Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Combined Clinical, Cross-Discipline Team Leader, and Division Director Summary Review

Application Type	Supplemental NDA
NDA/Supplement Number	NDA 022225 / S-014
Priority or Standard	Priority
Submit Date	June 12, 2024
PDUFA Goal Date	December 12, 2024
Division/Office	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/Office of Neuroscience/Office of New Drugs/CDER
Reviewer Names	Lisa Banta, MD, DAAP Rigoberto Roca, MD, Division Director, DAAP
Review Completion Date	December 11, 2024
Established or Proper Name	Sugammadex
Proprietary Name	BRIDION
Applicant	Merck, Sharp & Dohme LLC
Dosage Form/Strength	Injection/Strength: 200 mg/2 mL (100 mg/mL) and 500 mg/5 mL (100 mg/mL)
Applicant Proposed Dosing Regimens	For rocuronium and vecuronium: • 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. • 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation. 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.
Proposed Indication/Population	BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adult and pediatric patients undergoing surgery.
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including reviews by:	
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1. Benefit-Risk Assessment

Sugammadex is a modified γ cyclodextrin that forms a complex with the non-depolarizing neuromuscular blocking drugs rocuronium and vecuronium, thereby removing these agents from the neuromuscular junction and facilitating the return of muscle function. Given the mechanism of action of sugammadex, its efficacy profile holds true in pediatric subjects from ≥ 2 years old to < 17 years old, and therefore full pediatric extrapolation was utilized in these ages. Given the immaturity of multiple organ systems in patients < 2 years old including neonates, and in particular the neuromuscular system, the appropriate dose for efficacy, in addition to safety, needed to be established in the < 2-year-old patient population. Therefore, efficacy in subjects ages 0 to < 2 years old could not be extrapolated and was determined by the studies outlined in the Written Request (WR), which was formally made on October 28, 2016.

Neuromuscular blockade, also referred to as muscle relaxation, is a component of many surgical procedures. Neuromuscular blockade provides muscle relaxation and reduces patient movement which can be critical during procedures that require minimal to no movement. The reversal of neuromuscular blocking drugs usually occurs at the end of a surgical procedure, in which the anesthesiologist prepares a patient for "wake up" from a general anesthetic and to be ready for extubation. In order for this process to be successful, a patient must have recovery of muscle function and residual neuromuscular blockade should not be present. If there still remains residual neuromuscular blockade a patient may experience the following complications: respiratory failure, severe hypoxemia, airway obstruction, need for reintubation, increased risk of aspiration, generalized muscle weakness, difficulty swallowing, and difficulty speaking or drinking, prolonged recovery room stay, pneumonia, atelectasis.

Prior to FDA approval of sugammadex in 2015, the only drugs available to reverse neuromuscular blockade were anti-cholinesterase drugs, of which neostigmine is most commonly utilized. Neostigmine produces cholinergic side effects (e.g., bradycardia) and, therefore, needs to be administered concurrently with an anticholinergic drug (i.e., glycopyrrolate or atropine). Neostigmine has been shown to adequately reverse neuromuscular blockade in patients who have spontaneous recovery of at least one twitch in a train-of-four. Sugammadex offers a potential benefit over neostigmine, producing faster neuromuscular block reversal than neostigmine, as well as the ability to reverse deeper neuromuscular blockade than can be reversed with acetylcholinesterase inhibitors. Sugammadex, unlike neostigmine, does not inhibit acetylcholinesterase, therefore, cholinergic effects are not produced, and co-administration of an anticholinergic drug is not needed. Because co-administration of anticholinergic agents is not necessary with sugammadex, the use of sugammadex might be associated with fewer adverse effects than the use of traditional reversal agents. Also, since sugammadex can reverse profound levels of neuromuscular blockade, its availability could render the use of succinylcholine unnecessary. Succinylcholine has potentially serious adverse effects and a boxed warning regarding the risk of cardiac arrest in pediatric patients. Succinylcholine, the only available depolarizing agent also used for rapid intubation, carries the risk of side effects such as cardiac arrhythmias as well as the potential for rhabdomyolysis, hyperkalemia, and malignant hyperthermia, leading to the recommendation that succinylcholine is not to be used routinely in pediatric patients.

Study P169 evaluated the efficacy, safety, and pharmacokinetics of sugammadex in patients less than two years of age, which consisted of a Part A and Part B. The study objectives for Part A of the pharmacokinetics (PK) analyses were to (1) characterize PK parameter values following administration of 2- and 4-mg/kg sugammadex in pediatric participants aged from birth to <2 years; and (2) confirm the appropriateness of the 2- and 4-mg/kg doses for subsequent evaluation of sugammadex safety and efficacy for reversal of moderate and deep neuromuscular blockade (NMB), respectively, in pediatric participants aged

from birth to <2 years. The results of this study are summarized as follows: Study P169 demonstrated that in pediatric patients age birth to less than 2 years of age, sugammadex 2 mg/kg had a faster time to neuromuscular recovery when compared to neostigmine for the reversal of moderate neuromuscular blockade (1.4 minutes vs. 4.4 minutes). This was statistically significant with a p-value of 0.0021.

Clinical adverse events of special interest in Study P169, included clinically relevant bradycardia, hypersensitivity and anaphylaxis. Bradycardia is of particular concern in younger pediatric patients (i.e., birth to less than two years of age) as they may be most vulnerable to the effects of bradycardia compared to older pediatric patients and adults. In pediatric patients stroke volume (SV) is fixed due to less compliance of the myocardium, and therefore, cardiac output (CO) is heart rate (HR) dependent. Clinically relevant bradycardia, defined by the Applicant as any bradycardia event that occurs after administration of study treatment and requires intervention, as determined by investigator judgment. Treatment-emergent relative bradycardia was defined by the Applicant as a heart rate that decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment. In Study P169, events of clinically relevant bradycardia and treatment-emergent bradycardia were comparable among intervention groups (≤3 subjects per group). Treatment-emergent relative bradycardia occurred less frequently in the sugammadex groups (2 subjects per group) than in the neostigmine group (6 subjects). This is comparable to the data reviewed in older pediatric patients, with few events of clinically relevant bradycardia, and fewer events of treatment emergent and treatment emergent relative bradycardia in the sugammadex treatment groups compared to the neostigmine treatment group. Regarding anaphylaxis, the frequency of anaphylaxis was 0.3% in a randomized, double-blind adult study that examined the incidence of drug hypersensitivity reactions in healthy adult volunteers. In this adult study, the most common hypersensitivity adverse reactions reported were nausea, pruritus and urticaria and demonstrated a dose response relationship, occurring more frequently in the 16 mg/kg group compared to the 4 mg/kg and placebo groups. In Study P169 there were no adjudicated hypersensitivity or adjudicated anaphylaxis events reported at any timepoint, which also is comparable to the older pediatric age group with similar resulting data of no adjudicated cases of hypersensitivity or anaphylaxis in Study P089. Based on the information provided by the Applicant in the clinical study report, the Division concurs with this determination from the adjudication committee regarding hypersensitivity and anaphylaxis.

The benefit-risk assessment of sugammadex has been well-described in previous reviews that concluded with the approval of this product in both adult patients and pediatric patients from 2 to 17 years of age. The benefits of treating pediatric patients age birth to less than 2 years of age with sugammadex outweigh the risks due to the following six reasons:

1. TTNMR was faster in subjects who were administered sugammadex 2 mg/kg compared with neostigmine in the setting of moderate NMB; 1.4 minutes for sugammadex 2 mg/kg and 4.4 minutes for neostigmine (p=0.0021).
2. Sugammadex offers a potential benefit over neostigmine, producing faster neuromuscular block reversal than neostigmine, as well as the ability to reverse deep neuromuscular blockade.
3. Sugammadex, unlike neostigmine, does not inhibit acetylcholinesterase, therefore, cholinergic effects are not produced, and coadministration of an anticholinergic agent (glycopyrrolate or atropine) is not needed.
4. Because co-administration of anticholinergic agents is not necessary with sugammadex, the use of sugammadex might be associated with fewer adverse effects than the use of traditional reversal agents.
5. Sugammadex can reverse profound levels of neuromuscular blockade, and its availability could render the use of succinylcholine unnecessary.
6. Ability to avoid the use of succinylcholine (succinylcholine has potentially serious adverse effects and a boxed warning regarding the risk of cardiac arrest in pediatric patients).

The information provided in this supplement provides additional information to support the dose, efficacy, and safety that could be used in patients from birth to less than 2 years of age. Based on the totality of safety and efficacy information provided by the Applicant, the favorable benefit to risk ratio, and that no new safety signals were identified during Study P169 and postmarketing reports, the Division is granting approval to expand the pediatric dosing information for BRIDION to include pediatric patients from birth to less than 2 years of age for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide undergoing surgery.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Neuromuscular blockade, also referred to as muscle relaxation, is a component of many surgical procedures. Neuromuscular blockade provides muscle relaxation and reduces patient movement during surgical procedures that require minimal to no movement. This relaxation of muscles allows for optimal surgical conditions by improving visualization of the surgical field, and optimizing ventilation, which is critically important, especially during cranial, otolaryngology, cardiothoracic, laparoscopic, and abdominal surgeries. Neuromuscular blocking agents (NMBAs) are categorized into two types: depolarizing neuromuscular blocking agents (e.g., succinylcholine) and nondepolarizing neuromuscular blocking agents (e.g., rocuronium, vecuronium, atracurium, cisatracurium). Succinylcholine is the only available depolarizing agent. It is used for rapid sequence induction to secure the airway in patients with full stomachs, because it produces muscle paralysis rapidly within one minute. It also has a short duration of action, lasting several minutes, and requires no reversal agent to be given as it is eliminated by plasma cholinesterase and pseudocholinesterase. However, it has the risk of serious adverse events, such as cardiac arrhythmias, as well as the potential for rhabdomyolysis, hyperkalemia, and malignant hyperthermia, and according to the prescribing information, succinylcholine is not to be used routinely in pediatrics. Succinylcholine has a boxed warning that states that “ventricular dysrhythmias, cardiac arrest, and death from hyperkalemic rhabdomyolysis has occurred after use in apparently healthy pediatric patients.” Nondepolarizing muscle relaxants, such as rocuronium or vecuronium, are advantageous in pediatric anesthesia as intubation can occur within 45 seconds for most pediatric patients, but the duration of action can last 60 to 90 minutes. The depth of neuromuscular blockade (i.e., moderate, deep) and recovery is monitored using acceleromyography, also known as the train-of-four method. The depth of NMB can be monitored subjectively using a peripheral nerve stimulator device, which is most commonly used in clinical practice. The number of muscle twitches that occur after a peripheral nerve is stimulated indicates the percentage of blocked acetylcholine receptors at a neuromuscular junction, and therefore, can indicate to the clinician if the depth of neuromuscular blockade or recovery is adequate or not.	The importance of using a reversal agent to reverse NMB is to facilitate recovery of muscle function in order to breathe and prevent complications from occurring during extubation and recovery from anesthesia in the postoperative period. If residual neuromuscular blockade remains, either after a reversal agent is administered or not enough time is allowed for the neuromuscular blockade effects to wear off, a patient may experience the following complications: respiratory failure, severe hypoxemia, airway obstruction, need for reintubation, increased risk of aspiration, generalized muscle weakness, difficulty swallowing, and difficulty speaking or drinking, prolonged recovery room stay, pneumonia, atelectasis. Therefore, effective reversal of neuromuscular blockade is necessary to reduce the risks of untoward complications that can result from residual neuromuscular blockade.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The reversal of neuromuscular blocking drugs usually occurs at the end of a surgical procedure, in which the anesthesiologist prepares a patient for "wake up" from a general anesthetic and to be ready for extubation. In order for this process to be successful, a patient must have full recovery of muscle function and residual neuromuscular blockade should not be present.	
Current Treatment Options	In clinical practice, NMB reversal agents are typically administered at the end of a surgical procedure or after a period of intensive care to assist in the recovery of muscle function and to prevent residual neuromuscular block. The following reversal agents are available to reverse the effects of neuromuscular blockade: • Neostigmine • Sugammadex Neostigmine belongs to the class of drugs called acetylcholine esterase (AChE) inhibitors. Neostigmine inhibits acetylcholinesterase, the enzyme that metabolizes acetylcholine into choline and acetic acid, thereby allowing the buildup of acetylcholine at the neuromuscular junction to overcome the competitive inhibition of nondepolarizing blocking drugs. Neostigmine is indicated for the reversal of the effects of non-depolarizing neuromuscular blocking agents (NMBAs) after surgery and can be administered to all ages, including neonates and is administered to accelerate reversal of nondepolarizing neuromuscular blockade of nicotinic receptors located in the neuromuscular junction. This drug reverses neuromuscular blockade in patients who have spontaneous recovery of at least one twitch in a train-of-four, and therefore, is limited to the reversal of moderate NMB only. It does not reverse deep neuromuscular blockade. The AChE inhibitors have multiple side effects due to their nonselective potentiation of cholinergic neurotransmission, including significant side effects caused by increased acetylcholine concentrations outside the neuromuscular junction. Specifically, neostigmine produces cholinergic side effects (e.g., bradycardia hypotension, cardiac arrhythmias, abdominal cramps, bronchial constriction, increased salivation, vomiting, and diarrhea) and therefore, needs to be administered concurrently with an anticholinergic drug (i.e., glycopyrrolate or	The importance of using a reversal agent to reverse NMB is to facilitate the recovery of muscle function. This enables a patient to breathe spontaneously and maintain their own native airway at the end of surgery and prior to extubation. Adequate reversal prevents complications (e.g., respiratory distress, aspiration, airway obstruction, respiratory acidosis) in the immediate postoperative period. Although neostigmine is used as a reversal agent for neuromuscular blockade, it does have untoward side effects (i.e., bradycardia, serious reactions in patients with, coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myasthenia gravis). These adverse events can be especially important in younger pediatric patients whose cardiac output is heart rate dependent. Bradycardia in a young pediatric patient can quickly lead to cardiac arrest if not recognized and managed swiftly. Neostigmine is also contraindicated in patients with peritonitis or mechanical obstruction of the intestinal or urinary tract. Because neostigmine requires an anticholinergic drug to be concomitantly administered, the combination of the two (neostigmine and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	atropine). Although the concomitant administration of the anticholinergic decreases unwanted side effects, the anticholinergic drugs also may cause other side effects, such as tachycardia, dry mouth, cardiac arrhythmias, urinary retention, and blurred vision. According to the Prescribing Information (PI) for Neostigmine (BLOXIVERZ), which was most recently updated on October 27, 2023, there are serious reactions that may occur with certain coexisting conditions, such as coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myasthenia gravis. Prior to 2015, the only clinically available reversal agents were AChE inhibitors (neostigmine, edrophonium, and pyridostigmine). Sugammadex was approved by the FDA in 2015. Sugammadex is indicated for the reversal of neuromuscular blockade induced by rocuronium and vecuronium in adult and pediatric patients 2 years of age and older undergoing surgery. For pediatric patients less than two years of age, the only current treatment option available for reversal of neuromuscular blockade is neostigmine.	anticholinergic) is not always well-balanced and may lead to unwanted side effects. For example, the use of the anticholinergic can lead to tachycardia, dry mouth, cardiac arrhythmias, urinary retention, and blurred vision. In addition, it's not unusual for a younger pediatric patient to experience central nervous system (CNS) excitability when atropine is used with neostigmine, as atropine has the ability to cross the blood brain barrier due to its small molecular structure. This can make recovery from anesthesia challenging, especially for a young pediatric patient in the immediate post-operative period. At the present time, the only reversal agent approved for the reversal of neuromuscular blockade in pediatric patients less than two years of age is neostigmine.
Benefit	The benefits of sugammadex administration in pediatric patients from birth to less than 2 years of age undergoing surgery for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide include the following: • Produces faster neuromuscular blockade recovery than neostigmine • Ability to reverse deeper NMB than neostigmine • Less bradycardia than neostigmine • Can be administered as a sole reversal agent because no concomitant anticholinergic medication is required • May be associated with fewer adverse effects than the use of traditional reversal agents because cholinergic effects are not produced • May have the potential to limit the use of succinylcholine in pediatric patients	There are several benefits of sugammadex administration in the birth to less than 2 years of age pediatric population. The data from Study P-169 demonstrate that sugammadex is effective as a NMB reversal agent for the birth to less than 2-year-old population. The following benefits are noted: • Quicker time to neuromuscular recovery (TTNMR) with the use of sugammadex compared to neostigmine (1.4 minutes vs. 4.4 minutes) • Less bradycardia with sugammadex compared to neostigmine (4.5% vs. 9.7%)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		The approval of sugammadex in the birth to less than 2-year-old pediatric population may eliminate the need for succinylcholine. As stated above in the 'Analysis of Condition' Section, Succinylcholine is the only available depolarizing agent also used for rapid intubation. However, this paralytic drug carries the risk of side effects such as cardiac arrhythmias as well as the potential for rhabdomyolysis, hyperkalemia, and malignant hyperthermia, leading to the recommendation that succinylcholine is not to be used routinely in pediatrics, and has a black box warning that states that "ventricular dysrhythmias, cardiac arrest, and death from hyperkalemic rhabdomyolysis has occurred after use in apparently healthy pediatric patients" listed in the prescribing information. Having the ability to reverse deep levels of NMB would be beneficial to this youngest pediatric population by avoiding succinylcholine, as stated above, has many side effects, especially in the pediatric population. Unlike neostigmine, sugammadex acts completely independent of acetylcholine, thus avoiding associated autonomic side effects and obviating the need to administer a second agent to mitigate such effects. Therefore, sugammadex offers an important alternative to reversal of NMB in the practice of pediatric anesthesia. Because sugammadex is not contraindicated in coronary artery disease, cardiac arrhythmias, recent acute coronary syndrome or myasthenia gravis, as compared to neostigmine, it makes sugammadex a valuable treatment option in these

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		types of patients when clinician's need to choose a drug to reverse neuromuscular blockade. In addition, because this drug has been used off-label for many years in the pediatric population, clinicians are familiar with the benefits and risks, and will often choose this drug over approved drugs (e.g., neostigmine) based on adverse event profiles.
Risk and Risk Management	The primary risks associated with the administration of sugammadex include the following: • Vomiting • Pain • Nausea • Hypotension • Headache • Bradycardia Other risks associated with the administration of sugammadex, which occurred with an incidence of ≥2% in adult studies are: • Tachycardia • Bradycardia • Hypertension • Hypotension • Wound hemorrhage • Flatulence • Pyrexia • Chills • Dizziness • Myalgia • Insomnia • Anxiety • Pruritis • Erythema	Because sugammadex has been widely used (off-label) in the pediatric population, the risks of administration of sugammadex are well known and well-described in the published literature. Due to the known adverse events associated with the administration of sugammadex, risk mitigation strategies include administration by a trained anesthesia provider, adequate hemodynamic and cardiac monitoring, and immediate availability of emergency airway equipment and resuscitation medications. Clinicians should be vigilant about recognizing and managing the occurrence of serious adverse events, specifically bradycardia, hypersensitivity and anaphylactic reactions, during the perioperative period.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In pediatric patient studies age 2 to <17 years of age, according to the prescribing information for BRIDION, the following adverse events were reported with an incidence of ≥5% up to 7 days post-treatment: • Pain • Bradycardia • Vomiting • Nausea	

2. Background

This review will provide an overview of the regulatory and scientific facts of this supplemental application and issues that were identified during the course of the review of the submission. Aspects that will be discussed include the regulatory history, the adequacy of the data to support the supplemental application in terms of safety and efficacy, and the labeling requested by the Applicant. This review will also serve as the CDTL review and the Division Summary Review.

Sugammadex, also known as Org25969, is a neuromuscular blocking agent of the γ-cyclodextrin class. It was designed, by selective addition of functional groups around the structure, to bind rocuronium and vecuronium. It consists of ring-like structure with a lipophilic core and a hydrophilic outer surface. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center, and then held in place by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of the neuromuscular blocking agent from the neuromuscular junction will in effect reverse the paralysis.

Bridion® (sugammadex) injection was first approved on December 15, 2015, for reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery. At the time of approval, the following Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA), PMR 3003-1, was issued, which was a requirement to assess the efficacy and safety of sugammadex when used in pediatric patients.

PMR 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.

There were two Release from Postmarketing Requirement/New Postmarketing Requirement Letters issued: one on April 19, 2018, and one on July 11, 2018. The reasons for this release are described below:

April 19, 2018	The Applicant was released from PMR 3003-1. The Division determined that three studies were needed to attain information for the safe and effective use of sugammadex in the pediatric population. Specifically, the Division determined that the original PMR did not specify testing the higher dose regimen that is needed in some clinical scenarios. Three clinical PMRs were issued, 3003-5, 3003-6, and 3003-7, to evaluate sugammadex administration in the pediatric population.

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.

July 11, 2018	Regarding PMRs 3003-5 and 3003-6, typographical errors were made in the milestone dates in the April 19, 2018, Letter, and PMRs 3003-8 and 3003-9 were issued to replace PMRs 3003-5 and 3003-6.

Regarding PMR 3003-7, the Division determined there were practical and ethical difficulties in studying the 16 mg/kg dose in the pediatric population. Specifically, the Division determined that an evaluation of 16 mg/kg dose would not generate clinically meaningful data, and possibly expose children to greater than minimal risk. Therefore, PMR 3003-7 was released and was not replaced at that time.

The current PREA PMR for this NDA is as follows:

PMR 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.

Final Protocol Submission: 07/2018
Study Completion: 02/2023
Final Report Submission: 06/2024

In addition to the PMR, a Pediatric Written Request (PWR) was issued on October 28, 2016, based on the Sponsor's Proposed Pediatric Study Request dated July 1, 2016. The proposed pediatric studies under the PWR are intended to investigate the potential use of sugammadex in the treatment of reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients 0 to <17 years old. There were five amendments to the PWR, as noted below:

#1	May 24, 2017	Revisions to separate the protocols supporting the WR into two studies: Study Protocol 089 for 2 to less than 17 years old and Study Protocol 169 for birth to less than 2 years old.
#2	January 22, 2019	Revisions to remove the 16 mg/kg study dose. The Division had determined there were practical and ethical difficulties in studying the 16 mg/kg dose in the pediatric population. Specifically, the Division determined that an evaluation of 16 mg/kg dose would not generate clinically meaningful data, and possibly expose children to greater than minimal risk. Therefore, PMR 3003-7 was released and was not replaced at that time.
#3	November 23, 2019	Revisions of the study protocol that were minor.
#4	October 30, 2020	Revisions to change the primary efficacy endpoint for Part B of Study 2 to "time to neuromuscular recovery," defined as the interval from administration of reversal agent to time to neuromuscular recovery. Time to extubation, defined as the interval from administration of reversal agent to removal of the endotracheal tube, is now a secondary efficacy endpoint.
#5	August 30, 2023	Revisions to change the timeframe for submitting reports of the studies.

The following study was conducted to fulfill PMR 3003-9 and satisfy the PWR.

Study MK-8616 (Protocol 169-02 [Study P169]:
A Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to < 2 Years.

Study P169 was initiated on July 23, 2019, with the primary objective to describe the pharmacokinetic (PK) parameters of sugammadex when used for reversal of moderate neuromuscular blockade or deep neuromuscular blockade (Part A) and to evaluate the time to neuromuscular recovery of sugammadex in comparison to neostigmine for the reversal of moderate neuromuscular blockade (Part B). On November 2, 2022, the Division received Protocol amendment two.

On June 25, 2021, Supplement 8 was approved, and PMR 3003-8 was fulfilled. This expanded the indication in the prescribed labeling for BRIDION to include pediatric patients two years of age and older.

The pediatric program for BRIDION was comprised of three pediatric studies:

- Study P034
- Study P089
- Study P169

Study P034 was a multicenter, randomized, parallel dose-finding, safety-assessor blinded, placebo-controlled study designed to investigate four doses of sugammadex (0.5, 1.0, 2.0, and 4.0 mg/kg) and placebo for the reversal of rocuronium-induced (0.6 mg/kg) moderate NMB ("at the reappearance of T2") at different age groups of pediatric subjects. The study assessed children and adolescents across three age categories (infants- 28 days to 23 months, children- 2 to 11 years, and adolescents- 12 to 17 years). This study provided preliminary evidence that the intended doses (2 mg/kg and 4 mg/kg) would exhibit comparable exposures in the pediatric age cohorts when compared with adults.

Study P089 was a Phase 4, double-blind, randomized, active comparator-controlled, multicenter study that evaluated the efficacy, safety, and pharmacokinetics of sugammadex for reversal of neuromuscular blockade in pediatric patients aged 2 to less than 17 years of age, and was conducted to fulfill the requirements of PMR 3003-8. The results of Study P089 demonstrated that in pediatric patients aged 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.

Study P169 was conducted to further characterize the efficacy, safety, and PK of sugammadex in patients less than two years of age, which consisted of a Part A and Part B. The study objectives for Part A of the PK analyses were to (1) characterize PK parameter values following administration of 2- and 4-mg/kg sugammadex in pediatric participants aged from birth to <2 years; and (2) confirm the appropriateness of the 2- and 4-mg/kg doses for subsequent evaluation of sugammadex safety and efficacy for reversal of moderate and deep NMB, respectively, in pediatric participants aged from birth to <2 years. Pharmacokinetic samples were only collected for Part A of Study P169. This study was initiated on July 23, 2019. Details of the results of this study are located in Section 7 (Clinical/Statistical – Efficacy) and Section 8 (Safety) of this review document.

The Applicant submitted this supplement, S-014, on June 12, 2024, with the results of Study P169, which evaluated the efficacy, safety, and pharmacokinetics of sugammadex for the reversal of neuromuscular blockade in pediatric patients from birth to less and 2 years of age. The Applicant included an analysis of the results from Study P169, and their proposal for text for the package insert.

The following two tables, Table 1 and Table 2, provide summaries of key regulatory events that occurred during both the IND and NDA phases for BRIDION:

Table 1 Summary of Key Regulatory Events for IND 068029

Date	Communication Type	Key Event:
Feb. 13, 2013	Submission of the pediatric study plan	Submission included deferral request
July 1, 2016	Letter to Sponsor	Proposed Pediatric Study Request for BRIDION (sugammadex sodium injection), 100 mg/mL; intended to obtain 6-month exclusivity under BPCA
Sept. 8, 2016	Information Request	Proposed Pediatric Study Request (PPSR) - Clarification on location in submission of query of pediatric anesthesiologists (questions, responses) - Provide rationale for why premature infants, i.e., infants of a gestational age less than 37 weeks, are being excluded from your study. - Provide information on how primary efficacy endpoint "time to readiness for extubation" will be reproducible between different investigators. - Provide information on use of NMB in Pediatric Intensive Care Unit (PICU) and Neonatal Intensive Care Unit (NICU)
Oct. 28, 2016	Pediatric Written Request (PWR) issued to Applicant	Letter sent to Sponsor - FDA issued a WR to formally investigate the potential use of sugammadex in the treatment of reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients, birth to less than 17 years of age
Jan. 31, 2017	Sponsor requested amendment to the WR	WR Amendment #1
May 24, 2017	FDA granted Amendment to the WR	Amendment #1 separated the pediatric study protocols supporting the WR into two studies (P089 for 2 to less than 17 years old and P169 for birth to less than 2 years old)
Jan. 29, 2018	Sponsor submitted protocol to address the PMR 3003-09	FDA considered the Protocol for P169 complete on July 11, 2018
Oct. 19, 2018	Sponsor submitted Amendment (#2) to the PWR	To update the study designs of the 2 PMR studies
Jan. 11, 2019	Sponsor submitted Study Protocol P089 (Part A)	Part A of Protocol P089 submitted 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.
Jan. 22, 2019	FDA updates the PWR	For Amendment #2 to reflect changes to the interim pharmacokinetic and safety analysis for Part A of Study P089
Feb. 5, 2019	Study P169	Original study protocol submitted to the Division
Feb. 19, 2019	Advice Letter sent to Sponsor	Re: Sponsor must increase the dose to establish adequate PK matching in the 2- to 6-year-old cohort.
Apr. 9, 2019	Response from Sponsor received	The Sponsor 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. The Division determined this to be an acceptable approach.
July 17, 2019	Sponsor submitted Amendment, #3, to the PWR	To update the study objectives of the 2 PMR studies
July 23, 2019	Study P169 initiated	**Study MK-8616 (Protocol 169-02 [Study P169]):** *A Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to < 2 Years.*

Date	Communication Type	Key Event:
Mar. 17, 2020	Amendment to Study P169 Protocol	• Study endpoint of "time to neuromuscular recovery" moved to primary efficacy endpoint. • Study endpoint of "time to extubation" moved to secondary efficacy endpoint. • Protocol updated to assist sites with managing participant assignment in the case of delayed or rescheduled surgeries or clinical procedures
July 27, 2020	Sponsor submitted Amendment (#4) to PWR	To update the study design of P169
Aug 26, 2020	NDA Supplement 008 submission	Sponsor submitted NDA Supplement 008 for review with completed Study P089, for Section 8 of the labeling for pediatric patients; intent to fulfill PMR 3003-8.
Oct. 30, 2020	FDA updates the PWR	FDA updates the PWR for Amendment #4
Mar. 31, 2023	Sponsor submitted a Type D meeting request and background package	To discuss ending P169 prior to completion of subject enrollment in youngest age cohort
June 13, 2023	Teleconference	• The Division met via teleconference with the Sponsor to discuss the status of Study P169 and the possibility of ending enrollment in the youngest age cohort due to enrollment challenges. • The Sponsor also requested concurrence that this amended study will satisfy both PMR 3003-9 and the PWR when completed with the final report submission. • The Division did not agree with ending enrollment in the study as data from the target number of subjects are required to support the safe and efficacious use of sugammadex in the youngest pediatric patients, and to continue to enroll the study to completion. • The Division recommended that the Sponsor submit a PWR amendment with a proposal to extend the final study report submission date (currently August 31, 2023), noting that the final study report must be submitted 15 months prior to the existing exclusivity or patent expiration to support additional exclusivity.
June 23, 2023	Sponsor submitted Amendment (#5) to PWR	Sponsor submitted Pediatric Deferral Extension (DE) Request to complete Study P169 and Timeline Extension Request for the Pediatric Written Request
Aug. 29, 2023	DE request	The Pediatric Review Committee (PeRC) agreed with Division's recommendation to grant DE request and proposed timeline extension for PWR
Aug. 30, 2023	PWR Amendment #5	FDA updates PWR for Amendment #5 with extended timelines
Sept. 1, 2023	Communication to Sponsor	The Division granted the DE request for PMR 3003-9 and timeline extension request for PWR. Division proposed an extension of 10 months: Study Completion: December 2023 Final Report Submission: June 2024

Table 2 Summary of Key Regulatory Events for NDA 022225

Date	Communication Type	Key Event:
Dec. 15, 2015	NDA Approval	Approval of original NDA PMRs 3003-1, 3003-2, 3003-3, 3003-4 were issued
Jan. 13, 2017	Revised Written Request (WR) submitted	Revised Written Request submitted, proposed changes included: • Conduct two-part studies to include a pharmacokinetic component as well as efficacy and safety at 3 doses of sugammadex: 2 mg/kg, 4 mg/kg and 16 mg/kg
May 24, 2017	PWR Amendment	PWR Amendment #1 issued
Apr. 19, 2018	PMR update	Applicant was released from PMR 3003-1 Three PMRs were issued to replace PMR 3003-1 • 3003-5 • 3003-6 • 3003-7
July 11, 2018	PMR Update	The Division concurred with Applicant's position that studying the 16 mg/kg dose of sugammadex was not feasible or ethical in pediatric subjects. Applicant was issued a PMR Release and Reissue Letter • Released of PMR 3003-7 • New letter included two PMRs 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.
Aug. 26, 2020	PWR	Annotated Pediatric Written Request (PWR) for Study 1 (MK-8616-089; P089) submitted to the Agency
June 25, 2021	Approval of Supplement 8 and fulfillment of PMR 3003-08	Approval of pediatric labeling update to expand indication to include children ages 2 to 17 years of age. 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.
June 23, 2023	Applicant correspondence	Pediatric Deferral Extension Request (PREA Study) and Timeline Extension Request for the Pediatric Written Request
Aug. 30, 2023	PWR Amendment 5	PWR Amendment 5

Date	Communication Type	Key Event:
June 12, 2024	Applicant submitted Supplement 14	Intent to fulfill: • PMR 3003-9 • PWR • Expand indication down to birth
June 20, 2024	IR sent to Applicant	Requested Applicant to provide the associated efficacy data as median values of time to neuromuscular recovery in minutes for each treatment arm at each site, but not the number of events for the endpoint.
June 27, 2024	Response to IR received from Applicant	The Applicant submitted the requested data in Module 5.3.5.4
July 5, 2024	IR sent to the Applicant	**RE: Pediatric Exclusivity Determination request:** Requested Applicant to complete Annotated Written Request (WR) template.
July 16, 2024	Response received from Applicant to our IR sent July 5, 2024	Applicant provided the Division with information requested - updated template.
Aug. 19, 2024	Filing Communication	NDA filed 74-Day Letter sent to Applicant No filing review issues identified
Sept. 10, 2024	IR sent to Applicant	Requested Applicant to combine Study 1 (P-089) and Study 2 (P-169) into one document for the Annotated Written Request Template
Sept. 13, 2024	IR Response received from Applicant to our IR sent Sept. 10, 2024	Applicant requested an extension to submit Annotated Written Request Template. Extension request granted - document due by Sept. 20, 2024
Sept. 20, 2024	Response received from Applicant to IR sent Sept. 10, 2024.	Applicant provided an updated Annotated Written Request Template that included both Study 1 (P089) and Study 2 (P169) on one document.
Oct. 10, 2024	Statistics IR sent to Applicant	Recommendation sent to the Applicant to revise Table 14.2-1, Table 14.2-2, and Table 14.2-3 of the Clinical Study Report (CSR) for Study 169 submitted on June 12, 2024, to report p-values from your primary analyses that are based on the Cox regression models instead of from log rank tests from supportive analyses
Oct. 11, 2024	Clinical IR sent to Applicant	Requested Applicant to clarify data on residual NMB and recurrence of NMB
Oct. 14, 2024	Response to Clinical IR received from Applicant	The Applicant clarified the following: • Per Study Protocol MK-8616-169-02, reporting of spontaneous adverse events (AE) of recurrence should occur and this was monitored through routine medical monitoring. • During Investigator Meetings, study procedures were reviewed with sites and investigators, that residual NMB, recurrence of NMB, and adverse respiratory events (e.g., hypercapnia, dyspnea, hypoxia, and distress) should be collected via standard AE reporting. • No AEs of recurrence were reported by investigators for any subject
Oct. 16, 2024	Response to Statistics IR received from Applicant	The Applicant submitted to the Division updated tables regarding the requested information associated with the p-values from the primary analyses.

3. Product Quality

There was no new information submitted during this review cycle related to product quality.

4. Nonclinical Pharmacology/Toxicology

There were no pharmacology/toxicology data submitted with this supplement.

5. Clinical Pharmacology

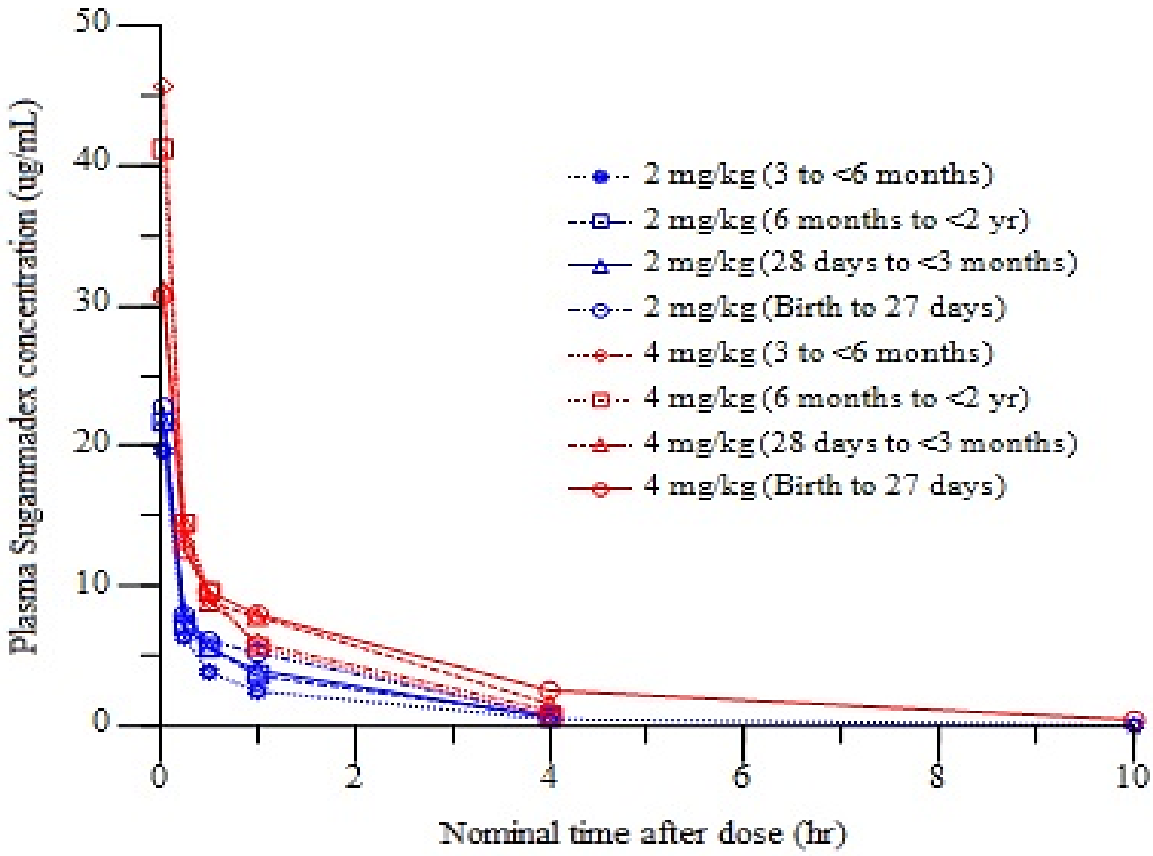
The following is a summary of the review completed by Drs. Srikanth C. Nallani, Deep Kwatra, and Mehul U. Mehta, dated November 19, 2024. For full details please refer to their completed review in DARRTS.

The PK analysis dataset included 47 subjects enrolled in Part A of Study P169 distributed across age categories and sugammadex treatments, contributing a total of 249 evaluable PK sample with more than 9 subjects included in each age cohort meeting the enrollment expectations for Part A of the trial.

The following figures (Figure 1 and Figure 2) and table (Table 3) from the Clinical Pharmacology review, are included here to summarize the PK profiles of sugammadex, individual values overlaid with Geometric mean (GM) values and corresponding 95% CIs for Cmax, and the descriptive statistics of the PK parameter estimates by treatment group.

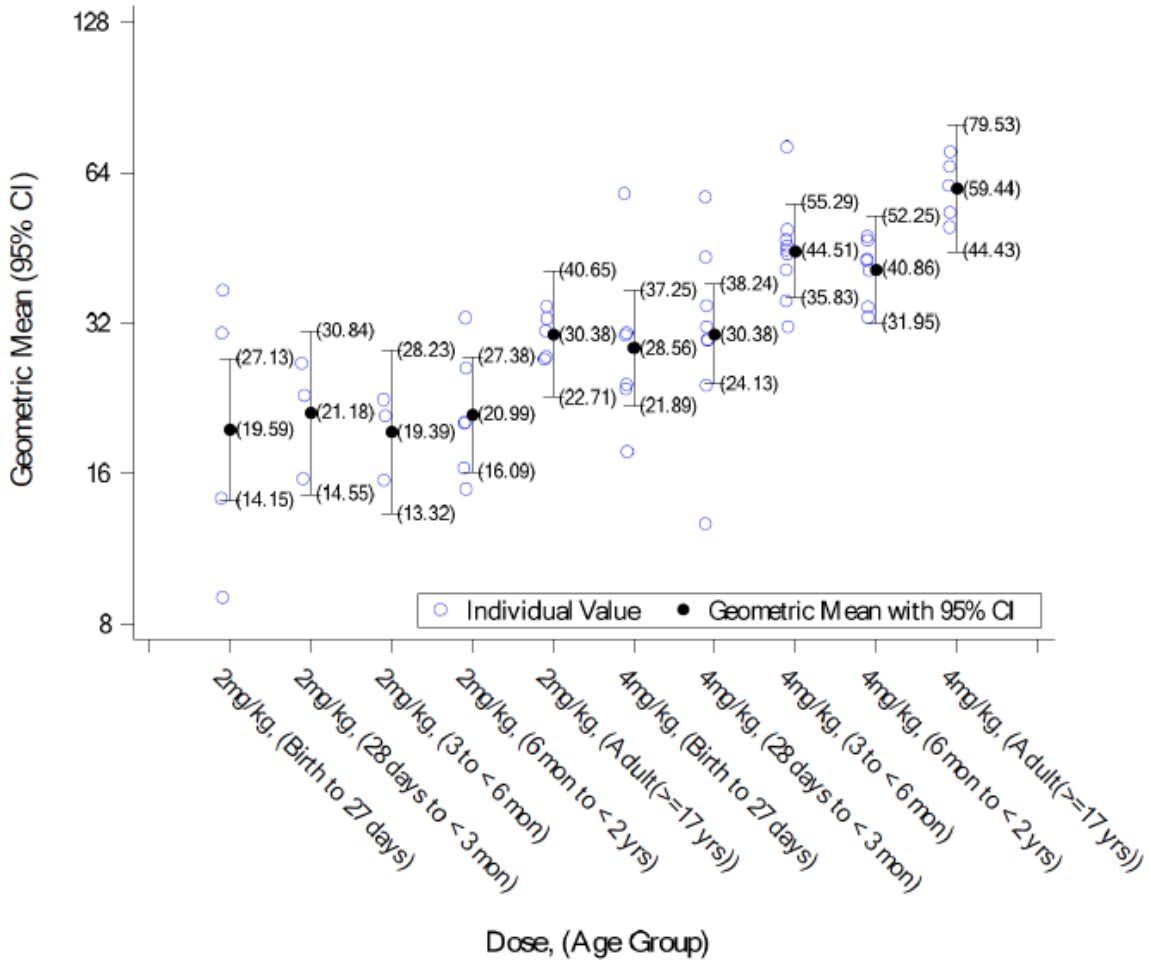
In Figure 1, below, the plasma concentration profiles of sugammadex following a single IV dose of 2 or 4 mg/kg administered in subjects grouped according to dose level and age.

Figure 1 Plasma Concentration Profiles of Sugammadex



In the following figure, Figure 2, below, Cmax (mcg/mL) values of sugammadex from Study P169 are following a single IV dose of 2 or 4 mg/kg administered in pediatric subjects from Study P169 (Grouped by dose level and age cohorts (Birth to 27 days, 28 days to <3 months, 3 months to < 6 months, and 6 months to < 2 years). The pediatric PK data are compared to adult PK data from Study P034, which was previously reviewed in a prior supplement from the Applicant. As stated in the Clinical Pharmacology review, "while the PK parameters in the pediatric patients were precise, it can be noted that Cmax and AUC are lower in these groups compared to adults (cross study) and "review of safety and efficacy data from Part A of the Study 2/P169 revealed that 2 mg/kg and 4 mg/kg doses can be evaluated in Part B."

Figure 2 Comparison of Cmax values from Study P169 and Study P034



y-axis values are logarithmically spaced.
CI=confidence interval; Cmax=maximum concentration; PK=pharmacokinetic; IV=intravenous.
Note: All PK parameters except for Cmax for one participant in 2mg/kg dose group (birth to 27 days) with an atypical concentration profile were excluded.

The following table below contains summary statistics of plasma PK parameters of sugammadex following a single IV dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric patients (P169, Part A: Birth to 27 days, 28 days to <3 months, 3 months to <6 months, and 6 months to <2 years).

Table 3 Summary Statistics of Plasma Pharmacokinetic Parameters of Sugammadex

Parameters	2 mg/ kg			4 mg/ kg		
	N	GM	95% CI	N	GM	95% CI
Birth to 27 days						
AUC0-inf (hr*µg/mL)[a]	2	13.40		6	39.09	(31.85, 47.98)
AUC0-1hr (hr*µg/mL)[a]	3	6.95	(5.38, 8.99)	6	12.38	(10.33, 14.85)
AUC0-4hr (hr*µg/mL)[a]	2	10.68		6	27.79	(22.95, 33.64)
Cmax (µg/mL)[a]	4	19.59	(14.15, 27.13)	6	28.56	(21.89, 37.25)
CL (L/hr)[a]	2	0.43		6	0.35	(0.28, 0.45)
Vd (L)[a]	2	1.14		6	1.22	(0.98, 1.52)
Vss (L)[a]	2	1.04		6	1.11	(0.92, 1.34)
Tlast (hr)[b]	3	4.54	(1.62, 10.00)	6	10.20	(4.16, 11.74)
MRT (hr)[c]	2	2.43		6	3.13	28.62
t1/2 (hr)[c]	2	1.84		6	2.39	27.34
28 days to <3 months						
AUC0-inf (hr*µg/mL)[a]	3	16.22	(12.14, 21.67)	6	31.90	(25.99, 39.16)
AUC0-1hr (hr*µg/mL)[a]	3	7.63	(5.90, 9.87)	7	14.39	(12.16, 17.02)
AUC0-4hr (hr*µg/mL)[a]	3	13.99	(10.67, 18.33)	6	27.16	(22.43, 32.89)
Cmax (µg/mL)[a]	3	21.18	(14.55, 30.84)	8	30.38	(24.13, 38.24)
CL (L/hr)[a]	3	0.66	(0.47, 0.92)	6	0.61	(0.48, 0.78)
Vd (L)[a]	3	1.45	(1.06, 1.98)	6	1.35	(1.08, 1.68)
Vss (L)[a]	3	1.23	(0.94, 1.60)	6	1.18	(0.98, 1.43)
Tlast (hr)[b]	3	5.23	(4.00, 10.91)	7	4.30	(1.00, 5.60)
MRT (hr)[c]	3	1.86	22.30	6	1.94	20.83
t1/2 (hr)[c]	3	1.52	20.21	6	1.53	16.42
3 to <6 months						
AUC0-inf (hr*µg/mL)[a]	3	11.50	(8.61, 15.37)	8	24.75	(20.73, 29.56)
AUC0-1hr (hr*µg/mL)[a]	3	6.10	(4.72, 7.88)	9	13.46	(11.61, 15.61)
AUC0-4hr (hr*µg/mL)[a]	3	10.13	(7.73, 13.27)	8	21.51	(18.23, 25.39)
Cmax (µg/mL)[a]	3	19.39	(13.32, 28.23)	9	44.51	(35.83, 55.29)
CL (L/hr)[a]	3	1.28	(0.91, 1.80)	8	0.97	(0.79, 1.19)
Vd (L)[a]	3	2.68	(1.96, 3.67)	8	2.16	(1.78, 2.62)
Vss (L)[a]	3	2.07	(1.59, 2.70)	8	1.69	(1.43, 1.98)
Tlast (hr)[b]	3	4.10	(4.05, 9.99)	10	4.50	(1.01, 11.12)
MRT (hr)[c]	3	1.62	31.73	8	1.74	27.64
t1/2 (hr)[c]	3	1.45	28.57	9	1.51	28.79
6 months to <2 years						
AUC0-inf (hr*µg/mL)[a]	5	14.07	(11.24, 17.61)	5	27.75	(22.17, 34.74)
AUC0-1hr (hr*µg/mL)[a]	6	7.31	(6.09, 8.76)	7	13.92	(11.76, 16.46)
AUC0-4hr (hr*µg/mL)[a]	5	12.57	(10.19, 15.50)	6	22.43	(18.52, 27.15)
Cmax (µg/mL)[a]	6	20.99	(16.09, 27.38)	7	40.86	(31.95, 52.25)
CL (L/hr)[a]	5	1.34	(1.03, 1.74)	5	1.27	(0.98, 1.65)
Vd (L)[a]	5	2.70	(2.11, 3.44)	5	2.77	(2.17, 3.53)
Vss (L)[a]	5	2.14	(1.74, 2.63)	5	2.18	(1.77, 2.68)
Tlast (hr)[b]	6	4.54	(1.03, 9.98)	7	5.19	(1.15, 10.00)
MRT (hr)[c]	5	1.60	17.99	5	1.71	23.47
t1/2 (hr)[c]	5	1.40	24.25	5	1.51	19.46

AUC0-1hr=area under the concentration-time curve from 0 to 1 hour; AUC0-4hr=area under the concentration-time curve from 0 to 4 hours; AUC0-inf=area under the concentration-time curve from 0 to infinity; CI=Confidence interval; CL=clearance ; Cmax=maximum concentration; GM=Geometric least-squares mean; MRT=Mean residence time ; Tlast= time of last measurable concentration; t1/2=half-life; Vd=apparent volume of distribution at terminal elimination phase; Vss=apparent volume of distribution at steady state.

Note: AUC0-inf and AUC0-1hr are model based in P034. AUC0-inf and AUC0-1hr are based on NCA for P169. Cmax is based on NCA for both P034 and P169.

N represents the number of participants with at least 4 evaluable PK samples per participant (as per protocol).

[a]Back-transformed least squares mean and CI from linear fixed effects model performed on natural log-transformed values.

[b]Median and range are provided.

[c]Geometric mean and geometric percent coefficient of variation are provided.

Note: All PK parameters except for Cmax for one participant in 2mg/kg dose group (Birth to 27 days) with an atypical concentration profile were excluded.

Source: NDA 022225/S-014, Summary of Clinical Pharmacology Studies, p. 22-23

The Clinical Pharmacology team made the following conclusions based on the PK results from Study P169:

- **Sugammadex PK data collected from pediatric participants birth to <2 years old in Part A of P169 permitted acceptable characterization of sugammadex PK parameter values when used for reversal of moderate or deep NMB. No dose dependent-trends or relevant deviations from dose linearity were observed. Additionally, sugammadex PK along with efficacy confirmed that no further PK data were required in Part B of P169.**

- **Sugammadex exposures (Cmax, AUC0-1hr) were broadly comparable for the age cohorts' birth to 27 days, 28 days to <3 months, 3 months to <6 months and 6 months to <2 years in comparison to next older age cohorts receiving equivalent sugammadex doses (2 mg/kg and 4 mg/kg).**

- **Based on both PK considerations evaluated in Part A, treatment with 2 or 4 mg/kg for reversal of moderate or deep block, respectively, in pediatric participants birth to <2 years old was supported in Part B of the study.**

- **PREA PMR 3003-09 is adequately addressed from a clinical pharmacology perspective.**

- **Sponsor has adequately addressed clinical pharmacology requirements specified in PWR in Part A of Study P169.**

The Division concurs with the assessment made by the Clinical Pharmacology review team.

6. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this supplemental application.

7. Clinical/Statistical- Efficacy

Overview of the Clinical Program

Sugammadex has been extensively evaluated in 62 completed clinical studies with a total of 6828 exposures to IV sugammadex in 5283 unique individuals and has a well-characterized safety and efficacy profile in adult and pediatric patients 2 to <18 years old, as stated by the Applicant in Section 1.5, p.9, of their Clinical Overview in their NDA 022225 supplement 14.

Three pediatric clinical studies have been completed to date:

- Study P034 (completed in 2009)
- Study P089 (completed in 2020)
- Study P169 (completed in 2024)

Study P034 was a multicenter, randomized, parallel dose-finding, safety-assessor blinded, pharmacokinetic study designed to investigate sugammadex across a dose range of 0.5 mg/kg to 4 mg/kg in three pediatric age cohorts: infants (28 days to 23 months inclusive [n = 8]); children (2 to 11 years inclusive [n = 26]); and adolescents (12 to 17 years inclusive [n = 30]). Although limited, the pediatric data from this study provided preliminary evidence that the intended doses (2 mg/kg and 4 mg/kg) would exhibit comparable exposures in the pediatric age cohorts when compared with adults, and that 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.

Study P089 was a Phase 4, double-blind, randomized, active comparator-controlled, multicenter study that evaluated the efficacy, safety, and pharmacokinetics of sugammadex for reversal of neuromuscular blockade in pediatric patients aged 2 to less than 17 years of age, and was conducted to fulfill the requirements of PMR 3003-8. The results of Study P089 demonstrated that in pediatric patients aged 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 and that routine sugammadex doses approved for adults (2 mg/kg and 4 mg/kg) were appropriate for pediatric subjects 2 to <17 years of age. According to the clinical review completed by Dr. Susan Yost on August 26, 2020, the following information regarding drug exposure and dose selection is noted (verbatim):

> **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 Cmax 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.**

Study P169 was a Phase 4, double-blind, randomized, active comparator-controlled, multicenter study, that was conducted to further characterize the efficacy, safety, and PK of sugammadex in patients less than two years of age, which consisted of a Part A and Part B. The study objectives for Part A of the PK analyses were to (1) characterize PK parameter values following administration of 2- and 4-mg/kg sugammadex in pediatric participants aged from birth to <2 years; and (2) confirm the appropriateness of the 2- and 4-mg/kg doses for subsequent evaluation of sugammadex safety and efficacy for reversal of moderate and deep NMB, respectively, in pediatric participants aged from birth to <2 years. Part A was subdivided into Panel 1 and Panel 2, as subjects were randomized to one of two groups in a 1:1 ratio, to evaluate two doses of sugammadex, to reverse moderate block. Panel 1 received sugammadex 2mg/kg to reverse moderate neuromuscular blockade, and Panel 2 received sugammadex 4 mg/kg to reverse deep neuromuscular blockade. Part B assessed the safety and efficacy of two doses of sugammadex (2 mg/kg and 4 mg/kg). In Part B of the study, sugammadex 2 mg/kg was compared to the active comparator neostigmine for the reversal of moderate neuromuscular blockade. This study was initiated on July 23, 2019.

Both Study P089 and Study P169 were multicentered studies, conducted at 39 centers in the following 12 countries: Australia, Belgium, Brazil, Denmark, Finland, France, Hungary, Malaysia, Mexico, Netherlands, Russian Federation, and the U.S.

On June 13, 2023, a teleconference between the Applicant and the Division was held to discuss the Applicant's proposal to end enrollment for the youngest age cohort (birth to 27-day olds) in Study P169. The Applicant discussed the hardships with attaining the required number of subjects due to the following factors:

- Unforeseen closures of study sites
- Political conflicts in Russia
- COVID-19 pandemic
- Logistical challenges with enrolling subjects in youngest age cohort

The Division acknowledged the difficulty with enrollment, however, the Division expressed concerns that the required number of subjects, especially in this youngest age cohort, is necessary, as the data may provide additional information to inform the safety for pediatric dosing. Therefore, the Division recommended to the Applicant that enrollment continue in the youngest age cohort to fulfill the required number of subjects. Per the Applicant's request, the PWR was amended to propose a change to the timeframe for submitting reports of the studies. The Applicant was successful with obtaining the required number of subjects for Study P169 and submitted the full clinical study report by June 27, 2024, the deadline written in the PWR Amendment #5.

Study Design of Study P169

Nonclinical Studies:
Based on review of the available non-clinical toxicology, no additional animal studies were required to support the clinical studies as described in Written Request Amendment 5.

Clinical Study:
The full title of Study P169 is "A Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years."

Study P169 was designed in two parts, Part A and Part B. Part A assessed PK and identified two doses of sugammadex to be used in Part B. Part A was further subdivided into Panel 1 and Panel 2, as subjects were randomized to one of two groups in a 1:1 ratio. Panel 1 received sugammadex 2mg/kg to reverse moderate neuromuscular blockade, and Panel 2 received sugammadex 4 mg/kg to reverse deep neuromuscular blockade.

Part B assessed safety and efficacy of the two doses of sugammadex (2mg/kg and 4 mg/kg). Subjects were randomized to the following groups in a 1:1:1 ratio:

- moderate block and reversal with 2 mg/kg sugammadex,
- moderate block and reversal with neostigmine + glycopyrrolate or atropine sulfate
- deep block and reversal with 4 mg/kg sugammadex

Moderate blockade with reversal of sugammadex 2 mg/kg dose was compared to the active control Neostigmine + glycopyrrolate or atropine. No active comparator was used for the sugammadex 4 mg/kg, as no active comparator exists to reverse deep neuromuscular blockade.

Randomization was stratified by age, beginning with the oldest age cohort (6 months to <2 years, 3 months to <6 months, 28 days to <3 months, and birth to 27 days) and NMBA (rocuronium or vecuronium).

The primary efficacy endpoint for Part B of Study P169 was "time to neuromuscular recovery," defined as the interval from administration of reversal agent to time to neuromuscular recovery. Time to neuromuscular recovery (TTNMR) was assessed using a Neuromuscular Transmission Monitoring (NMTM) device to monitor for moderate neuromuscular blockade (spontaneous recovery of T2 in a TOF) and deep blockade (at least 1 to 2 post-tetanic counts and no twitch responses to a TOF). Study P169 was designed to evaluate superiority of sugammadex to the active control arm (neostigmine) for the primary efficacy endpoint in subjects who were administered reversal for moderate neuromuscular blockade.

The secondary efficacy endpoint, time to extubation, was defined as the interval from administration of reversal agent to removal of the endotracheal tube.

The exploratory endpoints are listed as the following: The time to OR discharge, PACU discharge, and hospital discharge.

Results of Study P169

Primary Efficacy Endpoint

An assessment of the results of the primary efficacy endpoint is provided in the Statistical Team review and evaluation completed by Junyi Zhang, PhD (Primary Reviewer), Xinyu Tang, PhD, and Sue Jane Wang, PhD, completed on November 14, 2024. A summary of the analyses of the primary efficacy endpoint taken from the review by the Statistical Team is included in this section of the review for completeness. The Statistical Team concurred with the Applicant's statistical analyses performed, as the results from the supportive analysis and sensitivity analysis were consistent with the primary analysis findings.

Primary analyses for the primary efficacy endpoint:

Table 4 below, summarizes the results from the primary analysis for the primary efficacy endpoint, including the number of treated participants in Part B, the number of events, Kaplan-Meier estimate, hazard ratio (95% CI), and p-value. Based on Cox PH model, TTNMR was significantly faster (p=0.0021) in the sugammadex group compared with the neostigmine group (hazard ratio = 2.40, 95% CI: 1.37, 4.18).

Table 4 Primary Analysis Results of Primary Endpoint

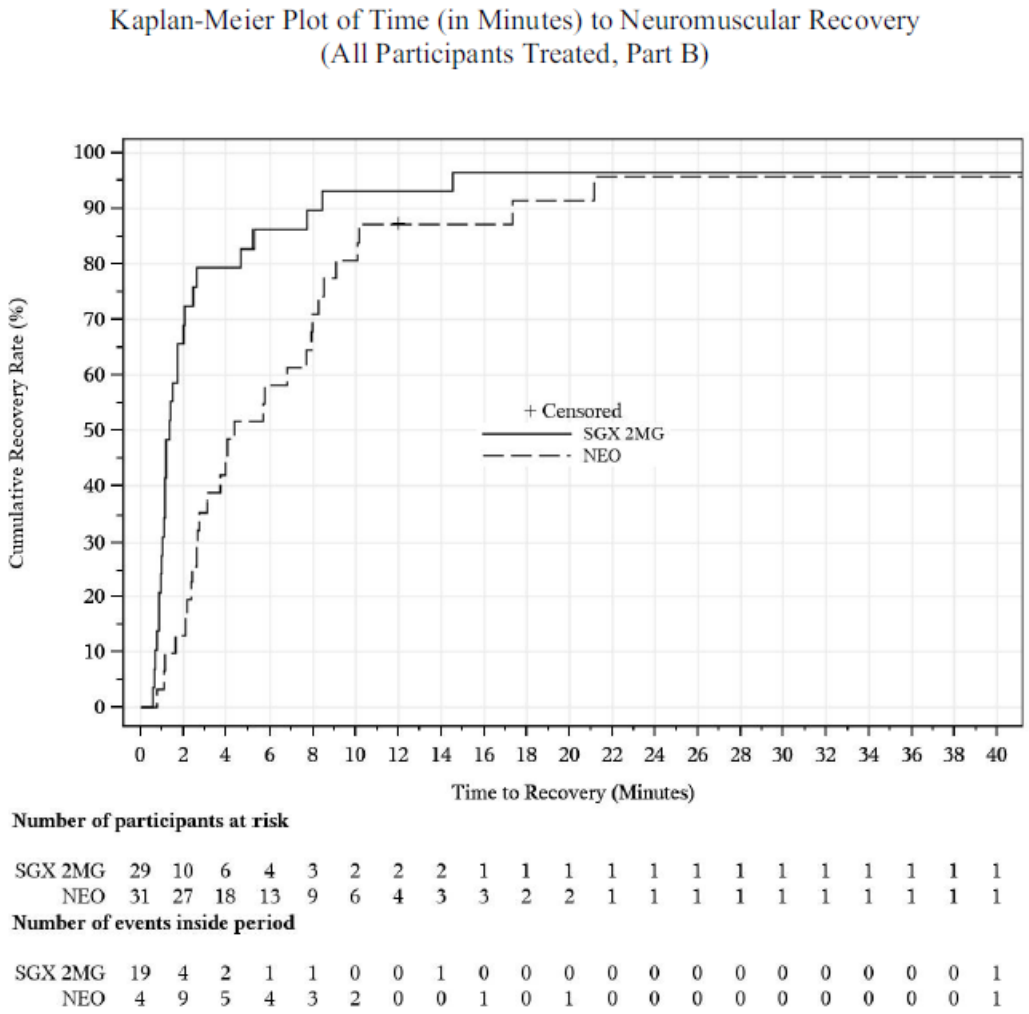
Treatment	N	Number of Events (%)	TTNMR (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	1.4 (1.1, 2.0) [1.0, 2.5]
Neostigmine + (Glycopyrrolate or Atropine)	31	30 (96.8)	4.4 (2.7, 7.9) [2.4, 8.5]

Pairwise Comparisons	Hazard ratio (95% CI[a])	p-value
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	2.40 (1.37, 4.18)	0.0021

N = the number of participants treated; CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile.
Hazard ratio (95% CI) and two-sided p-value were obtained based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous) and stratified by neuromuscular blocking agent.

Source: Sponsor's Response to FDA Information Request Regarding Primary and Secondary Endpoint Analysis, Table 2, received on Oct 16, 2024

Figure 3 Kaplan-Meier Plot of Time (in Minutes) to Neuromuscular Recovery



TTNMR is censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
TTNMR = time to neuromuscular recovery; SGX 2MG = sugammadex 2 mg/kg; NEO = neostigmine.
Source: NDA 022225/S-014, Clinical Study Report, p. 58

Sensitivity analyses for the primary efficacy endpoint:
Table 5 summarizes the results from the sensitivity analysis for the primary efficacy endpoint, including the number of treated participants in Part B, the number of events, Kaplan-Meier estimate, hazard ratio (95% CI), and p-value. The sensitivity analysis included all the treated participants with Neuromuscular Recovery Assessment Using Train of Four (TOF)/Peripheral Nerve Stimulator (PNS) Devices. Based on Cox PH model, the time to neuromuscular recovery was significantly faster (p=0.0043) in the sugammadex group compared with the neostigmine group (hazard ratio = 2.27, 95% CI: 1.29, 3.97). Based on Kaplan-Meier estimates, the median TTNMR is 1.4 minutes and 4.4 minutes in the sugammadex and neostigmine groups, respectively. These results are consistent with those from the primary analysis of the primary efficacy endpoint.

Table 5 Primary Efficacy Endpoint – Sensitivity Analysis Results

Treatment	N	Number of Events (%)	TTNMR† (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	1.4 (1.1, 2.0) [1.0, 2.5]
Neostigmine + (Glycopyrrolate or Atropine)	29	28 (96.6)	4.4 (2.7, 7.9) [2.4, 8.3]

Pairwise Comparisons	Hazard Ratio‡ (95% CI)‡	p-Value‡
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	2.27 (1.29, 3.97)	0.0043

† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on Cox regression model with Efron's method of tie handling with covariates for treatment, age (continuous) and stratified by neuromuscular blocking agent.
Per analysis plan, TTNMR is censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
CI = confidence interval; PNS = peripheral nerve stimulator; Q1 = the first quartile; Q3 = the third quartile; TOF = train-of-four stimulation; TTNMR = time to neuromuscular recovery.

Source: Sponsor's Response to FDA Information Request Regarding Primary and Secondary Endpoint Analysis, Table 3, received on Oct 16, 2024

Secondary Efficacy Endpoint
The table below provides the analysis of time to extubation for subjects dosed with sugammadex 2 mg/kg and neostigmine.

Table 6 Analysis of Time to Extubation

Treatment	N	Number of Events (%)	Time to Extubation (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	7.9 (5.7, 11.6) [4.7, 12.6]
Neostigmine + (Glycopyrrolate or Atropine)	31	31 (100.0)	10.5 (7.9, 13.5) [7.1, 17.4]

Pairwise Comparisons	Hazard ratio (95% CI)	p-value
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	1.30 (0.76, 2.21)	0.3381

N = the number of participants treated; CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile.
Hazard Ratio (95% CI) and two-sided p-value based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous), endotracheal extubation type (deep versus not deep) and stratified by neuromuscular blocking agent.

Source: Sponsor's Response to FDA Regarding Primary and Secondary Endpoint Analysis, Table 4, received on Oct 16, 2024

Time to extubation was comparable between the sugammadex and neostigmine groups.

Exploratory Efficacy Endpoints
The time to OR discharge, PACU discharge, and hospital discharge were also similar among subjects dosed with sugammadex 2 mg/kg or neostigmine.

Statistical analysis plan and major statistical issues

The following is an excerpt from the statistical review and evaluation completed by Junyi Zhang, PhD (Primary Reviewer), Xinyu Tang, PhD, and Sue Jane Wang, PhD, completed on November 14, 2024. For detailed information refer to their completed review.

> **Based on a stratified Cox regression model, TTNMR was shown statistically significantly faster in the sugammadex group compared to the neostigmine group (p=0.0021). The hazard ratio (sugammadex versus neostigmine) was estimated to be 2.4 (95% confidence interval [CI]:1.37, 4.18). The applicant performed a supportive analysis for TTNMR based on the product-limit (Kaplan-Meier) and log rank test. The applicant also performed a sensitivity analysis for TTNMR only including those with neuromuscular recovery assessment using train-of-four stimulation/peripheral nerve stimulator (TOF/PNS) devices. The results from the supportive analysis and sensitivity analysis were consistent with the primary analysis findings.**
>
> **Based on our statistical review, we agree that the efficacy results from Part B of Study 169 support the use of sugammadex for the reversal of moderate NMB in pediatric participants from birth to less than 2 years of age.**

Conclusion

The Division concludes that the Applicant provided substantial evidence of effectiveness to support approval for use in the birth to less than two years of age pediatric population. The Sponsor met their primary efficacy endpoint, “time to neuromuscular recovery” for Study P169. The results demonstrated that a sugammadex dose of 2 mg/kg has a faster time to neuromuscular recovery than the currently approved neostigmine for reversal of moderate neuromuscular blockade, and was statistically significant (p=0.0021, based on the Cox Regression Model analysis). The results were both statistically significant and clinically meaningful, as the amount of time to neuromuscular recovery was shorter in duration using sugammadex compared to neostigmine. A shorter time to neuromuscular recovery using sugammadex allows a patient to be able to maintain their own airway and breath spontaneously without artificial support quicker than using neostigmine, and therefore, there is less time spent in the vulnerable period at the end of a surgical procedure. During this vulnerable and critical time from transitioning from full ventilatory support via artificial mechanical ventilation to spontaneous native ventilation, a patient may be at increased risk for untoward adverse events, such as hypoxia, hypercapnia, aspiration, respiratory distress, respiratory failure, or inability to extubate, especially if adequate reversal of neuromuscular blockade had not been achieved. The secondary efficacy endpoint, time to extubation, was comparable between the sugammadex and neostigmine groups. The submission contained adequate information to demonstrate the efficacy of sugammadex when used as proposed by the Applicant.

8. Safety

The Applicant is relying on information from Study P169 to inform the safety profile of sugammadex when used for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in pediatric patients aged birth to less than 2 years old undergoing surgery. The discussion in this section will focus on the following: the adequacy of the safety database, safety endpoints and objectives, key safety results, as well as post-marketing and literature information.

The safety issues of greatest concern with the administration of sugammadex for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in patients undergoing surgery include bradycardia, hypersensitivity, and anaphylaxis, some of which are included in Section 5, Warnings and Precautions, of the prescribing information for BRIDION, based on both adult data and pediatric data in 2 to <17 years old. These events of clinical interest will be discussed further in this section of the review.

Safety Database

There was a total of 145 subjects enrolled in Study P169. The safety database in support of this supplement consisted of all randomized subjects from both Part A and Part B from all three treatment groups (sugammadex 2 mg/kg, sugammadex 4 mg/kg, and neostigmine) who received at least one dose of drug intervention. The total number of subjects that were treated was 138 (44 in the sugammadex 2 mg/kg group, 63 in the sugammadex 4 mg/kg group, and 31 subjects in the neostigmine group). Part A included 47 subjects (15 in sugammadex 2 mg/kg group and 32 in sugammadex 4 mg/kg group), and Part B included 91 subjects (29 in sugammadex 2 mg/kg group, 31 in sugammadex 4 mg/kg group, 31 in neostigmine group). As stated above in Section 7, which outlines the details of the design of Study P169, Part A characterized PK parameter values following administration of 2- and 4-mg/kg sugammadex and confirmed the 2- and 4-mg/kg doses for evaluation of sugammadex safety and efficacy for Part B. Part B assessed the safety and efficacy of the two doses of sugammadex (2 mg/kg and 4 mg/kg) and sugammadex 2 mg/kg was compared to the active comparator neostigmine for the reversal of moderate neuromuscular blockade.

Table 7 below, summarizes the subject demographics and characteristics, including study drug exposure, for all treatment groups in Study P169, in both Part A and Part B of Study P169:

Table 7 Study P169 - Demographics and Characteristics of Treatment Groups (Part A + Part 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	(%)
Participants in population	15		32		29		31		31		138	
Sex												
Male	9	(60.0)	20	(62.5)	24	(82.8)	20	(64.5)	19	(61.3)	92	(66.7)
Female	6	(40.0)	12	(37.5)	5	(17.2)	11	(35.5)	12	(38.7)	46	(33.3)
Age (Days)												
Birth to 27 days	4	(26.7)	6	(18.8)	7	(24.1)	6	(19.4)	5	(16.1)	28	(20.3)
28 days to < 3 months	3	(20.0)	8	(25.0)	6	(20.7)	9	(29.0)	9	(29.0)	35	(25.4)
3 months to < 6 months	2	(13.3)	11	(34.4)	8	(27.6)	8	(25.8)	8	(25.8)	37	(26.8)
6 months to < 2 years	6	(40.0)	7	(21.9)	8	(27.6)	8	(25.8)	9	(29.0)	38	(27.5)
Mean	197.4		135.7		164.0		162.9		179.3		164.3	
SD	200.1		120.4		176.1		164.5		193.8		168.0	
Median	144.0		108.5		113.0		102.0		94.0		100.5	
Range	2 to 649		4 to 492		1 to 564		3 to 543		1 to 720		1 to 720	
Race												
American Indian Or Alaska Native	0	(0.0)	2	(6.3)	4	(13.8)	1	(3.2)	4	(12.9)	11	(8.0)
Asian	2	(13.3)	4	(12.5)	5	(17.2)	8	(25.8)	8	(25.8)	27	(19.6)

	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	(%)
Black Or African American	0	(0.0)	0	(0.0)	0	(0.0)	2	(6.5)	1	(3.2)	3	(2.2)
Multiple	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	2	(6.5)	3	(2.2)
Black Or African American, White	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(6.5)	2	(1.4)
White, Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(0.7)
White	13	(86.7)	26	(81.3)	20	(69.0)	19	(61.3)	16	(51.6)	94	(68.1)
Race by Ethnicity												
Hispanic Or Latino	3	(20.0)	5	(15.6)	10	(34.5)	7	(22.6)	9	(29.0)	34	(24.6)
American Indian Or Alaska Native	0	(0.0)	2	(6.3)	4	(13.8)	1	(3.2)	4	(12.9)	11	(8.0)
Asian	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(0.7)
Multiple	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	1	(0.7)
White	3	(20.0)	3	(9.4)	6	(20.7)	5	(16.1)	4	(12.9)	21	(15.2)
Not Hispanic Or Latino	12	(80.0)	27	(84.4)	19	(65.5)	23	(74.2)	22	(71.0)	103	(74.6)
Asian	2	(13.3)	4	(12.5)	5	(17.2)	7	(22.6)	8	(25.8)	26	(18.8)
Black Or African American	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	1	(3.2)	2	(1.4)
Multiple	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	1	(3.2)	2	(1.4)
White	10	(66.7)	23	(71.9)	14	(48.3)	14	(45.2)	12	(38.7)	73	(52.9)
Not Reported	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(0.7)

	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	(%)
Black Or African American	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.2)	0	(0.0)	1	(0.7)
Weight (kg)												
Participants with data	15		32		29		31		31		138	
Mean	6.7		6.1		6.2		6.6		6.4		6.4	
SD	2.9		2.1		2.7		3.2		3.1		2.8	
Median	6.8		5.8		5.6		5.9		5.7		5.8	
Range	2.3 to 9.9		2.5 to 10.4		2.3 to 11.9		3.2 to 15.0		2.1 to 13.4		2.1 to 15.0	
ASA Class												
ASA Class 1	4	(26.7)	15	(46.9)	9	(31.0)	8	(25.8)	10	(32.3)	46	(33.3)
ASA Class 2	9	(60.0)	12	(37.5)	16	(55.2)	17	(54.8)	15	(48.4)	69	(50.0)
ASA Class 3	2	(13.3)	5	(15.6)	4	(13.8)	6	(19.4)	6	(19.4)	23	(16.7)
Type of Neuromuscular Blocking Agent (NMBA)												
Rocuronium	14	(93.3)	25	(78.1)	21	(72.4)	19	(61.3)	19	(61.3)	98	(71.0)
Vecuronium	1	(6.7)	7	(21.9)	8	(27.6)	12	(38.7)	12	(38.7)	40	(29.0)
Stratifications												
Rocuronium, Birth to 27 days	4	(26.7)	5	(15.6)	6	(20.7)	5	(16.1)	4	(12.9)	24	(17.4)
Rocuronium, 28 days to < 3 months	3	(20.0)	7	(21.9)	5	(17.2)	6	(19.4)	6	(19.4)	27	(19.6)
Rocuronium, 3 months to < 6	1	(6.7)	6	(18.8)	6	(20.7)	5	(16.1)	5	(16.1)	23	(16.7)

	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	(%)
months												
Rocuronium, 6 months to < 2 years	6	(40.0)	7	(21.9)	4	(13.8)	3	(9.7)	4	(12.9)	24	(17.4)
Vecuronium, Birth to 27 days	0	(0.0)	1	(3.1)	1	(3.4)	1	(3.2)	1	(3.2)	4	(2.9)
Vecuronium, 28 days to < 3 months	0	(0.0)	1	(3.1)	1	(3.4)	3	(9.7)	3	(9.7)	8	(5.8)
Vecuronium, 3 months to < 6 months	1	(6.7)	5	(15.6)	2	(6.9)	3	(9.7)	3	(9.7)	14	(10.1)
Vecuronium, 6 months to < 2 years	0	(0.0)	0	(0.0)	4	(13.8)	5	(16.1)	5	(16.1)	14	(10.1)
Neuromuscular Recovery Assessment Using TOF/PNS Devices												
Yes	14	(93.3)	32	(100.0)	29	(100.0)	31	(100.0)	29	(93.5)	135	(97.8)
No	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(6.5)	2	(1.4)
Missing	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
Extubation at Deep Sedation												
Yes	6	(40.0)	12	(37.5)	13	(44.8)	12	(38.7)	15	(48.4)	58	(42.0)
No	8	(53.3)	20	(62.5)	16	(55.2)	19	(61.3)	16	(51.6)	79	(57.2)
Missing	1	(6.7)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)

ASA = american society of anesthesiologists; PNS = peripheral nerve stimulator; SD = standard deviation; TOF = train-of-four stimulation.

Source: NDA 022225/S-014, Clinical Study Report, pp. 105 – 108

The baseline characteristics of subjects in Study P169 were generally comparable across all treatment groups. The percentage of male to female subjects was 66.7% to 33.3%, respectively. Although there was a higher percentage of male subjects, no sex differences were noted in this study, which is supported by previous data collected in adults and older children that did not reveal any gender-specific pharmacokinetic or pharmacodynamic differences. Therefore, the gender distribution between the male and female subjects is acceptable and does not impact the results of this study. The age distribution of subjects was evenly distributed across the birth to less than 2 years old study population. The Applicant enrolled the previously agreed-upon number of subjects within each age cohort and the subjects were evenly distributed by age within each age cohort, as per required by the PWR Amendment #5. Although, the Applicant attempted to request enrollment for the youngest age group to end prior to the required number of subjects enrolled (see Section 7, Overview of the Clinical Program, for details). The majority of subjects were of the ASA Physical Status Classification System (ASA-PS) ASA Class 2, which is 50% of the subjects in the study. Most subjects were administered rocuronium compared to vecuronium, 71% compared to 29%, respectively, which is consistent with clinical practice as rocuronium is used more commonly than vecuronium, especially in pediatric patients. Regarding neuromuscular recovery assessment, the most common method used for neuromuscular recovery assessment across all age subgroups was TOF/PNS devices. Two subjects had censored TTNMR, one subject in Part A (sugammadex 2 mg/kg Panel) and one subject in Part B (neostigmine intervention group). Review of these two cases with censored TTNMR revealed that the intervention drug was administered at an incorrect depth of block and therefore, those two subjects were censored. There was also missing data for one subject for which neuromuscular recovery assessment was not provided by the Investigator. This occurred in Subject number: (b) (6), Treatment Arm: Part B: Moderate block -reversal with sugammadex 2 mg/kg, who is also listed in this review as a subject who experienced a serious adverse event. The issue with the missing data occurred due to the presence of noise/artifacts during the neuromuscular transmission monitor (NMTM) reading, and therefore, that data were not reliable.

The Division concluded that the safety database is adequate to support the two doses for moderate block reversal (2 mg/kg) and deep block reversal (4 mg/kg) in the birth to less than 2 years of age pediatric population.

Safety Endpoints and Objectives

The primary safety objective of Study P169 was the assessment of safety and tolerability of sugammadex in pediatrics between the ages of birth to less than 2 years of age, which included the following parameters: adverse events, laboratory tests, and vital signs. Safety outcomes included physical exams, vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation), laboratory evaluations, and all adverse events.

Adverse events of special interest included hypersensitivity, anaphylaxis, and clinically-relevant bradycardia. Bradycardia was clearly defined with strict heart rate parameters, length of time it persists, and clinical significance (i.e., resultant hypotension) for each age cohort. The following criteria was used to define bradycardia by the Applicant:

- Clinically relevant bradycardia - any bradycardia event that occurs after administration of study treatment and requires intervention, as determined by investigator judgment.

- Treatment-emergent bradycardia – a heart rate generally below the first percentile for age that had also decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.

- Treatment-emergent relative bradycardia - a heart rate that decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.

Study Objectives

Table 8 below summarizes the study objectives and endpoint of Study P169.

Table 8 Study P169 - Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
Objective: To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	Pharmacokinetic parameters: Area under the plasma concentration-time curve (AUC), clearance (CL), apparent volume of distribution (Vz and V_{SS}), maximum plasma concentration (C_{max}), and half-life ($t_{1/2}$).
Objective: To evaluate the time to neuromuscular recovery of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B). Hypothesis: Sugammadex is superior to neostigmine in reversing moderate NMB as measured by time to neuromuscular recovery.	Time to neuromuscular recovery: Interval from administration of reversal agent to time to neuromuscular recovery.
Objective: To evaluate the safety and tolerability of sugammadex (data will be pooled across Part A and Part B of the study).	Number of participants experiencing adverse events.
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the time to extubation of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	Time to extubation: Interval from administration of reversal agent to removal of the endotracheal tube.

Source: NDA 022225/S-014, Applicant's Submission, Clinical Study Report, p. 4

Interim analyses were performed before moving to the next age cohort (a younger cohort) in Part A, and before proceeding to Part B of the Study. No dose adjustments were required based on the PK results in Part A.

In order to inform both the safety and pediatric dosing recommendations in labeling in the birth to less than 2 years of age pediatric population, the Division required that data from a required number of subjects would be needed to support the use of sugammadex in this pediatric population. Per Protocol Amendment Two, received on November 2, 2022, the proposed number of subjects per age cohort in Part A and Part B were agreed upon as follows:

- 6 months to <2 years: Part A - 9 subjects, Part B - 24 subjects
- 3 months to <6 months: Part A - 9 subjects, Part B - 24 subjects
- 28 days to <3 months: Part A - 9 subjects, Part B - 24 subjects
- Birth to 27 days: Part A - 9 subjects, Part B - 18 subjects

Key Safety Results

For Study P169, the following events were reported by the Applicant:

Deaths

There were no deaths reported by the Applicant during this study.

Adverse events

Table 9, below, is a modified table from the Clinical Study Report submitted by the Applicant in Supplement 14.

Table 9 Subjects with Specific Adverse Events by Maximum Intensity (All Subjects Treated, Part A + B, up to 14 Days Post-Treatment

	Intensity Grading	Sugammadex 2 mg/kg n	Sugammadex 2 mg/kg (%)	Sugammadex 4 mg/kg n	Sugammadex 4 mg/kg (%)	Neostigmine + (Glycopyrrolate or Atropine) n	Neostigmine + (Glycopyrrolate or Atropine) (%)
Cardiac disorders	**Total**	**3**	**(6.8)**	**0**	**(0.0)**	**3**	**(9.7)**
	Mild	1	(2.3)	0	(0.0)	2	(6.5)
	Moderate	2	(4.5)	0	(0.0)	1	(3.2)
Bradycardia	Total	2	(4.5)	0	(0.0)	3	(9.7)
	Mild	0	(0.0)	0	(0.0)	2	(6.5)
	Moderate	2	(4.5)	0	(0.0)	1	(3.2)
Tachycardia	Total	1	(2.3)	0	(0.0)	0	(0.0)
	Mild	1	(2.3)	0	(0.0)	0	(0.0)
Vomiting	Total	4	(9.1)	2	(3.2)	1	(3.2)
	Mild	4	(9.1)	2	(3.2)	1	(3.2)
Pain	Total	2	(4.5)	2	(3.2)	1	(3.2)
	Mild	1	(2.3)	1	(1.6)	1	(3.2)
	Moderate	1	(2.3)	1	(1.6)	0	(0.0)
Neuromuscular block prolonged	Total	0	(0.0)	0	(0.0)	1	(3.2)
	Moderate	0	(0.0)	0	(0.0)	1	(3.2)
Procedural pain	Total	18	(40.9)	34	(54.0)	10	(32.3)
	Mild	11	(25.0)	14	(22.2)	6	(19.4)
	Moderate	5	(11.4)	15	(23.8)	2	(6.5)
	Severe	2	(4.5)	5	(7.9)	2	(6.5)
Procedural vomiting	Total	3	(6.8)	1	(1.6)	0	(0.0)
	Mild	2	(4.5)	0	(0.0)	0	(0.0)
	Moderate	1	(2.3)	1	(1.6)	0	(0.0)
Oxygen saturation decreased	Total	0	(0.0)	0	(0.0)	1	(3.2)
	Mild	0	(0.0)	0	(0.0)	1	(3.2)
Hypoxia	Total	2	(4.5)	0	(0.0)	1	(3.2)
	Mild	0	(0.0)	0	(0.0)	1	(3.2)
	Moderate	2	(4.5)	0	(0.0)	0	(0.0)
Hypotension	Total	1	(2.3)	0	(0.0)	0	(0.0)
Hypotension	Mild	1	(2.3)	0	(0.0)	0	(0.0)

Source: NDA 022225/S-014, Clinical Study Report, Table 14.3-18, pp. 286-295, Modified by Reviewer

The most common adverse events were procedure pain (32.3% to 54.0%), and vomiting (1.6% to 9.1%) in all three treatment groups. Bradycardia was more common in the neostigmine group (9.7%) compared to the sugammadex 2 mg/kg group (4.5%). There was no bradycardia that was reported in the sugammadex 4 mg/kg group. Sugammadex was generally well-tolerated in this pediatric population and no new adverse drug reactions or safety signals were identified.

Serious adverse events

In reviewing all the case narrative reports that were submitted by the Applicant, it appears there were a total number of six subjects who had serious adverse events reported; two subjects in Part A, and four subjects in Part B. Below is a summary of each subject, the serious adverse events reported, and the Division's comments regarding the causality of each case:

Part A (2 subjects)

Subject number: (b) (6)

Treatment Arm: Part A/ Panel 2: Deep block and reversal with sugammadex 4 mg/kg

This is a 9-day-old male with a past medical history significant for a renal neoplasm, who was hospitalized and had a nephrectomy procedure. This subject was randomized and received sugammadex 4 mg/kg at the end of the procedure and was extubated. According to the case report, it appears that the subject had an uneventful hospital course with some moderate procedure pain that was medically treated and resolved. The subject was discharged home on day 4 with a nasogastric tube in place for oral intake. Two days after discharge the subject experienced diarrhea, progressive pain, and moderate hypophagia (nonserious), and was hospitalized due to accidental removal of the gastric tube, which was repositioned, and the subject was then discharged home. According to the case report, it appears the subject had several gastrointestinal issues with diarrhea and was later diagnosed with a cow milk allergy.

The investigator considered hemorrhagic diarrhea not related to sugammadex. The Division concurs with this assessment by the investigator that the serious adverse event was not related to the study drug, sugammadex.

Subject number: (b) (6)

Part A/ Panel 1: Moderate block and reversal with sugammadex 2 mg/kg

This is a 2-day old male with a past medical history significant for Trisomy 21, Hypokalemia, Hyponatremia, Jaundice, Hyperalbuminemia, who was hospitalized and had a colostomy procedure. The subject was randomized and received sugammadex 2 mg/kg. The subject was not extubated following surgery due to residual anesthesia. According to the case report, the subject had accidentally self- extubated during transport, caused by subject movement, which caused hypoxia (oxygen saturation: 85%) and moderate bradycardia (HR: 88 bpm). The subject was reintubated and vital signs returned to normal parameters. According to the case report, “On Day 3 atelectasis and hypocalcemia resolved. The participant had high digestive bleeding (large amount of “borraceous” secretion) and was diagnosed with mild GI hemorrhage.” Gastric lavage was performed, medical treatment administered, and the GI hemorrhage resolved within 24 hours. The etiology of altered coagulation tests was reported as unknown.

The investigator considered atelectasis, bradycardia, hypoxia, anesthetic complication, and GI hemorrhage not related to sugammadex. Bradycardia was considered an ECI.

It appears that the bradycardia that this subject experienced after the surgical procedure and after receiving sugammadex that occurred during transport from the operating room to the neonatal intensive care unit (ICU) was most likely due to hypoxia related to the endotracheal tube being dislodged from the trachea and not due to the study drug, sugammadex. The Division concurs with the investigator’s assessment for this subject.

Part B (4 subjects)

Subject number: (b) (6)

Treatment Arm: Part B: Deep block and reversal with sugammadex 4 mg/kg
This is a 9-day old male with a past medical history significant for Congenital megaureter, Congenital hydronephrosis, Decubitus ulcer, Polyuria, and Candida infection, who underwent a urethral valve resection. The subject was randomized and received sugammadex 4 mg/kg and was extubated. According to the case report, the subject made an uneventful recovery and was discharged home on Day 3. On Day 12, the subject was hospitalized with severe pyelonephritis and was treated with antibiotics.

The investigator considered pyelonephritis not related to sugammadex. The Division concurs with this assessment by the investigator that the serious adverse event was not related to the study drug, sugammadex.

Subject number: (b) (6)
Treatment Arm: Part B: Moderate block and reversal with sugammadex 2 mg/kg
This is 2-day old, with past medical history of hydrocephalus hospitalized due to an arachnoid cyst and had a ventriculostomy procedure. The subject was randomized and received sugammadex 2 mg/kg at and was extubated. Shortly after the procedure an ultrasound scan revealed severe bilateral cerebral hemorrhage, most likely a complication from the surgical procedure, at which time the subject had decreased oxygen saturation to 89% and 50%, and laboratory value results showed anemia and acidosis with a pH of 6.9.

The investigator considered cerebral hemorrhage not related to sugammadex. The Division concurs with this assessment by the investigator.

Subject number: (b) (6)
Treatment Arm: Part B: Moderate block and reversal with sugammadex 2 mg/kg
This is a 195-day old male with past medical history of congenital hydronephrosis and pyelonephritis, who had a pyeloplasty procedure. The subject was randomized and received sugammadex 2 mg/kg and was extubated. The subject experienced the following during the course of a six-day hospitalization: moderate procedural pain (postoperative) and mild constipation (both nonserious per the case report), and mild vomiting. Three days after discharge the subject was admitted with a diagnosis of severe urinoma and was treated with medications.

The investigator considered urinoma not related to sugammadex. The Division concurs with the investigator's assessment.

Subject number: (b) (6)
Treatment Arm: Part B: Moderate block and reversal with sugammadex 2 mg/kg
This is an 84-day old female with past medical history of nasopharyngitis who underwent a bladder exstrophy repair. The subject was randomized and received sugammadex 2 mg/kg and was extubated. However, there was a protocol deviation reported in this case as the study medication was not administered at the correct depth of block. It was also noted that the neuromuscular transmission monitor (NMTM) data were not reliable due to the presence of noise/artifacts during reading.

> The serious adverse event in this case was a mechanical device positioning issue on post operative day (POD) 1 that required reexploration in the operating room. On POD 5 the subject was diagnosed with a mild bacterial infection. Hospital course was complicated with mild anemia and moderate drug withdrawal syndrome from morphine withdrawal. The investigator considered mechanical device issue not related to sugammadex. The Division concurs with the investigator's assessment.

The age ranged from 2 days to 195 days old for the six subjects who experienced serious adverse events during Study P169. It's not unusual for neonates to have higher complications during the perioperative period versus older patients (i.e., dislodgement of endotracheal tube, bradycardia due to hypoxia, etc.) None of the serious adverse events reported were related to the study drug sugammadex. There did not appear to be any correlation with the serious adverse events, sex, or drug dosage administered.

Results of laboratory tests

No clinically meaningful changes from baseline in laboratory values were observed. No clinically meaningful findings were observed in the mean change from baseline in vital signs in all treated participants. The percentage of participants who met criteria for decreased heart rate (<age-defined criteria and at least 20% decrease from baseline) was more common in the neostigmine group than in the sugammadex groups (upper bound of the 95% CI <0).

Events of clinical interest (ECI)

The incidence of ECIs (≤2 participants) was comparable across the intervention groups.

Bradycardia

As stated prior in this review, the issue of bradycardia is especially important in younger pediatric patients, as cardiac output is heart rate dependent in this patient population. Bradycardia in a young pediatric patient can quickly lead to cardiac arrest if not recognized early and managed swiftly. Bradycardia was the only ECI with events reported.

The following criteria for bradycardia was defined earlier in this review, but it is repeated here for ease of review, especially with the discussion of Table 10 that follows the Applicant's definitions of bradycardia.

- Clinically relevant bradycardia - any bradycardia event that occurs after administration of study treatment and requires intervention, as determined by investigator judgment.
- Treatment-emergent bradycardia - a heart rate generally below the first percentile for age that had also decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.
- Treatment-emergent relative bradycardia - a heart rate that decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.

Table 10 Events of Bradycardia – All Subjects Treated, Part A+B, up to 30 minutes Post-Treatment

Treatment	n	(%)	Difference in % vs Neostigmine + (Glycopyrrolate or Atropine) Estimate (95% CI)†	p-value†
Participants in population				
Sugammadex 2 mg/kg	44			
Sugammadex 4 mg/kg	63			
Neostigmine + (Glycopyrrolate or Atropine)	31			
Clinically Relevant Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)	2.3 (-10.6, 13.5)	0.398
Sugammadex 4 mg/kg	0	(0.0)	0.0 (-12.3, 6.4)	>0.999
Neostigmine + (Glycopyrrolate or Atropine)	0	(0.0)		
Treatment-Emergent Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)	-8.0 (-25.5, 4.0)	
Sugammadex 4 mg/kg	2	(3.2)	-6.2 (-22.7, 3.6)	
Neostigmine + (Glycopyrrolate or Atropine)	3	(9.7)		
Treatment-Emergent Relative Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)		
Sugammadex 4 mg/kg	2	(3.2)		
Neostigmine + (Glycopyrrolate or Atropine)	6	(19.4)		

† Based on Miettinen & Nurminen method stratified by neuromuscular blocking agent and age group; if no participants are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.
Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.
CI = confidence interval.

Source: [P169MK8616: adam-adsl; adca]

Source: NDA 022225/S-014 Submission, Clinical Study Report, Table 14.3-45, p. 322

Treatment-emergent bradycardia was comparable between the sugammadex and neostigmine groups. Treatment-emergent relative bradycardia was reported in approximately 2% to 3% of subjects in the sugammadex groups and 19% of subjects in the neostigmine group.

There were two subjects in the sugammadex 2 mg/kg group who experienced clinically relevant bradycardia, defined as any bradycardia event that occurred after administration of study treatment and required intervention, during the study (11 minutes and 100 minutes after sugammadex administration). There were no bradycardia events that were reported as severe. Clinically relevant bradycardia and treatment-emergent bradycardia were comparable among intervention groups (≤3 subjects per group). Treatment-emergent relative bradycardia occurred less frequently in the sugammadex groups (≤2 participants per group) than in the neostigmine group (6 participants).

The data reported in Study P169 regarding the adverse event of bradycardia is similar to the data in adults. Per the most current prescribing information labeling for BRIDION (November 17, 2022), the adult data from pooled Phase 1 to 3 studies completed reported the incidence of bradycardia was 1% in subjects administered 2 mg/kg or 4 mg/kg of sugammadex, and 5% in adults administered a 16mg/kg dose.

Hypersensitivity, Anaphylaxis
There were no reported adjudicated hypersensitivity or anaphylaxis events.

The results from Study P169 are also consistent with that found in the adult data. According to the PI for BRIDION, hypersensitivity and anaphylaxis has been found to occur in 0.3% of adult patients.

Drug-induced liver injury (DILI)
No subjects met Hy's Law criteria, and therefore no DILI events were reported.

Recurrence of NMB
No AEs of recurrence were reported in Study P169. Compared to the adult data described in Section 5, Warnings and Precautions, of the BRIDION prescribing information, a small number of adults "experienced a delayed or minimal response to the administration of sugammadex." In the PI, it states that recurrence of neuromuscular blockade may occur due to the following scenarios:

- Displacement of rocuronium or vecuronium from sugammadex by other drugs
- When drugs which potentiate neuromuscular blockade are used in the post-operative phase
- When lower than recommended doses of sugammadex are administered

Although there were no reports of recurrence in Study P169, it may be important for clinicians to consider and be aware of the above scenarios when dosing sugammadex in younger pediatric patients.

Postmarketing experience: (US or foreign)

As reported in the Applicant's submission, the Applicant conducted a cumulative search of its global safety database for both spontaneous and noninterventional study reports received worldwide in patients less than 17 years of age and included the time period from July 31, 2008, through January 31, 2024. There was a total of 706 pediatric cases (205 serious and 501 nonserious) that were retrieved and contained 1,196 adverse events, which represented 8.0% (1,196/14,965) of all sugammadex adverse events reported during the span of 16 years.

Table 11 below provides a summary of the number of events and percentage of total events by seriousness and age group.

Table 11 Number of Adverse Events

Number of Events and Percentage of Total Events by Seriousness and Pediatric Age Group

Age Group	# Serious Events	# Nonserious Events	Total # of Events	% of Total Events
Neonates (Birth to 28 days)	14	37	51	4.9
Infants (29 days to <3 months)	12	39	51	4.9
Infants (3 months to <6 months)	15	42	57	5.4
Infants (6 months to 1 year)	20	93	113	10.8
Children (>1 year to <2 years)	1	40	41	3.9
Children (2 years to <17 years)	243	490	733	70
Total	**305**	**741**	**1046[1]**	

[1] Total number of events listed is less than total number of events (1,196) in the 706 cases involving all pediatric patients, as the total number of events for all pediatric patients included cases lacking age values as shown in [Table 2.7.4-nmbreversal: 15].

Source: NDA 022225, Module 2.7.4 Summary of Clinical Safety, p. 27

In the neonate age group (birth to 28 days) there were a total of 25 cases containing 51 adverse events with no fatal outcomes were reported. In the infant age group (29 days to < 3 months) there were a total of 28 cases containing 51 adverse events, with no fatal outcomes were reported. In the infant age group (3 months to < 6 months) there were a total of 26 cases containing 57 adverse events, with no fatal outcomes reported. In the infant age group (6 months to 1 year) there were a total of 49 cases containing 113 events, with no fatal outcomes reported. This age group appeared to have the highest total number of events as noted in the table below. Upon further review, it appears that 33% of the 113 events included off-label use, and almost 20% of total number of events were pyrexia, which is a common clinical finding in the perioperative period. In the age group children (>1 year to <2 years) there were a total of 23 cases containing 41 adverse events. In the age group children (2 years to <17 years) there were a total of 473 cases containing 733 events, which is approximately 70% of all the pediatric adverse events reported.

The most frequently reported clinical AEs are listed below according to age group:

- **Neonates (Birth to 28 days of age)** – off-label use (9 events), recurrence of neuromuscular blockade (6 events)
- **Infants (29 days to <3 months)** – off-label use (12 events), laryngospasm (3 events), and neuromuscular block prolonged (3 events)
- **Infants (3 months to <6 months)** – off-label use (16 events), bradycardia, erythema, recurrence of neuromuscular blockade, and respiratory arrest
- **Infants (6 months to 1 year)** – off-label use (27 events), pyrexia (22 events), vomiting (2 events), recurrence of neuromuscular blockade (4 events), anaphylactic reaction (2 events), bradycardia (2 events), and neuromuscular block prolonged (2 events)
- **Children (>1 year to <2 years)** - off-label use (10 events), pyrexia (3 events) and agitation postoperative (2 events)
- **Children (2 years to <17 years)** - recovered/resolved (386 events), and unknown (293 events).

There were 10 fatalities reported out of 733 events in the age group children (2 years to <17 years). The Applicant states that the 10 fatalities reported, were actually from a single case and described by the Applicant in their submission, below:

> *"A 4-year-old child who underwent surgery for adenoid removal* (b) (6) *The child was administered 45 mg of sugammadex (2.25 mg/kg). Approximately 3 to 5 minutes after extubation, the child developed bronchospasm (no rash), hemodynamic collapse, bradycardia, respiratory distress, and decreased arterial blood pressure. The child was administered cortisone and adrenaline in preparation for reintubation. However, 12 to 15 minutes later the "same events were repeated" and adrenaline was readministered. The child developed pulmonary edema due to hypoxemia. Oxygen and blood pressure were restored, but the child subsequently experienced a drop in arterial blood pressure and oxygen level. Cardiopulmonary resuscitation was continued for 2 hours, but the child did not respond to these measures and died."*

It is unclear whether the events in the case described above were due to sugammadex or to a complication related to extubation (i.e., hypoxia due to negative pressure pulmonary edema).

To compare the pediatric postmarketing reports with the adult reports, the following adult data search is included for completeness. A total of 4,244 cases (1,905 serious and 2,339 nonserious) containing 10,167 events (3,157 serious and 7,010 nonserious) were reported. Outcomes of the 10,167 events were reported as fatal (80; 51 cases), not recovered/not resolved (1,797), recovered/resolved (6,026), recovered/resolved with sequelae (32), recovering/resolving (555), and unknown (1,677). Of the 80 events reported with fatal outcomes, the three most frequently reported adverse events were: bradycardia (7), cardiac arrest (8), and death (10).

Literature Review

The Applicant conducted a cumulative literature search was performed from July 31, 2008, to March 19, 2024, for sugammadex. Review of the postmarketing literature identified no new safety concerns or an alternate safety profile in pediatric patients compared with the currently known safety profile in adults.

Conclusion

The information from the safety database is adequate to support the two doses for moderate block reversal (2 mg/kg) and deep block reversal (4 mg/kg). Cumulative review of the postmarketing spontaneous and noninterventional study AE reports for sugammadex in pediatric patients (from birth to <17 years of age) revealed that the safety profile of sugammadex in the pediatric population is generally similar to the profile observed in adults. In Study P169, the percentage of subjects who experienced one or more adverse events (AE) were similar across all three treatment groups (61.3% to 68.3%) and the adverse events were mild to moderate in severity. The percentage of subjects who experienced a drug-related AE were similar in the sugammadex and neostigmine groups and there were no drug-related serious adverse events (SAEs) reported in Study P169. No subjects were discontinued due to an AE. There were also no deaths reported in Study P169. The majority of the clinical AEs reported in this study are already listed in the prescribing information for BRIDION. Table 12

below provides a visual summary of adverse events for all subjects treated in Part A and Part B of Study P169 and included AEs up to 7 days post-treatment.

Table 12 Adverse Event Summary

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Participants in population	44		63		31	
with one or more adverse events	30	(68.2)	43	(68.3)	19	(61.3)
with no adverse event	14	(31.8)	20	(31.7)	12	(38.7)
with drug-related adverse events	1	(2.3)	0	(0.0)	3	(9.7)
with serious adverse events	3	(6.8)	1	(1.6)	0	(0.0)
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)

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

Source: [P169MK8616: adam-adsl; adae]

Source: NDA 022225/S-014 Submission, Module 2.5 Clinical Overview, p. 24

The most common adverse events reported in Study P169 were procedure pain (32.3% to 54.0%), and vomiting (1.6% to 9.1%). Sugammadex was generally well-tolerated in this pediatric population and no new adverse drug reactions or safety signals were identified.

9. Advisory Committee Meeting

There were no issues in this supplement that required presentation and discussion at an Advisory Committee meeting.

10. Pediatrics

The Division had two meetings with the PeRC and one meeting with the Pediatric Exclusivity Board from August 29, 2023, prior to the completion of this review. These details of these meetings are described below:

On August 29, 2023, the Division met with the PeRC to review the Applicant's request for Pediatric Deferral Extension (DE) Request (PREA Study) and Timeline Extension Request for the Pediatric Written Request. The PeRC agreed with the Division's recommendation to grant the DE request and the proposed timeline extension for the PWR, based on the following five reasons.

1. Additional data are needed in the youngest age cohort to inform the safety and efficacy profile of sugammadex use in the entire pediatric population.
2. There have been unforeseen challenges in completing enrollment in this study, such as the COVID-19 global pandemic and the political conflict in Ukraine.
3. Conducting clinical studies in the youngest age cohort is challenging, and particularly-so for this study given the need to evaluate subjects undergoing non-emergent surgeries. Specifically, the Division agrees with the Sponsor that many of the

procedures performed in the neonatal population are emergent and would therefore not qualify for participation in this study.

4. The Sponsor has continued with attempts to enroll subjects into the study, as evidenced by the additional four subjects enrolled from March to June 2023. The Division acknowledges there was over-enrollment in the three older age cohorts in Part A. In Part B, the Sponsor has successfully enrolled all age cohorts, with the exception of the birth to 27-day age cohort.
5. The Division is confident that with additional time, the additional subjects required for enrollment into the study can be successfully completed.

On October 16, 2024, the Division met with the Pediatric Exclusivity Board to determine whether the Applicant fulfilled the PWR, last amended on August 30, 2023 (Amendment 5), with the final clinical study report submission of Study P169, as well as the prior pediatric study that was submitted with Supplement-08. The Board determined that Pediatric Exclusivity shall be granted based on the Applicant fulfilling the requirements as stated in PWR Amendment #5.

On October 29, 2024, the Division met with the Pediatric Review Committee regarding whether the Applicant fulfilled PMR 3003-9 with the completion of Study P169 and the submission of the full clinical study report for Study P169. The PeRC concurred that the following PMR 3003-9 was fulfilled with the submission of the final study report (Study P169).

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.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) audits
On July 24, 2024, the Division made a request for the following clinical sites to be inspected: Site 3008 in Stanford, California, Site 3250 in Denmark, and Site 3014 in Houston, Texas.

The OSI primary reviewer, Dr. John Lee, completed the Clinical Inspection Summary (CIS) on November 27, 2024. The following is an excerpt of the results of the audit and the conclusions made by the OSI team. For full details refer to the OSI review completed by Dr. John Lee and submitted into DARRTS.

The information below is a summary of the CIS:

Inspection Results

1. Volker Classen, M.D.
   Blegdamsvej 9, 4013/14
   COPENHAGEN 2100

Denmark
Inspection Dates: 10/14 – 18, 2024

Site 3250: 10 subjects were screened and enrolled, and 10 completed the study. The study was audited for: protocol adherence, Institutional Review Board (IRB) oversight, site monitoring, staff training, study medication disposition, CI financial disclosure, and subject records.

No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

2. Maria Matuszczak, M.D.
   6431 Fannin Street, MSB 5.020
   Houston, TX 77030
   Inspection Dates: 10/1 – 4, 2024
   Site 3014: 17 subjects were screened and enrolled, and 17 completed the study. The study was audited for: protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, CI financial disclosure, and subject records.

   No significant GCP deficiencies or regulatory deviations were observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

3. Radhamangalam Ramamurthi, M.D.
   300 Pasteur Drive, Mc 5640 Rm H3580
   Stanford, CA 94305
   Inspection Dates: 9/16 – 20, 2024

   Site 3008: 17 subjects were screened and enrolled, and 15 completed the study. The study was audited for: protocol adherence, IRB oversight, site monitoring, staff training, study medication disposition, CI financial disclosure, and subject records.

   The following GCP deficiencies were observed:
   - One subject with an estimated glomerular filtration rate (eGFR) of 28 mL/min was enrolled, in violation of the subject selection criterion that specified exclusion for eGFR < 30 mL/min.
   - In obtaining informed consent (IC) for one subject not speaking English, the study personnel failed to adequately qualify/document the subject's English-speaking representative.

- The electronic case report forms (eCRFs) appeared not to consistently include all PDs; some minor PDs appeared not to have been reported in the NDA (data listing).

These observed GCP deficiencies appeared minor and unlikely to be important to data quality or subject safety/welfare. Significant GCP deficiency observations were otherwise not observed. The study records showed adequate compliance with applicable regulations and standards, including GCP for: informed consent; AE monitoring, management, and reporting; and PD monitoring, corrective actions, and reporting. The major safety and efficacy data were verifiable.

The Division concurs with the conclusions made by the primary reviewer of the OSI team.

12. Labeling

A review of both the label and labeling were completed by DMEPA on July 30, 2024. The following assessment is an excerpt from DMEPA's review:

> **Our evaluation of the proposed Bridion Prescribing Information (PI) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.**

Refer to the review completed by Sofanit Getahun and Valerie Vaughan for detailed information.

Prescribing Information

The Applicant's proposed prescribing information for BRIDION is to update Section 1, Section 6.1, Section 8.4, Section 12.3, and Section 14. Below is the proposed language by the Applicant for each of the relevant sections of the prescribed information in the labeling. Information in the labeling that is proposed to be removed is denoted with a strikethrough and new language is denoted in red text.

> **Section 1 - Indications and Usage**
> **BRIDION® is indicated for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adult and pediatric patients ~~aged 2 years and older~~ undergoing surgery.**
>
> **Section 6.1 - Clinical Trials Experience**
> ***Birth to <2 years of age***
> **The safety of BRIDION has been assessed in a randomized, double-blinded, active comparator-controlled study of pediatric patients from birth to <2 years of age, with 107 receiving treatment with BRIDION. Adverse events occurring in ≥5% of pediatric patients are presented in Table 4. The safety profile was generally**

consistent with that observed in pediatric patients from 2 to <17 years of age and adults.

Table 4: Pediatric Participants (Birth to <2 Years) with Specific 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	(%)
Participants in population	44		63	
with one or more specific adverse events	30	(68.2)	43	(68.3)
with no specific adverse events	14	(31.8)	20	(31.7)
Cardiac disorders	**3**	**(6.8)**	**0**	**(0.0)**
Gastrointestinal disorders	**6**	**(13.6)**	**4**	**(6.3)**
Vomiting	4	(9.1)	1	(1.6)
General disorders and administration site conditions	**5**	**(11.4)**	**6**	**(9.5)**
Pyrexia	3	(6.8)	3	(4.8)
Infections and infestations	**3**	**(6.8)**	**0**	**(0.0)**
Injury, poisoning and procedural complications	**19**	**(43.2)**	**35**	**(55.6)**
Procedural pain	18	(40.9)	34	(54.0)
Procedural vomiting	3	(6.8)	1	(1.6)
Metabolism and nutrition disorders	**3**	**(6.8)**	**2**	**(3.2)**
Respiratory, thoracic and mediastinal disorders	**5**	**(11.4)**	**3**	**(4.8)**

Every participant 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.

Section 8.4 – Pediatric Use

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~~ from birth and older. Use of BRIDION in these age groups is supported by evidence from adequate and well-controlled studies 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)].

Section 12.3 – Pharmacokinetics

Pediatric Patients

The pharmacokinetics of sugammadex in pediatric patients have been evaluated in 2 clinical studies following administration of intravenous doses of 2 or 4 mg/kg sugammadex administered for reversal of moderate or deep neuromuscular blockade, respectively. In one study, sugammadex pharmacokinetic parameters were estimated in pediatric patients 2 to <17 years of age with patients enrolled into 3 age groups (2 to <6, 6 to <12 and 12 to <17 years of age). In a second study, sugammadex pharmacokinetic parameters were estimated in pediatric patients birth to <2 years of age with patients enrolled into 4 age groups (birth to 27 days, 28 days to <3 months, 3 months to <6 months and 6 months to < 2 years).

Sugammadex exposure (AUC0-inf and Cmax) increased in a dose-dependent, linear manner following administration of 2 or 4 mg/kg across patients ~~2 to <17 years of age~~ birth 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)].

Both clearance and volume of distribution increase with increasing age in pediatric patients, whereas elimination half-life is generally similar across pediatric patients. As a result, 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. By comparison, observed steady-state volume of distribution of sugammadex is approximately 1 to 3 liters and clearance is approximately 38 to 95 mL/min with a half-life of approximately 1-2 hours in pediatric patients age birth to <2 years of age.

Section 14 – Clinical Studies

Birth to <2 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 145 randomized pediatric patients from birth to <2 years of age, of which 138 patients received treatment (92 boys and 46 girls; ASA class 1, 2, and 3; 68% were White; median weight was 5.8 kg; median age was 100.5 days). The primary efficacy objective was to evaluate the time to neuromuscular recovery of BRIDION in comparison to neostigmine for the reversal of moderate neuromuscular blockade.

Time to neuromuscular recovery was statistically significantly faster in participants dosed with BRIDION 2 mg/kg (N=29) compared with neostigmine (N=31) (median of 1.4 minutes for BRIDION 2 mg/kg and 4.4 minutes for neostigmine; hazard ratio=2.40, 95% CI: 1.37, 4.18). BRIDION 4 mg/kg achieved neuromuscular recovery with a median of 1.1 minutes. These effects were consistent across age cohorts studied (birth to 27 days, 28 days to <3 months, 3 months to <6 months, 6 months to <2 years of age).

During the review of the proposed labeling, the Division noted that (b) (6) . The Division sent an information request to the Applicant on December 2, 2024, to request the Applicant provide a rationale for the lack of consistency between these tables, specifically why this information is necessary to include for the youngest patient population. On December 3, 2024, a response was received back from the Applicant. The Applicant proposed to remove (b) (6) information as the safety profile is consistent across the study interventions. The Applicant's request to remove (b) (6)

(b) (6) information from the proposed labeling appears reasonable at this time.

(b) (6)

The proposed labeling was reviewed by all disciplines of the review team and the Division concurs with the proposed changes to the Applicant's labeling of BRIDION above. The determination was made that the Applicant's proposed prescribing information is compliant with the Physician's Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR).

13. Postmarketing Recommendations

None.

14. Recommended Comments to the Applicant

None.

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.

/s/

LISA M BANTA
12/11/2024 04:32:01 PM

RIGOBERTO A ROCA
12/11/2024 04:34:06 PM