EU RISK MANAGEMENT PLAN (RMP) FOR SUGAMMADEX

Solution for injection

RMP version to be assessed as part of this application:

RMP Version number: 9.0

Data lock point for this RMP: 09-FEB-2024

Date of final sign off: 06-DEC-2024

Rationale for submitting an updated RMP:

Completion of FDA post-marketing requirement (PMR) study (P169), PK, Safety and Efficacy of Sugammadex for the Reversal of Neuromuscular Blockade in Children aged birth to <2 years. This EU RMP is submitted as part of a Type II variation to extend the paediatric indication in the EU based on P169 data.

Summary of significant changes in this RMP:

This EU RMP was updated upon completion of a post-marketing requirement (PMR) required by the Food and Drug Administration (FDA), upon receipt of US approval:

- Completion of a global study (P169), Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years.

RMP Section	UPDATED INFORMATION
PART I: PRODUCT OVERVIEW	Updated indication to include all paediatric patients (birth to 17 years)
PART II: SAFETY SPECIFICATION	Not applicable
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Not applicable
PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION	Updated to correct dosing information in rabbits
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE	Updated with Post-Marketing Trial data

RMP Section	UPDATED INFORMATION
PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS	Updated with Post-Marketing Trial data; Removed infants and neonates from exclusion criterion (Table SIV.1.1)
PART II: MODULE SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program	Updated with Post-Marketing Trial data
PART II: MODULE SV - Post-authorization Experience	Updated patient exposure data
PART II: MODULE SVII.2 - New Safety Concerns and Reclassification With a Submission of an Updated RMP	Not applicable
PART II: MODULE SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks	Not applicable
PART II: MODULE SVII.3.2 Presentation of the Missing Information	Not applicable
PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS	Not applicable
PART III : MODULE III.1 Routine Pharmacovigilance Activities	A review of post marketing safety data in the paediatric population aged from birth will be included in the PSUR.
PART IV: Plans for Post-Authorization Efficacy studies	Not applicable
PART V: MODULE V.1 Routine Risk Minimization Measures	Not applicable
PART V: MODULE V.2 Additional Risk Minimization Measures	Not applicable
PART V: MODULE V.3 Summary of Risk Minimization Measures	Not applicable
PART VI: MODULE II.A List of Important Risks and Missing Information	Not applicable
PART VI: MODULE II.B Summary of Important Risks	Not applicable

Details of the currently approved RMP:

Version number: 8.0

Approved with procedure: EMEA/H/C/000885/II/0042

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QPPV name*:* Peter De Veene, MD

QPPV signature: see signature page

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LIST OF ABBREVIATIONS

ABW	Actual Body Weight
AChEIs	Acetylcholinesterase Inhibitors
ADR	Adverse Drug Reaction
AE	Adverse Experience
ASA	American Society of Anesthesiologists
ATC	Anatomical Therapeutic Chemical classification system
CD	Cyclodextrin
CrCl	Creatinine Clearance
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
INN	International Nonproprietary Name
IV	Intravenous(ly)
MOA	Mechanism of Action
NMB	Neuromuscular Blockade
NMBA	Neuromuscular Blocking Agent
NOAEL	No Adverse Effect Level
PAES	Post-authorization Efficacy Study
PRAC	Pharmacovigilance Risk Assessment Committee
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PTC	Post Tetanic Count
QPPV	Qualified Person for Pharmacovigilance
RI	Renal Impairment
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SRBA	Selective Relaxant Binding Agent

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s) **(INN or Generic name)**	Sugammadex
Pharmacotherapeutic group(s) (ATC Code)	V03AB35
Marketing Authorisation Holder	Marketing Authorization Holder Merck Sharp & Dohme B.V. Waarderweg 39 2031 BN Haarlem, The Netherlands
Number of medicinal products to which this RMP refers	One (1)
Invented name(s) in the European Economic Area (EEA)	BRIDION
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: Modified cyclodextrin (CD)
	Summary of mode of action: Cyclodextrins (CDs) are well known for their capability to form inclusion complexes with various drug molecules. Sugammadex resembles a donut like shape with a lipophilic core and a hydrophilic outer surface. The lipophilic steroidal part of the neuromuscular blocking agents (NMBA) rocuronium and vecuronium is attracted by the lipophilic core of sugammadex. Sugammadex has eight side-chains each connected to a sugar unit of the CD. The end of each side-chain has a negatively charged group. Once rocuronium or vecuronium has entered the lipophilic core of sugammadex, these negatively charged groups are attracted to the positively charged ammonium group of these NMBAs. As a result of van der Waals' forces and hydrophobic and electrostatic interactions, a very tight binding between the guest molecule and the host CD occurs. Upon complexation with an amino-steroidal neuromuscular blocker such as rocuronium or vecuronium, sugammadex reduces the amount of NMBA available to bind to nicotinic receptors in the neuromuscular junction, and hence results in the reversal of neuromuscular blockade (NMB). This concept is a completely new approach to reverse NMB. Important information about its composition: BRIDION 2 mL solution for injection Each 2 mL vial of BRIDION contains sugammadex sodium equivalent to 200 mg sugammadex. BRIDION 5 mL solution for injection Each 5 mL vial of BRIDION contains sugammadex sodium equivalent to 500 mg sugammadex. Excipients with known effect Contains up to 9.7 mg/mL sodium.

Table I.1: Product Overview

	Each solution for injection contains other following inactive ingredients: hydrochloric acid 3.7% and/or sodium hydroxide (to adjust pH) and water for injections.
Hyperlink to the Prescribing Information	See proposed Prescribing information in Module 1.3 from sequence 0149.
Indication(s) in the EEA	Current: Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years. Proposed: Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in paediatric patients from birth to 17 years.
Dosage in the EEA	**Current:** Sugammadex should only be administered by, or under the supervision of an anaesthetist. The use of an appropriate neuromuscular monitoring technique is recommended to monitor the recovery of neuromuscular blockade. The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed. The recommended dose does not depend on the anaesthetic regimen. Sugammadex can be used to reverse different levels of rocuronium or vecuronium induced neuromuscular blockade. *Adults* <u>Routine reversal:</u> A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post-tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 3 minutes. A dose of 2 mg/kg sugammadex is recommended if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T_4/T_1 ratio to 0.9 is around 2 minutes. Using the recommended doses for routine reversal will result in a slightly faster median time to recovery of the T_4/T_1 ratio to 0.9 of rocuronium when compared to vecuronium induced neuromuscular blockade. <u>Immediate reversal of rocuronium-induced blockade:</u> If there is a clinical need for immediate reversal following administration of rocuronium a dose of 16 mg/kg sugammadex is recommended. When 16 mg/kg sugammadex is administered 3 minutes after a bolus dose of 1.2 mg/kg rocuronium bromide, a median time to recovery of the T_4/T_1 ratio to 0.9 of approximately 1.5 minutes can be expected.

Table I.1: Product Overview

	There is no data to recommend the use of sugammadex for immediate reversal following vecuronium induced blockade. Re-administration of sugammadex: In the exceptional situation of recurrence of neuromuscular blockade post-operatively after an initial dose of 2 mg/kg or 4 mg/kg sugammadex, a repeat dose of 4 mg/kg sugammadex is recommended. Following a second dose of sugammadex, the patient should be closely monitored to ascertain sustained return of neuromuscular function. Re-administration of rocuronium or vecuronium after sugammadex: For waiting times for re-administration of rocuronium or vecuronium after reversal with sugammadex, refer to "Special warnings and precautions for use" in the SmPC. *Additional information on special population* Renal impairment: The use of sugammadex in patients with severe renal impairment (including patients requiring dialysis (CrCl < 30 mL/min)) is not recommended. Studies in patients with severe renal impairment do not provide sufficient safety information to support the use of sugammadex in these patients. For mild and moderate renal impairment (CrCl≥ 30 and < 80 mL/min): the dose recommendations are the same as for adults without renal impairment. Elderly patients: After administration of sugammadex at reappearance of T2 following a rocuronium induced blockade, the median time to recovery of the T4/T1 ratio to 0.9 in adults (18-64 years) was 2.2 minutes, in elderly adults (65-74 years) it was 2.6 minutes and in very elderly adults (75 years or more) it was 3.6 minutes. Even though the recovery times in elderly tend to be slower, the same dose recommendation as for adults should be followed. Obese patients: In obese patients, including morbidly obese patients (body mass index ≥ 40 kg/m 2), the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed. Hepatic impairment: Studies in patients with hepatic impairment have not been conducted. Caution should be exercised when considering the use of sugammadex in patients with severe hepatic impairment or when hepatic impairment is accompanied by coagulopathy. For mild to moderate hepatic impairment: as sugammadex is mainly excreted renally no dose adjustments are required. *Paediatric population* **Current:** The data for the paediatric population are limited (one study only for reversal of rocuronium induced blockade at reappearance of T2). Children and adolescents: For routine reversal of rocuronium induced blockade at reappearance of T2 in children and adolescents (2-17 years) 2 mg/kg sugammadex is recommended. BRIDION 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population. Other routine reversal situations have not been investigated and are therefore not recommended until further data become available.

Table I.1: Product Overview

	Immediate reversal in children and adolescents has not been investigated and is therefore not recommended until further data become available. Term newborn infants and infants: There is only limited experience with the use of sugammadex in infants (30 days to 2 years), and term newborn infants (less than 30 days) have not been studied. The use of sugammadex in term newborn infants and infants is therefore not recommended until further data become available. Method of administration Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing intravenous line. Sugammadex has only been administered as a single bolus injection in clinical trials. **Proposed:** *Paediatric population (birth to 17 years of age)* Bridion 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population. Routine reversal: A dose of 4 mg/kg sugammadex is recommended for reversal of rocuronium induced blockade if recovery has reached at least 1-2 PTC. A dose of 2 mg/kg is recommended for reversal of rocuronium induced blockade at reappearance of T_2. Immediate reversal: Immediate reversal has not been investigated in the paediatric population. Method of administration Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing intravenous line. Sugammadex has only been administered as a single bolus injection in clinical trials.
Pharmaceutical form(s) and strengths	**Current:** Solution for injection Each 2 mL and 5 mL vial solution for injection (100 mg/mL strength injection) is a clear and colourless to slightly yellow solution.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Reversal of neuromuscular blockade induced by rocuronium or vecuronium

Incidence and Prevalence:

Not applicable for the indication.

None of the potential and identified risks are prevalent conditions in the target population.

Demographics of the population in the indication:

Not applicable.

Risk factors for the disease:

Not applicable.

The main existing treatment options:

Traditionally, reversal of NMB has been achieved via the use of acetylcholinesterase inhibitors (AChEIs), that increase the availability of acetylcholine at the neuromuscular junction and reverse NMB, however these agents do not affect the metabolism or elimination of neuromuscular blocking agents (NMBAs) themselves. At maximal inhibition of acetylcholinesterase activity (deep NMB) neuronal release of acetylcholine becomes the rate limiting step in further restoration of muscle function, limiting the efficacy that can be achieved with AChEIs. Because of their indirect mechanism of action (MOA), AChEIs cannot reverse deep NMB, therefore, deep NMB cannot be maintained to the end of the surgical procedure. AChEIs also have unwanted side effects related to increased cholinergic activity. To help ameliorate these, anti-muscarinics, such as atropine or glycopyrrolate, are usually co-administered with AChEIs, but this practice leads to additional side effects. Finally, AChEIs are associated with risk for recurrence of NMB or post-operative residual paralysis.

Sugammadex is a modified γ cyclodextrin and a selective relaxant binding agent (SRBA), which has been developed to reverse any depth of NMB including deep NMB, induced by the NMBAs rocuronium or vecuronium bromide. Sugammadex acts by forming high affinity complexes with rocuronium or vecuronium, which prevents the complexed NMBAs from binding to nicotinic receptors in the neuromuscular junction, thus reversing NMB. This unique and direct mechanism of action distinguishes sugammadex from AChEI NMB reversal agents such as neostigmine, and frees sugammadex of the limitations associated with the use of AChEIs. Sugammadex does not cross the blood-brain-barrier and does not stimulate the cholinergic nervous system, thus avoiding the unwanted autonomic nervous system side effects associated with neostigmine and similar drugs, thereby negating the need

for concurrent administration of antimuscarinic drugs in an attempt to counteract AChEI-related side effects.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Not applicable.

Important co-morbidities:

Not applicable.

The target population consists of patients with an indication for surgery for which they receive NMB. Potentially, every individual in the general population can be part of this population. Therefore, the target population is considered to be the same as the general population.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage:

Overall, sugammadex has no identified risk based upon non-clinical evaluations.

Sugammadex was extensively evaluated in a series of nonclinical safety studies including genetic toxicology, safety pharmacology, developmental and reproductive toxicology, and in repeat-dose intravenous toxicology studies in rodent and non-rodent species. Relatively wide multiples exist between exposures associated the NOAEL (No Adverse Effect Level) in nonclinical species in comparison to exposures associated with intended clinical administration of sugammadex. Systemic exposures achieved in dogs following intravenous administration at 250 mg/kg/day (1075 $\mu g \bullet hr \bullet mL^{-1}$) were comparable to those in rats receiving sugammadex at 500 mg/kg/day (1050 $\mu g \bullet hr \bullet mL^{-1}$). Systemic exposures at these doses in nonclinical species provided approximately 26X greater exposure compared to systemic exposure after administration of 4 mg/kg in humans or approximately 7X greater exposure after administration of 16 mg/kg in humans.

Reproductive and developmental studies determined that sugammadex had no effect on male fertility and no effect on female fertility in rats following daily intravenous administration at 500 mg/kg/day. No effects on early embryonic or fetal development, and no effect on skeletal development, were noted following administration at 500 mg/kg/day to pregnant rats, or at 200 mg/kg/day to pregnant rabbits. Sugammadex had no untoward effect on prenatal and postnatal development of rats. Similarly, no effects on reproductive parameters, physical development, or neurobehavioral development were noted in the F_1 generation.

Nonclinical studies determined that sugammadex had no long-term consequence regarding bone quality, bone strength, or bone metabolism in juvenile rats and had no adverse effect on fracture repair or remodeling in young adult rats.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief Overview of Development

Overall, in the cumulative global database of 62 clinical studies, 36 were efficacy studies. Safety and tolerability were assessed based on data from 60 clinical trials in which IV sugammadex was administered. The Phase I studies were conducted to assess the initial safety and tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) effects of sugammadex in healthy subjects as well as special safety populations, including subjects with severe and moderate renal impairment. The potential for hypersensitivity to repeated exposure was investigated in two dedicated safety studies in healthy subjects. In the Phase 2, Phase 3 and post-marketing studies, populations that have been exposed to sugammadex were subjects undergoing surgery for which the use of an NMBA (neuromuscular blocking agent) was required or where an NMBA was indicated for anaesthetic purposes. Studies were conducted in several countries in Europe, Asia, and North America. There were 4 post-marketing clinical trials, involving American Society of Anesthesiologists (ASA) Class 3 and 4 subjects (Protocol 145), morbidly obese subjects where morbid obesity is defined as body mass index (BMI) ≥40 kg/m2 (Protocol 146), children and adolescents 2 to <17 years (Protocol 089) and neonates and infants aged birth to <2 years (Protocol 169).

SIII.2 Clinical Trial Exposure

All clinical trials with sugammadex that were sponsored by the MAH and that were completed as of 09-Feb-2024 are included below. The sugammadex clinical development program included 62 trials with a total of 9897 subject exposures to IV study medications (sugammadex, neostigmine or placebo,) in 7118 unique subjects. Of these, 6829 subject exposures were to IV sugammadex in 5283 unique subjects; 1981 subject exposures in 1396 unique subjects to IV placebo, and 1087 subject exposures in 1087 unique subjects to IV neostigmine. Subjects are unique within each treatment group, but the total number of unique subjects in each treatment group differs from the total number of unique subjects in the program as some subjects were in multiple treatment groups, (e.g., in the cross-over trials).

Three datasets were defined for analyses from the total of 62 trials conducted in the sugammadex clinical program. These include two key pooled datasets, Pooled Phase 1-3 trials and Pooled Phase 1 trials. The third dataset is a post-marketing clinical trial dataset that includes 4 completed trials in which the data are evaluated by trial.

The first key pooled dataset consists of:

Pooled Phase 1–3 Trials: these include data from all subjects (healthy subjects, and surgical subjects) who were administered anesthesia and/or a neuromuscular blocking agent (NMBA), and who were exposed to sugammadex, active comparators, or placebo. This dataset is referred to as "**Pooled Phase 1-3 Trials**". Trials represented in this dataset include both open-label/uncontrolled and blinded/active-comparator- or placebo-controlled trial designs. This dataset consisted of 42 trials. Note that a Phase 5 trial (P07981) is included in this dataset.

Within the Pooled Phase 1–3 Trials, two subsets of pooled studies were defined to characterize the safety profile of sugammadex relative to placebo and neostigmine:

a. Thirteen trials that compared sugammadex vs. placebo, referred to as "**Pooled Placebo-controlled**" trials, and

b. Eight trials which compared sugammadex vs. neostigmine, noted as "**Pooled Neostigmine-controlled**" trials.

The second key pooled dataset consists of:

Pooled Phase 1 Trials: The majority of subjects in this pooled group are healthy subjects, however, there are 21 unique subjects included in this group with renal impairment (RI) who participated in trial P105. All subjects in this pooled group were exposed to sugammadex and/or placebo but did not receive anesthesia and did not receive a NMBA, This dataset is referred to as the "**Pooled Phase 1**" trials. This dataset consists of 14 trials.

The third clinical trial dataset consists of:

Post-Marketing Trials: this dataset includes data from all subjects (surgical subjects) who were administered anesthesia and/or a NMBA, and who were exposed to sugammadex or active comparators. This dataset is referred to as "**Post-Marketing**" trials. The trials represented in this dataset include 4 blinded/active-comparator - controlled trials: protocol 145 (P145), protocol 146 (P146), protocol 089 (P089) and protocol 169 (P169). The clinical trials P145, P146, and P089 are presented in Annex 2 (tabular overview).

Adult and pediatric subjects were exposed to sugammadex in the following surgical procedures: female genital organ surgery; musculoskeletal system surgery; digestive system and spleen surgery; ear, nose, and larynx surgery; and urinary system, male genital organs, and retroperitoneal space surgery. In combination with all other types of surgery wherein exposure to sugammadex was studied, the MAH considers the studied population an adequate representation of the target population.

Clinical Trial Exposure

The numbers of exposures to IV sugammadex and comparators are presented in this section. An “exposure” is defined as each instance a subject received IV trial medication, and an individual subject may have had multiple exposures. For example, in the Phase 1 trials, several exposures of trial medication occurred in the cross-over trials where the same subject would receive differing doses of sugammadex or comparators. For the overall sugammadex program, a “unique” subject is an individual subject who received trial medication (sugammadex, neostigmine, or placebo) and was counted only once even if exposed to multiple trial medications in one study. Subjects are unique within each treatment group, but the total of unique subjects in each treatment group differs from the total of unique subjects in the program because some subjects were in multiple treatment groups, such as in the cross-over trials. This is also true for the definition of “unique” within each pooled subject population; subjects within each pooled group are unique to that group; the total of unique subjects in each pooled group differs from the total of unique subjects in the program. For

example, subjects in 19.4.109 were included in both the Pooled Phase 1-3 trials (19.4.109II) and in the Pooled Phase 1 trials (19.4.109III), these subjects contributed to the total number of unique subjects for both pools. The Phase 1 Renal PK study (P105) (open-label, single dose study) is a two-part study included in the Pooled Phase 1 safety database as studies 105A (Part 1) and 105B (Part 2). Preliminary PK data from the first 24 subjects in this study (now designated as Part 1) indicated that in some subjects, doses may not have been administered directly into the vein and likely infiltrated surrounding tissue based on substantial delays in Tmax and an apparent absorption phase in the pharmacokinetic profiles (105A). Therefore, Part 2 (105B) of the study was conducted because of dosing irregularities. Eligible subjects from Part 1 could enroll in Part 2 (n=9 subjects participated in both parts). There are 33 unique subjects in the study with a total of 42 subject exposures (n=24 exposures in 105A and n=18 exposures in 105B). All data from P105A and P105B are included in the exposure counts for Pooled Phase 1 studies.

In all Phase 2-3 trials and in Phase 1 trials 19.4.101 (Parts II and III), 19.4.102, 19.4.115, P06315, P06042, P05997, 19.4.112, 19.4.113, P07025, P07044, P101 and P105, the trial medication was administered as a rapid IV bolus (i.e., administered over ~10 seconds with the exception of P06042 where bolus was administered in less than 30 seconds). Subjects in the Phase 1 Trial 19.4.107 received a single IV bolus of 14C labeled sugammadex. In other Phase 1 trials, the trial medication was administered as a 2-min (19.4.105), 4-min (19.4.108 and 19.4.109), or 5-min (19.4.106) IV infusion. Because of the rapid dosing paradigm, duration of exposure is not included in the table displayed for exposure.

The number of unique subjects in the sugammadex, neostigmine, or placebo treatment groups and number of IV subject exposures to sugammadex, neostigmine, or placebo in each of the pooled datasets (as defined previously) are shown in Table SIII.2.1

Table SIII.2.1: Number of Subjects Exposed to Sugammadex, Placebo, or Neostigmine in the Overall Clinical Sugammadex Program

	Sugammadex		Placebo		Neostigmine		Total Clinical Program[a]	
	Unique subjects[b]	Subject exposures IV medication	Unique subjects[b]	Subject exposures IV medication	Unique subjects[b]	Subject exposures IV medication	Unique subjects[b]	Subject exposures IV medication
Total Clinical Program (N=62 Trials)[c]	5283	6829	1396	1981	1087	1087	7118	9897
Pooled Phase 1-3[d] (N=42 Trials)	3519	3601	544	544	930	930	4983	5075
Pooled Placebo-controlled (N=13 Trials)	1078	1078	544	544	---	---	1612	1622
Pooled Neostigmine-controlled (N=8 Trials)	871	871	---	---	881	881	1752	1752
Pooled Phase 1[e] (N=14 Trials)	937	2396	838	1424	---	---	1200	3820
Post-Marketing (N=4 Trials)	779	779	---	---	154	154	933	933

N = number of trials; IV = intravenous.

a Includes subjects exposed to any dose of sugammadex, neostigmine or placebo. *Because subjects in some studies could have multiple exposures in different treatment groups, the number of unique subjects in each treatment group does not equal the total number of unique subjects in the total clinical program.*

b The count for unique subjects includes both subjects exposed to IV administration as well as skin prick tests. In case a subject received sugammadex via skin testing the subject is counted once in the sugammadex group. When a subject was skin tested, but did not receive sugammadex, the subject is counted once in the placebo group. Furthermore, when a subject received sugammadex or placebo both via IV or skin testing, the subject is counted once in the sugammadex or placebo group, respectively. Skin prick tests were done in Phase I studies 19.4.106 (9 exposures/7 subjects), 19.4.110 (23 exposures/23 subjects), 19.4.115 (1 exposure/1 subject), and P06042 (191 exposures/190 subjects) for a total of 224 exposures and 221 subjects. *Because subjects in some studies could have multiple exposures in different pooled groups, the total across pooled groups does not equal the total number of unique subjects (or exposures) in the total clinical program.*

c Includes studies 19.4.110 and 19.4.109I (group B) in total counts of studies in program and exposures, but these studies are not included in any pooled groups.

d Includes subjects in Phase 5 study P07981 and studies using anesthesia and/or NMB.

e Includes Phase 1 studies without anesthesia or NMB.

Clinical Trial Exposure by Dose

Regardless of the trial phase, each trial which included a placebo or active control group was either blinded or there was a blinded safety assessor responsible for identification and assessment of adverse events (AEs). Therefore, it is considered appropriate to pool the safety-related data of these studies as defined previously.

Sugammadex has been administered to subjects in doses ranging from <2 mg/kg to 32 mg/kg in Phases 2-3 trials and from <2 mg/kg to 96 mg/kg in Phase 1 trials.

The number of adult subject exposures to IV sugammadex at each dose of sugammadex used in the Pooled Phase 1-3 trials is presented in Table SIII.2.2. There were 3601 total subject exposures to sugammadex (in 3519 unique subjects) at doses up to 32 mg/kg.

Most subject exposures (n=1921) were at the 4 mg/kg dose of sugammadex followed by 895 subject exposures at the 2 mg/kg dose of sugammadex, which are the proposed recommended doses for routine reversal of moderate and deep NMB. A total of 98 subject exposures occurred at the 16 mg/kg dose of sugammadex, which is only recommended if there is an urgent or emergent need to reverse NMB following administration of rocuronium.

Table SIII.2.2: Number of Adult Subject Exposures to Placebo or Sugammadex by Dose in Pooled Phase 1-3 Trials

Study Phase	Placebo (mg/kg)	Sugammadex (mg/kg)										
	0	<2	2	3	4	6	8	12	16	20	32	Total[a]
	N	n	n	n	n	n	n	n	n	n	n	N
Phase 1	77	4	26	0	89	0	3	0	5	4	168	299
Phase 2	84	250	212	9	167	28	122	39	38	0	1	866
Phase 3[b]	383	40	657	17	1665	0	0	0	55	2	0	2436
Total	**544**	**294**	**895**	**26**	**1921**	**28**	**125**	**39**	**98**	**6**	**169**	**3601**

n= number of subject exposures at each dose; N=total number of exposures per treatment group and phase
[a] Total Sugammadex = number of subject exposures to intravenous sugammadex across all doses.
[b] Includes Phase 5 study P07981

As noted previously, all subjects in the Pooled Phase 1 group were exposed to sugammadex and/or placebo but did not receive anesthesia and did not receive a NMBA. Table SIII.2.3 shows the number of subjects exposed to the various doses of sugammadex or placebo in these Phase 1 trials.

Table SIII.2.3: Number of Adult Subject Exposures to Sugammadex or Placebo by Dose (mg/kg) in Pooled Phase 1 Trials

Study Phase	Placebo 0 mg/kg	Sugammadex (mg/kg)										Total[a] Sugammadex
		<2	2	3	4	8	12	16	32	64	96	
	N	n	n	n	n	n	n	n	n	n	n	N
Phase 1	1424	46	6	2	1162	31	1	969	155	12	12	2396

N = number of exposures per treatment group; n=number of subject exposures at each dose.
[a] Total column includes subjects exposed to all doses of intravenous sugammadex (<2 to 96 mg/kg).

The number of subjects included in the post-marketing trial P145 are presented in Table SIII.2.4. All subjects were adult and were exposed to IV sugammadex at doses ranging from 2 mg/kg to 16 mg/kg. Table SIII.2.5 shows the clinical trial exposure to sugammadex by duration for P145.

Table SIII.2.4: Clinical Trial Exposure to Sugammadex by Dose (Post-Marketing Trial P145: Study on ASA Class 3 and 4 Treated Subjects)

Dose of Exposure	Subjects	Subject Time (years)
Any dose	280	0.7666
≥ 0 mg/kg to < 2 mg/kg	12	0.0329
≥ 2 mg/kg to < 3 mg/kg	94	0.2574
≥ 3 mg/kg to < 4 mg/kg	39	0.1068
≥ 4 mg/kg to < 5 mg/kg	68	0.1862
≥ 5 mg/kg to < 15 mg/kg	0	0.0000
≥ 15 mg/kg to < 16 mg/kg	24	0.0657
≥ 16 mg/kg to < 17 mg/kg	43	0.1177

Each subject is counted once on each applicable dose category row.
One subject who actually received the planned dose 16 mg/kg was included in the ≥ 0 mg/kg to < 2 mg/kg category due to a confirmed non-critical data entry error identified post database lock.

Table SIII.2.5: Clinical Trial Exposure to Sugammadex by Duration (Post-Marketing Trial P145: Study on ASA Class 3 and 4 Treated Subjects)

Duration of Exposure	Subjects	Subject Time (years)
1 day	280	0.7666
Each subject is counted once on each applicable duration category row.		

The number of subjects included in the post-marketing trial P146 are presented in Table SIII.2.6 All subjects were adult and were exposed to IV sugammadex at doses ranging from 2 mg/kg to 4 mg/kg based upon actual body weight (ABW) or ideal body weight (IBW). Table SIII.2.7 shows the clinical trial exposure to sugammadex by duration for P146.

Table SIII.2.6: Clinical Trial Exposure to Sugammadex by Dose (Post-Marketing Trial P146: Study on Morbidly Obese Treated Subjects)

Dose of Exposure	Subjects	Subject Time (years)
Any dose	150	0.4107
≥ 0 mg/kg to < 2 mg/kg	57	0.1561
≥ 2 mg/kg to < 3 mg/kg	55	0.1506
≥ 3 mg/kg to < 4 mg/kg	7	0.0192
≥ 4 mg/kg to < 5 mg/kg	31	0.0849
Each subject is counted once on each applicable dose category row.		

Table SIII.2.7: Clinical Trial Exposure to Sugammadex by Duration (Post-Marketing Trial P146: Study on Morbidly Obese Treated Subjects)

Duration of Exposure	Subjects	Subject Time (years)
1 day	150	0.4107
Each subject is counted once on each applicable duration category row.		

The number of subjects included in the post-marketing trial P089 are presented in Table SIII.2.8 Subjects were aged 2 to <17 years and were exposed to IV sugammadex at doses ranging from 2 mg/kg to 4 mg/kg. Table SIII.2.9 shows the clinical trial exposure to sugammadex by duration for P089.

Table SIII.2.8: Clinical Trial Exposure to Sugammadex by Dose (Post-Marketing Trial P089: Study on Age 2 to <17 Years Treated Subjects)

Dose of Exposure	Subjects	Subject Time (years)
Any dose	242	0.6626
≥ 0 mg/kg to < 2 mg/kg	1	0.0027
≥ 2 mg/kg to < 3 mg/kg	50	0.1369
≥ 3 mg/kg to < 4 mg/kg	27	0.0739
≥ 4 mg/kg to < 5 mg/kg	164	0.4490
Each subject is counted once on each applicable dose category row.		

Table SIII.2.9: Clinical Trial Exposure to Sugammadex by Duration (Post-Marketing Trial P089: Study on Age 2 to <17 Years Treated Subjects)

Duration of Exposure	Subjects	Subject Time (years)
1 day	242	0.6626
Each subject is counted once on each applicable duration category row.		

The numbers of pediatric subjects exposed to IV sugammadex at doses ranging from 2 mg/kg to 4 mg/kg in post-marketing trial P169 are presented in Table SIII.2.10. Table SIII.2.11 shows the clinical trial exposure to sugammadex by duration for P169.

Table SIII.2.10: Clinical Trial Exposure to Sugammadex by Dose (Post-Marketing Trial P169: Study on Age Birth to <2 Years Treated Subjects)

Dose of Exposure	Subjects	Subject Time (years)
Any dose	107	0.2930
≥ 0 mg/kg to < 2 mg/kg	7	0.0192
≥ 2 mg/kg to < 3 mg/kg	37	0.1013
≥ 3 mg/kg to < 4 mg/kg	5	0.0137
≥ 4 mg/kg to < 5 mg/kg	58	0.1588
Each subject is counted once on each applicable dose category row.		

Table SIII.2.11: Clinical Trial Exposure to Sugammadex by Duration (Post-Marketing Trial P169: Study on Age Birth to <2 Years Treated Subjects)

Duration of Exposure	Subjects	Subject Time (years)
1 day	107	0.2930
Each subject is counted once on each applicable duration category row.		

Clinical Trial Exposure by Age Group and Gender

Table SIII.2.12 presents cumulative exposure to sugammadex in subjects by age group and gender. Age-specific trials in elderly and pediatric populations were conducted. In the elderly subject trial (19.4.305), elderly subjects received 2 mg/kg at re-appearance of T2 after rocuronium was administered. For reversal of NMB induced by vecuronium there are limited data for elderly (≥65 years) subject populations.

In the post-marketing trials P089 and P169, doses up to 4 mg/kg sugammadex were studied in 349 subjects aged birth to <17 years. In a previous trial (Protocol 19.4.306), infants, children, and adolescents with doses up to 4 mg/kg sugammadex had been studied. This group (51 pediatric subjects) has been excluded from the other exposure counts and tables.

Table SIII.2.12: Cumulative Subject Exposure to Sugammadex from Completed Clinical Trials by Age and Gender

	Number of Subjects		
Age Range (year)	**Male**	**Female**	**Total**
28 days–23 months	77	36	113
2–11 years	108	93	201
12–17 years	49	37	86
18 to 65	2795	2630	5425
66 to 75	328	304	632
76 and older	166	206	372
Total Pediatric (<18 years)	**234**	**166**	**400**
Total Adults	**3289**	**3140**	**6429**
Total	**3523**	**3306**	**6829**
Note: Data from completed trials			

Data by age and gender for the recommended sugammadex doses of 2, 4 or 16 mg/kg are shown in Table SIII.2.13 and Table SIII.2.14 for the Pooled Phase 1-3 trials and the Pooled Phase 1 trials. Data by age and gender in Table SIII.2.15, Table SIII.2.16, Table SIII.2.17 and Table SIII.2.18 are shown for the post-marketing trials (P145, P146, P089, and P169), respectively.

Table SIII.2.13: Demographic and Baseline Characteristics of Exposures for Adult Subjects who Received Anesthesia and/or NMBA and Placebo or Sugammadex in Pooled Phase I-III Studies by mg/kg Dose of Sugammadex

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total sugammadex
Parameter	Statistic/ Category					
Age (n [%])	n	544	895	1921	98	3601
	18-64 yr	345 (63)	692 (77)	1339 (70)	87 (89)	2766 (77)
	65-74 yr	118 (22)	132 (15)	349 (18)	9 (9)	516 (14)
	>=75 yr	81 (15)	71 (8)	233 (12)	2 (2)	319 (9)
Gender (n [%])	n	544	895	1921	98	3601
	Male	284 (52)	448 (50)	893 (46)	37 (38)	1776 (49)
	Female	260 (48)	447 (50)	1028 (54)	61 (62)	1825 (51)

Table SIII.2.14: Demographic and Baseline Characteristics of Exposures for Adult Healthy Volunteers who Received Placebo or Sugammadex in Phase I Studies Without NMBA and Without Anesthetics by mg/kg dose of Sugammadex

		0 mg/kg (Placebo)	2 mg/kg	4mg/kg	16 mg/kg	Total Sugammadex
Parameter	Statistic/ Category					
Age (n [%])	n	1424	6	1162	969	2396
	18-64 yr	1423 (100)	6 (100)	1138 (98)	969 (100)	2371 (99)
	65-74 yr	1 (0)	0 (0)	21 (2)	0 (0)	22 (1)
	>=75 yr	0 (0)	0 (0)	3 (0)	0 (0)	3 (0)
Gender (n [%])	n	1424	6	1162	969	2396
	Male	781 (55)	6 (100)	640 (55)	518 (53)	1306 (55)
	Female	643 (45)	0 (0)	522 (45)	451 (47)	1090 (45)

Table SIII.2.15: Clinical Trial Exposure to Sugammadex by Age Category and Gender (Post-Marketing Trial P145: Study on ASA Class 3 and 4 Treated Subjects)

Age Category (years)	Subjects			Subject Time (years)		
	Male	Female	Total	Male	Female	Total
< 65	54	35	89	0.1478	0.0958	0.2437
65 to 74	58	35	93	0.1588	0.0958	0.2546
> 74	54	44	98	0.1478	0.1205	0.2683
Total	166	114	280	0.4545	0.3121	0.7666

Table SIII.2.16: Clinical Trial Exposure to Sugammadex by Age Category and Gender (Post-Marketing Trial P146: Study on Morbidly Obese Treated Subjects)

Age Category (years)	Subjects			Subject Time (years)		
	Male	Female	Total	Male	Female	Total
65 and younger	36	98	134	0.0986	0.2683	0.3669
66 to 75	3	11	14	0.0082	0.0301	0.0383
76 and older	1	1	2	0.0027	0.0027	0.0055
Total	40	110	150	0.1095	0.3012	0.4107

Table SIII.2.17: Clinical Trial Exposure to Sugammadex by Age Category and Gender (Post-Marketing Trial P089: Study on Age 2 to <17 Years Treated Subjects)

Age Category (years)	Subjects			Subject Time (years)		
	Male	Female	Total	Male	Female	Total
2 to <6 years	60	42	102	0.1643	0.1150	0.2793
6 to <12 years	41	38	79	0.1123	0.1040	0.2163
12 to <17 years	34	27	61	0.0931	0.0739	0.1670
Total	135	107	242	0.3696	0.2930	0.6626

Table SIII.2.18: Clinical Trial Exposure to Sugammadex by Age Category and Gender (Post-Marketing Trial P169: Study on Age Birth to <2 Years Treated Subjects)

Age Category (years)	Subjects			Subject Time (years)		
	Male	Female	Total	Male	Female	Total
Birth to 27 days	17	6	23	0.0465	0.0164	0.0630
28 days to < 3 months	17	9	26	0.0465	0.0246	0.0712
3 months to < 6 months	18	11	29	0.0493	0.0301	0.0794
6 months to < 2 years	21	8	29	0.0575	0.0219	0.0794
Total	73	34	107	0.1999	0.0931	0.2930

Clinical Trial Exposure by Racial/Ethnic Origin

In the Phase 3 trials, race was collected as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White, and ethnicity was collected as Hispanic or Latino and not Hispanic or Latino. In Phase 1 and Phase 2 trials, however, race was collected as Asian, Caucasian, Black, and Other. Therefore, the race categories for the Phase 3 trials were mapped to the Phase 1 and Phase 2 race categories.

In the Post-Marketing trials, race was collected Black or African American, Native Hawaiian or Other Pacific Islander, and White, and ethnicity was collected as Hispanic or Latino and not Hispanic or Latino.

The majority of adult subjects exposed to sugammadex were Caucasian. Table SIII.2.19 and Table SIII.2.20 presents the sugammadex exposure in subjects by racial group for the Pooled Phase 1-3 trials and the Pooled Phase 1 trials, respectively. Data by race and ethnicity are shown in Table SIII.2.21 to Table SIII.2.28 for the post-marketing trials (P145, P146, P089, and P169), respectively.

Table SIII.2.19: Demographic and Baseline Characteristics of Exposures for Adult Subjects who Received Anesthesia and/or NMBA and Placebo or Sugammadex in Pooled Phase I-III Studies by mg/kg Dose of Sugammadex

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total sugammadex
Parameter	Statistic /Category					
Race (n [%])	n	544	895	1921	98	3601
	Asian	25 (5)	227 (25)	169 (9)	4 (4)	503 (14)
	Black	0 (0)	30 (3)	52 (3)	12 (12)	99 (3)
	Caucasian	513 (94)	632 (71)	1685 (88)	82 (84)	2975 (83)
	Other	6 (1)	6 (1)	14 (1)	0 (0)	23 (1)
	Missing	0	0	1	0	1
Ethnicity Hispanic or Latino (n [%])	n	544	895	1921	98	3601
	Yes	5 (1)	22 (3)	43 (2)	15 (25)	86 (3)
	No	485 (99)	739 (97)	1787 (98)	45 (75)	2993 (97)
	Missing	54	134	91	38	522

Table SIII.2.20: Demographic and Baseline Characteristics of Exposures for Adult Healthy Volunteers who Received Placebo or Sugammadex in Phase I Studies Without NMBA and Without Anesthetics by mg/kg Dose of Sugammadex

		0 mg/kg (Placebo)	2 mg/kg	4mg/kg	16 mg/kg	Total Sugammadex
Parameter	Statistic /Category					
Race (n [%])	n	1424	6	1162	969	2396
	Asian	39 (3)	0 (0)	14 (1)	35 (4)	79 (3)
	Black	69 (5)	0 (0)	85 (7)	71 (7)	158 (7)
	Caucasian	1269 (89)	6 (100)	1027 (88)	836 (86)	2096 (87)
	Other	47 (3)	0 (0)	36 (3)	27 (3)	63 (3)
	Missing	0	0	0	0	0
Ethnicity Hispanic or Latino (n [%])	n	1424	6	1162	969	2396
	Yes	348 (25)	0 (0)	326 (29)	294 (31)	621 (27)
	No	1031 (75)	0 (0)	813 (71)	644 (69)	1639 (73)
	Missing	45	6	23	31	136

Table SIII.2.21: Clinical Trial Exposure to Sugammadex by Race (Post-Marketing Trial P145: Study on ASA Class 3 and 4 Treated Subjects)

Race	Subjects	Subject Time (years)
Black Or African American	14	0.0383
Native Hawaiian Or Other Pacific Islander	1	0.0027
White	265	0.7256
Total	280	0.7666

Table SIII.2.22: Clinical Trial Exposure to Sugammadex by Ethnicity (Post-Marketing Trial P145: Study on ASA Class 3 and 4 Treated Subjects)

Ethnicity	Subjects	Subject Time (years)
Hispanic Or Latino	6	0.0164
Not Hispanic Or Latino	272	0.7447
Not Reported	1	0.0027
Unknown	1	0.0027
Total	280	0.7666

Table SIII.2.23: Clinical Trial Exposure to Sugammadex by Race (Post-Marketing Trial P146: Study on Morbidly Obese Treated Subjects)

Race	Subjects	Subject Time (years)
Black Or African American	10	0.0274
Native Hawaiian Or Other Pacific Islander	1	0.0027
White	139	0.3806
Total	150	0.4107

Table SIII.2.24: Clinical Trial Exposure to Sugammadex by Ethnicity (Post-Marketing Trial P146: Study on Morbidly Obese Treated Subjects)

Ethnicity	Subjects	Subject Time (years)
Hispanic Or Latino	8	0.0219
Not Hispanic Or Latino	140	0.3833
Not Reported	1	0.0027
Unknown	1	0.0027
Total	150	0.4107

Table SIII.2.25: Clinical Trial Exposure to Sugammadex by Race (Post-Marketing Trial P089: Study on Age 2 to <17 Years Treated Subjects)

Race	Subjects	Subject Time (years)
American Indian Or Alaska Native	1	0.0027
Asian	9	0.0246
Black Or African American	6	0.0164
Multiple	6	0.0164
White	215	0.5887
NULL	5	0.0137
Total	242	0.6626

Table SIII.2.26: Clinical Trial Exposure to Sugammadex by Ethnicity (Post-Marketing Trial P089: Study on Age 2 to <17 Years Treated Subjects)

Ethnicity	Subjects	Subject Time (years)
Hispanic Or Latino	26	0.0712
Not Hispanic Or Latino	203	0.5558
Not Reported	4	0.0110
Unknown	9	0.0246
Total	242	0.6626

Table SIII.2.27: Clinical Trial Exposure to Sugammadex by Race (Post-Marketing Trial P169: Study on Age Birth to <2 Years Treated Subjects)

Race	Subjects	Subject Time (years)
American Indian Or Alaska Native	7	0.0192
Asian	19	0.0520
Black Or African American	2	0.0055
Multiple	1	0.0027
White	78	0.2136
Total	107	0.2930

Table SIII.2.28: Clinical Trial Exposure to Sugammadex by Ethnicity (Post-Marketing Trial P169: Study on Age Birth to <2 Years Treated Subjects)

Ethnicity	Subjects	Subject Time (years)
Hispanic Or Latino	25	0.0684
Not Hispanic Or Latino	81	0.2218
Not Reported	1	0.0027
Total	107	0.2930

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Populations that have been exposed to sugammadex in clinical trials are healthy subjects and subjects undergoing surgery for which the use of an NMBA was required or where an NMBA was indicated for anaesthetic purposes. The administration of multiple doses of sugammadex has been limited to Phase 1 studies. Post-marketing exposure is limited to patients undergoing surgery for which the use of an NMBA (rocuronium or vecuronium) was indicated for anaesthetic purposes.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Hypersensitivity to cyclodextrins (including sugammadex)	Population cannot be treated with sugammadex because of expected allergic reactions which may lead to serious and/or life-threatening events	No	Information is labelled
Patients with severe renal impairment	Minimize data variability and improve efficiencies of the study logistics	No	Sugammadex is not recommended for use in patients with severe (CrCl <30 mL/min) renal impairment including those requiring dialysis.
Patients with significant hepatic dysfunction	Minimize data variability and improve efficiencies of the study logistics	No	Sugammadex is neither metabolized nor excreted by the liver; therefore, dedicated studies in patients with hepatic impairment have not been conducted. This information is labelled.
Anatomical malformations that would preclude intubation	Minimize data variability and improve efficiencies of the study logistics	No	Anatomical malformations may decrease the capability of patients to complete the treatment and also would result in data variability.
Medical or physical conditions expected to interfere with neuromuscular monitoring	Minimize data variability and improve efficiencies of the study logistics	No	Subjects who have a condition, or received medication, known to interfere with NMBAs, implies that there is no dedicated data on the efficacy and safety of sugammadex in these subjects. The SmPC holds warnings regarding the use of sugammadex in combination with drugs that potentiate NMB.
Known or suspected neuromuscular disorders impairing NMB	Minimize data variability and improve efficiencies of the study logistics	No	Subjects who have a neuromuscular disorder, known to interfere with NMBAs, implies that there are no data on the efficacy and safety of sugammadex in these subjects. The SmPC holds warnings regarding the use of sugammadex in combination with drugs that potentiate NMB

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Known or suspected to have a (family) history of malignant hyperthermia	Minimize data variability and improve efficiency of the study logistics	No	Administering the study drug to such patients might confound the results or have an impact on the efficacy of the study drug, as malignant hyperthermia may be triggered by anesthetic agents.
Pregnancy and lactation	• No studies have been carried out in patients with childbearing potential not using any of the following methods of birth control: condom or diaphragm with spermicide, vasectomized partner (>6 months), Intrauterine Device (IUD), and abstinence. • Excretion of sugammadex in human milk has not been studied. Based on pre-clinical data, excretion in human milk is to be expected.	No	Information is included in the SmPC, that no clinical data related to sugammadex exposure during pregnancy are available. It is unknown whether sugammadex is excreted in human breast milk.
Prior participation in the trial	Minimize data variability and improve efficiencies of the study logistics	No	Protect patient from potential drug interactions because of residual of previous investigational drug. Unknown drug interactions may induce safety concern and/or an impact on the efficacy of the study drug.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table SIV.2.1: Limitations of Clinical Trial Program

Ability to Detect Adverse Reactions	Limitation of Trial Program	Discussion of Implications for Target Population
Which are rare (it may be appropriate to choose other adverse drug reaction (ADR) frequencies)	In completed Phase 1-3 trials with anaesthesia and/or NMBA, there were 3601 adult and 51 pediatric exposures to IV sugammadex following administration of rocuronium, vecuronium, or pancuronium. Two post-marketing trials with 349 pediatric exposures to IV sugammadex have also been completed.	The sample size for pediatric subjects is not large enough to allow the detection of rare adverse experiences occurring with a frequency of at least 1 in 10,000.
Due to prolonged exposure	Limited exposure to administration of sugammadex is available; lifetime clinical exposure data do not exist.	Not applicable
Due to cumulative effects	Dosing was performed in up to three repeated IV bolus sugammadex doses within the program.	Cumulative effects were examined in the healthy volunteer hypersensitivity studies P06042 and P101 with three exposures of drug in dosing periods separated by approximately five weeks to allow potential sensitization to develop. More than 3 doses of IV sugammadex were not examined.
Which have a long latency	Not applicable because of short half-life of drug.	Half-life of drug is ~2 hrs with concentrations not measurable at 24 hours postdose in subjects with normal renal function and hence, clinical monitoring in the clinical program would have captured ADRs over this interval and likely exceeded this interval.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure Total number of subjects	
Pregnant women and breastfeeding women	• No clinical trial data on exposed pregnancies are available. • Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. The SmPC includes a warning that caution is to be exercised when administrating sugammadex to pregnant women. • Excretion of sugammadex in human milk has not been studied. Based on pre-clinical data, excretion in human milk is to be expected. The SmPC holds a warning that caution is to be exercised when administrating sugammadex to breastfeeding women.	
Patients with hepatic impairment including hepatic impairment accompanied by coagulopathy	• Sugammadex is neither metabolized nor excreted by the liver; therefore, dedicated studies in patients with hepatic impairment have not been conducted and, in addition, there is no information on the use of sugammadex in patients with known coagulopathies. • In the pooled Phase 1-3 placebo-controlled trials there were 43 (4%) of 1078 subject exposures to sugammadex.	
Patients with renal impairment (GFR < 80 mL/min)	Baseline blood sample GFR estimated by Cockcroft-Gault	379 subjects exposed to sugammadex
	Dedicated study[a] (19.4.304)	15 subjects exposed to sugammadex
	Dedicated study[a] (19.4.328)	37 subjects exposed to sugammadex
	Dedicated study[a] (19.4.333)	6 subjects exposed to sugammadex
	Dedicated study[a] (P105)	33 subjects exposed to sugammadex
Patients with cardiovascular impairment	Dedicated study[a] (19.4.309)	76 subjects exposed to sugammadex
Patients with pulmonary impairment	Dedicated study[a] (19.4.308)	68 subjects exposed to sugammadex
Immunocompromised (IC) patients	• No clinical trial data on immunocompromised patients are available. • Given the unique safety profile and risks associated with surgery in IC patients, these population was excluded from clinical trials during sugammadex development.	
American Society of Anesthesiologists classification (ASA) Class 4	• ASA class 4 definition: A patient with an incapacitating systemic disease that is a constant threat to life. • Post-marketing trial completed in 2020 that specifically evaluated the safety of sugammadex in ASA Class 3 or 4 subjects. Trial concluded 1) At doses of 2- or 4-mg/kg sugammadex, the incidences of treatment-emergent sinus bradycardia and sinus tachycardia are generally lower than neostigmine + glycopyrrolate and 2) sugammadex 2-, 4-, and 16-mg/kg is well tolerated in reversing moderate or deep levels of rocuronium or vecuronium-induced NMB. • 280 subjects were exposed to sugammadex in the post-marketing trial and 2 subjects were exposed to sugammadex in the Pooled Phase 1-3 trials.	

Table SIV.3.1: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure Total number of subjects
Morbidly obese patients	• Post-marketing trial completed in 2019 which specifically evaluated sugammadex dosing of morbidly obese patients based on actual body weight (ABW) vs. ideal body weight (IBW). Trial concluded 1) Time to recovery to a TOF ratio ≥0.9 with sugammadex is faster for subjects dosed with sugammadex according to ABW vs IBW; 2) Sugammadex is well tolerated when dosed according to ABW or IBW, pooled across depth of block and NMBA and 3) Treatment-emergent bradycardia, treatment-emergent tachycardia, and other treatment-emergent arrhythmias occur with similar incidences when sugammadex was dosed according to ABW or IBW. • 150 subjects were exposed to sugammadex.
Exposure in children and adolescents	• Post-marketing trial completed in 2020 that specifically evaluated the efficacy, safety, and pharmacokinetics of sugammadex in patients aged 2 to <17 years. Trial concluded 1) Time to recovery to a TOF ratio of ≥0.9 is faster when dosed with sugammadex 2 mg/kg compared to neostigmine for the reversal of moderate NMB. 2) Times to recovery to TOF ratios of ≥0.7, ≥0.8, and ≥0.9 are rapid when dosed with sugammadex 4 mg/kg (no formal comparator) for the reversal of deep NMB and is consistent with those observed in the moderate block setting. 3) Sugammadex is well tolerated by pediatric participants aged 2 to <17 years. 4) Incidences of clinically relevant bradycardia and treatment-emergent bradycardia are generally balanced across treatment groups. • 242 subjects were exposed to sugammadex in the post-marketing trial and 51 subjects were exposed to sugammadex from one study in the Pooled Phase 1-3 trials.
Exposure in infants and neonates	• Post-marketing trial completed in 2024 that specifically evaluated the efficacy, safety, and pharmacokinetics of sugammadex in patients aged birth to <2 years. Trial concluded 1) Sugammadex 2 mg/kg is superior to neostigmine in reversing moderate NMB as measured by time to neuromuscular recovery. 2) Sugammadex 2 mg/kg is similar to neostigmine in time to extubation. 3) Sugammadex 2 mg/kg and 4 mg/kg are well tolerated by pediatric participants aged birth to <2 years when used to reverse moderate or deep levels of rocuronium- or vecuronium-induced NMB. 4) Incidences of clinically relevant bradycardia and treatment-emergent bradycardia are generally balanced across treatment groups. • 107 subjects were exposed to sugammadex in the post-marketing trial.

[a] Renal status known in the trials 19.4.304, 19.4.308, 19.4.309, 19.4.328, 19.4.333, and P105
Note: Renal status is unknown in trials P05768, P05775, P06101, P194203, P194206, P194207, P194210, P194313, P194316, P194318, P194319, and P194334

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure estimates for sugammadex were calculated from information gathered and maintained by IMS (IQVIA) data from 25-Jul-2008 to 31-Jan-2014. Patient exposure estimates from 01-FEB-2014 to 31-JAN-2024 were calculated from our Company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area (FSA) database. These data provide a more complete and consistent methodology for the estimate of patient exposure worldwide for current Company products. Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

SV.1.2 Exposure

The estimated number of vials of sugammadex distributed worldwide from product launch through 31-JAN-2024[a] is 130,625,120**.** Patient-years of treatment are not provided, as this is not an appropriate measure of patient exposure for a product dosed in a non-chronic manner.

Strength	Number of Vials
1ML	147,640
2ML	124,834,614
5ML	5,642,866
Total	**130,625,120**

[a] This estimate of patient exposure is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated from market introduction to 31-DEC-2023, rather than until 31-JAN-2024.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Sugammadex is available only through prescribing physicians and other health care providers with prescriptive authority. Neither sugammadex, nor its components are known to possess addictive properties.

The MAH has not been made aware of any reports for misuse for illegal purposes.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not Applicable

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Not applicable as there are no Important Identified or Important Potential Risks included in the RMP.

SVII.3.2 Presentation of the Missing Information

Not applicable as the RMP does not contain any safety concerns as Missing Information.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

A review of post marketing safety data in the paediatric population aged from birth will be included in the PSUR.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance studies that are required for sugammadex.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not Applicable

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for sugammadex.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

Not applicable

V.1 Routine Risk Minimization Measures

Not applicable

V.2 Additional Risk Minimization Measures

Not applicable

V.3 Summary of Risk Minimization Measures

Not applicable

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for BRIDION (sugammadex)

This is a summary of the risk management plan (RMP) for BRIDION. The RMP details important risks of BRIDION, how these risks can be minimised, and how more information will be obtained about BRIDION 's risks and uncertainties (missing information).

BRIDION's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how BRIDION should be used.

This summary of the RMP for BRIDION should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BRIDIONS's RMP.

I. The Medicine and What it is Used For

BRIDION is authorised for the routine reversal of neuromuscular blockade (NMB) in adults, children and adolescents. Refer to the SmPC for the full indication. It contains sugammadex as the active substance and it is available as solution for injection (100 mg/mL) for administration as a single IV bolus at doses of 2 mg/kg, 4 mg/kg and 16 mg/kg.

Further information about the evaluation of BRIDION's benefits can be found in BRIDION's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/BRIDION

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of BRIDION, together with measures to minimise such risks and the proposed studies for learning more about BRIDION 's risks, are outlined here after.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC addressed to healthcare professionals;
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the HCP can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of BRIDION are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BRIDION. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Not applicable.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of BRIDION.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for BRIDION.

REFERENCES

Not Applicable

ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable

ANNEX 6 – DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not Applicable