adult dosing (2

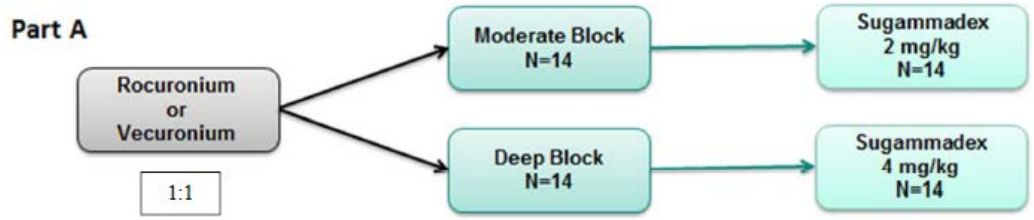
mg/kg for moderate block reversal, 4 mg/kg for deep block reversal). No additional efficacy benefits were expected from higher doses than those recommended in adults. Based on adult trial data, the use of doses lower than recommended in adults may lead to an increased risk of recurrence in neuromuscular blockade after reversal.

The limited PK data collected from a Study P034, (Plaud, B. et al., 2009) a randomized controlled trial that evaluated rocuronium induced moderate NMB reversed with sugammadex in pediatric patients age 28 days to 17 years, provided preliminary PK data that were generally consistent with the adult data. Because of the preliminary evidence adult doses of sugammadex will exhibit comparable exposures in pediatric patients, it is reasonable that the Applicant chose the recommended adult doses for Part A of Study P089.

Dose selection for Part B was based on the results of the PK studies from Part A. Sugammadex exposure increased in a dose dependent linear manner following administration of 2 and 4 mg/kg to pediatric patients, similar to adults. However, the AUC and $C_{max}$ were about 40% lower in patients 2 to < 6 years old following administration of either 2 or 4 mg/kg of sugammadex compared to pediatric patients 6 to < 17 years old. However, this difference was not found to be clinically relevant. The efficacy was similar for the 2 to less than 6-year-old age group to the older children. Therefore, the doses selected for Part B remained sugammadex 2 mg/kg for moderate block reversal and 4 mg/kg for deep block reversal.

Approximately 30% of the overall sample was planned to receive vecuronium. For Part A, patients were randomized 1:1 to moderate block and reversal with sugammadex 2 mg/kg OR deep block and reversal with sugammadex 4 mg/kg

**Figure 2: Part A Patient Randomization**




Source: Applicant Submission August 26, 2020, CSR, p 29

In addition, each subgroup was stratified by age as follows:

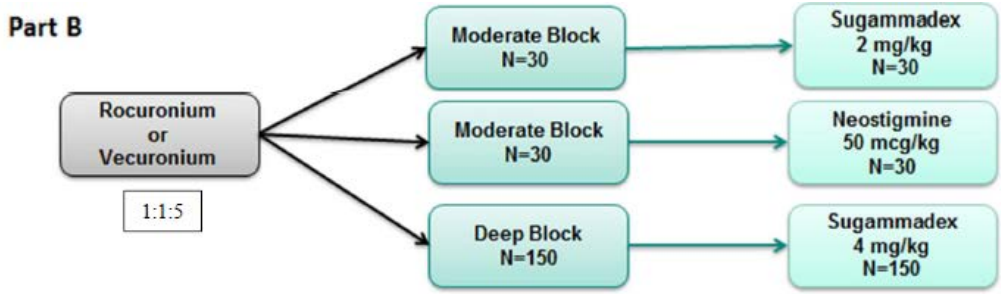
- 2 to less than 6 years old
- 6 to less than 12 years old
- 12 to less than 17 years old

Following completion of Part A of the study, an interim analysis was performed to evaluate PK and safety data. The PK and safety data were evaluated by a standing internal Data Monitoring Committee (siDMC) and safety data was reviewed by an eDMC (external DMC). In addition, PK and efficacy data were submitted to FDA for review. Following review, FDA agreed to continue evaluation of 2 mg/kg and 4 mg/kg doses for Part B

For Part B, moderate block reversal with an active comparator was added to the treatment groups (see Figure 3).

- Moderate block and reversal with sugammadex 2 mg/kg
- Deep block and reversal with sugammadex 4 mg/kg
- Moderate block and reversal with neostigmine (active comparator) 50 mcg/kg to a max of 5 mg + atropine or glycopyrrolate

**Figure 3: Part B Patient Randomization**




Source: Applicant Submission August 26, 2020, CSR, p 29

Patients in Part B were randomly assigned in a 1:1:5 ratio to the type of block and treatment group. However, to ensure adequate safety database sample sizes were reached, the allocation ratios varied slightly by age, so the youngest age cohort had the largest sample size.

- 1:1:6 ratio for the 2 to less than 6 years old cohort
- 1:1:5 ratio for the 6 to less than 12 years old cohort
- 1:1:4 ratio for the 12 to less than 17 years old cohort

*Study Treatments*
Following administration of the planned neuromuscular blocking agent (NMBA) for intubation, additional doses of NMBA were administered as clinically required for the duration of the surgery to maintain the assigned depth of block, either moderate or deep neuromuscular blockade. Depth of block was assessed via continuous neuromuscular transmission monitoring using the TOF Watch SX®. Patients were maintained in either a moderate or deep neuromuscular blockade (NMB) intraoperatively until the time of reversal according to the assigned treatment plan.

- For patients randomized to moderate block: after the last dose of administered NMBA and within 2 minutes of reappearance of a second twitch referred to as T2, the second twitch on the train of four with the lower limit of train of four (TOF) count 1 and upper limit of TOF count of 4, study medication sugammadex or neostigmine was administered
- For patients randomized to deep block: after last dose of administered NMBA and within 2 minutes of detection of a target of 1-2 post tetanic contraction referred to as PTC with a range of 1-5 PTC at the train of four or TOF count of 0, study medication sugammadex, was administered
- Neuromuscular monitoring continued until the patient reached the endpoint of TOF ≥0.9, or for at least 30 minutes following study drug administration.

*Blinding*
Out of necessity, the pharmacist preparing the medications was unblinded. The study drug was provided to the anesthesiologist in masked syringes. The anesthesiologist present in the operating room, who administered the study drug, was blinded in the moderate block group. In the deep block group, there was no blinding since there was no active comparator for this group.

A Blinded Safety Assessor (BSA) was blinded to the study treatment assignment and depth of block for each patient. They were not present during surgery nor was the individual part of the anesthesia team. The BSA completed the postanesthetic safety visit (Visit 3) and completed the causality assessment for all AEs.

*Administrative Structure*
A standing internal Data Monitoring Committee (siDMC) consisting of internal Applicant personal, was unblinded. The siDMC was responsible analyzing the interim results of Part A of the study.

An external Data Monitoring Committee (DMC) monitored interim data from Part A of the trial. The members of the committee were external to the Applicant. Following review of interim data, the DMC made recommendations to the Executive Oversite Committee to proceed with the trial according to protocol.

The Neuromuscular Monitoring Adjudication Committee (NMAC) reviewed all TOF traces to assess overall data quality. The Committee provided confirmation of the acceptability of the investigative site TOF-operator's interpretation or provided a separate interpretation to be used as part of the efficacy analysis.

A Clinical Adjudication Committee (CAC) consisted of independent consultants, independently assessed events of hypersensitivity and anaphylaxis, and determined if there were any

confounding factors.

*Procedures and Schedules*
The table below presents the schedule of events for screening, Day 1 (Day of Surgery), Days 1 to 2 (4 to 36 hours post study drug administration), and 14-day Follow-up Safety Contact.

**Table 3: Schedule of Events, Study P089**

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

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

Source: Applicants Submission, August 26, 2020, Protocol Amendment 089-01, p 103-10

## Table 3 Continued

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

Abbreviations: AE = adverse event, β-hCG = β-human chorionic gonadotropin, ECI = event of clinical interest, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, NMBA = neuromuscular blocking agent, SAE = serious adverse event, SCr = serum creatinine, TOF = train-of-four

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

Source: Applicants Submission, August 26, 2020, Protocol Amendment 089-01, p 103-106

Because sugammadex is a single dose medication, monitoring vital signs and assessing PK parameters frequently at the time immediately following dosing is imperative.

Vital signs (heart rate, blood pressure, oxygen saturation, respiratory rate, and temperature) were assessed as follows:

- Screening visit
- Prior to administration of NMBA
- After final dose of NMBA is administered, prior to study drug administrations
- At 2, 5, 10, and 30 minutes following study drug administration
- Post-anesthetic visit
- During the peri-anesthetic time, ECG was continuously monitored for 5 minutes prior to, during and for 30 minutes following study drug administration

PK samples (Part A only) were drawn from a separate location than the study drug administration at 2, 15, 30 and 60 minutes, and 5- and 10-hours following study drug administration.

The following table shows additional laboratory tests performed.

**Table 4: Safety Laboratory Assessments**

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

[a] For participants with history of renal impairment only: SCr will be required for Screening (Visit 1), to calculate eGFR (using revised Schwartz estimate).
[b] Fasting or non-fasting glucose values are acceptable.
Abbreviations: ALT/SGPT = alanine aminotransferase/serum glutamic-pyruvic transaminase, AST/SGOT = aspartate aminotransferase/serum glutamic-oxaloacetic transaminase, β-hCG = β-human chorionic gonadotropin, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, MCH = mean corpuscular hemoglobin, MCV = mean corpuscular volume, RBC = red blood cell, SCr = serum creatinine, WBC = white blood cell

Source: Applicant's Submission, August 26, 2020, CSR, Protocol p 67

Investigators were required to document review of each laboratory safety report.

*Concurrent medications*

Patients were administered the steroidal neuromuscular blocking agents that bind to sugammadex, rocuronium and vecuronium. No other neuromuscular blocking agents were given, including succinylcholine. All of the patients underwent a general anesthetic and the medications administered according to the requirements of the anesthetic and surgical procedure. However, toremifene or fusidic acid use were prohibited within 24 hours before or 24 hours after the administration of the study drug. Both of these drugs have a potential displacement reaction with sugammadex, thereby lengthening the duration of a neuromuscular blocking agent.

*Treatment Compliance*

Dosage was assessed based on the actual and planned dosage of the study medication. Any dosage that deviated more than 10% from the planned dosage was considered a medication error. No statistical tests were planned or performed with respect to treatment compliance**.** No patients were discontinued from the study due to dosage deviation.

*Rescue medications*

No rescue medications were specified to be used in this study.

*Patient completion*
Signing of informed consent was considered the beginning of the study. The overall study ended when the last patients completed the final study related phone-call or visit. Once the patient received the study medication at Visit 2 (Surgery Day) all applicable procedures followed the flow chart from Figure 1. If a patient withdrew, a treated patient with analysis in progress at the time of the request was used as part of the study data. Patients discontinued from the study were not replaced.

**Study Endpoints**
Primary Efficacy Endpoint

- The time to recovery to a TOF ratio of ≥0.9
  A TOF ≥0.9, is thought to correlate with essentially complete clinical recovery from the effects of neuromuscular blockade.

Secondary Efficacy Endpoints

- Time to recovery to a TOF ratio of ≥0.8
- Time to recovery to a TOF ratio of ≥0.7
  Hypoxic ventilatory responses are impaired at TOF ratios of <0.7.

Tertiary/Exploratory Efficacy Endpoints

- Time to Extubation: interval from the administration of reversal agent to removal of the endotracheal tube
- Time to OR discharge
- Time to PACU discharge
- Time to hospital discharge
- Incidence of delayed recovery

Primary Safety Endpoint

- Number of participants experiencing adverse events
  The following were identified as events of clinical interest (ECI):
  - **Hypersensitivity and/or anaphylaxis**. An external Adjudication committee reviewed potential hypersensitivity and/or anaphylaxis events.
    Sugammadex is known to cause hypersensitivity and anaphylaxis.
  - **Clinically relevant bradycardia**, defined as any bradycardia event necessitating intervention as determined by the investigator.
    Sugammadex is known to cause bradycardia.

  In addition, the incidence of treatment emergent bradycardia and treatment emergent relative bradycardia were assessed.
  - **Treatment-emergent relative bradycardia** was defined as a heart rate that has decreased 20% or greater as compared to the patient's pre-dose baseline heart

rate value, sustained for at least 30 seconds, and occurring after the administration of the study drug.

- **Treatment-emergent bradycardia** is defined as a heart rate generally below the 1st percentile for age that has also decreased 20% or greater as compared to the patient's pre-dose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of the study drug.

Primary Pharmacokinetic Endpoint (Part A only)

- To describe pharmacokinetic parameters: AUC, CL, $V_Z$, $C_{max}$, and $t_{1/2.}$ The sugammadex PK parameters were estimated to predict dosing. After interim analysis, the dosing was determined for Part B.

**Statistical Analysis Plan**

The key elements of the statistical analysis plan are summarized in Table 5 that follows.

**Table 5: Statistical Analysis Plan Summary for Study P089**

| | |
|---|---|
| **Study Design Overview** | A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants |
| **Treatment Assignment** | In Part A, participants will be randomized to 2 doses of sugammadex in a 1:1 ratio with NMBA and age as stratification factors:<br>• 2 mg/kg sugammadex for moderate NMB and reversal<br>• 4 mg/kg sugammadex for deep NMB and reversal<br>In Part B, participants will be randomized to the following treatment groups in a 1:1:5 ratio (overall) with NMBA and age as stratification factors:<br>• 2 mg/kg sugammadex for moderate NMB and reversal<br>• 50 mcg/kg neostigmine for moderate NMB and reversal<br>• 4 mg/kg sugammadex for deep NMB and reversal |
| **Analysis Populations** | **Pharmacokinetic:** Pharmacokinetic (PK) Set<br>**Safety**: All Participants as Treated (APaT)<br>**Efficacy**: All Participants Treated (APT) |
| **Primary Endpoint(s)** | **Pharmacokinetic**: Area under the plasma concentration-time curve (AUC), clearance (CL), volume of distribution ($V_z$), maximum plasma concentration ($C_{max}$), and half-life ($t_{1/2}$)<br>**Safety**: Adverse event (AE) reporting, laboratory and vital sign assessments.<br>**Efficacy**: The time to recovery to a train-of-four (TOF) ratio of ≥0.9 |
| **Secondary Endpoints** | The time to recovery to a TOF ratio of ≥0.8<br>The time to recovery to a TOF ratio of ≥0.7 |
| **Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses** | **Pharmacokinetic**: Separately for each PK parameter, individual values of CL, AUC, $C_{max}$, and $V_z$, will be natural log-transformed and evaluated with a fixed effects model containing terms dose and age group. At each dose, 95% CIs of geometric means for each parameter will be provided. Descriptive summary statistics will be provided for PK parameters including AUC, $C_{max}$, dnAUC, dn$C_{max}$, CL, $V_z$ and $t_{1/2}$.<br>**Efficacy**: The efficacy hypothesis will be evaluated within Part B by comparing sugammadex to neostigmine in the setting of moderate block using log-transformed time-to-recovery values via Analysis of Variance (ANOVA), adjusting for neuromuscular blocking agent (NMBA) and age. |
| **Statistical Methods for Key Safety Analyses** | P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the stratified Miettinen and Nurminen method [1] |
| | with NMBA and age group as stratification factors. |
| **Interim Analyses** | One interim analysis (IA) will be performed in this study to evaluate PK and safety data. PK and safety data will be reviewed by a standing internal Data Monitoring Committee (siDMC) and safety data will be reviewed by an external Data Monitoring Committee (eDMC). This interim analysis is summarized below. Details are provided in Section 3.2.<br>• Timing: When Part A has been completed, prior to the commencement of enrollment of Part B.<br>• Testing: IA will evaluate PK and safety data. No formal efficacy analyses are planned. |
| **Multiplicity** | No multiplicity adjustment is planned as there is a single comparison of sugammadex versus neostigmine in the setting of moderate block using 1 endpoint in the primary efficacy hypothesis. |
| **Sample Size and Power** | The planned sample size is 238 participants, based on minimum safety database requirement. There will be 30 participants per treatment arm (sugammadex and neostigmine) in the setting of moderate block for efficacy analysis. For time to recovery to TOF ≥0.9, the trial has >99% power to demonstrate that sugammadex 2mg/kg is superior to neostigmine at an overall two-sided 5% alpha-level. |

Source: Applicant's Submission, August 26, 2020, CSR, Documentation of Statistical Methods p 3-4

- All efficacy analyses were based on All Participants Treated (APT) population. The APT

population consisted of randomized patients who were dosed with both a NMBA and at least one dose of the study drug.

- A formal test for efficacy to compare sugammadex to neostigmine for reversal of moderate neuromuscular blockade was conducted for Part B of the study.
- Primary efficacy analysis compared efficacy of sugammadex to neostigmine using time to recovery of a TOF ratio ($T_4/T_1$) ≥0.9 after study drug administration.
- Log transformed time to recovery values were analyzed by analysis of variance (ANOVA) adjusting for NMBA and age.
- The same set of analysis for the primary endpoint was also utilized for the secondary endpoints.
- Additional supportive analysis included a stratified log-rank test and a Kaplan-Meir curve for time to recovery to a TOF ratio of ≥0.9.

- All safety analyses were based on All Subjects as Treated (ASaT) population, consisting of all randomized patients from bot Part A and Part B who received a dose of study drug.
    - Safety analysis were subject to a tiered approach. The following table shows the tiers for adverse events.
    - Tier 1 adverse events were subject to inferential testing for statistical significance with 95% confidence intervals, using between-group comparisons.
    - Tier 2 parameters were assessed via point estimates with 95% confidence intervals, using between-group comparisons.
    - Tier 3 parameters were assessed by point estimates by treatment groups.

**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 |
| | Grouped AE | | X | X |
| | Specific AEs, SOCs, or PDLCs[b] (incidence ≥4 participants in 1 of the treatment groups) | | X | X |
| Tier 3 | Specific AEs, SOCs or PDLCs[b] (incidence <4 participants in all of the treatment groups) | | | X |
| | Change from Baseline Results (Labs, Vital Signs) | | | X |
| | Treatment-emergent relative bradycardia | | | X |

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

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

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

Source: Applicant's Submission, August 26, 2020, CSR, Documentation of Statistical Methods p 13

- For Part A only, the population for PK population for data analysis was defined as all participants with data at the following time points following study drug administration: 2, 15, 30, and 60 minutes, and 4 to 6 hours, and 10 to 12 hours (10 to 12 hour sample was optional).
    - For each PK parameter, individual values of CL, AUC, $C_{max}$, and $V_Z$ were assessed; descriptive statistics were calculated for all plasma PK parameters (AUC, Cmax, dose normalized AUC, dose normalized Cmax, CL, Vz, and t1/2) for sugammadex by age group. Sample size (N), arithmetic mean (AM), standard deviation (SD), arithmetic coefficient of variation (ACV), median (Med), minimum (Min), maximum (Max), geometric mean (GM), and geometric CV (GCV) were provided for all PK parameters by age group.

**Protocol Amendments**

Protocol Amendment 1:

The purpose of this amendment was the following:

- Clarification of the safety endpoint treatment-emergent relative bradycardia. The definition of treatment emergent relative bradycardia was added to align with FDA requested requirements.

- The eDMC will charter will contain the details of the stopping criteria

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**
Per the study report body:

> "This study was conducted in conformance with the ethical principles originating from the Declaration of Helsinki, GCP requirements, and applicable country and/or local statutes and regulations regarding IEC review, informed consent and the protection of human participants in biomedical research, as stated in the MSD Code of Conduct for Interventional Clinical Trials in the study protocol."

**Financial Disclosure**
Frank J. Real, Executive Director, Global Regulatory Affairs and Clinical Safety, signed FDA form 3454 on August 4, 2020, certifying that he had not entered into any financial arrangements with any of the listed clinical investigators where the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, he certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b), did not disclose any such interests. He further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

**Patient Disposition**
Initially, 299 patients were screened, and 288 patients were randomized from both Parts A and B of the study combined. From 288 randomized patients, 276 patients were treated. The following table shows patients who were excluded from treatment following randomization.

**Table 7: Subjects Excluded from All Subjects Treated (AST) All Randomized Subjects Parts A + B**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 54 | | 199 | | 35 | | 288 | |
| Included in All Subjects Treated (AST) | 51 | (94.4) | 191 | (96.0) | 34 | (97.1) | 276 | (95.8) |
| Excluded from AST | 3 | (5.6) | 8 | (4.0) | 1 | (2.9) | 12 | (4.2) |
| Not treated by study medication | 3 | (5.6) | 8 | (4.0) | 1 | (2.9) | 12 | (4.2) |
| The All Subjects Treated (AST) population consists of the randomized subjects who receive at least 1 dose of study treatment and are included in the treatment group to which they are randomized.<br>A subject with multiple exclusion reasons for a population exclusion is counted a single time for that population exclusion. | | | | | | | | |

Source: Applicant Submission, August 26, 2020, CSR p 40

Of the 12 patients who were not treated, 3 did not receive study intervention because of TOF Watch-SX issues. Other reasons for treatment exclusion were consent withdrawal, change of

anesthesia method by surgeon, surgery cancellation and concern for risk of pregnancy.

Efficacy analyses were based on the AST (APT) population seen in the table above (any patient who received one dose of study drug and NMBA). Safety analyses were based patients who received one dose of the study drug (APaT). For this study, the APT and the APaT populations are identical.

The treated patients were randomized as follows:

- Part A
    - Sugammadex 2 mg/kg (moderate block reversal) – 18 patients
    - Sugammadex 4 mg/kg (deep block reversal) – 22 patients

- Part B
    - Sugammadex 2 mg/kg (moderate block reversal) – 33 patients
    - Sugammadex 4 mg/kg (deep block reversal) – 169 patients
    - Neostigmine 50 mcg/kg up to 5 mg + glycopyrrolate or atropine – 34 patients

Of the 288 randomized patients, 272 patients completed the study, 16 patients discontinued. No patients were discontinued due to an adverse event. Two patients withdrew from the study (one in the sugammadex 2 mg/kg group and one in the 4 mg/kg group). The other remaining patients discontinued for reasons such as lost to follow up and physician decision. The data from patients that may be missing from patients lost to follow up would be data following patient discharge. These would be adverse events occurring during the seven-day postoperative period. Those events, though treatment emergent adverse events, are not likely to be drug related. Table 8 summarizes the patient disposition for study P089.

**Table 8: Patient Disposition, Study P089**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Not Randomized | | | | | | | 11 | |
| Subjects in population | 54 | | 199 | | 35 | | 288 | |
| **Study Disposition** | | | | | | | | |
| Completed | 50 | (92.6) | 189 | (95.0) | 33 | (94.3) | 272 | (94.4) |
| Discontinued | 4 | (7.4) | 10 | (5.0) | 2 | (5.7) | 16 | (5.6) |
| Lost To Follow-Up | 1 | (1.9) | 2 | (1.0) | 1 | (2.9) | 4 | (1.4) |
| Physician Decision | 1 | (1.9) | 2 | (1.0) | 1 | (2.9) | 4 | (1.4) |
| Randomized By Mistake Without Study Treatment | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.3) |
| Withdrawal By Parent/Guardian | 1 | (1.9) | 1 | (0.5) | 0 | (0.0) | 2 | (0.7) |
| Other | 1 | (1.9) | 4 | (2.0) | 0 | (0.0) | 5 | (1.7) |
| Each subject is counted once for Study Disposition based on the latest corresponding disposition record. One subject was enrolled twice. The first enrollment discontinued before treatment, while the second enrollment completed the study. | | | | | | | | |

Source: Applicant's Submission, August 26, 2020, CSR, p 36

All patients who received one dose of the study drug and NMBA were evaluated for efficacy per the Applicant. However, Part A was for PK evaluation only; Part B, the inclusion of the 4 mg/kg of sugammadex arm in the setting of deep block was limited for efficacy review because the active comparator, neostigmine, only reverses moderate block. Therefore, all efficacy analyses were based on the two moderate block groups in Part B: sugammadex 2 mg/kg and neostigmine. Initially, 70 patients were randomized, then 67 patients received a NMBA and one dose of study drug. The table below, generated by the Statistical team, summarizes the patient disposition for efficacy.

**Table 9: Patient Disposition for Part B Efficacy**

| | Part A | | Part B | | | Total |
|---|---|---|---|---|---|---|
| | Sugammadex 2mg/kg (Moderate block) | Sugammadex 4mg/kg (Deep block) | Sugammadex 2mg/kg (Moderate block) | Sugammadex 4mg/kg (Deep block) | Neostigmine (Moderate block) | |
| Randomized | 19 | 23 | 35 | 176 | 35 | 288 |
| **Analysis Population** | | | **33** | | **34** | **67** |
| Completed | | | 32 | | 33 | 65 |

Source: Statistical Team's Review

**Protocol Violations/Deviations**

The Applicant defined Important protocol deviations as those that may significantly impact the quality or integrity of key trial data or affect the patient's safety or rights. Clinically important protocol deviations were defined as those that may compromise critical data analysis pertaining to endpoints or patient safety.

Although important protocol deviations were reported for 10 patients in this study, 8 patients had clinically important deviations. However, no patient data was excluded from analysis due to

any important or clinically important protocol deviation. The two tables below summarize important protocol deviations not considered clinically important, and clinically important protocol deviations for all randomized subjects.

There were two patients with important protocol deviations, not clinically important from both Parts A and B. One patient from the sugammadex 2mg/kg, Part B, had a safety event that was not reported per the timelines outlined in the Protocol. The other patient from Part B, sugammadex 4mg/kg was dispensed study intervention other than what was assigned in the allocation schedule. The Applicant did not submit further information regarding these two patients.

**Table 10: Summary of Clinically Important Protocol Deviations, Part A + B**

| | Part A: Sugammadex 2 mg/kg | | Part A: Sugammadex 4 mg/kg | | Part B: Sugammadex 2 mg/kg | | Part B: Sugammadex 4 mg/kg | | Part B: Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 19 | | 23 | | 35 | | 176 | | 35 | | 288 | |
| With one or more clinically important protocol deviations | 2 | (10.5) | 0 | (0.0) | 1 | (2.9) | 4 | (2.3) | 1 | (2.9) | 8 | (2.8) |
| With no clinically important protocol deviations | 17 | (89.5) | 23 | (100.0) | 34 | (97.1) | 172 | (97.7) | 34 | (97.1) | 280 | (97.2) |
| **Safety Reporting** | **0** | **(0.0)** | **0** | **(0.0)** | **1** | **(2.9)** | **1** | **(0.6)** | **1** | **(2.9)** | **3** | **(1.0)** |
| Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol. | 0 | (0.0) | 0 | (0.0) | 1 | (2.9) | 1 | (0.6) | 1 | (2.9) | 3 | (1.0) |
| **Study Intervention** | **2** | **(10.5)** | **0** | **(0.0)** | **0** | **(0.0)** | **3** | **(1.7)** | **0** | **(0.0)** | **5** | **(1.7)** |
| Study treatment was administered at >= 3 minutes after reaching the minimal level of recovery specified by the assigned depth of block. | 2 | (10.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |
| Study treatment was administered at the incorrect depth of block as assigned at the time of randomization. Examples: For moderate block cases, study treatment administration at <T1 For moderate block cases, study treatment administration at PTC 0, 1, 2, 3, 4, or 5 For deep block cases, study treatment administration at <1 PTC | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (1.7) | 0 | (0.0) | 3 | (1.0) |
| Every subject is counted a single time for each applicable row and column. | | | | | | | | | | | | |

Source: Applicant's Submission, August 26, 2020, CSR p 28

In this table, the Applicant provided definitions for clinically important protocol deviations for safety reporting and study intervention. The most common clinically important protocol deviation was study treatment was administered at the incorrect depth of block as assigned at randomization. The example given was for a moderate block, the study treatment was administered at less than T1. For deep block, the study drug was administered at PTC <1.There were three patients in the Sugammadex 4 mg/kg group where this protocol deviation occurred. Because sugammadex 4 mg/kg was not used to assist in labeling for efficacy, this will not change the outcome. The dose of drug administered is important for safety, not the timing of the dose, therefore, this protocol deviation does not affect safety.

There were two patients in the sugammadex 2 mg/kg group where the study treatment was administered ≥3 minutes after reaching the minimal level of recovery specified by the assigned depth of block. Both patients were administered the study drug at 3 minutes after reaching the minimal level of recovery specified by the protocol. Although this was a protocol deviation, in clinical practice, this is usually not meaningful.
Three other patients had safety events that were not reported per protocol timelines. Two

events were treatment emergent relative bradycardia events that were not reported per timelines outlined in the protocol but were still reported and included in the safety data. The third patient had worsening abdominal pain, a reportable SAE that was not reported within 24 hours.

**Demographics and Baseline Characteristics**
All patients enrolled in this study were at least 2 years old and less than 17 years old. The intervention groups were balanced for all baseline characteristics. The majority of the patients were white (89.5%), had a an eGFR >90mL/min/1.73m$^2$(91.3%), and were ASA class 1 (63.4%). There were slightly more male patients than female (55.4% versus 44.6%).

The Applicant included 19 patients with a lower eGFR. These patients were important to be included as sugammadex is primarily renally excreted. There was a slightly higher percentage of patients with a lower eGFR in the neostigmine group, however, the numbers were so small, it is unlikely this affected outcome. Also, the predominance of white patients is not clinically meaningful since neuromuscular junction physiology is not affected by race. Furthermore, there were minimal differences in demographic characteristics across treatment populations that are not clinically meaningful.

The Applicant included Body Mass Index (kg/m$^2$) as a demographic. In the pediatric population, BMI is age and sex specific. It is usually defined as a percentile for age and sex. Therefore, the BMI alone as a demographic is not useful in determining obesity in pediatric patients and the dose

The following table outlines the full demographics of the treated population.

**Table 11: Patient Characteristics, All Treated, Part A + B**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | | 276 | |
| **Gender** | | | | | | | | |
| Male | 31 | (60.8) | 104 | (54.5) | 18 | (52.9) | 153 | (55.4) |
| Female | 20 | (39.2) | 87 | (45.5) | 16 | (47.1) | 123 | (44.6) |
| **Age (Years)** | | | | | | | | |
| 2 to <6 years | 22 | (43.1) | 80 | (41.9) | 12 | (35.3) | 114 | (41.3) |
| 6 to <12 years | 15 | (29.4) | 64 | (33.5) | 13 | (38.2) | 92 | (33.3) |
| 12 to <17 years | 14 | (27.5) | 47 | (24.6) | 9 | (26.5) | 70 | (25.4) |
| Mean | 7.7 | | 7.8 | | 8.5 | | 7.9 | |
| SD | 4.6 | | 4.4 | | 4.3 | | 4.4 | |
| Median | 7.0 | | 7.0 | | 8.0 | | 7.0 | |
| Range | 2 to 16 | | 2 to 16 | | 2 to 16 | | 2 to 16 | |
| **Race** | | | | | | | | |
| American Indian Or Alaska Native | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.4) |
| Asian | 2 | (3.9) | 7 | (3.7) | 2 | (5.9) | 11 | (4.0) |
| Black Or African American | 2 | (3.9) | 4 | (2.1) | 0 | (0.0) | 6 | (2.2) |
| Multiple | 2 | (3.9) | 4 | (2.1) | 0 | (0.0) | 6 | (2.2) |
| Black Or African American, White | 2 | (3.9) | 0 | (0.0) | 0 | (0.0) | 2 | (0.7) |

**Table 11 Continued**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| White, Asian | 0 | (0.0) | 4 | (2.1) | 0 | (0.0) | 4 | (1.4) |
| Unknown | 1 | (2.0) | 4 | (2.1) | 0 | (0.0) | 5 | (1.8) |
| White | 44 | (86.3) | 171 | (89.5) | 32 | (94.1) | 247 | (89.5) |
| **Race by Ethnicity** | | | | | | | | |
| Hispanic Or Latino | 7 | (13.7) | 19 | (9.9) | 5 | (14.7) | 31 | (11.2) |
| Black Or African American | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.4) |
| White | 7 | (13.7) | 18 | (9.4) | 5 | (14.7) | 30 | (10.9) |
| Not Hispanic Or Latino | 40 | (78.4) | 163 | (85.3) | 28 | (82.4) | 231 | (83.7) |
| American Indian Or Alaska Native | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.4) |
| Asian | 2 | (3.9) | 7 | (3.7) | 2 | (5.9) | 11 | (4.0) |
| Black Or African American | 2 | (3.9) | 3 | (1.6) | 0 | (0.0) | 5 | (1.8) |
| Multiple | 2 | (3.9) | 4 | (2.1) | 0 | (0.0) | 6 | (2.2) |
| Unknown | 0 | (0.0) | 3 | (1.6) | 0 | (0.0) | 3 | (1.1) |
| White | 34 | (66.7) | 145 | (75.9) | 26 | (76.5) | 205 | (74.3) |
| Not Reported | 1 | (2.0) | 3 | (1.6) | 0 | (0.0) | 4 | (1.4) |
| Unknown | 1 | (2.0) | 0 | (0.0) | 0 | (0.0) | 1 | (0.4) |
| White | 0 | (0.0) | 3 | (1.6) | 0 | (0.0) | 3 | (1.1) |
| Unknown | 3 | (5.9) | 6 | (3.1) | 1 | (2.9) | 10 | (3.6) |
| Unknown | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.4) |
| White | 3 | (5.9) | 5 | (2.6) | 1 | (2.9) | 9 | (3.3) |

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| **Body Mass Index (BMI) (kg/m$^2$)** | | | | | | | | |
| <15 | 8 | (15.7) | 40 | (20.9) | 7 | (20.6) | 55 | (19.9) |
| ≥15 to <25 | 37 | (72.5) | 134 | (70.2) | 24 | (70.6) | 195 | (70.7) |
| ≥25 | 6 | (11.8) | 17 | (8.9) | 3 | (8.8) | 26 | (9.4) |
| Subjects with data | 51 | | 191 | | 34 | | 276 | |
| Mean | 18.5 | | 18.3 | | 18.7 | | 18.4 | |
| SD | 4.2 | | 4.9 | | 4.4 | | 4.7 | |
| Median | 17.1 | | 16.6 | | 17.8 | | 16.8 | |
| Range | 13.6 to 32.4 | | 11.3 to 46.3 | | 12.7 to 31.2 | | 11.3 to 46.3 | |
| **Weight (kg)** | | | | | | | | |
| Subjects with data | 51 | | 191 | | 34 | | 276 | |
| Mean | 34.1 | | 33.7 | | 35.4 | | 34.0 | |
| SD | 21.4 | | 21.6 | | 21.8 | | 21.6 | |
| Median | 24.0 | | 24.0 | | 29.0 | | 25.0 | |
| Range | 11.0 to 85.0 | | 10.0 to 130.0 | | 11.0 to 99.0 | | 10.0 to 130.0 | |
| **Estimated Glomerular Filtration Rate[§] (mL/min/1.73m$^2$)** | | | | | | | | |
| >30 to ≤60 | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.4) |
| >60 to ≤90 | 3 | (5.9) | 10 | (5.2) | 5 | (14.7) | 18 | (6.5) |

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| >90 | 46 | (90.2) | 177 | (92.7) | 29 | (85.3) | 252 | (91.3) |
| Missing | 2 | (3.9) | 3 | (1.6) | 0 | (0.0) | 5 | (1.8) |
| Subjects with data | 49 | | 188 | | 34 | | 271 | |
| Mean | 128.2 | | 126.8 | | 118.5 | | 126.0 | |
| SD | 22.6 | | 29.1 | | 21.0 | | 27.2 | |
| Median | 129.0 | | 121.9 | | 117.8 | | 123.0 | |
| Range | 83.0 to 184.5 | | 57.3 to 264.9 | | 81.1 to 170.8 | | 57.3 to 264.9 | |
| **ASA Class** | | | | | | | | |
| ASA Class 1 | 30 | (58.8) | 121 | (63.4) | 24 | (70.6) | 175 | (63.4) |
| ASA Class 2 | 13 | (25.5) | 52 | (27.2) | 9 | (26.5) | 74 | (26.8) |
| ASA Class 3 | 8 | (15.7) | 18 | (9.4) | 1 | (2.9) | 27 | (9.8) |
| **Type of Neuromuscular Blocking Agent (NMBA)** | | | | | | | | |
| Rocuronium | 37 | (72.5) | 123 | (64.4) | 20 | (58.8) | 180 | (65.2) |
| Vecuronium | 14 | (27.5) | 68 | (35.6) | 14 | (41.2) | 96 | (34.8) |
| **Stratifications** | | | | | | | | |
| Rocuronium, 2 to <6 years | 15 | (29.4) | 46 | (24.1) | 6 | (17.6) | 67 | (24.3) |
| Rocuronium, 6 to <12 years | 11 | (21.6) | 41 | (21.5) | 8 | (23.5) | 60 | (21.7) |
| Rocuronium, 12 to <17 years | 11 | (21.6) | 36 | (18.8) | 6 | (17.6) | 53 | (19.2) |

**Table 11 Continued**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | | Total | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| Vecuronium, 2 to <6 years | 7 | (13.7) | 34 | (17.8) | 6 | (17.6) | 47 | (17.0) |
| Vecuronium, 6 to <12 years | 4 | (7.8) | 23 | (12.0) | 5 | (14.7) | 32 | (11.6) |
| Vecuronium, 12 to <17 years | 3 | (5.9) | 11 | (5.8) | 3 | (8.8) | 17 | (6.2) |
| **Dosage of NMBA Received in Subjects Stratified to Rocuronium (mg/kg)** | | | | | | | | |
| Subjects with data | 37 | | 123 | | 20 | | 180 | |
| Mean | 1.30 | | 2.86 | | 1.97 | | 2.44 | |
| SD | 1.75 | | 7.16 | | 3.66 | | 6.11 | |
| Median | 0.83 | | 1.05 | | 0.71 | | 0.97 | |
| Range | 0.38 to 10.71 | | 0.34 to 52.08 | | 0.17 to 12.96 | | 0.17 to 52.08 | |
| **Dosage of NMBA Received in Subjects Stratified to Vecuronium (mg/kg)** | | | | | | | | |
| Subjects with data | 14 | | 68 | | 14 | | 96 | |
| Mean | 0.18 | | 0.30 | | 0.20 | | 0.27 | |
| SD | 0.12 | | 0.42 | | 0.17 | | 0.37 | |
| Median | 0.13 | | 0.19 | | 0.13 | | 0.16 | |
| Range | 0.05 to 0.42 | | 0.06 to 3.40 | | 0.09 to 0.67 | | 0.05 to 3.40 | |
| § Estimated glomerular filtration rate is based on Schwartz formula. | | | | | | | | |

Source: Applicant Submission, August 26, 2020, CSR p 42-46

Because efficacy analysis was done on a subset of the total population, the Statistical team also analyzed the demographics for the patients from that population. Among the 67 patients treated, the mean age was 8 years old, 57% were male and 92% were white. The table below is from the Statistical team's review.

**Table 12: Demographic and Baseline Characteristics for Part B, Efficacy Analysis**

| | Sugammadex 2mg/kg (n=33) | Neostigmine (n=34) | Total |
|---|---|---|---|
| **Age (Years)** | | | |
| Mean (Standard Deviation) | 8.0 (4.5) | 8.5 (4.3) | 8.3 (4.4) |
| Median (Range) | 7 (2, 15) | 8 (2, 16) | 8 (2, 16) |
| **Age Group** | | | |
| 2 to <6 years | 13 (39%) | 12 (35%) | 25 (37%) |
| 6 to <12 years | 10 (30%) | 13 (38%) | 23 (34%) |
| 12 to <17 years | 10 (30%) | 9 (26%) | 19 (28%) |
| **Gender** | | | |
| Male | 20 (61%) | 18 (53%) | 38 (57%) |
| Female | 13 (39%) | 16 (47%) | 29 (43%) |
| **Race** | | | |
| White | 29 (91%) | 32 (94%) | 61 (92.4%) |
| Others | 3 (9%) | 2 (6%) | 5 (7.6%) |
| **Weight (kg)** | | | |
| Mean (Standard Deviation) | 35.0 (22.1) | 35.4 (21.8) | 35.2 (21.8) |
| Median (Range) | 27 (11, 85) | 29 (11, 99) | 29 (11, 99) |
| **Region** | | | |
| United States | 9 (27%) | 5 (15%) | 14 (21%) |
| Others | 24 (73%) | 29 (85%) | 53 (79%) |
| **ASA** | | | |
| 1 | 24 (73%) | 24 (71%) | 48 (72%) |
| 2 | 6 (18%) | 9 (26%) | 15 (22%) |
| 3 | 3 (9%) | 1 (3%) | 4 (6%) |
| **NMBA** | | | |
| Rocuronium | 20 (61%) | 20 (59%) | 40 (60%) |
| Vecuronium | 13 (39%) | 14 (41%) | 27 (40%) |

Source: Statistical team Review

Although the demographic characteristics differ slightly from the overall study population, this is a minor difference and should not affect efficacy extrapolation to the pediatric population

ages 2 to less than 17 years.

*Other Baseline Characteristics*
The patient population included pediatric patients age 2 years to less than 17 years undergoing a surgical or medical procedure requiring a neuromuscular blocking agent. The most frequently performed procedures were, when grouped together, dental procedures (10.9%). Dental procedures under general anesthetic are common in pediatrics. The other most frequently performed surgeries were typical for the pediatric population; adenotonsillectomy (7.6%), adenoidectomy (6.5%), and tonsillectomy.

Medical history conditions reported in ≥5% of the patients overall included adenoid hypertrophy (13.4%), tonsil hypertrophy (9.8%), dental caries (9.8%), cleft palate (8.0%), tonsillitis (7.2%), otitis media (6.9%), and sleep apnea syndrome (6.5%). These conditions are common in the pediatric population and are consistent with the predominant procedures performed for this study.

**Concomitant Medications**
All patients received prior treatment with anesthetics and NMBAs. The most frequently reported anesthetic medications were propofol (88.4%), sevoflurane (58.7%) and remifentanil hydrochloride (33.3%). The most frequently reported medications prior to anesthetic delivery were fentanyl, midazolam, and acetaminophen. The anesthetics and prior medications are typical for the procedures and surgeries performed in the pediatric population.

In addition to anesthetics and analgesics, other medications consistent with the surgical setting included blood replacements or fluid replacement, antiemetics and antibiotics. The Applicant reported the medications administered were balanced across the intervention groups.

None of the agents would interfere with the reversal of neuromuscular blockade.

**Efficacy Results – Primary Endpoint**
Primary Endpoint: The time to recovery to a TOF ratio of ≥0.9 for a comparison of sugammadex to neostigmine for the reversal of moderate neuromuscular blockade.

The efficacy analysis was done for all patients treated, Part B. The time to recovery to a TOF ratio of ≥0.9 was significantly faster ($p<0.0001$) in pediatric patients ages 2 to less than 17 years when dosed with sugammadex 2mg/kg compared to neostigmine with a geometric mean 1.6 minutes compared to 7.5 minutes.

**Table 13: Analysis of Time (in Minutes) to Recovery of the TOF Ratio ≥0.9 (Primary Analysis)**

| Treatment | N | Mean (SD) | Median Range | Geometric Mean (95% CI) |
|---|---|---|---|---|
| Sugammadex 2 mg/kg | 33 | 2.1 (2.4) | 1.4 (0.7, 14.8) | 1.6 (1.3, 2.0) |
| Neostigmine + (Glycopyrrolate or Atropine) | 34 | 10.4 (9.3) | 7.8 (1.1, 42.3) | 7.5 (5.6, 10.0) |
| **Pairwise Comparisons** | | | *Ratio of Geometric Mean ‡ (95% CI)‡* | *p-Value ‡* |
| Sugammadex 2 mg/kg versus Neostigmine + (Glycopyrrolate or Atropine) | | | 0.22 (0.16, 0.32) | <0.0001 |

Per analysis plan, explicit imputation is used if the recovery time is missing.
‡Based on analysis of variance (ANOVA) for log-transformed time to recovery values, adjusting for neuromuscular blocking agent and age. P-value is two-sided.
SD: Standard Deviation. CI: confidence interval.

Source: Applicant's Submission, August 26, 2020, CSR, p 50

The Statistical team verified the Applicant's primary analysis: however, the team evaluated the model based on geometric least squares means with which yielded the following results:

**Table 14: Statistical Team Analysis of Time to Recovery of TOF Ratio ≥0.9, (Table 5 from the Statistical Team Review)**

| Endpoint | Sugammadex 2mg/kg (n=33) Geometric LS Mean (95% CI) | Neostigmine (n=34) Geometric LS Mean (95% CI) | Ratio of Geometric LS Means (95% CI) | p-Value |
|---|---|---|---|---|
| Primary Endpoint: Time to recovery to a TOF Ratio of 0.9 or above | 1.7 (1.3, 2.1) | 7.4 (5.8, 9.6) | 0.2 (0.2, 0.3) | <0.0001 |

Source: Statistical team Review

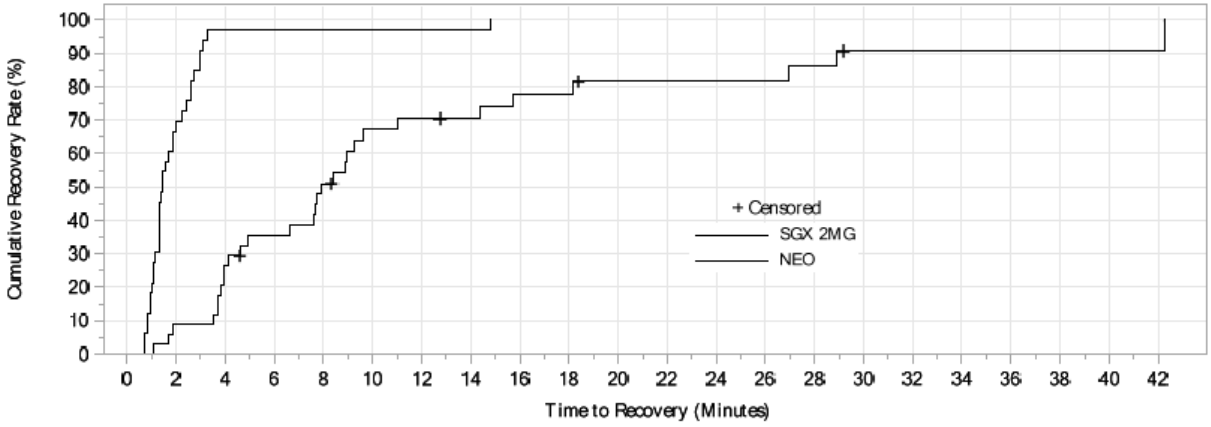
Following discussion with the Applicant, they agreed the Statistical team's results would appear in the label. The Statistical Team's analysis used the Applicants data for all participants treated in Part B for the above table. All the statistics were based on ANOVA of log transformed time to recovery values, which were adjusted for age and NMBA. From the Statistical team review:

> The geometric LS mean for each treatment group in Table 5 differs slightly from the observed geometric mean reported in Table 11-1 (Primary Analysis) of the applicant's clinical study report. The difference between observed geometric means and geometric LS means is that geometric LS means are adjusted by NMBA and age in this case. Therefore, geometric LS means are more comparable and should be reported in the statistical comparison results.

The Statistical team considered the differences in analysis important for labeling, and the recommendations will be further discussed section in section 10, Labeling Recommendations.

The Applicant concluded based on Kaplan-Meier estimates, 90.9% (30/33) patients dosed with sugammadex recovered to a TOF ration of 0.9 or greater within 3 minutes compared with 8.8% (3/34) participants in the neostigmine group. Figure 4 illustrates the Kaplan-Meier curves for the primary endpoint.

**Figure 4: Kaplan-Meier Curves for Primary Endpoint**




Source: Applicants Submission, August 26, 2020, p 52

The active comparator group, neostigmine, demonstrated delayed time to recovery for all age groups when compared with sugammadex 2 mg/kg for reversal of moderate neuromuscular blockade.

**Efficacy Results – Secondary and other relevant endpoints**

Secondary key endpoints: The secondary key endpoints evaluated the time to recovery to a TOF ratio of ≥0.8 and ≥0.7. As with the primary endpoint, the time to recovery to a TOF ratio of ≥0.8 and ≥0.7 was significantly faster than neostigmine for the pediatric patients in the study.

The table below demonstrate the Statistical team's analysis of the time to recovery of the TOF of ≥0.8 and ≥0.7. The times in minutes are the same as the Applicant's, the confidence intervals differ slightly.

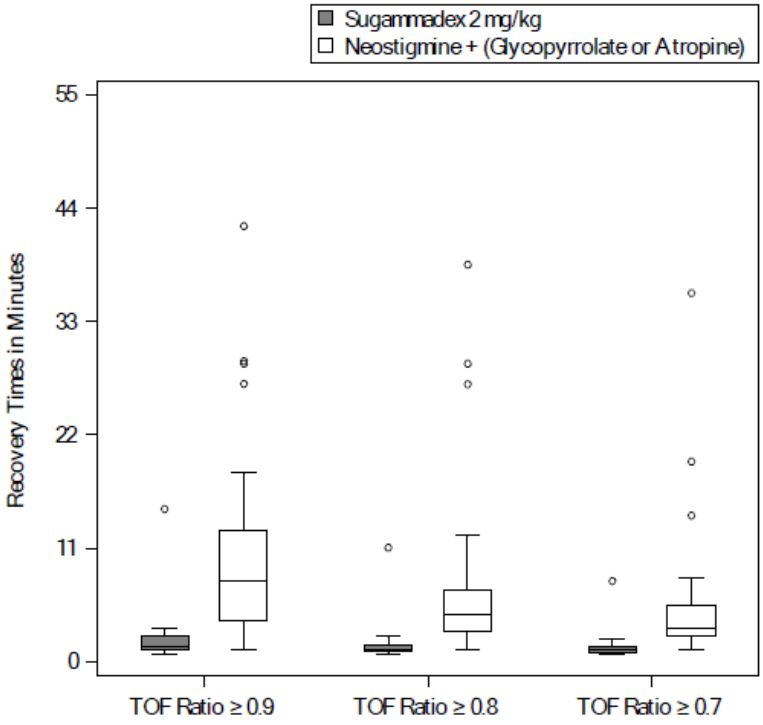
**Table 15: Statistical Team Analysis of Secondary Endpoints**

| Endpoint | Sugammadex 2mg/kg (n=33) Geometric LS Mean (95% CI) | Neostigmine (n=34) Geometric LS Mean (95% CI) | Ratio of Geometric LS Means (95% CI) | p-Value |
|---|---|---|---|---|
| Secondary Endpoint: Time to recovery to a TOF Ratio of 0.8 or above | 1.3 (1.1, 1.7) | 5.0 (4.0, 6.4) | 0.3 (0.2, 0.4) | <0.0001 |
| Secondary Endpoint: Time to recovery to a TOF Ratio of 0.7 or above | 1.1 (0.9, 1.4) | 3.7 (3.0, 4.6) | 0.3 (0.2, 0.4) | <0.0001 |

Source: Statistical team review, Statistical team's analysis using applicant's data for all participants treated in Part B.

The boxplot in the figure below provides visual demonstration of the rapid recovery times for patients dosed with sugammadex when compared with neostigmine, consistent with the primary analyses above.

**Figure 5: Boxplot for Recovery time, All Subjects Treated, Part B**




Source: Applicant's Submission, August 26, 2020, CSR, p 59

Other Endpoints:

Delayed Recovery: The Applicant defined delayed recovery as any observation of the TOF ratio to ≥0.9 that is > 3 times the geometric mean recovery time of the TOF ratio to ≥0.9 within each treatment group.

**Table 16 : Patients with Delayed Recovery, All Subjects Treated, Part A + B**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | |
| Delayed Recovery | 1 | ( 2.0) | 14 | ( 7.3) | 3 | ( 8.8) |
| Delayed recovery is any observation of the TOF ratio to ≥ 0.9 (in the original scale) that is > 3 times the geometric mean recovery time of the TOF ratio to ≥ 0.9 within each treatment group. | | | | | | |

Source: Applicant's Submission, August 26, 2020, CSR p. 61

The sugammadex 2 mg/kg group had the least number of patients with a delayed recovery. Based on their review of the trace data, the Applicant suggests that this may be due measurement anomaly to suboptimal set-up with a high baseline T1 or slow drug administration. The significance of the difference in delayed recovery between treatment groups is unclear due to the small numbers.

Time to Recovery to TOF Ratios - Moderate and Deep Block: The Applicant pooled results for the time to recovery of TOF for Parts A and B. The sugammadex 4 mg/kg group was included in these data; however, no active comparator exists for this dose. The table below shows the time to recovery for the TOF ratios for all patients treated, Parts A and B.

**Table 17: Summary of Time in Minutes to Recovery of TOF Ratios, All Subjects Treated, Parts A + B**

| TOF Ratio | Treatment | N | Mean (SD) | | Median | Range | Geometric Mean | (95% CI) |
|---|---|---|---|---|---|---|---|---|
| TOF Ratio ≥ 0.9 | Sugammadex 2 mg/kg | 51 | 2.1 | (2.2) | 1.6 | (0.7, 14.8) | 1.6 | (1.4, 1.9) |
| | Sugammadex 4 mg/kg | 191 | 3.8 | (10.0) | 1.7 | (0.4, 118.1) | 2.0 | (1.8, 2.3) |
| | Neostigmine + (Glycopyrrolate or Atropine) | 34 | 10.4 | (9.3) | 7.8 | (1.1, 42.3) | 7.5 | (5.6, 10.0) |
| TOF Ratio ≥ 0.8 | Sugammadex 2 mg/kg | 51 | 1.6 | (1.6) | 1.3 | (0.4, 11.1) | 1.3 | (1.1, 1.5) |
| | Sugammadex 4 mg/kg | 191 | 2.8 | (8.8) | 1.3 | (0.4, 111.1) | 1.5 | (1.3, 1.7) |
| | Neostigmine + (Glycopyrrolate or Atropine) | 34 | 7.3 | (8.2) | 4.6 | (1.1, 38.5) | 5.0 | (3.8, 6.7) |
| TOF Ratio ≥ 0.7 | Sugammadex 2 mg/kg | 51 | 1.3 | (1.1) | 1.1 | (0.4, 7.8) | 1.1 | (0.9, 1.3) |
| | Sugammadex 4 mg/kg | 191 | 2.4 | (8.2) | 1.1 | (0.4, 105.1) | 1.3 | (1.1, 1.4) |
| | Neostigmine + (Glycopyrrolate or Atropine) | 34 | 5.2 | (6.5) | 3.2 | (1.1, 35.8) | 3.7 | (2.9, 4.8) |

SD: Standard Deviation. CI: confidence interval.
Per analysis plan, explicit imputation is used if the recovery time is missing.

Source: Applicant's Submission, August 26, 2020, CSR, p 62

In general, patients dosed with sugammadex 4 mg/kg had a rapid time to recovery of the TOF as shown in the table above. However, as there was no active comparator, these data were not used for primary efficacy determination and will not be included in the label.

Pharmacokinetic Endpoints: Sugammadex PK parameters were estimated in Part A to determine dosing in Part B. Following analysis of the PK data from Part A, the Applicant and the Division determined that no further PK data were required in Part B. In addition, the dosing would remain at sugammadex 2 mg/kg and 4 mg/kg for all age groups. See the Clinical Pharmacology section 4.5 for further information.

**Data Quality and Integrity**

There were no medication errors or dosage deviations reported in either Part A or Part B of Study P089. Three patients were administered the study drug at the incorrect depth of block, i.e., before the appropriate number of twitches were seen on the TOF. In addition, two patients were administered the study medication ≥3 minutes after reaching the minimal level of recovery described in the protocol. Section 6.1.1 describes the recovery of TOF and the timing for dose administration. These five incidents were reported as protocol deviations however, the data from these patients were included in the final analyses. These protocol deviations the Applicant included as clinically important though are likely not clinically significant.

There were no premature unblinding events related to investigative site personnel. However, there were 9 incidents involving 9 patients where potentially unblinding or biasing information was disclosed to the Merck personnel who were blinded to the study intervention. The treatment with sugammadex could be inferred from the depth of block or number of doses

administered, however, the actual sugammadex dose remained blinded. These incidents were considered by the Applicant not to be significant issues impacting data validity or reliability. A clinician may be able to infer from dosing of NMBA the depth of block, based on frequency of dosing or the amount of NMBA used. Therefore, discerning sugammadex treatment, especially with a deep block, would not be difficult.

**Dose/Dose Response**
Although two doses of sugammadex were studied, 2 mg/kg and 4 mg/kg, only a single dose is administered during the study.

**Durability of Response**
Sugammadex is a given as a single dose. There is no expectation for an extended duration of response.

**Persistence of Effect**
Sugammadex is a single dose, short acting drug. There is no expectation for persistence of effect.

**Additional Analyses Conducted on the Individual Trial**
The Applicant included median times to extubation, operating room discharge, post-anesthesia care unit discharge, and hospital discharge as exploratory endpoints. There was no statistical difference between the sugammadex 2 mg/kg group and the neostigmine group for any of these exploratory endpoints. It is interesting to note, although patients recovered the TOF faster, the time to extubation was not significantly different. These same phenomena were also noted with operating room discharge, post-anesthesia care unit, and hospital discharge. In summary, NMB reversal times only led to faster return of complete neuromuscular function. The table below shows the difference in times to extubation for sugammadex 2 mg/kg and neostigmine.

**Table 18: Analysis of Time in Minutes to Extubation, All Subjects Treated, Part B**

| Treatment | N | Number of Events (%) | Time to Extubation† (Minutes) Median (95% CI) [Q1, Q3] |
|---|---|---|---|
| Sugammadex 2 mg/kg | 33 | 33 (100.0) | 20.0 (12.2, 25.0) [11.5, 34.8] |
| Neostigmine + (Glycopyrrolate or Atropine) | 34 | 34 (100.0) | 24.2 (15.7, 31.9) [15.5, 41.1] |
| | | | |
| **Pairwise Comparisons** | | *Hazard Ratio*‡ (95% CI)‡ | *p-Value*§ |
| Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine) | | 1.24 (0.75, 2.03) | 0.5040 |

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with treatment and age as covariates and stratified by neuromuscular blocking agent.
§ Two-sided p-value based on log-rank test stratified by neuromuscular blocking agent and age groups.
CI: confidence interval. Q1: the first quartile. Q3: the third quartile.

Source: Applicant's Submission, August 26, 2020, CSR, p 238

# 7. Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

This this NDA supplement is supported by a single study. This section is not relevant to this NDA supplement.

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

Approval of this supplement to NDA 022225 will extend the use of sugammadex to the pediatric population ages 2 to less than 17 years of age.

### 7.2.2. Other Relevant Benefits

There are no other relevant benefits for this NDA.

## 7.3. Assessment of Effectiveness

The rationale for PMR 3003-8 was to determine the correct dosing for pediatric patients 2 to <17 years of age. Study P089 was conducted to fulfill the PMR. Part A was conducted for PK evaluation only and to select doses for Part B. Efficacy evaluation was based on evaluation of 67 patients randomized to moderate block and reversal with sugammadex 2 mg/kg or neostigmine 50 mcg/kg.

The Applicant has demonstrated that sugammadex 2 mg/kg produced statistically significant earlier recovery ($p<0.0001$) to a TOF ratio of ≥0.9 in pediatric patients 2 years to less than 17 years old when compared with neostigmine. There were no apparent differences across neuromuscular blocking agents or demographic characteristics. The geometric least square mean (in minutes) for sugammadex 2 mg/kg was 1.7 minutes compared to 7.4 minutes for neostigmine for the primary endpoint.

Additionally, the efficacy of sugammadex 2 mg/kg dose for moderate block reversal in pediatric patients 2 years to less than 17 years old was further supported by the Applicant's secondary endpoints. The patients administered sugammadex 2 mg/kg achieved the designated TOF recovery milestones (recovery to a TOF ratio of ≥0.8 and ≥0.7) faster than patients administered neostigmine 50 mcg/kg (see Table 14).

Finally, the sugammadex 2 mg/kg had less patients with delayed recovery, defined recovery as any observation of the TOF ratio to ≥0.9 that is > 3 times the geometric mean recovery time of the TOF ratio to ≥0.9 within each treatment group. The significance is unclear due to the small

numbers in the sugammadex 2 mg/kg group and the neostigmine group.

Regarding efficacy for deep block reversal with sugammadex 4 mg/kg; because no active comparator exists for this group, it was not included in evaluation of efficacy for this supplemental NDA.

In summary, Study P089 supports the use of sugammadex 2 mg/kg for the reversal of (b) (4) neuromuscular blockade in pediatric patients age 2 to less than 17 years old.

# 8. Review of Safety

## 8.1. Safety Review Approach

The evaluation of the safety information will be done based on the data that was provided by the Applicant from Study P089 to determine whether sugammadex dosing at 2 mg/kg and 4mg/kg is acceptable for pediatric patients ages 2 to < 17 years of age. The review will look at safety issues of highest interest, clinically relevant bradycardia (bradycardia requiring intervention), hypersensitivity and anaphylaxis and drug induced hepatic injury (tier 2).

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

The safety analyses were based on 288 randomized patients from Parts A and B. There were 276 patients who received the study drug or the active comparator for reversal of neuromuscular blocking agent at the completion of a medical or surgical procedure requiring muscle relaxation. A total of 242 patients received sugammadex 2 mg/kg or 4 mg/kg and 34 patients received the active comparator, neostigmine. The table that follows demonstrates the exposure by dose of study drug.

**Table 19: Patient Exposure by Dose, Part A + B**

| Treatment Group | Medication | Total Subjects | Dosage in mg | | Dosage in mg/kg | |
|---|---|---|---|---|---|---|
| | | | Mean (SD) | Median (Range) | Mean (SD) | Median (Range) |
| Sugammadex 2 mg/kg | Sugammadex | 51 | 68.3 (42.9) | 48.0 (22.0 to 170.0) | 2.00 (0.00) | 2.00 (2.00 to 2.00) |
| Sugammadex 4 mg/kg | Sugammadex | 191 | 134.6 (86.6) | 96.0 (40.0 to 520.0) | 4.00 (0.02) | 4.00 (3.76 to 4.00) |
| Neostigmine + (Glycopyrrolate or Atropine) | Neostigmine | 34 | 1.8 (1.1) | 1.5 (0.6 to 5.0) | 0.05 (0.00) | 0.05 (0.05 to 0.05) |
| Neostigmine + (Glycopyrrolate or Atropine) | Glycopyrrolate | 24 | 0.4 (0.3) | 0.3 (0.1 to 1.0) | 0.01 (0.00) | 0.01 (0.01 to 0.02) |
| Neostigmine + (Glycopyrrolate or Atropine) | Atropine | 10 | 0.4 (0.1) | 0.4 (0.2 to 0.5) | 0.02 (0.00) | 0.02 (0.01 to 0.02) |
| Dosage in mg is calculated as: (# of ml administered / # of ml prepared) x prepared dosage in mg.<br>Dosage in mg/kg is calculated as: (# of ml administered / # of ml prepared) x prepared dosage in mg / weight in kg. | | | | | | |

Source: Applicant's Submission, August 26, 2020, p 48

#### 8.2.2. Relevant characteristics of the safety population:

The study population was pediatric patients ages 2 to less than 17 years. This population includes all patients as treated from Part A and Part B. The safety population had the same demographic population as previously discussed in section 6.1.1 "Demographics and Baseline Characteristics". Full demographics are described in Table 11: Patient Characteristics, All Treated, Part A + B.

#### 8.2.3. Adequacy of the safety database:

The safety database is adequate for this postmarketing pediatric supplement. There is no other study that will be integrated into this evaluation.

### 8.3. Adequacy of Applicant's Clinical Safety Assessments

#### 8.3.1. Issues Regarding Data Integrity and Submission Quality

As previously described in section 4.1, Office of Scientific Investigations, Site 6 was chosen for inspection using a risk-based approach. This included number of enrolled subjects, site efficiency, protocol deviations, and prior inspection history. The site was inspected March 23-29, 2021.

No significant deficiencies were observed. The inspector noted the Investigator at the site correctly imputed missing TOF data. There were no issues regarding the data integrity or the overall quality of the submission.

The safety information provided by the Applicant was organized and easy to locate. The Applicant submitted an ISS in Module 5 in addition to the Summary of Clinical Safety in Module 2.

#### 8.3.2. Categorization of Adverse Events

The Applicant appropriately defined adverse events as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. All adverse events were coded with MeDRA, Version 22.1.
The adverse events of clinical interest with sugammadex for this study were the following

- Hypersensitivity and anaphylaxis
- Clinically relevant bradycardia (defined as bradycardia necessitating intervention)
- Drug induced liver injury (tier 2 event)

These adverse events have been seen following administration of sugammadex in the general adult population. Although seen in the adult population, bradycardia is of particular concern in

the pediatric population, especially younger children whose cardiac output is heart rate dependent.

Event severity should be utilized for rating the intensity of the event. Event severity was defined as follows:

- Mild: An event easily tolerated by the participant
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Determination of causality also appeared to be appropriate.

Serious adverse events were defined as an adverse event that:

- Resulted in death
- Was life threatening
- Required inpatient hospitalization or prolonged hospitalization
- Resulted in persistent or significant disability
- Resulted in a congenital anomaly or birth defect.

The Applicants definitions of severity and SAE's are appropriate. In addition, the assessment of causality was based on exposure, time course and likely cause related to the adverse event.

There was some splitting of the safety signals. For example, the Applicant split bradycardia into two terms, bradycardia and sinus bradycardia. For this study, they are the same, and should be considered as the same adverse event when reviewing incidences of bradycardia.

#### 8.3.3. Routine Clinical Tests and Safety Assessments

All assessments were conducted following the scheduled assessments described in Table 3: Schedule of Events, Study P089 and Table 4: Safety Laboratory Assessments Table.

## 8.4. Safety Results

### 8.4.1. Deaths

No deaths were reported during the study.

### 8.4.2. Serious Adverse Events

The percentage and number of patients with SAEs was small, 8/276 (3.3%). No SAE occurred more than once in the study population. There were no SAEs reported in the 12 to less than 17 years age group. None of the events were related to the study drug.

**Table 20: Patients with Serious Adverse Events, All Patients Part A + B**

| *Age Group* | *Sugammadex 2 mg/kg* | *Sugammadex 4 mg/kg* | *Neostigmine+ Glyco/Atropine* |
|---|---|---|---|
| Total Population | 3/51 (5.9%) | 3/191 (1.6%) | 2/34 (5.9%) |
| 2 to < 6 years | 3/22 (13.6%) | 2/80 (2.5%) | 1/12 (8.3%) |
| 6 to < 12 years | 0/15 | 1/64 (1.6%) | 1/13 (7.7%) |
| 12 t0 < 17 years | 0/14 | 0/47 | 0/9 |

Source: Reviewer generated

A brief description of the serious adverse events, in order of age, for each patient follows.

- Patient Number (b) (6): A 2-year-old male, randomized to the moderate block group and reversal with sugammadex 2 mg/kg, underwent hepaticojejunostomy for duodenal atresia. He had a PMH of Trisomy 21. The patient developed a post-surgical bile leak that resolved on Day 8. The event was considered severe and not related to the study drug. I concur with the assessment.
- Patient Number (b) (6): A 2-year-old female, randomized to the moderated block and reversal with sugammadex 2 mg/kg, underwent laparoscopy due to unilateral hydronephrosis. On Day 6, the patient was hospitalized due to a urinary tract infection. She was treated with gentamycin and ampicillin and discharged on Day 10. The event was considered severe and not related to the study drug. I concur with the assessment.
- Patient Number (b) (6): A 3-year-old male, randomized to the deep block and reversal with sugammadex 4 mg/kg group, underwent laparotomy for malrotation. The patient was discharged on Day 4. On Day 6, he was admitted due to abdominal pain and constipation. Following a complex course, including GI tube placement, resolved on Day 19. The abdominal pain was considered severe and not related to the study drug. I concur with the assessment.
- Patient Number (b) (6): A 3-year-old male, randomized to the moderate block and reversal with neostigmine, had an adenotonsillectomy for sleep apnea syndrome. The patient had laryngospasm following extubation, 45 minutes after study drug administration. The laryngospasm was considered severe and not related to the study medication. I concur with the severity, however, without knowing how many twitches the patient had at the time of extubation I cannot determine whether it was related to study drug administration (inadequate reversal) or not.
- Patient Number (b) (6): A 4-year-old male, randomized to the deep block and reversal with sugammadex 4 mg/kg, underwent femoral derotation osteotomy. On Day 4, the patient was noted to have hip pain and calf swelling. An x-ray confirmed a femoral neck fracture, which was surgically repaired on the same day. The event was considered severe and not related to the study medication. I concur with the assessment.
- Patient Number (b) (6): A 5-year-old male randomized to the moderate block and reversal with sugammadex 2 mg/kg had an adenoidectomy for otitis media. On Day 4, the patient was hospitalized for post-surgical bleeding and discharged on Day 5

following resolution. The event was considered mild and not related to the study medication. I concur with the assessment.

- Patient Number (b) (6): A 9-year-old female, randomized to the moderate block and reversal with neostigmine, underwent cleft lip repair. On Day 4, she was admitted with dehydration due to pain and discharged the following day. The event was found to be severe and not related to the study drug. I concur with this assessment.
- Patient Number (b) (6): An 11-year-old male, randomized to the deep block with sugammadex 4 mg/kg group, underwent alveolar bone graft with iliac crest bone for cleft lip and palate repair. The patient developed pyrexia on Day 2 which resolved on Day 3. He was discharged on Day 4. The event was found to be moderate and not related to the study drug. I concur with this assessment.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients dropped out or discontinued Study P089 due to an adverse event.

### 8.4.4. Significant Adverse Events

There were no significant adverse events other than those defined by the Applicant as Adverse Events of Special Interest. Those will be discussed in section 8.5, Analysis of Submission Specific Safety Issues.

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A majority of the patients in all of the treatment groups experienced an adverse event up to seven days post treatment. None of the patients discontinued the study due to any type of adverse event, drug related, serious, or serious drug related. None of the patients died during the study. The tables below present a summary of the overall adverse event occurrences and the adverse event occurrences by age group.

**Table 21: Adverse Event Summary, All Patients Treated Parts A + B**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | |
| with one or more adverse events | 40 | (78.4) | 143 | (74.9) | 33 | (97.1) |
| with no adverse event | 11 | (21.6) | 48 | (25.1) | 1 | (2.9) |
| with drug-related[T] adverse events | 4 | (7.8) | 5 | (2.6) | 4 | (11.8) |
| with serious adverse events | 3 | (5.9) | 3 | (1.6) | 2 | (5.9) |
| with serious drug-related adverse events | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| who died due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to an adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to a drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to a serious adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| discontinued drug due to a serious drug-related adverse event | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[T] Determined by the investigator to be related to the drug.

Source: Applicant's Submission, August 26, 2020, CSR p 65

**Table 22: Adverse Event Summary by Age Group, All Patients Treated Parts A + B**

| *Treatement* | *Total Patients* | *One or More Adverse Events* | *No Adverse Events* | *Drug Related Adverse Events ** | *Serious Adverse Events* | *Seriouse Drug Related Adverse Events** |
|---|---|---|---|---|---|---|
| **Total Patients Treated, Parts A + B** | | | | | | |
| Sugammadex 2 mg/kg | 51 | 40 (78%) | 11 (21.6%) | 4 (7.8%) | 3 (5.9%) | 0 |
| Sugammadex 4 mg/kg | 191 | 143 (74.9%) | 33 (97.1%) | 5 (2.6%) | 3 (1.6%) | 0 |
| Neostigmine + Glyco or Atopine | 34 | 33 (97.1%) | 1 (2.9%) | 4 (11.8%) | 2 (5.9%) | 0 |
| **2 to less than 6 years old** | | | | | | |
| Sugammadex 2 mg/kg | 22 | 18 (81.8%) | 4 (18.2%) | 2 (9.1%) | 3 (13.6%) | 0 |
| Sugammadex 4 mg/kg | 80 | 60 (75%) | 20 (25%) | 0 | 2 (2.5%) | 0 |
| Neostigmine + Glyco or Atopine | 12 | 12 (100%) | 0 | 1 (8.3%) | 1 (8.3%) | 0 |
| **6 to less than 12 years old** | | | | | | |
| Sugammadex 2 mg/kg | 15 | 12 (80%) | 3 (20%) | 2 (13.3%) | 0 | 0 |
| Sugammadex 4 mg/kg | 64 | 48 (75%) | 16 (25%) | 1 (1.6%) | 1 (1.6%) | 0 |
| Neostigmine + Glyco or Atopine | 13 | 12 (92%) | 1 (7.7%) | 2 (15.4%) | 1 (7.7%) | 0 |
| **12 to less than 17 years old** | | | | | | |
| Sugammadex 2 mg/kg | 14 | 10 (71.4%) | 4 (28.6%) | 0 | 0 | 0 |
| Sugammadex 4 mg/kg | 47 | 35 (74.5%) | 12 (25.5%) | 4 (8.5%) | 0 | 0 |
| Neostigmine + Glyco or Atopine | 9 | 9 (100%) | 0 | 1 (11.1%) | 0 | 0 |

*Determined by the investigator to be related to the drug
Source: Adapted from Applicant's Submission, August 26, 2020, CSR p 247-259

Overall adverse event occurences are similar within a treatment group across all age cohorts. Drug related adverse events did not follow a pattern within the sugammadex 2 mg/kg vs 4 mg/kg treated groups. However, overall, drug related adverse events were lower in the sugammadex treated groups than the neostigmine treated group, particularly in the sugammadex 4 mg/kg treated group.

The most frequently reported adverse event up to seven days post treatment in all intervention groups was procedural pain, as would be expected in a surgical population. Also frequently reported was nausea and vomiting and bradycardia. The following table presents specific adverse events.

**Table 23: Patients with Specific Adverse Events (Incidence ≥5% in One or More Treatment Groups) All Patients Treated, Part A + B, Up to 7 Days Post-Treatment**

| | ***Sugammadex 2 mg/kg*** | ***Sugammadex 4 mg/kg*** | ***Neostigmine + Glyco/Atropine*** |
|---|---|---|---|
| *Subjects in Population* | | | |
| With one or more specific adverse events | 40 (78.4%) | 143 (74.9%) | 33 (97%) |
| With no specific adverse events | 11 (22.6%) | 48 (26.1%) | 1 (3%) |
| Total Subjects | 51 | 191 | 34 |
| *Cardiac Disorders* | | | |
| Bradycardia/Sinus Bradycardia | 5 (9.8%) | 13 (6.8%) | 5 (14.7%) |
| Other | 0 | 3 (1.6%) | 0 |
| *Gastrointestinal Disorders* | | | |
| Nausea/procedural nausea | 5 (9.8%) | 21 (11%) | 2 (5.9%) |
| Vomiting/procedural vomiting | 7 (13.7%) | 25 (13.1%) | 3 (8.8%) |
| Other | 4 (7.8%) | 3 (1.6%) | 0 |
| *Pain* | | | |
| Incision site pain/procedural pain | 33 (64.7%) | 117 (61.3%) | 25 (75.7%) |
| *Eye Disorders* | | | |
| | 3 (5.9%) | 3 (1.6%) | 3 (8.8%) |
| *Infections and Infestations* | | | |
| | 1 (2%) | 3 (1.6%) | 3 (8.8%) |
| *General Disorders, Administrative Site Conditions, and Investigations* | | | |
| Pyrexia | 0 | 2 (1%) | 2 (5.9%) |
| Body temperature increased | 0 | 1 (0.5%) | 2 (5.9%) |
| Other | 1 (2%) | 10 (5.2%) | 2 (5.9%) |
| *Musculoskeletal and Connective Tissue Disorders* | | | |
| Muscle Spasms | 0 | 0 | 2 (5.9%) |
| *Nervous System Disorders* | | | |
| | 2 (3.9%) | 4 (2.1%) | 3 (8.8%) |
| *Respiratory, Thoracic and Mediastinal Disorders* | | | |
| | 1 (2%) | 3 (1.6%) | 3 (8.8%) |

Source: Adapted from Applicant's Submission, August 26, 2020, CSR p 67-69

Overall, there were no clincally meanigful diffferences in adverse event incidences between sugammadex and neostigmine.

The Applicant separated bradycardia and sinus bradycardia. For safety evaluation, they are the same adverse event, they are combined in the above adverse event table. In addtion bradycardia and sinus bradycardia were combined in the label in Section 6.1. Nausea and procedural nausea and vomiting and procedural vomitting were grouped together in this table, however, they were not grouped in the final label, similar to the adults. They have been combined here to give the reader a clearer picture of the incidence of these adverse events without splitting.

The following table shows adverse events the Applicant attributes to study intervention.

**Table 24: Patients with Drug-Related Adverse Events, All Patients Treatment, Part A + B, Up to 7 Days Post-Treatment**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | |
| with one or more drug-related adverse events | 4 | (7.8) | 5 | (2.6) | 4 | (11.8) |
| with no drug-related adverse events | 47 | (92.2) | 186 | (97.4) | 30 | (88.2) |
| **Cardiac disorders** | **4** | **(7.8)** | **3** | **(1.6)** | **3** | **(8.8)** |
| Bradycardia | 3 | (5.9) | 2 | (1.0) | 2 | (5.9) |
| Sinus bradycardia | 1 | (2.0) | 1 | (0.5) | 1 | (2.9) |
| **Gastrointestinal disorders** | **0** | **(0.0)** | **1** | **(0.5)** | **1** | **(2.9)** |
| Vomiting | 0 | (0.0) | 1 | (0.5) | 1 | (2.9) |
| **Respiratory, thoracic and mediastinal disorders** | **0** | **(0.0)** | **1** | **(0.5)** | **0** | **(0.0)** |
| Tachypnoea | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) |
| Every subject is counted a single time for each applicable row and column. | | | | | | |

Source: Applicant's Submission, August 26, 2020, CSR p 71

In addition to bradycardia, there was one event of vomiting and one event of tachypnea in the sugammadex 4 mg/kg group the Applicant attributed to the study drug. The Applicant supplied narratives for clinically relevant bradycardia, however, no information was provided by the Investigator regarding causlity of vomitting. There are many reasons why a patient may have vomiting during the postoperative period and causality may be difficult to determine. There are also many reasons why a patient may have tachypnea in the post operative period. The most plausable reasons for study drug related tachypnea may be layrngospasm, bronchospasm or incomplete reversal. Without a more granular explanation into the mechanism of tachypnea, causality is difficult to determine.

### 8.4.6. Laboratory Findings

There were laboratory findings pertinent to this NDA.

#### 8.4.7. Vital Signs

No clinically meaningful findings were observed in the mean changes from baseline vital signs in any treated patients. Regarding the safety concern of bradycardia in the pediatric population, heart rate decreases (<age defined criteria and at least 20% decrease from baseline) were more common in the neostigmine group.

#### 8.4.8. Electrocardiograms (ECGs)

This section is not relevant to this NDA. No twelve lead ECGs were obtained during the study.

#### 8.4.9. QT

QT interval studies were submitted under the original NDA.

#### 8.4.10. Immunogenicity

Sugammadex is not a therapeutic protein, nor does it cause an immune mediated response. This section is not relevant to this NDA.

### 8.5. Analysis of Submission-Specific Safety Issues

Bradycardia and hypersensitivity and anaphylaxis are known adverse reactions following administration of sugammadex. Bradycardia is of particular concern in the pediatric population, particularly in younger patients whose cardiac output is heart rate dependent.

The following were identified as events of clinical interest (ECI):

- Sugammadex is known to cause bradycardia. Clinically relevant bradycardia, defined as any bradycardia event necessitating intervention as determined by the investigator
- Sugammadex is known to cause hypersensitivity and anaphylaxis. An external Adjudication committee reviewed potential hypersensitivity and/or anaphylaxis events.

In addition, patients were monitored for evidence of drug-induced hepatic injury as a tier 2 safety endpoint.

#### 8.5.1. Bradycardia

Bradycardic events were defined as follows:

- Clinically relevant bradycardia – Bradycardia necessitating intervention
- Treatment-emergent bradycardia – Heart rate generally below the first percentile for age that had also decreased 20% or greater as compared to the patient's pre-dose baseline heart rate value, sustained for at least 30 seconds.

- Treatment-emergent relative bradycardia – Heart rate that decreased 20% or greater as compared to the patients' pre-dose baseline heart rate value, sustained for at least 30 seconds

The table below describes the Applicant's review of all bradycardic events that occurred during Study P089, whether they were considered drug related or not.

**Table 25: Analysis of Bradycardic Events, All Patients Treated Parts A + B, Up to 45 Minutes Post-Treatment**

| Treatment | n | (%) |
|---|---|---|
| **Subjects in population** | | |
| Sugammadex 2 mg/kg | 51 | |
| Sugammadex 4 mg/kg | 191 | |
| Neostigmine + (Glycopyrrolate or Atropine) | 34 | |
| **Clinically Relevant Bradycardia** | | |
| Sugammadex 2 mg/kg | 1 | (2.0) |
| Sugammadex 4 mg/kg | 3 | (1.6) |
| Neostigmine + (Glycopyrrolate or Atropine) | 2 | (5.9) |
| **Treatment-Emergent Bradycardia** | | |
| Sugammadex 2 mg/kg | 2 | (3.9) |
| Sugammadex 4 mg/kg | 10 | (5.2) |
| Neostigmine + (Glycopyrrolate or Atropine) | 4 | (11.8) |
| **Treatment-Emergent Relative Bradycardia** | | |
| Sugammadex 2 mg/kg | 8 | (15.7) |
| Sugammadex 4 mg/kg | 29 | (15.2) |
| Neostigmine + (Glycopyrrolate or Atropine) | 14 | (41.2) |

Source: Applicant's Submission, August 26, 2020, CSR, p 79

The number of patients with bradycardia, clinically relevant and treatment – emergent, up to 45 minutes following study drug administration, was verified by JMP Clinical data manipulation.

The percentage of patients with treatment emergent bradycardia was slightly higher in the sugammadex 4 mg/kg group. However, clinically relevant and treatment emergent relative bradycardia were fairly equal between sugammadex 2 mg/kg and 4 mg/kg treatment groups.

Sugammadex had a lower percentage of bradycardia of any type than neostigmine. None of the events of bradycardia were reported as severe.

It is interesting to note events clinically relevant bradycardia, an Event of Clinical Interest, occurred within 45 minutes of study drug administration. The individual patients will be discussed below.

**Table 26: Patients with the Clinically Relevant Bradycardia, All Patients Treated Parts A + B, Up to 7 Days Post-Treatment**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | |
| with one or more adverse events of clinical interest | 1 | (2.0) | 3 | (1.6) | 2 | (5.9) |
| with no adverse events of clinical interest | 50 | (98.0) | 188 | (98.4) | 32 | (94.1) |
| **Cardiac disorders** | **1** | **(2.0)** | **3** | **(1.6)** | **2** | **(5.9)** |
| Bradycardia | 0 | (0.0) | 2 | (1.0) | 0 | (0.0) |
| Sinus bradycardia | 1 | (2.0) | 1 | (0.5) | 2 | (5.9) |

Every subject is counted a single time for each applicable row and column.

Source: Applicant's Submission, August 26, 2020, CSR p 376

Patients in the youngest age group, 2 to less than 6 years old, are dependent on heart rate for their cardiac output. This age group might be the most vulnerable to the effects of bradycardia from a study drug. The following are patients with clinically relevant bradycardia up to 7 days post treatment by age cohort.

- Sugammadex 2 mg/kg
  - 2 to < 6 years =1/22 (4.5%)
- Sugammadex 4 mg/kg
  - 6 to < 12 years = 1/64 (1.6%)
  - 12 to < 17 years = 2/47 (4.3%)
- Neostigmine with glycopyrrolate or atropine
  - 6 to < 12 years = 2/13 (15.4%)

As can be seen above, the number of patients in any group is small, however, the only patient in the 2 to less than 6 years age group that experienced clinically relevant bradycardia was in the sugammadex 2 mg/kg group. No discernable pattern could be found in the age distribution for clinically relevant bradycardia.

The following are narratives for the six events of clinically relevant bradycardia, in order of age.

- Patient Number (b) (6): A 4-year-old male, randomized to the moderate block and reversal with sugammadex 2 mg/kg, underwent adenotonsillectomy. Approximately 6 minutes after administration of the study medication, patient experienced clinically relevant bradycardia, with a heart rate of 81, and a blood pressure of 90/37. The patient

was treated with atropine. The bradycardia resolved after 13 minutes. At the time of recovery, his heart rate was 133 and blood pressure was 100/53. The investigator considered the event to be mild and related to the study medication. I concur with this assessment.

- Patient Number (b) (6): A 6-year-old female, randomized to deep block and reversal with sugammadex 4 mg/kg, underwent dental surgery for dental plaque. Approximately 7.5 minutes after study drug administration, the patient experienced clinically relevant bradycardia with a heart rate of 66 and a blood pressure of 113/46. The patient was treated with atropine. The investigator considered the bradycardia to be due to a painful stimulus during surgery and decrease of anesthetic depth at the same time. Although a young patient of 6 years old may have a parasympathetic response to a painful stimulus under light anesthesia, the close temporal proximity to administration of a high dose of sugammadex cannot rule out the study drug's contribution to bradycardia. Therefore, I do not fully concur with the assessment of the Investigator, and believe it was a combination of events occurring simultaneously that caused the patient's bradycardia.
- Patient Number (b) (6): A 10-year-old male, randomized to moderate block and reversal with neostigmine, underwent dental surgery for dental plaque. The patient experienced moderate, clinically relevant bradycardia 17.5 minutes following study drug administration. The investigator determined the bradycardia not related to the study medication. Based on the narrative and the CRF, it is difficult to discern causality.
- Patient Number (b) (6): An 11-year-old female, randomized to moderate block and reversal with neostigmine, underwent adenotonsillectomy. His pre-dose heart rate was 74 beats per minute. Approximately 5 minutes following study drug administration, the patient experienced clinically relevant bradycardia, with a heart rate of 66 beats per minute and a blood pressure of 99/45. He was treated with atropine. The Investigator considered the event related to the study medication. I concur with this assessment.
- Patient Number (b) (6): A 15-year-old male, randomized to deep block and reversal with sugammadex 4 mg/kg, underwent tympanoplasty. His vital signs pre-dose was a heart rate of 87 beats per minute and blood pressure of 94/56. The patient experienced clinically relevant bradycardia, with a heart rate of 68 beats per minute and a blood pressure of 70/45 approximately 11 minutes after study drug administration. He was treated with atropine. The bradycardia resolved after 57 seconds. The investigator concluded the bradycardia was related to the study drug. I concur with this assessment.
- Patient Number (b) (6): A 15-year-old male, randomized to deep block and reversal with sugammadex 4 mg/kg, underwent spinal laminectomy for severe lumbar stenosis. His pre-dose heart rate was 79 and his blood pressure was 84/46. Two minutes following study drug administration, the patient experienced clinically significant sinus bradycardia, with a heart rate of 63 beats per minute and a blood pressure of 77/31. The heart rate was lowest at 50 beats per minute, 27 minutes following study drug administration. He was treated with glycopyrrolate. By 30 minutes following study drug

administration his heart rate was 76 meats per minute and his blood pressure was 113/50. The investigator considered the event related to the study drug. I concur with this assessment.

Four of these events were associated with study drug administration, one patient received 2 mg/kg of sugammadex, two patients received 4 mg/kg of sugammadex, and one patient received neostigmine. Determination of causality is difficult from the narrative and the CRF for the other two patients, although it is likely the study drugs may have played a role in the bradycardia for both patients due to the timing of the events.

Because the numbers were small for both sugammadex and the active comparator, it is difficult to make a final assessment. However, when reviewing treatment emergent bradycardia, it is more evident that sugammadex had fewer incidences of bradycardia than neostigmine.

### 8.5.2. Adjudicated Hypersensitivity and Anaphylaxis

Overall, six cases were submitted for adjudication and review by an independent external adjudication committee There were no adjudicated cases of hypersensitivity or anaphylaxis for Study P089. The table below shows the cases the number of cases submitted for each group.

**Table 27: Participants with Cases Submitted for Adjudication, All Patients Treated, Parts A + B, Up to 7 Days Post - Treatment**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | | Neostigmine + (Glycopyrrolate or Atropine) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Subjects in population | 51 | | 191 | | 34 | |
| with no cases submitted for adjudication | 49 | (96.1) | 189 | (99.0) | 32 | (94.1) |
| with one or more cases submitted for adjudication | 2 | (3.9) | 2 | (1.0) | 2 | (5.9) |
| Number of cases submitted for adjudication | 2 | | 2 | | 2 | |
| Number of cases adjudicated as: | | | | | | |
| **Hypersensitivity** | | | | | | |
| Yes | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| No | 2 | (100.0) | 2 | (100.0) | 2 | (100.0) |
| Unable to adjudicate | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| **Anaphylaxis** | | | | | | |
| Yes | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| No | 2 | (100.0) | 2 | (100.0) | 2 | (100.0) |
| Unable to adjudicate | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

Percent of sub-category levels is calculated using the total number in that sub-category as the denominator.
There may be multiple AEs within one case submitted for adjudication.

Source: Applicant's Submission, August 26, 2020, CSR p 77

#### 8.5.3. Hepatic Safety

There was no evidence of drug-induced liver injury and no pattern of elevated liver function tests.

### 8.6. Safety Analyses by Demographic Subgroups

The Applicant did not perform safety analyses by demographic subgroups, though efficacy was similar across race and gender.

### 8.7. Specific Safety Studies/Clinical Trials

There were no safety specific studies or clinical trials conducted for this NDA.

### 8.8. Additional Safety Explorations

#### 8.8.1. Human Carcinogenicity or Tumor Development

This section is not relevant to this application.

#### 8.8.2. Human Reproduction and Pregnancy

This section is not relevant to this application.

#### 8.8.3. Pediatrics and Assessment of Effects on Growth

This section is not relevant to this application.

#### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This section is not relevant to this application.

### 8.9. Safety in the Postmarket Setting

#### 8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant conducted a cumulative review of postmarketing cases, spontaneous and noninterventional, in patients less than 17 years old, for the period of July 31, 2008 to January 1, 2020. The Applicant found a total of 292 cases (out of 3486 cases reported) containing 443 events reported during the time. The following table is the number of events by age group.

**Table 28: Number of Events and Percentage of Total Events by Age Group**

| Age Group | # Serious Events | # Nonserious Events | Total # of Events | % of Total Events |
|---|---|---|---|---|
| Children (2 years to <6 years) | 34 | 73 | 107 | 24% |
| Older Children (6 years to <12 years) | 64 | 145 | 209 | 47 % |
| Adolescent (12-<17 years) | 72 | 55 | 127 | 29% |
| **Total** | **170** | **273** | **443** | **100%** |

Source: Applicant's Submission, August 26, 2020, Summary of Clinical Safety, p 27

**2 to less than 6 years old**

A total of 72 cases containing 107 events occurred in the youngest age group. The most frequently reported adverse events were related to procedural events or related to product use (off-label use and product administered to patients of inappropriate age).

The most frequently reported clinical AE's were bronchospasm, anaphylactic reaction, and recurrence of neuromuscular blockade. There were 45 events that were associated with off-label use, 39 associated with a single literature source from Italy describing the use of sugammadex 4 mg/kg in children 5 to 10 years of age. See Table 29 for a complete list of the most common adverse events seen.

There were 10 fatal events from one case. The patient was an approximately 4-year-old female who underwent an adenoidectomy. The patient received sugammadex 2.25 mg/kg. Approximately 3 to 5 minutes after extubation, the patient had bronchospasm with hemodynamic collapse, bradycardia, and respiratory distress. The patient was reintubated. She was administered cortisone and epinephrine a good response. After 15-20 minutes, the same events recurred. Epinephrine was again administered. She developed pulmonary edema; however, blood pressure and oxygenation were restored. Despite this, the patient expired the next day.

**6 to less than 12 years old**

There was a total of 153 cases with 209 events reported in the 6 to less than 12-year-old age group. The most frequently reported AEs in this age group were procedural or events associated with product use (off label use and no AE). The most frequently reported clinical AEs were related to hypersensitivity and anaphylaxis (anaphylactic reaction, urticaria, anaphylactic shock, and erythema). There were 111 cases of off-label, 102 were from a single literature source from Italy describing the use of sugammadex 4 mg/kg in children 5 to 10 years of age. From the other 9 cases, there was one case described of a recurrence of a neuromuscular blockade.

**12 to less than 17 years old**

There was a total of 67 cases with 127 events reported in the 12 to less than 17 years old age group. The most frequently reported AEs in this age group were procedural events or events associated with product use. These were off-label use, product use issues and delayed recovery from anesthesia. The most frequently reported clinical adverse events were associated with anaphylaxis and hypersensitivity (anaphylactic reaction, rash, anaphylactic shock and urticaria).

**Discussion and Conclusion**

The Applicant found in their cumulative review to January 1, 2020 for sugammadex use in patients 2 to less than 17 years old that the majority of AEs reported were associated with product use, already listed AE or signs or consequences of listed AE's. Therefore, no new safety signals were noted.

**Table 29: The Most Frequent Adverse Events Reported by Age Group**

| Age Group | Preferred terms (PT) | Listed in CCDS (U/L*) | Total # of Events | # of Serious events | # Nonserious |
|---|---|---|---|---|---|
| **Child (2 to <6 years of age)** | | | | | |
| | Off-label use | Unlisted | 45 | 0 | 45 |
| | Bronchospasm | Listed | 5 | 4 | 1 |
| | Anaphylactic reaction | Listed | 4 | 4 | 0 |
| | Recurrence of neuromuscular blockade | Listed | 4 | 1 | 3 |
| | Laryngospasm | Unlisted | 3 | 2 | 1 |
| | Product administered to patient of inappropriate age | Unlisted | 3 | 0 | 3 |
| | Bradycardia | Listed | 2 | 2 | 0 |
| | Drug ineffective | Unlisted | 2 | 0 | 2 |
| | Dyspnoea | Unlisted | 2 | 0 | 2 |
| | Erythema | Unlisted | 2 | 1 | 1 |
| | Heart rate increased | Listed | 2 | 0 | 2 |
| | Hypoxia | Unlisted | 2 | 2 | 0 |
| | Musculoskeletal stiffness | Unlisted | 2 | 2 | 0 |
| | Postoperative respiratory distress | Unlisted | 2 | 2 | 0 |
| | Rash | Listed | 2 | 0 | 2 |
| | Urticaria | Listed | 2 | 0 | 2 |
| | **Subtotal** | | **84** | **20** | **64** |
| **Older Child (6 to <12 years of age)** | | | | | |
| | Off-label use | Unlisted | 111 | 0 | 111 |
| | Anaphylactic reaction | Listed | 10 | 10 | 0 |
| | Urticaria | Listed | 8 | 4 | 4 |
| | Anaphylactic shock | Listed | 7 | 7 | 0 |
| | Erythema | Unlisted | 6 | 4 | 2 |
| | No adverse event | Listed | 5 | 0 | 5 |
| | Epilepsy | Unlisted | 4 | 4 | 0 |
| | Asthma | Unlisted | 3 | 2 | 1 |
| | Hypersensitivity | Listed | 3 | 3 | 0 |
| | Product use issue | Unlisted | 3 | 0 | 3 |
| | Rash | Listed | 3 | 1 | 2 |
| | **Subtotal** | | **163** | **35** | **28** |

Source: Applicant's Submission, August 26, 2020, Clinical Safety Summary, p 31-32

**Table 29 Continued**

| Age Group | Preferred terms (PT) | Listed in CCDS (U/L*) | Total # of Events | # of Serious events | # Nonserious |
|---|---|---|---|---|---|
| **Adolescent (12 to <17 years of age)** | | | | | |
| | Anaphylactic reaction | Listed | 20 | 18 | 2 |
| | Rash | Listed | 9 | 2 | 7 |
| | Anaphylactic shock | Listed | 6 | 6 | 0 |
| | Urticaria | Listed | 6 | 3 | 3 |
| | Off-label use | Unlisted | 4 | 0 | 4 |
| | Erythema | Unlisted | 3 | 2 | 1 |
| | Headache | Unlisted | 3 | 0 | 3 |
| | Hypersensitivity | Listed | 3 | 1 | 2 |
| | Product use issue | Unlisted | 3 | 0 | 3 |
| | Pruritus | Unlisted | 3 | 1 | 2 |
| | **Subtotal** | | **60** | **33** | **27** |

*U=Unlisted, L=Listed
# = number

Source: Applicant's Submission, August 26, 2020, Clinical Safety Summary, p 31-32

### 8.9.2. Expectations on Safety in the Postmarket Setting

This section is not relevant to this NDA.

### 8.9.3. Additional Safety Issues from Other Disciplines

There were no other safety issues identified from other disciplines.

## 8.10. Integrated Assessment of Safety

Study P089 was conducted to determine the safety and efficacy of sugammadex in pediatric patients ages 2 to less than 17 years old. The Applicant presented data comparing dosing across different NMBA and age cohorts.

There were no deaths during the study. There were no SAE's related to study drug administration. There were no adjudicated cases of anaphylaxis or hypersensitivity.

The event of clinical interest that occurred in the pediatric population was bradycardia. Although bradycardia is usually associated with larger doses of sugammadex, the only incidence of clinically relevant bradycardia in the 2 to less than 6-year-old age group was in the sugammadex 2 mg/kg group. There was no apparent pattern among age group distribution.

Overall, there was a small number of patients that had clinically relevant bradycardia (n=6) from all treatment groups.

A larger percentage of patients had treatment emergent bradycardia, specifically, 11.8% in the neostigmine group versus 5.2% in the sugammadex 4 mg/kg group and 3.9% in the sugammadex 2 mg/kg group. Again, these numbers were small, however it is apparent that sugammadex had a lower percentage of bradycardia than neostigmine.

Finally, a much larger percentage of patients in the neostigmine group had treatment emergent relative bradycardia in the neostigmine group (40%) versus in either sugammadex group (15% for both groups).

In summary, sugammadex was well tolerated in the pediatric population at the doses studied. The safety profile of sugammadex in the pediatric population was similar across age groups and doses. Furthermore, no new safety signals were identified.

# 9. Advisory Committee Meeting and Other External Consultations

No advisory committee meetings were convened for this NDA submission because there were no issues that required a meeting.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

This application provided data to support the proposed label for a subpopulation of pediatric patients ages 2 to less than 17 years of age. The current sugammadex label recommends dosing adults according to actual body weight and doses 2 mg/kg for reversal of moderate neuromuscular blockade and 4 mg/kg for reversal of deep neuromuscular blockade.
The efficacy from Study P089 demonstrated a statistically significant difference in the time to recovery of TOF ≥0.09 for pediatric patients ages 2 to less than 17 years when dosed with sugammadex 2 mg/kg for reversal of moderated neuromuscular blockade when compared with neostigmine. The treatment emergent adverse event of bradycardia is seen less frequently when dosed with sugammadex than with neostigmine. The Applicant is recommending no changes in dosing in the approved label for sugammadex 2 mg/kg and 4 mg/kg. I concur with these recommendations.

The final language is still being negotiated with the Applicant; however, these language changes are minor. Therefore, the final label may differ slightly from this review.

Labeling Changes by Section

*Indications and Usage (Also repeated in Section 1)*
Approval of Supplement 008 extends the use of sugammadex to patients 2 years and older.

BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults and pediatric patients aged 2 years and older undergoing surgery. (1)

*DOSAGE AND ADMINISTRATION (repeated in section 2.2)*
Sugammadex 16 mg/kg was not studied in pediatric patients.

For rocuronium only:
- 16 mg/kg is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium. Immediate reversal in pediatric patients has not been studied. (2.2)

*Adverse Reactions*
The following bullet was added:

- Most common adverse reactions (reported in ≥10% of pediatric patients 2 to <17 years of age at BRIDION doses of 2 or 4 mg/kg) were pain, vomiting, and nausea. (6.1)

*2.1 Important Dosing and Administration*
The Applicant added preparation of dilution for pediatric uses. DMEPA and CMC had interaction with the Applicant for clarification of safe dilution of Bridion for pediatric uses. The current label reads as follows:

Preparation of dilution for pediatric use:
BRIDION 100 mg/mL may be diluted to a concentration of 10 mg/mL, using 0.9% sodium chloride injection, USP, to increase the accuracy of dosing in the pediatric population.

- To prepare the required dose, aseptically transfer all the contents of the 2 mL vial of BRIDION 2-mL single-dose vials containing 200 mg sugammadex (100 mg/mL) to a bottle (or intravenous bag) containing 18 mL of 0.9% (9 mg/mL) sodium chloride injection, to achieve a final concentration of 10 mg/mL sugammadex.
- BRIDION injection is a single-dose sterile solution without preservatives. Discard any unused portion from the vial.
- If not used immediately, the diluted solution can be stored up to 48 hours refrigerated (5°C; 41°F) or at room temperature (25°C; 77°F).

For further details, please see the review from DMEPA.

*6.1 Clinical Trials Experience*

The Applicant added the adverse event profile of patients treated with sugammadex 2 mg/kg or 4 mg/kg. The Division requested the adverse events of bradycardia and sinus bradycardia be combined as they represent one adverse event. The Applicant complied.

Pediatric Patients

The safety of BRIDION has been assessed in a randomized, active-controlled study of pediatric patients 2 to <17 years of age, with 242 receiving treatment with BRIDION. Adverse events occurring in ≥5% of pediatric patients are presented in Table 3. The safety profile was generally consistent with that observed in adults.

**Table 3: Pediatric Patients with Adverse Events Incidence ≥5% in One or More Treatment Groups Up to 7 Days Post-Treatment**

| | Sugammadex 2 mg/kg | | Sugammadex 4 mg/kg | |
|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** |
| Subjects in population | 51 | | 191 | |
| with one or more specific adverse events | 40 | (78) | 143 | (75) |
| with no specific adverse events | 11 | (22) | 48 | (25) |
| **Cardiac disorders** | **5** | **(10)** | **16** | **(8)** |
| Bradycardia* | 5 | (10) | 13 | (7) |
| **Eye disorders** | **3** | **(6)** | **1** | **(1)** |
| **Gastrointestinal disorders** | **8** | **(16)** | **35** | **(18)** |
| Nausea | 1 | (2) | 12 | (6) |
| Vomiting | 4 | (8) | 20 | (10) |
| **Injury, poisoning and procedural complications** | **34** | **(67)** | **121** | **(63)** |
| Incision site pain | 3 | (6) | 6 | (3) |
| Procedural nausea | 4 | (8) | 9 | (5) |
| Procedural pain | 30 | (59) | 111 | (58) |
| Procedural vomiting | 3 | (6) | 5 | (3) |

*Combines preferred terms of bradycardia and sinus bradycardia

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears in this table only if its incidence in one or more of the columns meets the incidence criterion in the table title, after rounding.

*8.4 Pediatric Use*

The Applicant added the results of the safety and effectiveness of sugammadex from Study P089 to address the use in pediatric patients ages 2 years and older.

The safety and effectiveness of BRIDION for reversal of neuromuscular blockade induced by rocuronium bromide or vecuronium bromide have been established in pediatric patients aged 2

years and older. Use of BRIDION in these age groups is supported by evidence from an adequate and well-controlled study of BRIDION *[see Clinical Pharmacology (12.3) and Clinical Studies (14.1)].* In pediatric patients aged 2 years and older, the safety profile is generally consistent with that observed in adults *[see Adverse Reactions (6.1)]*.

Safety and effectiveness in patients younger than 2 years of age have not been established.

*12.3 Pharmacokinetics*

There have been several modifications to this section, however, Dr. Nallini's comments have been accepted by the Applicant.

Pediatric Patients

Sugammadex pharmacokinetic parameters were estimated in pediatric patients 2 to <17 years of age with patients enrolled into 3 age groups and intravenous doses of 2 or 4 mg/kg sugammadex administered for reversal of moderate or deep neuromuscular blockade, respectively. Both clearance and volume of distribution increase with increasing age in pediatric patients.

Sugammadex exposure ($AUC_{0\text{-}inf}$ and $C_{max}$) increased in a dose-dependent, linear manner following administration of 2 and 4 mg/kg across patients 2 to <17 years of age. Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant *[see Clinical Studies (14.1)]*.

The observed steady-state volume of distribution of sugammadex is approximately 3 to 10 liters and clearance is approximately 38 to 95 mL/min resulting in a half-life of approximately 1-2 hours in pediatric patients 2 to <17 years of age.

*14.1 Clinical Studies*

The Applicant did not clarify that the efficacy portion of Study P089 was performed on 67 patients, 33 in the sugammadex 2 mg/kg group and 34 patients in the neostigmine group. In addition, the Statistical team indicated that the use of a p value in the label was not appropriate and the Applicant should use the geometric least squares mean to for their comparison of sugammadex 2 mg/kg and neostigmine. The changes were made in the second paragraph of this section.

Comparative Study of BRIDION versus Neostigmine as a Reversal Agent for Neuromuscular Blockade Induced by Rocuronium or Vecuronium in Pediatric Patients 2 to <17 Years of Age

Time to recovery from neuromuscular blockade induced by rocuronium or vecuronium followed by administration of BRIDION or neostigmine was assessed in a randomized, double-blind, active comparator-controlled study. The study was conducted in 288 randomized pediatric patients 2 to <17 years of age, of which 276 patients received treatment (153 boys and 123 girls; ASA class 1, 2, and 3; 89.5% were Caucasian; median weight was 25 kg; median age was 7 years). The primary efficacy objective was to evaluate the effect of BRIDION compared to neostigmine for reversal of moderate neuromuscular blockade as measured by time to recovery to a TOF ratio of ≥0.9.

Recovery to a TOF ratio of ≥0.9 was statistically significantly faster in pediatric patients 2 to <17 years of age dosed with BRIDION 2 mg/kg (N=33) compared with neostigmine (N=34) for reversal of moderate block based on a geometric mean of 1.7 minutes for BRIDION 2 mg/kg and 7.4 minutes for neostigmine (ratio of geometric means was 0.22, 95% CI (0.16, 0.32)). These effects were

consistent across age cohorts studied (2 to <6; 6 to <12; 12 to <17 years of age) and neuromuscular blocking agent (rocuronium and vecuronium).

### 10.2. Nonprescription Drug Labeling

This is a prescription drug. This section is not relevant to this NDA.

## 11. Risk Evaluation and Mitigation Strategies (REMS)

There are no REMS for this NDA.

## 12. Postmarketing Requirements and Commitments

There are no postmarketing requirements or commitments for this NDA.

## 13. Appendices

### 13.1. References

Plaud B, Meretoja O, Hofmockel R, Raft J, Stoddart PA, van Kuijk JH, Hermens Y, Mirakhur RK. Reversal of rocuronium-induced neuromuscular blockade with sugammadex in pediatric and adult surgical patients. *Anesthesiology.* 2009 Feb;110(2):284-94.

## 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): A Phase 4 Double-Blinded, Randomized, Active-Comparator Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Patients (Study ID 8616-089)**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes X | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 148 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

APPEARS THIS WAY ON ORIGINAL

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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RIGOBERTO A ROCA on behalf of SUSAN D YOST
06/25/2021 01:22:19 PM

RIGOBERTO A ROCA
06/25/2021 01:23:00 PM