NDA 22225: Sugammadex Injection
Anesthetic and Analgesic Drug Products
Advisory Committee (AC) Meeting
November 6, 2015
Sugammadex AC Briefing Document

ADVISORY COMMITTEE BRIEFING MATERIALS
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Sugammadex Advisory Committee Briefing Document

Sugammadex Injection

NDA 22225

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

November 6, 2015

Merck Sharp & Dohme Corporation

Kenilworth, New Jersey, U.S.A.

ADVISORY COMMITTEE BRIEFING MATERIALS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
AC	Adjudication Committee
AChEIs	Acetylcholinesterase inhibitors
AE	Adverse Event
ASA	American Society of Anesthesiologists
aPTT	Activated Partial Thromboplastin Time
BMI	Body Mass Index
BP	Blood Pressure
Cmax	Maximum Concentration
CI	Confidence Interval
CPR	Cardiopulmonary resuscitation
CrCl	Creatinine Clearance
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
HCP	Healthcare Provider
IDT	Intradermal Skin Test
IMS	Intercontinental Marketing Services
IV	Intravenous
MedDRA	Medical Dictionary For Regulatory Activities
mg/kg	Milligrams per Kilogram
min	Minutes
mL	Milliliters
mL/min	Milliliter per Minute
NMB	Neuromuscular Blockade
NMBA	Neuromuscular Blocking Agent
OSI	Office of Scientific Investigations
PEA	Pulseless Electrical Activity
PEF	Peak Expiratory Flow
PHDS	Perioperative Health Documentation System
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
PT(INR)	Prothrombin Time (International Normalized Ratio)
PTC	Post-Tetanic Count
QT	QT Interval
QTc	Corrected QT Interval
SAEs	Serious Adverse Events
SMQ	Standardized MedDRA Query
SOC	System Organ Class

Abbreviation/Term	Definition
SPT	Skin Prick Test
SRBA	Selective relaxant binding agent
T1, T2, T3, T4	First (T1), Second (T2), Third (T3) or Fourth (T4) Twitch in Response to Train of Four (TOF) Stimulation
T4/T1 ratio	TOF Ratio: Ratio of the Height of T4 Over the Height of T1 in the Recording of the Response to TOF Stimulation. Ratio expressed in decimals (e.g., 0.7 or 0.8).
THA	Targeted Hypersensitivity Assessment
TOF	Train-of-Four
TOF-Watch® SX	Acceleromyograph used for objective neuromuscular monitoring
WAO	World Allergy Organization
WFRS	Worldwide Financial Repository System
Xa	Activated Coagulation Factor X

1 EXECUTIVE SUMMARY

An unmet need exists in anesthesia for a neuromuscular blockade (NMB) reversal agent that acts quickly, with minimal side effects, and with low risk for residual or recurrent paralysis following surgery. Currently, reversal of NMB is achieved via the use of acetylcholinesterase inhibitors (AChEIs), which 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 novel 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.

The Proposed Indication and Dosing recommendations for sugammadex are as follows:

Indication

Sugammadex is a selective relaxant binding agent indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

Dosing and Administration

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- A dose of 4 mg/kg is recommended if recovery has reached 1-2 post-tetanic counts (PTC), train-of-four (TOF)-count 0 (deep blockade) following administration of rocuronium- or vecuronium-induced blockade.
- A dose of 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.

- A dose of 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

Efficacy

The efficacy of sugammadex was assessed in 33 trials. Twenty-four trials evaluated sugammadex at 2 mg/kg or 4 mg/kg in the setting of reversal of moderate or deep NMB, respectively, for routine use; two trials evaluated 16 mg/kg for urgent or emergent use; the remaining seven trials evaluated sugammadex at depths of NMB or time points other than the currently recommended deep NMB (1-2 PTC) or moderate NMB (reappearance of T2). In all pooled trials, rocuronium or vecuronium were the NMBAs, sugammadex was administered at the recommended dose for the depth of NMB being studied, and a key pre-specified efficacy endpoint was recovery from NMB defined as a "train of four" [TOF] T4/T1 ratio of 0.9. Note that because trial 19.4.318 utilized sugammadex 2 mg/kg as well as sugammadex 4 mg/kg, the trial is accounted for in the tally of both moderate NMB and deep NMB trials, respectively.

- The 2 mg/kg dose, intended for reversal of moderate block (when spontaneous recovery had reached the reappearance of T2), was investigated in 16 of the 26 efficacy trials (12 trials with rocuronium and four trials with both rocuronium and vecuronium as NMBA).
- The 4 mg/kg dose, intended for reversal of deep block (when recovery had reached 1-2 (PTC, or TOF count of 0), was investigated in nine of the 26 efficacy trials (six trials with rocuronium and three trials with both rocuronium and vecuronium as NMBA).
- The 16 mg/kg dose, intended for urgent or emergent use in life-threatening situations, was evaluated in two efficacy trials. Because such situations cannot be studied directly, these trials induced NMB with rocuronium at a high dose of 1.2 mg/kg in surgical patients, followed by reversal with sugammadex three minutes later, assessing speed of recovery to an endpoint representing the ability to breathe spontaneously.

The results of the pivotal trials and pooled efficacy analyses demonstrate that following sugammadex administration, complete recovery (TOF ratio $\geq$0.9) was achieved within five minutes for >95% of patients treated with either rocuronium or vecuronium. The results of these studies demonstrate that for moderate and deep NMB, sugammadex consistently provided markedly more rapid and complete recovery of NMB than either placebo or neostigmine.

Compared with currently available treatments, the effectiveness of sugammadex offers the following advantages:

- Only sugammadex can reverse deep NMB induced by rocuronium or vecuronium.
- Compared with spontaneous reversal of the effects of the depolarizing NMBA succinylcholine (with short duration of action currently used for rapid sequence induction), the data demonstrate that sugammadex 16 mg/kg resulted in significantly

faster and more reliable reversal of rocuronium-induced NMB when given three minutes after the administration of rocuronium 1.2 mg/kg, providing the potential to reduce anoxia and poor outcomes when urgent or emergent reversal of rocuronium-induced NMB is required.

- Residual NMB and recurrence of NMB following reversal were infrequent with the use of sugammadex at recommended doses as compared to usual care, implying reduced risk for complications post-operatively.

Safety and Tolerability:

Safety and tolerability were assessed in data from 56 clinical trials in which IV sugammadex was administered, comprising 5999 exposures in 4453 unique adult subjects. Within these 56 trials, two pooled datasets were defined:

- Pooled Phase 1-3 dataset (42 of the 56 clinical trials): surgical subjects or healthy subjects receiving IV sugammadex *with* anesthesia and/or NMBA. Two subsets were defined from the Pooled Phase 1-3 data set for head-to-head comparisons between sugammadex and placebo or neostigmine, respectively.

- Pooled Phase 1 dataset (14 of the 56 clinical trials): subjects receiving IV sugammadex without anesthesia or NMBAs.

Experience informing safety is also available from routine clinical use, as sugammadex is currently approved and marketed in more than 50 countries worldwide, with approximately 11.5 million patients exposed as of 31-Mar-2015.

In clinical studies, the use of sugammadex was generally safe and well tolerated. No clinically important differences were observed between sugammadex and placebo in the Pooled Phase 1-3 datasets for the incidence of AEs, SAEs, AEs with severe intensity, deaths, or discontinuation due to AEs. The most commonly reported AEs were primarily related to the surgical process and/or general anesthesia in both groups (e.g., procedural pain, nausea, wound complication), and evidence did not suggest increased frequency or severity of AEs with increased dose (2 mg/kg, 4 mg/kg and 16 mg/kg). No clinically relevant effects of sugammadex were observed for laboratory or vital signs in Phase 1 subjects who were not anesthetized and who did not receive an NMBA. In subjects who received an NMBA in the Pooled Phase 1-3 trials, observed changes in vital signs were consistent with those expected in a population of surgical subjects. Infrequent reports of potential hypersensitivity reactions prompted a request from the FDA for further characterization of these AEs prior to approving sugammadex. The approach taken to address this request, as well as the results of further assessment of hypersensitivity, are described below.

Extensive post-marketing safety experience of sugammadex in approximately 11.5 million patients has confirmed the potential for hypersensitivity reactions in exposed patients. In addition, rare cases of bradycardia have been reported in the postmarketing environment that appear to be responsive to usual anticholinergic therapy. No other safety issues have been identified in the postmarketing experience of sugammadex use.

Hypersensitivity (including anaphylaxis)

Based on the initial review of the original NDA for sugammadex submitted in 2007, in 2008 the FDA requested further characterization of hypersensitivity reactions, particularly with regard to the safety of repeat exposure to the drug and the potential mechanism underlying the pathophysiology of the reactions. To address the FDA's request, a dedicated trial (Trial P06042) was conducted to investigate the frequency and time course as well as the immunological basis of the events. However, based on audits conducted for the 2012 NDA resubmission, elements of study conduct, including maintenance of the blind, monitoring and documentation were found to fall short of clinical trial standards. Thus, the Sponsor conducted an additional dedicated hypersensitivity trial (Trial P101). Due to the potential impact of the conduct issues on interpretation of the clinical data from Trial P06042, the focus of this document will be on Trial P101. Mechanistic investigations including serum and urine biomarkers as well as skin tests were analyzed from both studies. In addition, a review of the cumulative clinical trial database to identify cases of hypersensitivity was conducted, followed by adjudication of potential events by an external adjudication committee. Finally, all post-marketing reports of anaphylaxis and serious reports of hypersensitivity were reviewed and systematically evaluated by an independent external adjudication committee. Based on conservative estimates of reporting rates and use, the incidence of these events in clinical use was estimated and compared to epidemiological information about the general incidence of anaphylaxis in the peri-operative setting. The results of the full assessment are summarized below.

Dedicated Hypersensitivity Trial (Trial P101)

Trial P101 was a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the incidence of hypersensitivity after repeated single-dose administrations of sugammadex. In this trial, 375 healthy awake subjects, who did not receive NMBAs or anesthetics, were randomized to treatment with three successive single doses (separated by approximately five weeks to allow potential sensitization to develop) of one of the following treatments in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex, or placebo, respectively. An important aim of the trial was to understand whether repeated administration of sugammadex was associated with increasing risk for hypersensitivity and anaphylaxis. For this reason, the trial was designed to maximize the likelihood of detecting all hypersensitivity events, irrespective of their immediate clinical significance, and used an intensive case-finding methodology to elicit signs and symptoms consistent with a hypersensitivity reaction. Subjects were evaluated at least three times over the 24 hours after each dose with a targeted hypersensitivity assessment (THA) that included elicitation of AEs potentially related to hypersensitivity, as well as a focused physical examination. Subjects with predefined symptoms or signs of hypersensitivity were referred for adjudication to a blinded external adjudication committee for determination of confirmed hypersensitivity reactions, and whether such reactions were anaphylaxis as defined by the Sampson Criterion 1 **[1]**, which is the definition that the FDA division of Pulmonary, Allergy and Rheumatology Products has usually employed to identify cases of anaphylaxis in the evaluation of new molecular entities. The FDA agreed to the design of the trial before it was conducted.

In this trial, both 4 mg/kg and 16 mg/kg sugammadex were associated with a higher incidence (6.6% and 9.5%, respectively) of hypersensitivity as compared to placebo (1.3%). The majority (91%) of hypersensitivity reactions were mild (as judged by the adjudication committee), started within minutes after dose administration, and resolved spontaneously within minutes to hours of onset of symptoms; three cases required treatment, all in the 16 mg/kg treatment arm, and all responded quickly to antihistamine and/or corticosteroid, and no cases required treatment with epinephrine. There was one case adjudicated as anaphylaxis that was mild in severity (sneezing, nasal congestion, conjunctival edema, urticaria, and swelling of the uvula, and a transient decrease in peak expiratory flow to ~30% below baseline, that responded to treatment with antihistamine and corticosteroid). This case, in which the subject displayed no signs of hypotension, occurred in the 16 mg/kg arm after the subject's first dose of sugammadex. No cases of anaphylaxis were observed in the 4 mg/kg or placebo arms. There was no increase in the frequency or severity of hypersensitivity with repeated administration of sugammadex, providing evidence that sensitization and hence increased clinical risk does not occur with repeated administration of sugammadex.

Studies to Evaluate Underlying Mechanism of Hypersensitivity

A number of studies were conducted to elucidate the mechanism of the hypersensitivity reaction, including measurements of serum tryptase (a biomarker for mast cell degranulation) and assays for sugammadex-specific IgG and IgE antibodies. Based on the measurement of serum tryptase, the evidence did not suggest mast cell degranulation in any of the adjudicated cases of hypersensitivity and anaphylaxis. Specific IgE antibody development was not detected, although one subject with adjudicated hypersensitivity did appear to develop IgG after exposure, and another subject had measurable IgG prior to first exposure but was negative in assays conducted after exposure to sugammadex. In Trial P06042, skin testing was also employed, as well as serum and urine biomarkers for the complement pathway, the contact system, endothelial and neutrophil activation, and ex-vivo measurements of histamine release from basophils. The results for these additional tests did not identify a specific mechanism for the hypersensitivity reactions. Thus, based on the totality of the mechanistic and clinical data, the events of hypersensitivity, including anaphylaxis, are not consistent with Type 1 immune-mediated (IgE) hypersensitivity and the mechanism of hypersensitivity to sugammadex is undetermined.

Review of Safety Database and Adjudication of Hypersensitivity Events

The risk for hypersensitivity and anaphylaxis was also investigated in the cumulative safety database of controlled clinical trials. Potential cases of hypersensitivity or anaphylaxis (Sampson Criterion 1) **[1]** were identified through searches using Standardized MedDRA Queries (SMQs) for hypersensitivity and for anaphylaxis. Each identified event was then adjudicated by members of an independent external adjudication committee blinded to treatment assignment. The results of the two dedicated hypersensitivity trials (P101 and P06042) are considered separately. In the Pooled Phase 1 dataset of subjects receiving 715 exposures of sugammadex alone from 0.1 to 96 mg/kg (with neither anesthesia nor NMBA) there were four (0.6%) events of confirmed hypersensitivity and no events of anaphylaxis as determined by the external adjudication committee. There were no events adjudicated as

hypersensitivity or anaphylaxis in the placebo group. In the Pooled Phase 1-3 studies in surgical patients and healthy subjects receiving sugammadex, neostigmine or placebo together with anesthesia and/or NMBA, the incidence of adjudicated hypersensitivity-related events in sugammadex-treated patients was low (0.2%) and similar to the placebo group (0.6%) and neostigmine group (0.3%), and there were no events reported or adjudicated as anaphylaxis. As this database includes more than 3,000 individuals who received sugammadex, these results provide evidence that the upper bound for the 95% confidence interval for the true incidence of anaphylaxis associated with sugammadex in the surgical setting based on the Pooled Phase 1-3 studies is 0.1%.

Review of Postmarketing Data:

As of 31 March 2015, approximately 11.5 million patients have received sugammadex. The post-marketing safety database was reviewed and a total of 273 anaphylaxis cases were identified (i.e., 259 anaphlyaxis reports and 14 serious hypersensitivity reports that were adjudicated as anaphylaxis). The most commonly described clinical features in the 273 anaphylaxis reports were mucocutaneous manifestations and decreased blood pressure/hypotension, which resolved spontaneously or were responsive to usual treatment using methods readily available in an operating room or post-operative care setting. Based on 273 reported cases in 11.5 million doses, anaphylaxis is estimated to occur at a rate of approximately 24 per 100,000 (or 0.024%) doses of sugammadex, assuming that 10% of cases are reported. Since this rate is derived from reporting of anaphylaxis in a setting where multiple agents may be causative, a precise estimate of the rate attributable to sugammadex alone is not possible, but these post-marketing data suggest that anaphylaxis with sugammadex is rare (reporting rate <0.1%). This result is consistent with that observed in the Pooled Phase 1-3 studies presented above (i.e. the risk for anaphylaxis associated with sugammadex is $\leq 0.1\%$).

To contextualize these results, it is useful to consider the risk for anaphylaxis that patients undergoing surgery with general anesthesia face. The background rate of anaphylaxis associated with other drugs used in anesthesia and other potential precipitants routinely present in the perioperative setting where NMBAs have been administered has been reported in the literature (15-34 per 100,000), corresponding to a risk of 0.015% to 0.034%. Thus, any sugammadex-associated increase in risk for anaphylaxis above reported background rates in the surgical setting in which it is used is limited (reporting rate in the post-marketing safety database of 0.024% for sugammadex and 0.015% – 0.034% for background).

Conclusions on Hypersensitivity/Anaphylaxis:

Analyses of clinical trial results and post-marketing safety reports provide evidence that sugammadex is associated with hypersensitivity, including anaphylaxis. The data suggest that the risk for anaphylaxis may be greater in the 16 mg/kg dose (only recommended for urgent/emergent use) as compared with the usual doses of 2 mg/kg and 4 mg/kg. The data further suggest that anaphylaxis associated with sugammadex, when it occurs, responds to usual interventions and can be treated effectively. Evidence from Trial P101 did not suggest increased risk of hypersensitivity with repeated exposure. In the clinical database of surgical patients, events of hypersensitivity were infrequent and occurred at an incidence similar to

placebo, and no cases of anaphylaxis were identified in clinical trials with surgical patients based on adjudication of potential cases by an independent external adjudication committee. Additionally, no clinical factors that increase risk for anaphylaxis have been identified in any of the databases examined.

The estimates for incidence of hypersensitivity and anaphylaxis in the healthy volunteer trial P101 compared with those in the overall clinical trials database and the post-marketing clinical setting differ. This may be related to several factors, but probably arises, most importantly, from the different objectives and methodologies in the different databases: in particular, the healthy volunteer trial P101 employed very intense scrutiny and prospective case-finding in awake subjects to capture all signs and all symptoms, irrespective of clinical risk, in order to characterize even subtle cases of hypersensitivity to determine the potential for sensitization with repeated administration of sugammadex, which was not observed. Thus, that trial likely identified as cases some individuals who would not have come to attention in the sugammadex patient studies and the post-marketing reports, because in these databases, cases would typically be identified in a fashion more similar to what occurs in usual clinical practice, that is, on the basis of prominent signs in anesthetized patients.

As a result of these factors, the different databases had different reporting thresholds, which is an important consideration in assessing how results from each analysis compare to background rates reported in the literature. In this regard, the results from the overall sugammadex clinical trial database and the post-marketing safety database, whose estimates incorporate clinician judgments about clinical importance, are likely most comparable to literature reports for anaphylaxis when individuals undergo general anesthesia, where cases have typically been identified based on significant clinical events reported to a registry or ascertained by chart review.

Thus in terms of providing a context for assessing the magnitude of risk associated with sugammadex in clinical use, the Pooled Phase 1-3 clinical trial database and the post-marketing safety database both provide estimates for the frequency of anaphylaxis in sugammadex-treated patients of less than 0.1%, which does not suggest a marked increase over estimates of background rates derived from the literature reviewed above. This does not imply that there is no incremental risk of anaphylaxis associated with sugammadex, but does suggest that the magnitude of any additional risk, relative to other factors in the surgical setting, is small.

The mechanism underlying the sugammadex hypersensitivity reaction is unknown, but is unlikely to represent a Type 1 IgE-mediated hypersensitivity response as the clinical results did not demonstrate sensitization after repeated sugammadex administration, and anti-sugammadex IgE production was not seen after repeated exposures in the dedicated hypersensitivity trial.

Appropriate labeling will alert clinicians to be prepared to treat potential hypersensitivity reactions, including anaphylaxis.

Cardiac Safety

The FDA requested further evaluation of the cardiovascular safety profile, particularly related to additional studies to further explore whether sugammadex, alone or in association with agents commonly used during anesthesia, has effects on QT prolongation or is associated with cardiac arrhythmias.

The effect of sugammadex on the QT/QTc interval was studied in three dedicated trials of sugammadex alone, sugammadex in combination with rocuronium or vecuronium, and sugammadex with either propofol or sevoflurane. In none of these studies was there evidence of a clinically relevant effect of sugammadex on the QT interval. Meta-analyses of healthy subject data and all Phase 2-3 trials were also conducted to look for clinical evidence of cardiac effects. In the Pooled Phase 1-3 studies cardiac arrhythmia-related AEs for sugammadex were infrequent (~5%), similar to the incidence observed with placebo (~4%) and lower than that observed with neostigmine (~8%) or succinylcholine (~9%). There were no reported cases of Torsade de Pointes.

Review of the post-marketing safety database suggests that in rare instances sugammadex may be associated with bradycardia requiring intervention, with isolated cases progressing to cardiac arrest. Importantly, review of the post-marketing safety reports of these episodes suggest that when such bradycardia occurs, it is responsive to usual treatment (e.g. intervention with an anticholinergic agent such as atropine). The postmarketing safety database, however, did not suggest an increased reporting rate of cardiac arrhythmias beyond expected background rates as reported in the literature for the population of patients undergoing surgery with general anesthesia. In general, with the exception of bradycardia, individual cardiac events in the post-marketing safety database were heterogeneous in nature and without evidence suggesting a common underlying causal etiology.

Conclusion

Sugammadex is a new drug developed for reversal of NMB induced by either rocuronium or vecuronium, and has been studied for reversal of moderate or deep NMB at doses of 2 or 4 mg/kg, respectively. The results of the studies conducted in the development program show that sugammadex acts rapidly and completely to reverse NMB of any depth. Because of its effectiveness at reversing NMB, sugammadex allows anesthesiologists to maintain deep NMB until the end of the procedure, as necessary, to improve surgical conditions and safety by ensuring more complete muscle relaxation and preventing unwanted patient movement. The rapidity and completeness of NMB reversal after sugammadex administration also reduces the risk of recurrent or residual NMB post-operatively. Because residual block has been associated with post-operative respiratory complication **[2]**, this is an important potential safety advantage over current practice.

Sugammadex has also been studied at a dose of 16 mg/kg for use when urgent or emergent reversal of rocuronium is required. In this setting, the ability of sugammadex to terminate NMB quickly can reduce the potential for anoxia, which is likely to be brain-sparing and lifesaving for some patients, as has been reported in several case reports in the literature **[3]**.

The identified increase in risk of hypersensitivity and anaphylaxis associated with sugammadex is limited and quickly recognizable in the highly monitored setting in which sugammadex is used, and responsive to standard treatments. In addition, rare cases of bradycardia that appear to be related to sugammadex administration can be quickly identified in the highly monitored setting in which sugammadex is used, and are also responsive to usual therapy. Thus, overall, the benefits of sugammadex markedly outweigh its risks in the settings in which it is proposed for use. Sugammadex has the potential to become an important addition to the pharmacologic interventions available for patients undergoing anesthesia with NMB.

2 BACKGROUND INFORMATION

Overview

This background document summarizes the clinical, mechanistic and post-marketing data for sugammadex, submitted by the Sponsor to the FDA in NDA resubmissions made in October 2014 and June 2015 in response to Complete Response letters received in September 2013 and April 2015 from the FDA. These resubmissions included the results from an additional hypersensitivity trial (Trial P101) conducted by the Sponsor to characterize hypersensitivity reactions to repeated exposure to sugammadex as well as sensitivity analyses of Trial P101 as requested by FDA. This background document contains a summary of the results of this hypersensitivity trial, and a review of the safety and tolerability of sugammadex based on the cumulative clinical database of 56 clinical trials in subjects with exposure to IV sugammadex as well as a summary of results of additional mechanistic research. It also contains updated analyses of the post-marketing experience derived from > 12.1 million vials of sugammadex sold in > 50 countries where sugammadex has been approved and marketed, resulting in an estimated 11.5 million patients receiving sugammadex (assuming 95% usage of vials sold).

The cumulative clinical database includes 8900 subject exposures to IV sugammadex, neostigmine, or placebo in 6121 unique adult subjects. Among these, the IV sugammadex subset is comprised of 5999 subject exposures in 4453 unique adult subjects. Depending on the design of the trials, subjects could be exposed only once or more than once to study drug in one trial, or they could receive the investigational drug or a comparator in cross-over designs at different time points during a trial. Whenever an analysis is based on a data set that included subjects with more than one exposure, the analysis is therefore based on "exposures" as the basis for calculations. If a data set included for a particular analysis only subjects with one exposure, the analysis is based on "unique subjects." This approach is consistent with the approach taken in the original NDA and subsequent NDA resubmissions to the FDA.

These 56 clinical trials are the basis of the safety and tolerability assessments in the clinical trial database. As the trial populations, comparators and primary scope of the trials varied, additional subsets of trials for efficacy and safety have been defined for specific purposes:

Efficacy Analysis

For the analyses of efficacy, a total of 26 trials were included. Of those 26 trials, 24 trials form the basis of the integrated summaries of efficacy in routine situations (reversal at reappearance of T2 at 2 mg/kg or at 1-2 PTC at 4 mg/kg), and had the time to a TOF ratio of 0.9 as a pre-specified endpoint. In 23 of these 24 trials, the time to full recovery (a TOF ratio of 0.9) was the primary efficacy endpoint of the trial; one trial (19.4.210) had a primary objective of comparing recovery between two different maintenance anesthetic agents (propofol and sevoflurane) after rocuronium infusion at T1 3-10% and the time to a TOF ratio of 0.9 as a secondary objective. Two trials investigated the efficacy of sugammadex using 16 mg/kg at three minutes after a rocuronium dose of 1.2 mg/kg. Subjects with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) and pediatric subjects (<18 yrs) were excluded from the pooled efficacy analysis.

Figure 1 provides an overview of the efficacy trials and the pooling strategy. Trial 19.4.318 utilized sugammadex at 2 mg/kg as well as at 4 mg/kg and therefore is reflected in both the moderate NMB and deep NMB groupings in the figure, respectively. Also note that seven sugammadex trials used both vecuronium and rocuronium as NMBAs, and those seven trials are displayed in the figure under each NMBA for the respective level of block (but are not double counted in the totals for the number of pooled trials by level of block).

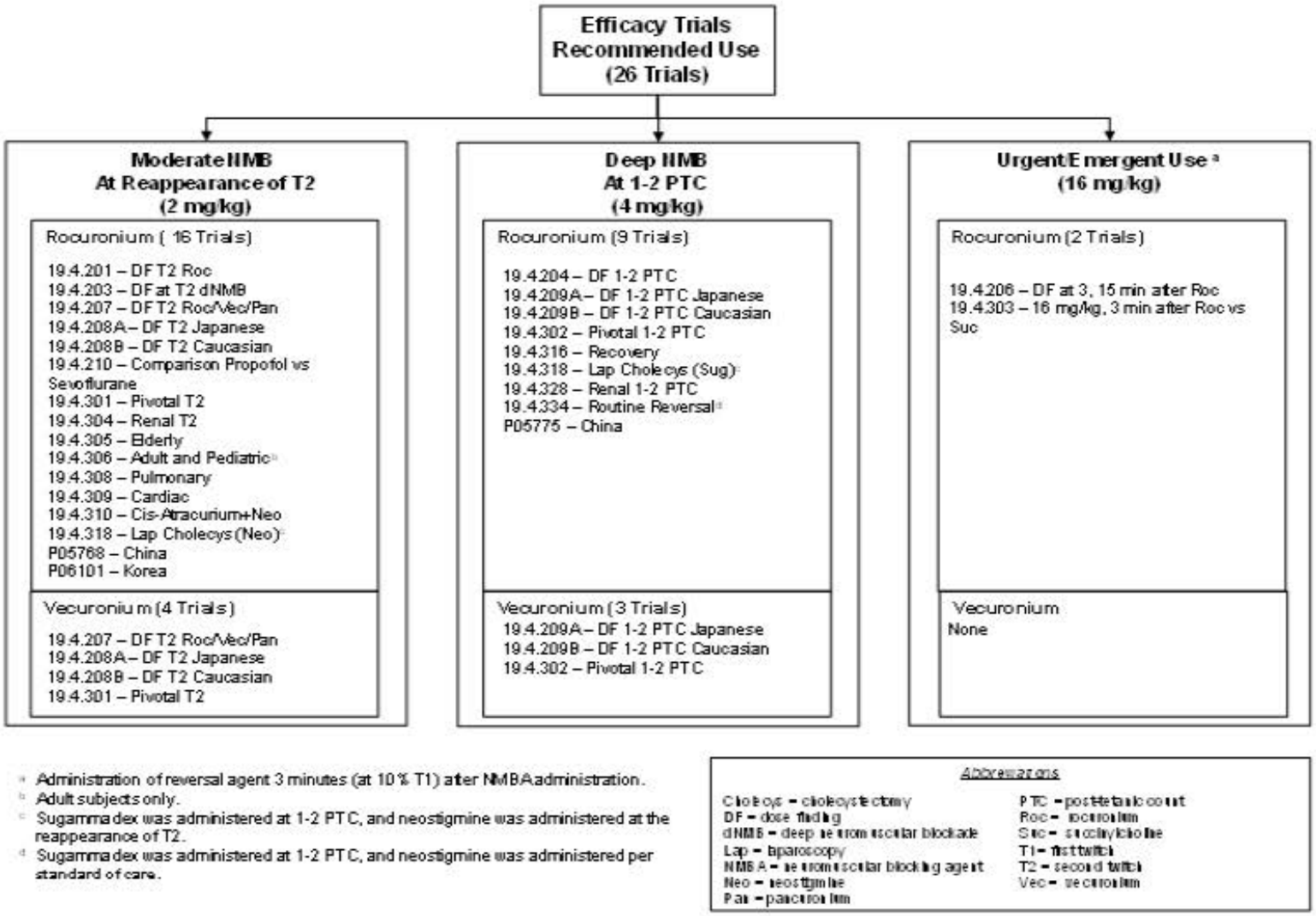


Figure 1 Overview of Efficacy Trials in the Populations of Intended Recommended Use at the Three Recommended Doses for Sugammadex

Safety Analysis

For the analyses of safety, two key pooled datasets were defined in alignment with FDA recommendations, from the total of 56 clinical trials conducted in the clinical program using IV sugammadex.

- The first key pooled dataset consists of the **Pooled Phase 1–3 Trials:** This dataset includes data from all subjects (healthy volunteers and surgical subjects) who were administered anesthesia and/or an NMBA and who were exposed to IV sugammadex (across all doses), active comparators, or placebo in 42 clinical trials. Trials included in this dataset include both blinded, placebo- or active-controlled trials and open-label/uncontrolled trials. In order to better characterize the safety profile of sugammadex relative to placebo and neostigmine, two subsets were defined within the Pooled Phase 1-3 Trials:
  - **Pooled Placebo-controlled Trials**: 13 trials that compared sugammadex versus placebo directly in randomized controlled trials, and in which either rocuronium or vecuronium were used as NMBA.
  - **Pooled Neostigmine-controlled Trials**: Eight trials which compared sugammadex versus neostigmine directly in randomized controlled trials, and in which either rocuronium or vecuronium were used as NMBA.
- The second key pooled dataset consists of **Pooled Phase 1 Trials**: This dataset includes subjects in 14 Phase 1 trials (including dedicated hypersensitivity trials: P101 and P06042) who were exposed to IV sugammadex, but who did not receive anesthesia and did not receive an NMBA.

Figure 2 displays an overview of the pooled datasets and the number of unique subjects in each pooled dataset; unless otherwise indicated, in this figure the number of subject exposures to sugammadex is equal to the number of unique subjects. The safety database consists of a broad age range of subjects and with comparable percentages of men and women. In addition, most subjects were in lower anesthesia risk categories by American Society of Anesthesiologists (ASA) class, with a smaller number of patients in the more severe risk categories.

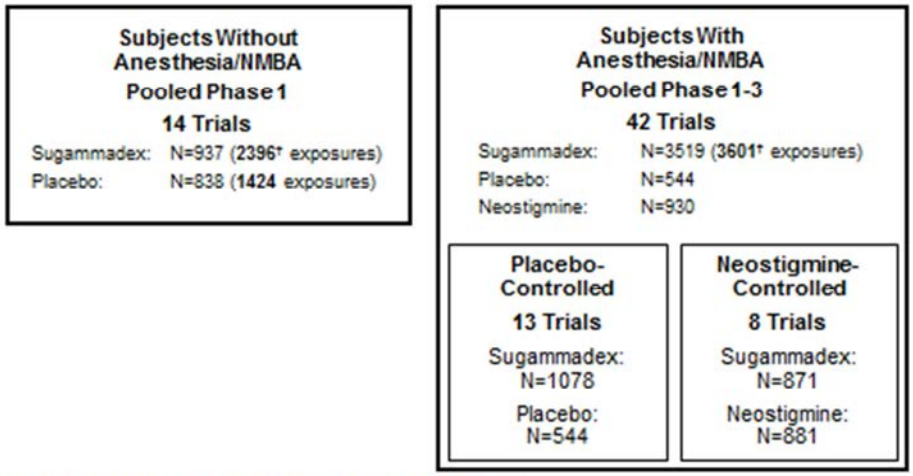


Figure 2 Overview of Trials and Unique Adult Subjects in the Cumulative Clinical Trial Database Exposed to Sugammadex, Placebo or Neostigmine

Note that the entire clinical development program included a total of 58 trials. Two trials were not included in the pooled data of 56 trials because one trial did not include sugammadex (the moxifloxacin arm of a QT trial, which was designated as a separate trial) and the other did not include any use of IV sugammadex (as it was a skin testing trial).

One safety, efficacy and pharmacokinetic trial (Trial 19.4.306) included pediatric patients (ages 28 days to 17 years inclusive) as well as adult patients. The pediatric data from this trial are not discussed in this background document since the data presented in this document are limited to the intended recommended use in the adult population.

Extensive experience is also available from routine clinical practice, as sugammadex is approved and marketed in more than 50 countries worldwide, with an estimated 11.5 million patients who received sugammadex as of 31-Mar-2015.

US Regulatory History

The original NDA for sugammadex was submitted in 2007. On 11-Mar-2008, sugammadex was discussed at the Anesthetics and Life Support Advisory Committee (now known as Anesthetic and Analgesic Drug Products Advisory Committee). While the committee voted with a positive vote (10/0) in favor of the safety and efficacy of sugammadex, the issue of potential for hypersensitivity was not fully discussed. Subsequently, the FDA issued a Not Approvable letter, citing two clinical issues that needed to be further addressed:

1) The potential for repeated sugammadex administration to increase risk of potential hypersensitivity reactions, and

2) The potential for sugammadex to affect coagulation and/or bleeding risk.

The Sponsor conducted three dedicated trials to address these two issues, and resubmitted the NDA in December 2012. After review of the 2012 resubmission, FDA issued a Complete Response letter indicating that the potential of hypersensitivity upon repeated dosing had not been adequately addressed due to issues associated with conduct of the clinical hypersensitivity trial, including incomplete maintenance of the blind, and deficiencies in study monitoring and documentation falling short of clinical trial standards. The NDA was resubmitted in October 2014 with a new hypersensitivity trial (Trial P101) and following review, the FDA issued a second Complete Response letter where the FDA asked for the conduct of a number of sensitivity analyses in several patient subgroups in Trial P101. The NDA resubmission in June 2015 included these sensitivity analyses. The results of these analyses are consistent with the overall trial results and support the interpretations and conclusions of the hypersensitivity trial (Trial P101) as previously reported.

3 PRODUCT DEVELOPMENT RATIONALE

3.1 Pharmacological Profile of Sugammadex

Sugammadex is a modified γ cyclodextrin and a novel selective relaxant binding agent (SRBA), which has been developed to reverse any depth of NMB including deep NMB, with select NMBAs, specifically induced by rocuronium or vecuronium bromide. Sugammadex forms high affinity complexes with the NMBAs rocuronium or vecuronium, with a very low dissociation constant, resulting in a rapid decrease in rocuronium or vecuronium free concentrations in the neuromuscular junction (NMJ). The complexed NMBAs cannot bind to nicotinic receptors in the NMJ leading to a reversal of NMB (**Figure 3**); this complex is then eliminated by the kidneys. This unique mechanism of action distinguishes sugammadex from the class of AChEI reversal agents. 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 and negating the need for concurrent administration of anti-muscarinic drugs.

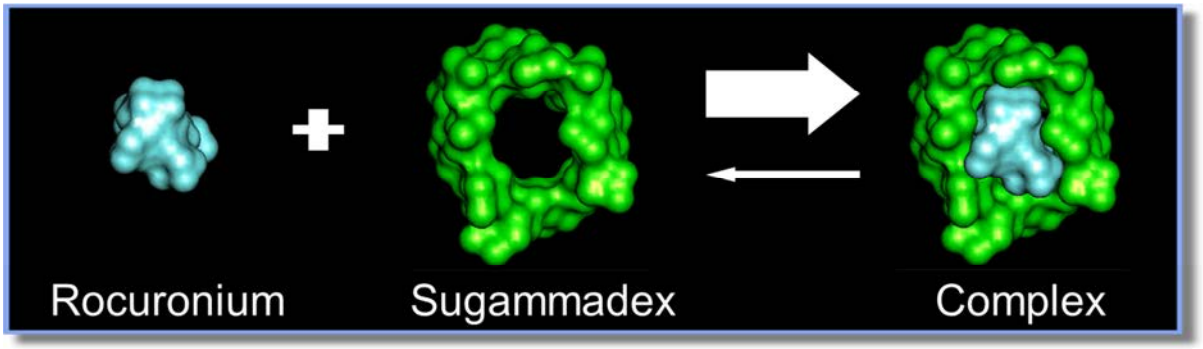


Figure 3 Mechanism of Action of Sugammadex

3.2 Unmet Medical Need

An unmet need exists for a NMB reversal agent that will act quickly, with minimal side effects and with low risk for residual or recurrent paralysis. Acetylcholinesterase inhibitors increase the availability of acetylcholine at the neuromuscular junction by slowing its

degradation, but do not affect the metabolism or elimination of NMBAs themselves. With maximal inhibition of acetylcholinesterase activity, neuronal release of acetylcholine becomes the rate-limiting step in further restoration of muscle function, limiting AChEI efficacy. Further, AChEIs cannot reverse deep NMB, which therefore cannot be maintained to the end of the procedure. Finally, AChEIs are associated a considerable risk for recurrence of NMB or post-operative residual paralysis. Sugammadex, interacting directly with NMBA's, does not suffer these limitations. Acetylcholinesterase inhibitors also have unwanted side effects related to increased cholinergic activity. Co-administration of anti-muscarinics such as atropine or glycopyrrolate can help ameliorate these, but this practice has its own side effects. By contrast, sugammadex does not stimulate the cholinergic nervous system, avoiding unwanted autonomic nervous system side effects and obviating the need for concurrent administration of anti-muscarinic drugs.

3.3 Proposed Indication and Dosing

The Sponsor is seeking approval to market sugammadex with the following proposed Indication and dosing recommendations:

Proposed Indication

Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

Proposed Dosing and Administration

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- A dose of 4 mg/kg is recommended if recovery has reached 1-2 post-tetanic counts (PTC), train-of-four (TOF)-count 0 (deep blockade) following administration of rocuronium- or vecuronium-induced blockade.
- A dose of 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.
- A dose of 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

4 SUMMARY OF CLINICAL PHARMACOLOGY

The sugammadex clinical pharmacology program included 21 Phase 1 trials; 14 of the pooled Phase 1 trials included 937 unique subjects (2396 exposures) who did not receive anesthesia and/or NMBA, the remaining Phase 1 trials included subjects who received anesthesia and/or NMBA. These studies assessed the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of sugammadex, including studies assessing hypersensitivity and potential for QTc prolongation. Further details on safety are provided in Section 6.

The PK of sugammadex following single doses from 0.1 mg/kg to 96 mg/kg were evaluated including the effects of intrinsic factors and extrinsic factors (drug-drug interactions) on

sugammadex PK and/or PD taking into account the nature of the product, results of in vitro studies, and data obtained during the development program. The analysis of PK-PD included population-based analyses across many of the clinical pharmacology studies and clinical trials to assess potential covariate effects on PK-PD variability. The results indicate that sugammadex is not metabolized, rather it is renally eliminated with a clearance approximating the glomerular filtration rate, resulting in a plasma half-life of 2 hours in adults with normal renal function. In general, there is a low potential for drug-drug interactions with sugammadex. Sugammadex PK is linear over doses of 0.1 to 96 mg/kg and no clinically meaningful differences in sugammadex PK based upon intrinsic factors (i.e., gender, age, race) have been observed with similar PK observed for anesthetized surgical patients and non-anesthestized healthy subjects such that no dose adjustments are necessary based upon these factors. However, owing to renal elimination, exposure to this drug increases with declining renal function, resulting in substantially higher exposure in patients with severe renal impairment (~8-10 times) compared to those with normal renal function. By comparison, patients with mild and moderate renal impairment show modest increases (~2 to 3-times) in sugammadex exposure. Based upon the PK and clinical efficacy and safety data, sugammadex is not recommended in patients with severe renal impairment or end stage renal disease, and no dose adjustment is necessary in patients with mild or moderate renal impairment.

5 OVERVIEW OF EFFICACY

The efficacy of sugammadex was assessed in 33 clinical trials by measuring the effect of reversal with sugammadex on various depths of NMB induced by rocuronium and vecuronium. The program assessed efficacy in three clinical settings: the first two (i.e., routine use) were for the reversal of moderate or deep NMB, and the third setting was for urgent/emergent use. Of 33 trials, 26 assessed sugammadex reversal in the setting of moderate or deep block at recommended doses, and for urgent or emergent reversal; the other seven trials were dose-finding trials or trials which used specific timepoints or utilized alternative endpoints as part of the trial. Of those 26 trials, 24 trials form the basis of the integrated summaries of efficacy in routine use situations (reversal at reappearance of T2 at 2 mg/kg or at 1-2 PTC at 4 mg/kg), and had the time to a TOF ratio of 0.9 as either the primary (in 23 trials) or secondary (in one trial) pre-specified endpoint. Two trials investigated the efficacy of sugammadex for urgent or emergent reversal using 16 mg/kg sugammadex after a rocuronium dose of 1.2 mg/kg. In all 26 studies, time to a TOF ratio of 0.9 was a pre-specified endpoint for sugammadex treated patients.

Recommended Routine Use

Efficacy was assessed at 2 mg/kg for reversal of moderate NMB induced by rocuronium or vecuronium, and at 4 mg/kg for reversal of deep NMB induced by rocuronium or vecuronium. The primary pre-specified efficacy endpoint in 23 (of 24) trials was the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9, a marker of complete recovery from NMB **[4]**. Efficacy was assessed by measuring recovery of neuromuscular function with a TOF stimulus using the TOF Watch® SX (acceleromyography). The comparators were placebo and/or neostigmine. In support of the indications for reversal of moderate and deep neuromuscular blockade, key efficacy results

from the two registration trials for routine use (Trial 19.4.301 and Trial 19.4.302) are presented in **Figure 4** and **Figure 5** below.

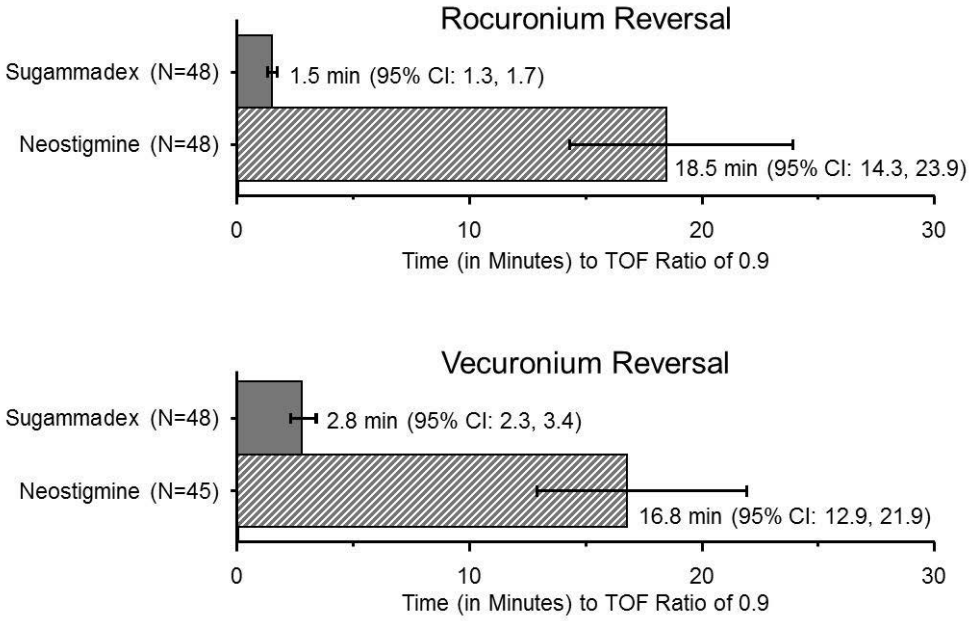


Figure 4 **Trial 19.4.301: Sugammadex 2 mg/kg Superior to Neostigmine in Reversal of Moderate Blockade (Intent-to-Treat Analysis)**

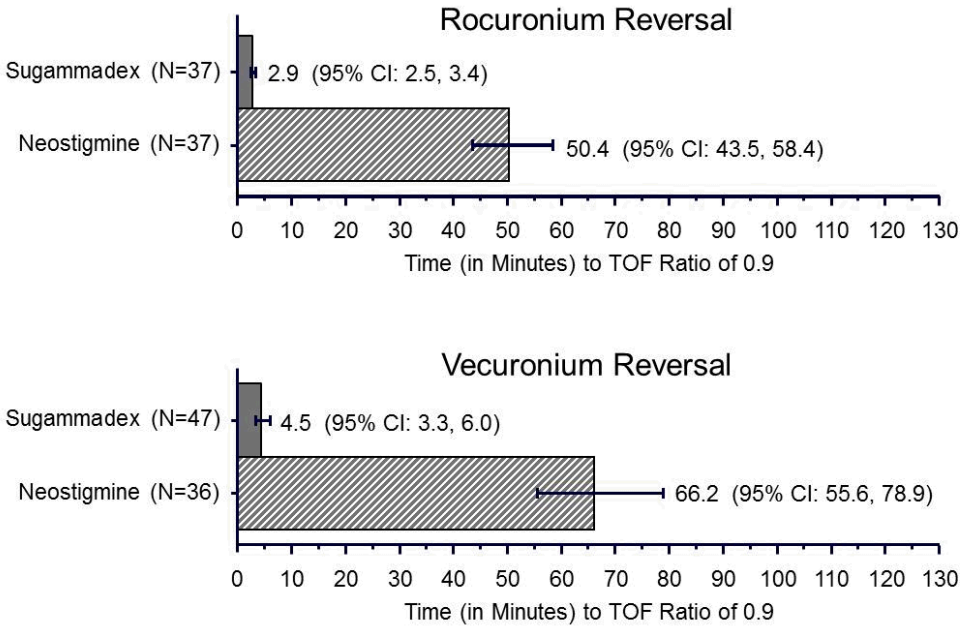


Figure 5 **Trial 19.4.302: Sugammadex 4 mg/kg Superior to Neostigmine in Reversal of Deep Blockade (Intent-to-Treat Analysis)**

These results demonstrate that sugammadex consistently provided markedly more rapid and complete recovery than neostigmine in the settings of both moderate and deep NMB.

For the pooled analyses of all routine use efficacy trials (n=24), the results for sugammadex reversal of NMB were similar to those observed in the two pivotal trials described above (**Appendix 1** and **Appendix 2**). Following sugammadex administration, complete recovery (TOF ratio ≥0.9) was achieved within five minutes for >95% of patients administered either rocuronium or vecuronium for NMB. In addition, the occurrence of residual block (defined as TOF ratio < 0.9), which poses a risk for adverse airway events and postoperative pulmonary complications, was substantially lower after reversal of rocuronium-induced deep NMB with sugammadex as compared to neostigmine in the setting of usual care. Speed of recovery after sugammadex administration was impacted by several baseline factors including the NMBA used (rocuronium or vecuronium), trial region, and renal clearance, but none of these effects were large enough to predict a clinically important reduction of efficacy or necessitate dose adjustment. Other factors that were examined but did not meaningfully affect efficacy included age, weight or Body Mass Index (BMI), ASA class, race, ethnicity, surgery type, number of maintenance doses of the NMBA, or maintenance with inhalational anesthetic agents.

As compared with placebo or the standard-of-care neostigmine, sugammadex provides a more rapid and reliable means of reversing NMB. Compared with neostigmine, sugammadex has the additional advantage of not inducing unwanted anti-cholinergic effects. Further, through its unique ability to reverse deep NMB, for which no currently available reversal agent is efficacious, sugammadex meets an important unmet medical need.

The speed and effectiveness with which sugammadex acts provides clear advantages over current standard of care at the end of a surgical procedure by providing, firstly, the ability to terminate NMB effects quickly, and secondly, the ability to reverse deep NMB. Together these factors allow deep NMB to be used throughout the surgical procedure, which provides the advantages of reduced patient movement (an important safety advantage), relaxed muscle tone throughout the entire procedure, and improved surgical field conditions. In addition, the fact that complete recovery is attained rapidly reduces risks associated with residual blockade in the immediate post-operative period. Residual block has been shown to be associated with an increased risk for respiratory complications, and therefore, reduction of residual block by sugammadex is another potential safety advantage over current standard of care. Thus, overall, sugammadex has the potential to provide several distinct, important new benefits in the surgical setting.

Urgent/Emergent Use

In addition to the two routine uses (reversal of moderate and deep NMB block), the efficacy of sugammadex to reverse NMB in close proximity to the administration of the NMBA rocuronium was also studied, in order to understand its ability to reliably reverse NMB rapidly in an urgent or emergent situation. Because such situations occur unpredictably and are life-threatening, efficacy was assessed by simulating a clinical situation that could broadly inform use in these settings.

Reversal of NMB is most difficult within the first few minutes after administration, when rocuronium plasma concentrations peak. Therefore the efficacy of sugammadex 16 mg/kg in reversing NMB was studied at three minutes after rocuronium administration in surgical patients **[5**], a time selected to approximate the time it would take to recognize an urgent or emergent situation and react. The control condition was a matched treatment group in which NMB was induced with succinylcholine, a short-acting NMBA for which no reversal agent exists. The primary outcome measure was defined as the mean time after study drug administration to recovery of T1 to 10% (first TOF twitch [T1] to 10%), a parameter chosen for its correlation with restoration of diaphragmatic activity, and hence with the ability for spontaneous respiration **[6, 7].** TOF ratios were not used as endpoints for this trial because succinylcholine is a depolarizing NMBA. A key secondary outcome was the proportion of patients for whom T1 10% had returned within five minutes after NMB administration, as this represents a critical window beyond which the brain is increasingly at risk for anoxic damage. The results of this trial (Trial 19.4.303) strongly favored sugammadex and are shown in **Figure 6**.

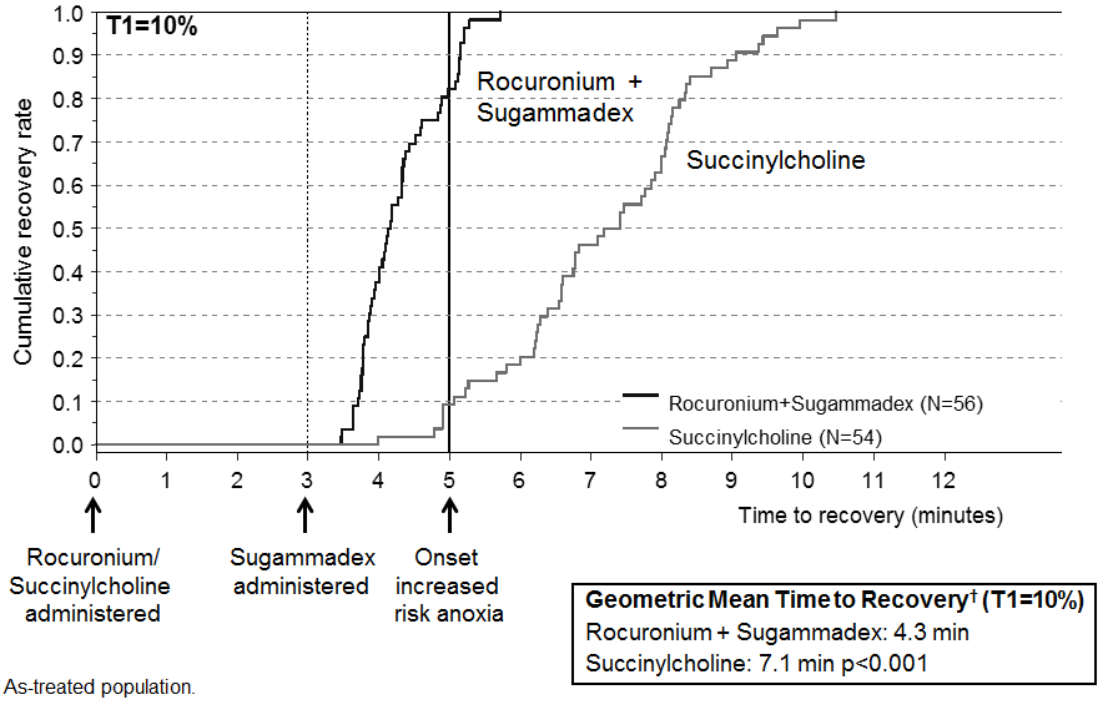


Figure 6 Trial 19.4.303: Sugammadex 16 mg/kg reverses Blockade Within the Critical Window for Anoxia

The identification of the 16 mg/kg dose for use in the setting of urgent or emergent use was based on preliminary dose-finding work aimed at establishing the dose of sugammadex that would most reliably lead to full recovery, defined as a TOF ratio of 0.9, for the greatest proportion of patients. The rationale for this approach was to limit the possibility of outliers who fail to reach quick and full recovery, given the potential serious morbidity or mortality that could occur if NMB reversal was inadequate in these settings. The conclusion of this

assessment was that while the lower doses of sugammadex were associated with rapid mean recovery to a TOF ratio of 0.9 for most patients, they were also associated with more outliers as compared with the 16 mg/kg dose.

In summary, the efficacy of sugammadex has been systematically studied for reversal of moderate and deep NMB and shown to be superior to that of usual care, providing advantages during surgical procedures as well as in the post-operative recovery period. Sugammadex has also been shown to be effective at 16 mg/kg for urgent or emergent reversal of NMB following administration of rocuronium when definitive reversal is clinically indicated to avert life-threatening anoxic injury.

Recurrence of Neuromuscular Blockade

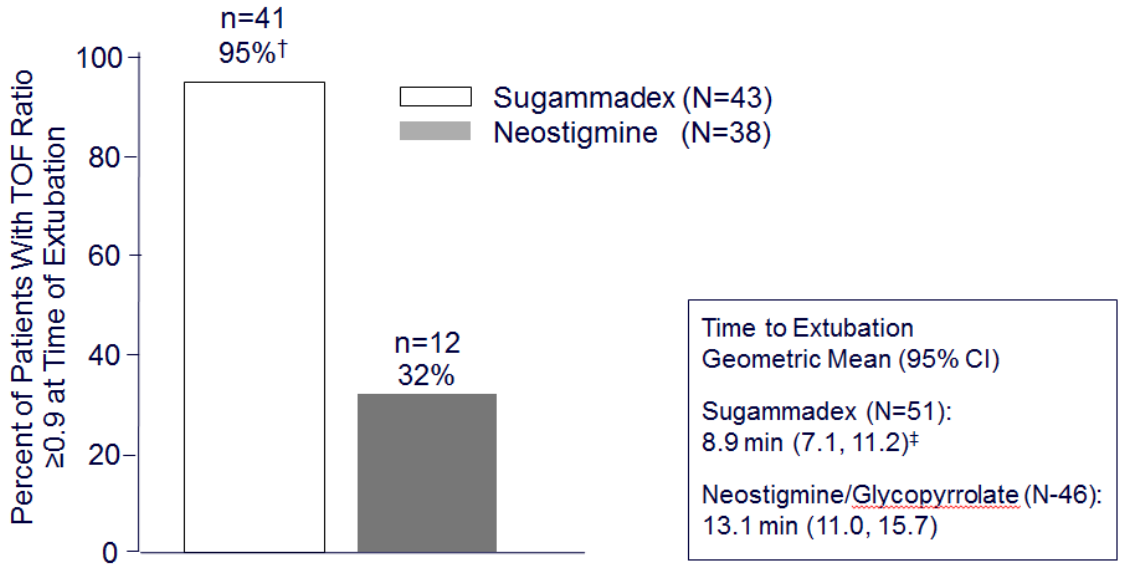
Recurrence of NMB (defined as a decline in the TOF ratio from ≥0.9 to <0.8 in at least 3 consecutive TOF values) was systematically examined in pooled Phase 2-3 clinical trials in a surgical setting, using pre-defined criteria. The observed incidence of recurrence of NMB when using sugammadex at a recommended dose for the appropriate depth of NMB was 0.20% (4 cases out of 2022 subjects met this criterion). For placebo, no cases of recurrence of NMB were observed, and for neostigmine three cases were reported, for an incidence of 0.34%.

Residual Neuromuscular Blockade

Residual NMB is defined as a TOF ratio below 0.9 at the time of tracheal extubation. In order to assess the comparative risk for residual block after NMB reversal with sugammadex as compared to neostigmine, a dedicated trial (Trial 19.4.334) was conducted in patients undergoing abdominal surgery. Patients were randomized to reversal with either sugammadex 4 mg/kg administered at 1-2 PTC, or to neostigmine 50 µg/kg plus glycopyrrolate given according to usual care. The decision to extubate was made as per usual care, on the basis of clinical parameters alone by an anesthesiologist blinded to the TOF ratio. The primary objective of the trial was to compare the incidence of residual NMB at the time of tracheal extubation after reversal of rocuronium bromide-induced NMB with sugammadex compared with neostigmine. Residual NMB was defined as T4/T1 ratio of <0.9.

The results of the trial are displayed in **Figure 7** and indicate that at the time of extubation, the majority (95%) of sugammadex-treated patients had fully recovered to a TOF Ratio ≥0.9. Conversely, only about a third (32%) of neostigmine treated patients had reached that level of recovery. The treatment effect was statistically significant (p <0.0001).

Based on the geometric mean time to extubation (8.9 minutes for sugammadex and 13.1 minutes for neostigmine) from the time of administration of each reversal agent, patients reversed with sugammadex were ready to be extubated faster than those receiving neostigmine. This finding is additionally notable because sugammadex-treated patients were reversed from deep NMB (at 1-2 PTC), whereas neostigmine-treated patients were reversed later according to usual care (at moderate block).



† p<0.0001 vs. neostigmine (completers analysis); ‡ p=0.009 vs. neostigmine (intent-to-treat analysis). TOF=train-of-four.

Figure 7 Less Residual Blockade at Extubation After Reversal With Sugammadex vs. Neostigmine (Trial 19.4.334)

In pooled efficacy trials (N=26) the incidence of residual NMB was 0% in sugammadex treated subjects. For neostigmine/placebo an incidence of 14%-100% residual NMB was reported and existed even 30 minutes after exposure to neostigmine or placebo. Additionally, in two recent studies, sugammadex also had a low incidence of residual NMB at 0% and 4.6% for those treated with sugammadex in each of the studies respectively, as compared to 43.4% and 68.4% for those treated with neostigmine in each of the studies, respectively.

In summary, both residual NMB and recurrence of NMB following reversal were infrequent with the use of sugammadex at recommended doses as compared to usual care, predicting reduced risk for complications post-operatively.

6 OVERVIEW OF SAFETY

Safety and tolerability was studied in the cumulative data set of clinical trials. The sugammadex clinical development program consists of 56 trials with IV sugammadex exposure, and the cumulative database for IV sugammadex includes 5999 exposures in 4453 unique adult subjects.

6.1 Pooling Strategies

In alignment with FDA recommendations, two key pooled datasets were defined for analyses from the total of 56 trials with IV sugammadex exposure conducted in the sugammadex clinical program (see **Figure 2**).

1) Pooled Phase 1-3 Trials

There were 3601 exposures to IV sugammadex in 3519 unique subjects treated with sugammadex in combination with anesthesia and/or NMBA at doses up to 32 mg/kg in the Pooled Phase 1-3 dataset. Among the proposed recommended doses for sugammadex use, there were 895 exposures to the 2 mg/kg dose, 1921 exposures to the 4 mg/kg dose of sugammadex, and 98 exposures to the 16 mg/kg dose of sugammadex.

a) Pooled Placebo-controlled Trials

This subset of the Pooled Phase 1-3 trial dataset is comprised of 13 placebo-controlled trials consisting of two Phase 1 trials, seven Phase 2 trials, and four Phase 3 trials. In this pooled subset of data, the number of unique subjects is the same as the number of exposures to IV sugammadex, which accounts for a total of 1078 exposures to sugammadex and 544 exposures to placebo.

b) Pooled Neostigmine-controlled Trials

This subset of the Pooled Phase 1-3 trial dataset is comprised of data from eight randomized, neostigmine-controlled trials (seven Phase 3 trials and one Phase 5 trial). In this pooled subset of data, the number of unique subjects is the same as the number of exposures to IV sugammadex, which accounts for 871 exposures to sugammadex and 881 exposures to neostigmine.

2) Pooled Phase 1 Trials

In the pooled Phase 1 trials without anesthesia or NMBA, some subjects received more than one exposure to treatment, therefore there were 2396 exposures to sugammadex in 937 unique subjects and 1424 exposures to placebo in 838 unique subjects.

6.2 Summary of Disposition

In the Pooled Phase 1-3 trials, six subjects exposed to sugammadex (out of the total 3601 exposures) discontinued from the trial due to an AE (<1%) and the discontinuation incidence was similar in the placebo group (one out of 544 exposures [<1%]). In the Pooled Phase 1 trials, 22 (1%) subjects exposed to sugammadex (out of 2396 exposures) discontinued a trial due to an AE, and the incidence was similar in the placebo group (19 out of 1424 exposures [1%]).

6.3 Overview of Adverse Events

Adverse events and SAEs were evaluated in a blinded fashion. In studies that were not double-blind or in which efficacy measures could be potentially unblinding, the protocols directed that a blinded safety assessor be used. Any event that started after study drug administration was included in the integrated analyses (unless otherwise noted). The follow-up period after study drug administration was generally seven days (and at least 14 days in the dedicated coagulation trial (Trial P07038). For subjects who were female and became pregnant during the trial (N=3), there was an additional follow-up contact at least 30 days

after study drug administration. As an overview **Table 1** displays a summary of AEs for subjects exposed to sugammadex (at all doses of IV sugammadex [<2 to 32 mg/kg]), placebo, succinylcholine or neostigmine in the Pooled Phase 1-3 dataset. **Table 2** displays a summary of AEs for subjects exposed to sugammadex (at all doses of IV sugammadex [<2 to 32 mg/kg]) or placebo in the Pooled Phase 1-3 placebo-controlled dataset.

For the Pooled Phase 1 trials there were 853 of 2396 (35.6%) subject exposures with at least one AE in the sugammadex group. Thirty of 2396 (1%) subject exposures in the sugammadex group discontinued a trial due to an AE, of which the investigator considered 14 (0.6%) to be drug-related. Of the six (0.3%) subject exposures associated with SAEs in the total sugammadex group, three were considered by the investigator to be drug-related. There were no deaths in the Pooled Phase 1 trials. For details refer to Section 6.3.5.

Table 1 Adverse Event Summary for Subjects Exposed to Sugammadex or Placebo in Pooled Phase 1-3 Trials

	Placebo	**Sugammadex[c]**
	(N=544)	**(N=3601)**
	n (%)	**n (%)**
Subjects with AEs	447 (82.2)	2849 (79.1)
Deaths[a]	3 (0.6)	4 (0.1)
Subjects with SAEs	38 (7.0)	190 (5.3)
Subjects who discontinued due to AEs	1 (0.2)	6 (0.2)
Subjects with drug-related AE[b]	51 (9.4)	430 (11.9)
Subjects with AEs of known severe intensity	46 (8.5)	304 (8.4)

AEs=Adverse Events; SAEs=Serious Adverse Events; N=Number of Exposures; n=Number of Subject Exposures with AEs

a. Irrespective of time point of death.

b. Considered by the investigator to be possibly, probably, or definitely related to trial medication.

c. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

Table 2 Adverse Event Summary for Subjects Exposed to Sugammadex or Placebo in Pooled Placebo-Controlled Trials

Event type	Placebo (N=544) n (%)	Sugammadex[c] (N=1078) n (%)
Subjects with AEs	447 (82.2)	793 (73.6)
Deaths [a]	3 (0.6)	1 (0.1)
Subjects with SAEs	38 (7.0)	67 (6.2)
Subjects who discontinued due to AEs	1 (0.2)	1 (0.1)
Subjects with drug-related AEs [b]	51 (9.4)	126 (11.7)
Subjects with AEs of known severe intensity	46 (8.5)	59 (5.5)

AEs=Adverse Events; SAEs=Serious Adverse Events; N=Number of Exposures; n=Number of Subject Exposures with AEs

a. Irrespective of time point of death.

b. Considered by the investigator to be possibly, probably, or definitely related to trial medication.

c. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

6.3.1 Deaths

In the Pooled Phase 1-3 trials (with anesthesia and/or NMBA), a total of eight deaths were reported (see **Table 3**). No cases of death occurred in the Phase 1 trials. In all cases in the other trials, death was considered unlikely or not drug-related according to the reporting investigators. Among the eight subjects, four subjects died after exposure to sugammadex (out of 3601 exposures), one subject died after exposure to neostigmine (out of 881 exposures), and three subjects died after exposure to placebo (out of 544 exposures). Review of the cases post-sugammadex exposure did not suggest a role of sugammadex in the fatal outcome (none were considered to be drug related according to the investigator) for the respective subjects, as serious medical conditions such as malignancy, pulmonary embolism, multi-organ failure or terminal multi-morbidity were prominent factors in all cases. In addition, deaths occurred days after administration of study drug. **Table 3** provides details of the eight subject deaths.

Table 3 Adverse Events with Fatal Outcome

Trial	Dose	Day of Death[a]	Adverse Event
19.4.203	Sugammadex 0.5mg/kg	Day 42	Cardiogenic shock
			Myocardial infarction
			Pulmonary edema
19.4.208B	Sugammadex 2 mg/kg	Day 18	Pulmonary embolism
19.4.333	Sugammadex 4 mg/kg	Day 5	Pulmonary hemorrhage
19.4.333	Sugammadex 4 mg/kg	Day 3	Cardiac failure
			Hepatic failure
			Intestinal ischemia
P07038	Placebo	Day 8	Ventricular fibrillation
P07038	Placebo	Day 61	Metastatic renal cell carcinoma
19.4.309	Placebo	Day 12	Post procedural edema
			Brain edema
			Cerebral hemorrhage
			Hydrocephalus
P07038	Neostigmine 50 ug/kg	Day 43	Cardiac arrest

[a] Day of death relative to study drug administration

6.3.2 Pooled Phase 1-3 Trials

Adverse Events (AEs)

In general, no dose-related trends were apparent for the incidence of individual AEs in the Pooled Phase 1-3 dataset, however, a slightly higher incidence of AEs were reported across the System Organ Classes (SOCs) for the sugammadex 4 mg/kg dose (84.5%) than for the 2 mg/kg dose (77.4%). Fewer subjects were exposed to 16 mg/kg (N=98) relative to the lower doses, thus the incidence of AEs reported in the 16 mg/kg dose group (80.6%) should be interpreted with caution.

The highest incidences of AEs were observed in the SOC 'Injury, poisoning, and procedural complications' with 52.9% for the total sugammadex group and 51.5% in the placebo group. Procedural pain was the AE with the highest incidence in this SOC with 45.7% of subject exposures in the sugammadex 4 mg/kg group (39.8% for total sugammadex) and 35.1% of subject exposures in the placebo group. Most subjects experienced AEs that were mild to moderate in intensity as determined by the investigators. No clear dose-response relationship was found for the incidence of individual AEs. A tabulation of AEs by dose for the Pooled Phase 1-3 trials with an incidence of at least 2% of sugammadex or placebo subject exposures by SOC can be found in **Appendix 3**.

Serious Adverse Events (SAE)

A total of 5.3% of subjects exposed to any dose of sugammadex experienced at least one SAE. No dose response for exposure to sugammadex was apparent for the overall incidence

of SAEs, with 38 (7%) for placebo, 47 (5%) at 2 mg/kg, 116 (6%) at 4 mg/kg, and five (5%) at 16 mg/kg. Post-procedural hemorrhage was the most frequent SAE, occurring in 10 (<1%) subject exposures across the sugammadex doses and in two (<1%) subject exposures in the placebo group. Serious adverse events that were considered to be related to study drug occurred in 13 (1%) subject exposures in the sugammadex group and three (<1%) in the placebo group, the highest incidences of which was for Electrocardiogram (ECG) QT prolonged (three subject exposures to sugammadex and one for placebo). Note that QT prolongations were to be reported as serious AEs in trials performed at the time of the original submission.

6.3.3 Pooled Phase 1-3: Placebo-Controlled Trials

Adverse Events

Adverse events that occurred with an incidence of at least 5% of sugammadex or placebo subject exposures in the 13 Pooled Placebo-controlled trials are summarized in **Table 4**. The incidence of subject exposures with at least one AE was lower for sugammadex (73.6%) than for placebo (82.2%). Adverse events that occurred with an incidence of at least 2% of sugammadex or placebo subject exposures by SOC and preferred terms are displayed in **Appendix 4**.

Table 4 Number (%) of Subject Exposures with Adverse Events in Pooled Placebo-Controlled Trials (Incidence ≥5% in Either Treatment Group)

	Placebo	Sugammadex [a]
Adverse Events (AEs)	**(N=544)**	**(N=1078)**
	n (%)	**n (%)**
At least one AE (Total)	**447 (82.2)**	**793 (73.6)**
Procedural pain	191 (35.1)	268 (24.9)
Wound complication	32 (5.9)	71 (6.6)
Anaemia postoperative	51 (9.4)	54 (5.0)
Procedural nausea	31 (5.7)	21 (1.9)
Nausea	96 (17.6)	169 (15.7)
Vomiting	43 (7.9)	100 (9.3)
Constipation	73 (13.4)	74 (6.9)
Chills	27 (5.0)	41 (3.8)
Arthralgia	42 (7.7)	47 (4.4)
Headache	42 (7.7)	53 (4.9)
Sleep disorder	56 (10.3)	45 (4.2)
Anaemia	50 (9.2)	47 (4.4)
Hypokalaemia	27 (5.0)	20 (1.9)

N=Number of Exposures; n=Number of Subject Exposures with AEs

a. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

There were no clinically important differences between the AEs reported for the sugammadex and placebo groups. Most subjects experienced AEs that were assessed by investigators as mild to moderate in intensity. Most reported AEs appear primarily related to the surgical process and/or general anesthesia in both groups. For severe AEs, the highest incidences for the sugammadex group were reported for the AEs procedural pain (11 [1%] for sugammadex, six [1%] for placebo) and abdominal pain (five [<1%] for sugammadex, one [<1%] for placebo). Only in a small number of AEs were the incidences higher with sugammadex than placebo, and most of these events were reported with an incidence of less than 4%. No apparent dose response relationship was seen in this data set, in which most patients were treated at doses recommended for routine use (2 mg/kg and 4 mg/kg).

The assessment of AEs observed in the pooled randomized, placebo-controlled trials support the conclusion that the use of sugammadex in the intended target patient population is generally safe and well tolerated.

Serious Adverse Events

The incidence of SAEs in the Pooled Placebo-controlled trials was similar between the groups, with 67 (6%) and 38 (7%) reported in the sugammadex and placebo groups, respectively. The highest incidence of SAEs were reported in the Injury, Poisoning and Procedural complications SOC, with 17 subject exposures (2%) reported for those in the sugammadex group and 15 subject exposures (3%) in the placebo group. In the sugammadex group, 2% (n=17 exposures) reported SAEs in the Investigations SOC, which were mostly events related to ECG abnormalities (1%, n=16), while the incidence was <1% (n=2 exposures) for the placebo group. In the gastrointestinal SOC, eight (1%) SAEs were reported for subjects in the sugammadex group and three (1%) SAEs for subjects in the placebo group; within this SOC, two SAEs of small intestinal perforation were reported in the sugammadex group and none were in the placebo group. These two subjects on sugammadex underwent laparoscopic rectosigmoidectomy and were administered 2 mg/kg and 1 mg/kg sugammadex, respectively. Both events were not considered related to the study drug by the investigator, and the subjects recovered from the SAEs. Post-procedural hemorrhage occurred in three (<1%) sugammadex and two (<1%) placebo subjects in each treatment group.

Serious AEs that were considered to be related to study drug occurred in only seven (1%) of subject exposures in the sugammadex group and three (1%) in the placebo group; of these, ECG QT prolongation was reported in three subject exposures to sugammadex and one for placebo. Of note, per protocol definition, any QT abnormality was considered as an SAE, regardless of whether it met the standard criteria for a SAE. In the sugammadex group, one drug-related SAE of abnormal QT interval was reported for the same subject who also had an SAE of prolonged QT interval. Other drug-related SAEs in the sugammadex group included post procedural haemorrhage, subcutaneous haematoma, haematoma, and hypotension. In the placebo group, other drug-related SAEs included hematoma, wound haemorrhage, wound secretion [two subject exposures] and anaemia.

6.3.4 Pooled Phase 1-3: Neostigmine-Controlled Trials

Adverse Events

The incidence of AEs was similar for sugammadex (83.9%) and neostigmine (87.2%) in the Pooled Neostigmine-controlled trials. The overall incidences of AEs were similar between the two treatment groups for each SOC, with no apparent dose relatedness for sugammadex. Adverse events occurring at more than 10% were procedural pain, nausea, constipation, vomiting and pain for both treatment groups.

Serious Adverse Events

In the eight neostigmine-controlled trials, all of which were Phase 3 trials, there were 44 (5%) and 59 (7%) subject exposures in the sugammadex and neostigmine groups, respectively, associated with at least one SAE. Only four subject exposures in the neostigmine group (procedural pain, acute myocardial infarction, pneumonia, delayed recovery) and two in the sugammadex group (post-procedural hemorrhage and hematoma) resulted in an SAE that was considered to be related to study drug by the investigator.

6.3.5 Pooled Phase 1 Trials

Adverse Events

For Pooled Phase 1 data without NMB or anesthesia, there was a clear association between sugammadex and AEs of dysgeusia and nausea, and these effects were also observed in increasing incidence with increasing sugammadex dose. In Pooled Phase 1-3 trials with anesthesia and/or NMBA there was no increased incidence in dysgeusia or nausea with sugammadex, as the events would not normally be reported by patients in the surgical setting. An overview of the AEs in the healthy subject population (not receiving general anesthesia or NMBA) is given in **Table 5**.

Serious Adverse Events

There were six subject exposures (0.3%) associated with SAEs in the total sugammadex group of which two occurred at the 4 mg/kg dose, three at the 16 mg/kg dose and one at the 32 mg/kg dose; the SAEs were reported within several SOCs. SAEs were reported for four (0.3%) subject exposures to placebo. Three of the subject exposures associated with SAEs were considered to be drug-related by the study investigators: two subject exposures in the 16 mg/kg sugammadex group were associated with SAEs of anaphylactic shock (urticaria, hypotension, tachycardia and flushing) and "electrocardiogram QT prolonged" and one subject exposure in the 32 mg/kg with events of feeling hot, dysgeusia, and headache (subject with an accidental overdose who actually received 27 mg/kg instead of the intended 16 mg/kg dose). The case of anaphylactic shock occurred in the previous hypersensitivity trial P06042. There were no reported SAEs in the placebo group considered to be related to study drug by investigators.

Table 5 Number (%) of Subject Exposures Associated with Adverse Events by Sugammadex Dose (mg/kg) in Pooled Phase 1 Trials (Incidence ≥2% in One or More Treatment Groups)

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total Sugammadex[a]
		(N=1424)	(N=6)	(N=1162)	(N=969)	(N=2396)
		n (%)	n (%)	n (%)	n (%)	n (%)
At least one AE	Total	300 (21.1)	1 (16.7)	351 (30.2)	379 (39.1)	853 (35.6)
Nervous system disorders	Total	101 (7.1)	0 (0.0)	137 (11.8)	227 (23.4)	433 (18.1)
	Dysgeusia	7 (0.5)	0 (0.0)	34 (2.9)	156 (16.1)	242 (10.1)
	Headache	72 (5.1)	0 (0.0)	77 (6.6)	71 (7.3)	161 (6.7)
Gastrointestinal disorders	Total	46 (3.2)	0 (0.0)	75 (6.5)	107 (11.0)	223 (9.3)
	Nausea	13 (0.9)	0 (0.0)	38 (3.3)	79 (8.2)	134 (5.6)
General disorders and administration site conditions	Total	58 (4.1)	0 (0.0)	55 (4.7)	50 (5.2)	134 (5.6)
Infections and infestations	Total	57 (4.0)	0 (0.0)	53 (4.6)	41 (4.2)	103 (4.3)
	Nasopharyngitis	29 (2.0)	0 (0.0)	17 (1.5)	23 (2.4)	45 (1.9)
Skin and subcutaneous tissue disorders	Total	15 (1.1)	0 (0.0)	36 (3.1)	49 (5.1)	96 (4.0)
Respiratory, thoracic and mediastinal disorders	Total	44 (3.1)	0 (0.0)	36 (3.1)	37 (3.8)	90 (3.8)

N=Number of subject exposures per treatment group. n =Number of Subject Exposures with AEs

[a] Total column includes subjects exposed to all doses of sugammadex (<2, 2, 4, 8, 16, 32, 64 and 96 mg/kg).

6.3.6 Assessment of Bleeding Risk

Based on dedicated clinical trials in at-risk subjects being treated with anti-thrombotic prophylaxis, the cumulative clinical safety database, and postmarketing surveillance data, the limited and transient effects of sugammadex on Activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (International Normalized Ratio)PT(INR), which appear to be mediated mainly by a reversible inhibition of Activated Coagulation Factor X (Factor Xa) activity, are not associated with an increased bleeding risk in surgical subjects. Further evaluation of potential effects of IV sugammadex on coagulation was not requested in the Complete Response letter received from FDA on 20-Sep-2013. Updated review of clinical and post-marketing data support the conclusions of the dedicated trial (Trial P07038) in

orthopedic patients on antithrombotic prophylaxis, which showed no clinically meaningful differences in the proportion patients experiencing serious bleeding between the sugammadex and usual care groups as described in the 2012 resubmission.

6.4 Overview of Postmarketing Safety

There has been extensive experience with sugammadex since its initial approval in the European Union in 2008. Sugammadex is currently approved and marketed in more than 50 countries worldwide. As of 31-March-2015, 12.1 million vials of sugammadex have been sold. For the purposes of this application, the estimated usage rate of sugammadex has been assumed to be 95% based on the following data: 1) conservatively allowing for as much as three month stockpile in the distribution channels over the 84 months of sales corresponds to a 96% usage rate; and 2) fewer than 2% of doses have been returned to the Sponsor. This usage rate translates to approximately 11.5 million patients exposed to sugammadex since market introduction.

Out of 11.5 million patient exposures, a total of 1200 (538, 45% serious) postmarketing AE reports for sugammadex were identified in the Merck Adverse event Reporting and Review System (MARRS) pharmacovigilance database from market introduction through 22-Apr-2015. These 1200 reports included 2301 AEs, of which less than half were serious (N=1066, 46%).

The ten most common AEs associated with sugammadex are shown in **Table 6**.

Table 6 Most Common Postmarketing Adverse Events (25-Jul-2008 to 22-Apr-2015)

Preferred Term	Number of Events
Anaphylactic shock	106
Anaphylactic reaction	104
Blood pressure decreased	88
Urticaria	88
Drug ineffective	63
Bradycardia	61
Erythema	59
Nausea	57
Off label use	48
Rash	47

The ten most common serious AEs associated with sugammadex are shown in **Table 7**.

Table 7 Most Common Postmarketing Serious Adverse Events (25-Jul-2008 to 22-Apr-2015)

Preferred Term	Number of Events
Anaphylactic shock	106
Anaphylactic reaction	85
Blood pressure decreased	60
Urticaria	33
Anaphylactoid reaction	31
Bronchospasm	30
Cardiac arrest	30
Erythema	26
Recurrence of neuromuscular blockade	25
Hypotension	22

As shown, the most common AEs, both overall and serious, appear to be related to hypersensitivity reactions.

6.4.1 Postmarketing Reports of Patients with Fatal Outcome

A total of 13 postmarketing reports in patients with fatal outcomes have been received since market introduction of sugammadex. These reports can be divided into three groups: fatalities associated with anaphylaxis (4), fatalities associated with cardiac arrhythmia (3, plus an additional two which are contained in the anaphylaxis grouping of 4), and a heterogeneous group (6) of generally medically complicated patients who do not fit any particular clinical pattern. Detailed information on these 13 reports can be found in **Appendix 5**.

Four fatal reports (Fatal reports #1-4) containing terms consistent with anaphylaxis have been received by the Sponsor since market introduction. These reports are discussed in greater detail in section 6.5.4, and are described at length in **Appendix 5**. The reports describe patients with complicated medical conditions and courses, with multiple risk factors for poor outcomes, and it is not clear in these cases whether sugammadex played a causal role, either in whole or in part. Although these reports all had terms included in either the narrow Anaphylactic reaction or Anaphylactic shock SMQ, after review, none of these reports were adjudicated by the independent Adjudication Committee to represent anaphylaxis or hypersensitivity.

A total of three fatal reports (Fatal reports #5-7) associated with terms of cardiac arrhythmia have been received by the Sponsor. An additional two reports with an arrhythmia event (Fatal reports #3 and #4) are also associated with anaphylaxis, and are addressed in the discussion of hypersensitivity. The three fatalities associated with cardiac arrhythmia all had significant underlying morbidities, and are reviewed below in the cardiac arrhythmia discussion, and provided in greater detail in **Appendix 5**.

An additional six fatal reports (Fatal reports #8-13) were received by the Sponsor, and are described briefly below. These reports are heterogeneous in nature, and do not represent a

consistent clinical pattern that might suggest an association with sugammadex. These six reports are briefly described below and are described in more detail in **Appendix 5**.

- A 78 year-old patient with aortic valve stenosis and diabetes mellitus who experienced decreased blood pressure shortly after sugammadex that resolved with epinephrine and percutaneous cardiopulmonary support. The patient died of complications of aortic valve stenosis on postoperative Day #5;
- A 60 year-old patient with hepatitis B and hepatocellular carcinoma with uncomplicated use of sugammadex following microwave coagulo-necrotic therapy, died of liver failure three months post surgery;
- A 79 year-old patient with renal failure, aortic valve insufficiency, and craniopharyngioma who experienced two episodes of decreased blood pressure, one 15 minutes after sugammadex administration, and one 2-3 hours later with subsequent multi-organ failure 30 hours after surgery. Died seven days after surgery of unknown cause;
- A 78 year-old patient with hypertension and lung cancer with intermittent hemoptysis, had uncomplicated use of sugammadex following removal of a lumbar cord tumor. Four days post surgery underwent bronchial artery embolization for severe hemoptysis and was managed with mechanical ventilation. The patient subsequently developed pneumonia and pulmonary edema and died 11 days after the initial surgery;
- A 70 year-old patient with bladder cancer, hypertension and an unspecified cardiovascular disorder underwent two surgeries five days apart (transurethral resection (TUR) and cystectomy), with uncomplicated use of sugammadex following TUR. Received radiation therapy and died two months after surgeries due to an unspecified respiratory complication;
- A female of unknown age with inoperable tracheal and esophageal carcinoma underwent tracheal stenting with uncomplicated use of sugammadex. Enroute to the recovery room, she developed grave ST segment depression that was managed with nitroglycerine and a beta blocker. She later developed pulmonary edema and died the day of surgery.

6.4.2 Postmarketing Mortality Rates

Fatalities are expected to occur in the perioperative period because of the risks of the procedures and the medically complicated patient population. The 13 total fatalities reported among 11.5 million treated patients in the sugammadex postmarketing database translates into an estimated rate of 1.1 fatalities per 100,000 exposures, assuming that 10% of cases are reported. For context, a published systematic meta-analysis of perioperative mortality estimated a rate in developed countries of 2.5 per 100,000 for mortality solely attributable to anesthesia, 8.5 per 100,000 for mortality partially related to anesthesia, and 110 per 100,000 surgeries for total perioperative mortality regardless of anesthesia. [**8**]. Thus, the number of deaths reported in the sugammadex post-marketing database is of a similar order of magnitude to the number of deaths expected to occur in the perioperative period.

6.5 Hypersensitivity/ Anaphylaxis

In the Complete Response letter of 20-Sep-2013, the FDA stated that an audit conducted during routine inspection by the Office of Scientific Investigations (OSI) indicated protocol deviations and other findings that could impact the validity, reliability, or integrity of the data from Trial P06042, a dedicated hypersensitivity trial. Since Trial P06042 was conducted to address the questions the FDA had previously raised about hypersensitivity, these questions remained unresolved. The Sponsor therefore conducted Trial P101, a hypersensitivity trial similar in overall design to Trial P06042. The FDA requested characterization of sugammadex safety on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. The FDA also requested that the Sponsor attempt to define the physiological basis of hypersensitivity reactions as well as to perform a comprehensive analysis of available clinical data. Prior to finalizing the trial design, the Sponsor discussed the trial with the FDA, and it was agreed that the mechanistic work in the new hypersensitivity Trial, P101, would be limited to measurements of serum tryptase and assays for sugammadex-specific IgG and IgE antibodies.

As noted in the 2003 Report of the Nomenclature Review Committee of the World Allergy Organization (WAO), the terminology used to characterize allergic and allergy-like reactions is confusing, so it is important to define the terms being used. As recommended by the WAO, "… the term hypersensitivity should be used to describe objectively reproducible symptoms and signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons." In the Pooled Phase 1 trials, the doses of sugammadex ranged up to 96 mg/kg and the majority of subjects tolerated the dose range. Additionally in this report of the Nomenclature Review Committee, "… anaphylaxis is a severe, life-threatening generalized or systemic hypersensitivity reaction." Thus anaphylaxis by this definition is a subset of hypersensitivity reactions, and encompasses both *allergic anaphylaxis,* that is, anaphylaxis caused by an immunologic mechanism such as IgE, as well as *non-allergic anaphylaxis* **[9]**.

The body of data now available to assess hypersensitivity and anaphylaxis risk and sugammadex includes:

- A dedicated hypersensitivity trial in healthy subjects (Trial P101) investigating the incidence of hypersensitivity and anaphylaxis after three repeated administrations of doses of 4 mg/kg sugammadex, 16 mg/kg sugammadex, or placebo in 375 healthy subjects randomized in a 2:2:1 ratio with independent blinded adjudication of hypersensitivity cases.
- Studies to elucidate the mechanism of action of hypersensitivity reactions based on the results of the biomarkers included in Trial P101 and Trial P06042 (skin testing, anti-sugammadex IgE/IgG assay, serum tryptase evaluation, basophil histamine release testing, activation of contact and complement system, and parameters of neutrophil or cytokine activation).
- Analyses of the cumulative pooled clinical trial database (including post-hoc adjudication of AE reports suggestive of hypersensitivity/ anaphylaxis).
- A review of the extensive post-marketing experience (including post-hoc adjudication of post-marketing reports suggestive of hypersensitivity/ anaphylaxis).

– Epidemiological data and published literature regarding risks of anaphylaxis in the surgical setting.

6.5.1 Evaluation of Hypersensitivity After Repeat Exposure (Trial P101)

Trial P101 was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the incidence of hypersensitivity after repeated single-dose administrations of sugammadex. In the trial, 375 healthy awake subjects, who did not receive NMBAs or anesthetics, were randomized to one of three parallel arms assigned to treatment with three successive single doses of one of the following treatments in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex or placebo (151, 148 and 76 subjects, respectively) and shown in **Figure 8**. Dosing periods were spaced apart by approximately five weeks to allow potential sensitization to develop. After each dose, each subject was examined at 0.5, 4 and 24 hours for signs and/or symptoms of hypersensitivity according to a standardized Targeted Hypersensitivity Assessment (THA), which included a semi-structured interview to elicit symptoms of hypersensitivity and also contained a focused physical examination. Strict blinding procedures were specified by the protocol and carefully monitored during the trial. In particular, after the pharmacist prepared the study drug, an opaque label was used to mask the contents of the syringe, and no subject in P101 was assessed with the THA by the same person who administered the masked dose of study drug.

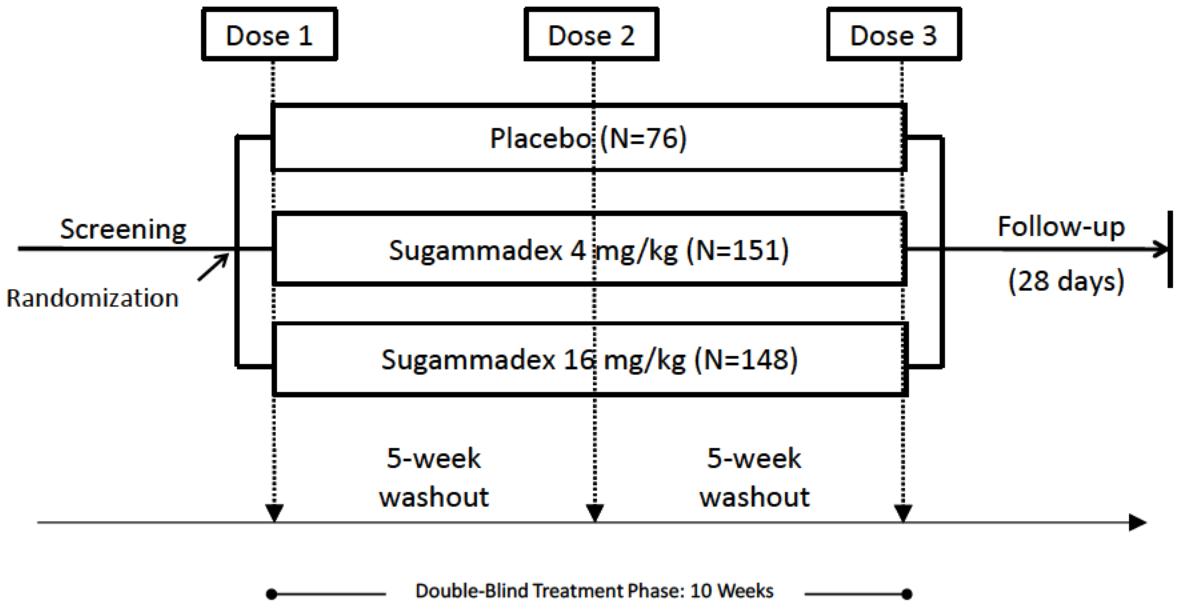


Figure 8 Overview of the Trial Design of P101

Adjudication of Hypersensitivity/Anaphylaxis

Cases with protocol-defined signs and symptoms of hypersensitivity found through THAs were referred to the external blinded adjudication committee (AC), composed of experts in allergy and/or anesthesia. In addition to referrals based on findings by investigators on the THAs, the Sponsor conducted periodic review of safety data including AEs, which resulted in five additional referrals to the AC. The AC determined whether events were true

hypersensitivity, rated the severity of hypersensitivity (independent of the rating of severity of individual AEs by the investigator), and determined whether the events met the definition of anaphylaxis. For Trial P101, the definition of anaphylaxis according to Sampson (Criterion 1, as in **Table 8**) was employed, as this was the criterion used by the FDA to analyze previous events of hypersensitivity to sugammadex.

Table 8 Anaphylaxis According to Sampson Criterion 1

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

BP=Blood Pressure; PEF=Peak Expiratory Flow

Sampson et al, 2006 **[1]**

Incidence of Adjudicated Hypersensitivity and Anaphylaxis with Repeated Administration of 16 mg/kg Sugammadex, 4 mg/kg Sugammadex or Placebo

A total of 94 subjects (45, 35 and 14 subjects in the 16 mg/kg sugammadex, the 4 mg/kg sugammadex and the placebo treatment groups, respectively) were referred to the AC for evaluation. Among these 94 subjects, the AC identified 25 subjects with adjudicated hypersensitivity after receiving at least one dose of study drug. The incidence of adjudicated hypersensitivity was 6.6% (95% CI [3.2%, 11.8%], 10 of 151 subjects) in the 4 mg/kg sugammadex treatment group, 9.5% (95% CI [5.3%, 15.4%], 14 of 148 subjects) in the 16 mg/kg sugammadex treatment group, and 1.3% (95% CI [0.0%, 7.1%], one of 76 subjects) in the placebo treatment group. Only one case was adjudicated as anaphylaxis, with the first dose of 16 mg/kg sugammadex, which corresponds to an incidence of 0.7% (95% CI [0.0%, 3.7%]). This case was also classified as severe hypersensitivity by the AC, although the individual AEs were characterized by the investigator as mild to moderate. This subject had onset of the initial AEs immediately after dose administration: mild sneezing, nasal congestion and conjunctival edema, and moderate urticaria and swelling of the uvula, and a transient decrease in peak expiratory flow (decrease from baseline 810 L/min to 470 L/min at 27' with increase to 570 L/min at 29' and 730 L/min at ~4 hrs), but with no change in oxygen saturation and a respiratory rate within four breaths per minute of baseline and no hypotension. The investigator treated these symptoms with IV antihistamine and corticosteroid. The symptoms improved rapidly with resolution of all symptoms within three hours of receiving sugammadex except for conjunctival edema which did not resolve until nine hours after the dose administration. There were no abnormal lung sounds noted in the THAs for this case. This subject was discontinued from the trial per protocol for having received treatment for hypersensitivity symptoms, and did not receive additional doses of sugammadex. No subject in either the 4 mg/kg sugammadex treatment group or the placebo treatment group had adjudicated anaphylaxis, which corresponds to a within group upper bound of the 95% CI of 2.4% and 4.7% for the 4 mg/kg sugammadex, and placebo groups, respectively.

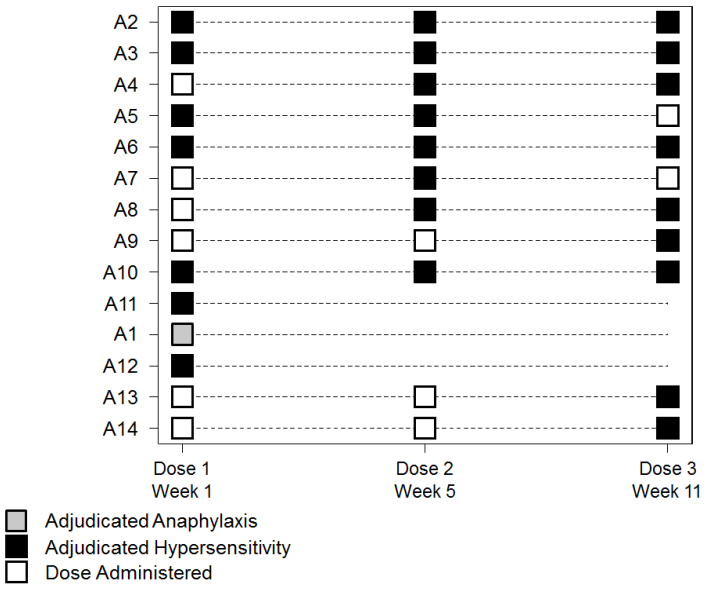
Adverse Events in Subjects with Adjudicated Hypersensitivity

In Trial P101, all AEs in subjects treated with sugammadex were rated as mild to moderate in intensity by the investigators; there were two AEs rated as severe in the placebo treatment group. Of the 25 subjects with adjudicated hypersensitivity (coded case numbers of A1 to A25 with A indicating adjudicated), 11 had more than one adjudicated hypersensitivity event and each event for a given subject had a similar time course and pattern of AEs. Clinical signs and symptoms of hypersensitivity and/or anaphylaxis occurred soon after sugammadex administration, generally within 10 minutes of bolus administration. Symptoms and signs that did occur resolved quickly and spontaneously for the majority of cases. Three subjects with adjudicated hypersensitivity (including subject A1 with adjudicated anaphylaxis) in the 16 mg/kg treatment group received and responded to treatment with antihistamines and corticosteroids. No subjects required treatment with epinephrine. No subjects in the 4 mg/kg treatment group or in the placebo group required treatment for adjudicated hypersensitivity. There was one subject in the 4 mg/kg group who did not have adjudicated hypersensitivity and received treatment for moderate nausea, which was defined by the protocol as a symptom of hypersensitivity and was treated with ondansetron. These four subjects who received treatment for AEs defined in the protocol as sign/symptoms of hypersensitivity were discontinued. Most subjects with adjudicated hypersensitivity (21 of 25) had dermatologic symptoms, which included pruritus, urticaria, erythematous rash or erythema alone or in some combination. Many of the subjects (nine of 25) had involvement of the respiratory system, including sneezing, throat irritation, nasal congestion or discomfort, rhinorrhea or pharyngeal edema. Several of the subjects (seven of 25) had gastrointestinal symptoms, typically nausea and/or vomiting. No subject had hypotension, cardiovascular collapse, or respiratory failure.

Frequency and Severity of Adjudicated Hypersensitivity and Anaphylaxis Over Time

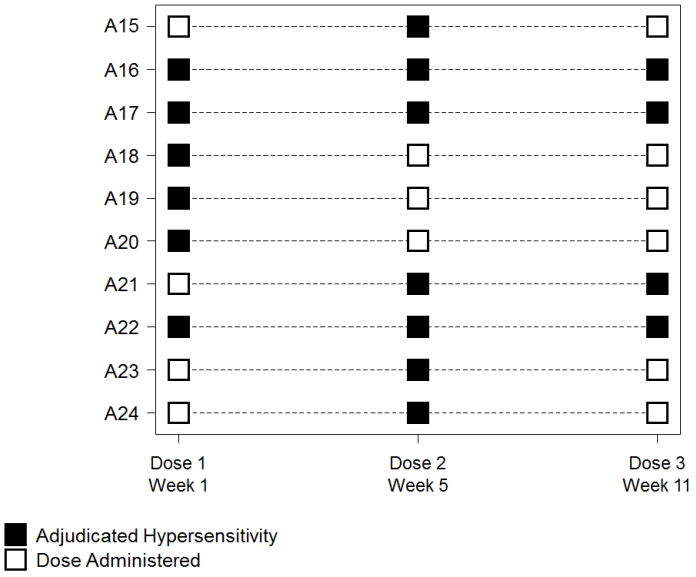
Overall the incidence of adjudicated hypersensitivity was similar in each dosing occasion for each treatment group. Graphical presentations of the time course of adjudicated hypersensitivity events for each subject by sugammadex treatment groups, showing time point(s), repeated occurrence of adjudicated hypersensitivity, duration of trial participation, and premature discontinuations, are shown in **Figure 9** for subjects treated with 16 mg/kg and in **Figure 10** for those treated with 4 mg/kg. One subject exposed to placebo also had adjudicated hypersensitivity in Treatment Period 3 (data not shown). The incidence of hypersensitivity did not increase with repeated administration of sugammadex, and no subject who received sugammadex had adjudicated anaphylaxis on retreatment with sugammadex. Among subjects with adjudicated hypersensitivity, several subjects continued in the trial and received additional doses of sugammadex. As seen in **Figure 9** and **Figure 10**, responses patterns varied. There were subjects with adjudicated hypersensitivity with each administration of sugammadex, and subjects with a single event of adjudicated hypersensitivity with no further events on sugammadex retreatment. Furthermore, there was no pattern of increasing severity of adjudicated hypersensitivity; of seven subjects with adjudicated hypersensitivity on all three dosing occasions, six had adjudicated hypersensitivity rated as mild by the AC on each dosing occasion. There was one subject who had mild hypersensitivity on the first dosing occasion and moderate hypersensitivity on

the second and third dosing occasion. The pattern of events does not suggest the development of sensitization with repeated exposures to sugammadex.



A1 – A14 are the subject's coded case numbers. The squares indicate a dose administered and the filled in squares either represent adjudicated hypersensitivity following dosing or adjudicated anaphylaxis (in the case of A1). The horizontal lines represent the treatment period from first dosing occasion up to last dosing occasion.

Figure 9 Adjudicated Hypersensitivity over Time for Sugammadex 16 mg/kg



A15 – A25 are the subject's coded case numbers. The squares indicate a dose administered and the filled in squares represent adjudicated hypersensitivity following dosing. The horizontal lines represent the treatment period from first dosing occasion up to last dosing occasion.

Figure 10 Adjudicated Hypersensitivity over Time for Sugammadex 4 mg/kg

Trial P06042

The design of Trial P101 was similar to Trial P06042, which was included in the 2012 NDA resubmission, with regard to the size of the active treatment arms, the doses of sugammadex administered (4 mg/kg and 16 mg/kg administered as three repeated single bolus doses separated by approximately five weeks), and the use of a blinded independent AC composed of experts on hypersensitivity, although detection of potential cases of hypersensitivity depended on AE reporting as opposed to the THA in Trial P101.

In Trial P06042, there were eight cases of adjudicated hypersensitivity; zero in the placebo treatment group, one in the 4 mg/kg treatment group, and seven in the 16 mg/kg treatment group. Among these eight cases of hypersensitivity, there were three cases of adjudicated anaphylaxis all with the first dose of sugammadex in the 16 mg/kg sugammadex treatment group. One case of anaphylaxis was a case of anaphylactic shock and required treatment of hypotension with epinephrine and antihistamine, and the other two cases resolved spontaneously.

6.5.2 Biomarkers related to potential mechanisms of hypersensitivity

In both hypersensitivity studies, exploratory biomarkers were employed to address potential mechanisms of hypersensitivity. In both trials P101 and P06042, serum tryptase, a biomarker for mast cell degranulation, and assays for sugammadex-specific IgG and IgE antibodies were measured. Additional tests employed in Trial P06042 were skin testing (intradermal and skin prick), measurements of serum and urine biomarkers of the complement and contact systems as well as neutrophil and endothelial activation, and ex-vivo basophil histamine testing. The protocol deviations in Trial P06042 did not affect the mechanistic biomarkers measured in the trial. The Sponsor proposed not to repeat these additional tests in Trial P101, and the FDA concurred.

Tryptase

Tryptase is a serine protease stored in mast cell granules and released along with other mediators when mast cells are activated. It is useful as a measure of mast cell degranulation as the half-life of tryptase at approximately two hours is much longer than the two minute half-life of histamine **[10]**. Thus, an increase in serum tryptase is highly suggestive of mast cell activation **[11]**. In both trials P06042 and P101, the ImmunoCAP® assay (Phadia, Uppsala, Sweden) was employed to measure tryptase before dosing (baseline) and after dosing. The protocol-defined criteria for analysis was a value above 11 ng/mL based on the 95th percentile of the baseline tryptase in normal individuals **[11]** or a change from baseline of greater than 2 ng/mL based on a study in which tryptase measurements were conducted in subjects upon challenge with a known allergen **[12]**.

In Trial P101, none of the 25 subjects with adjudicated hypersensitivity had a post dose tryptase measurement that was > 11 ng/mL. Only one subject in Trial P101 with adjudicated hypersensitivity met the prespecified criteria of an increase >2 ng/mL (this subject had a 3 ng/mL increase from baseline). In Trial P06042, seven of the eight subjects with adjudicated hypersensitivity were evaluated (tryptase samples were missing for one subject)

and none had a post dose tryptase measurement > 11 ng/mL. Only one subject in Trial P06042 met the prespecified criteria of an increase > 2 ng/mL (this subject had a 3 ng/mL increase from baseline).

Anti-sugammadex Antibodies

A 3-step tiered assay was developed and validated for the detection of sugammadex-specific IgG and IgE antibodies, and was first employed in Trial P06042. The assay was updated, revalidated and employed for Trial P101.

In Trial P101, assays for the presence of anti-sugammadex IgG and IgE were carried out at baseline and approximately 4-5 weeks after each dose (subjects who completed all three dosing periods were tested four times) in all subjects with adjudicated hypersensitivity (n=25), subjects referred to the AC but without adjudicated hypersensitivity (n=69), and in a set of control subjects (n=91) from all treatment groups lacking evidence of potential hypersensitivity.

No subjects in Trial P101 had measurable anti-sugammadex IgE. There were two subjects with adjudicated hypersensitivity with measurable anti-sugammadex IgG. The first subject (A6 in 16 mg/kg dose group) had anti-sugammadex IgG at baseline, but did not have measurable anti-sugammadex IgG after the first, second and third doses. The second subject (A23 in 4 mg/kg dose group) was negative at baseline, but then had anti-sugammadex IgG in samples drawn after each dose.

In Trial P06042, the eight subjects with adjudicated hypersensitivity and 94 subjects without adjudicated hypersensitivity were tested for the presence of sugammadex specific IgG and IgE. All eight subjects with adjudicated hypersensitivity were negative for anti-sugammadex IgG and IgE. There was one subject without adjudicated hypersensitivity in the 4 mg/kg dose group that had anti-sugammadex IgG in samples drawn at baseline before exposure and after exposure to sugammadex.

Skin Testing

In Trial P06042, both skin prick (SPT) and intradermal tests (IDT) with appropriate positive (histamine) and negative (normal saline solution) controls were performed in the eight subjects with adjudicated hypersensitivity and in 173 subjects without adjudicated hypersensitivity. Seven of the eight subjects with adjudicated hypersensitivity showed adequate response to positive (histamine) and negative control (diluent) to be evaluated by SPT. All seven of these subjects were negative to sugammadex in the SPT test. Five of the eight subjects with adjudicated hypersensitivity showed adequate response to positive and negative controls and could be evaluated by IDT. One subject was positive to sugammadex. This was the same subject that had adjudicated anaphylaxis according to the Sampson criteria after a dose of 16 mg/kg sugammadex. The IDT was positive at a 1:10 dilution of sugammadex (10 mg/ml) and negative at lower dilutions. This concentration of sugammadex is approximately 50-fold higher than the expected Cmax of a 16 mg/kg dose of sugammadex. One hundred seventy three (173) subjects without adjudicated hypersensitivity were evaluated by SPT; one of these subjects was positive in the test. There were 120 subjects

without adjudicated hypersensitivity that were evaluated by IDT; one of these subjects was positive in this test.

Additional mechanistic studies

There were additional studies in Trial P06042 including an ex-vivo basophil histamine release assay, and serum and urine biomarkers for examination of the contact and complement system, and neutrophil and endothelial activation. There was no evidence of sugammadex-induced release of histamine from basophils of subjects with adjudicated hypersensitivity. There was no meaningful difference in the serum and urine biomarkers between subjects with adjudicated hypersensitivity and control subjects in Trial P06042, indicating that there was no evidence of contact system, complement system, endothelial cell or neutrophil activation associated with adjudicated hypersensitivity in Trial P06042.

Altogether these mechanistic results suggest that sugammadex-associated hypersensitivity is unlikely to be caused by a Type 1 immune-mediated (allergic) reaction. The mechanistic results are consistent with the observed clinical pattern of hypersensitivity observed in the adjudicated cases in the dedicated hypersensitivity trials, where there was no apparent sensitization to repeated administration of sugammadex.

6.5.3 Clinical Database Review of AEs Potentially Suggestive of Hypersensitivity (Including Anaphylaxis)

Potential events of hypersensitivity including anaphylaxis were investigated in all 56 clinical trials conducted by the Sponsor in the clinical development program for sugammadex (IV administration). For the analysis of hypersensitivity/anaphylaxis data in the clinical trial database, a number of sensitivity analyses were performed, and the results from the adjudication of events suggestive of hypersensitivity are summarized here.

In order to allow a more sensitive and specific analysis of hypersensitivity/anaphylaxis, an independent adjudication committee was tasked with retrospectively adjudicating all potential events of hypersensitivity/anaphylaxis in the clinical trial database in trials in which a dedicated AC did not perform such adjudication during the trial. For the post-hoc adjudication of potential hypersensitivity, identification of cases for referral to the AC was conducted using the Standardized MedDRA Query (SMQ) for 'hypersensitivity' and 'anaphylactic reaction'. The AC processed these cases in the same manner as events sent for adjudication during the clinical trials, with anaphylaxis defined by the Sampson Criteria **[1]**. The results of all adjudication across the clinical trial database for hypersensitivity and for anaphylaxis by the AC are presented in **Table 9** and **Table 10**. The AC was presented with all potential events in a fashion strictly blinded to treatment assignment, allowing unbiased comparisons across treatments. The results of the post hoc adjudication of events suggestive of hypersensitivity and/or anaphylaxis were as follows:

- In the Pooled Phase 1 trials in subjects that received sugammadex alone (with no anesthesia and no NMBA) excluding the dedicated hypersensitivity studies (Trials P101 and P06042), there were no dosing events adjudicated as anaphylaxis and four dosing

events (0.6%) adjudicated as hypersensitivity (all considered drug-related). There were no dosing events adjudicated as hypersensitivity or anaphylaxis in the placebo group.

- In the Pooled Phase 1-3 trials in subjects who received sugammadex or placebo with anesthesia and/or NMBA, the AC determined that adjudicated hypersensitivity occurred in nine dosing events (0.2%) in the sugammadex group, three dosing events (0.6%) in the placebo group, and three dosing events in the neostigmine group (0.3%). No events in these trials were reported or adjudicated as anaphylaxis. This is the clinical trial database with individuals who most closely resemble the population of anesthetized surgical patients treated with NMBAs likely to receive sugammadex; based on seeing no cases of anaphylaxis in this database of over 3,000 individuals, the upper bound for the 95% confidence interval on the true incidence of anaphylaxis in this population of patients receiving sugammadex is 0.1%.

Table 9 Adjudication Results for Exposure for Subjects in Pooled Phase 1-3 Database (Surgical Patients and Healthy Subjects with Anesthesia and/or NMBA)

Adjudication outcome	0 mg/kg (Placebo) (N=544)		<2 mg/kg (N=294)		2 mg/kg (N=895)		3 mg/kg (N=26)		4 mg/kg (N=1921)		6 mg/kg (N=28)		8 mg/kg (N=125)		12 mg/kg (N=39)		16 mg/kg (N=98)		20 mg/kg (N=6)		32 mg/kg (N=169)		Neostigmine (N=930)		Total Sugammadex (N=3601)	
	N	%	n	%	n	%	N	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Anaphylaxis	0		0		0		0		0		0		0		0		0		0		0		0		0	
Hypersensitivity	3	0.6	0		5	0.6	0		4	0.2	0		0		0		0		0		0		3	0.3	9	0.2

N = number of Exposures by group; n = number of exposures.

Table 10 Adjudication Results for Exposure for Subjects in Pooled Phase 1 Database (Subjects with No Anesthesia and No NMBA) Excluding Dedicated Hypersensitivity Trials (P101 and P06042)

Adjudication outcome	0 mg/kg (Placebo) (N=305)		<2 mg/kg (N=46)		2 mg/kg (N=6)		4 mg/kg (N=315)		8 mg/kg (N=31)		16 mg/kg (N=139)		32 mg/kg (N=154)		64 mg/kg (N=12)		96 mg/kg (N=12)		Total Sugammadex (N=715)	
	n	%	n	%	n	%	N	%	N	%	n	%	n	%	n	%	n	%	n	%
Anaphylaxis present	0		0		0		0		0		0		0		0		0		0	
Hypersensitivity present	0		0		0		1	0.3	1	3.2	0		2	1.3	0		0		4	0.6

N = number of Exposures by group; n = number of exposures.

6.5.4 Epidemiological and Postmarketing Data

To provide a context for understanding the frequency of anaphylaxis as it may be related to sugammadex, the epidemiologic literature describing anaphylaxis in the surgical setting is reviewed below, as are the results of a study conducted at the Cleveland Clinic.

Background Incidence Summary

The epidemiologic literature is limited but overall the available data suggest that the background rate for anaphylaxis (i.e., allergic and non-allergic anaphylaxis) is approximately 15 to 34 adjudicated cases per 100,000 operations (0.015% to 0.034%) in surgical patients receiving NMBA **[13; 14; 15; 16]**. Mortality rates due to anaphylaxis are approximately 0.5 to 1.5 deaths per 100,000 operations [**17]**. The epidemiological studies are limited by the rarity of anaphylaxis and the difficulty with diagnosing anaphylaxis accurately. The observed rate depends on whether the case definition includes hypersensitivity as well as anaphylaxis, whether all grades of severity are included, the degree of active surveillance, and the rigor of case adjudication. Although the studies did report rates in surgeries that used NMBA in association with anesthesia, some of the literature is over a decade old so it may not reflect current practices.

Background Incidence: NMBA Exposed Patients

A study in Norway **[13]** examined anaphylactic reactions after general anesthesia that were referred to a specialist center for evaluation from 1996-2001 and found 19 NMBA-associated anaphylactic cases in approximately 56,500 anesthesia exposures (34 per 100,000 exposures).

Another study in Norway **[14]** studied serious intraoperative problems associated with general anesthesia during the period 1996-2000. Serious intraoperative problems were defined as "an event that requires one or more measures either to prevent further complications, or to treat a situation that is currently or potentially serious, and which does not routinely occur during the conduct of anesthesia." The problems were then graded according to severity: Grade 1 (trivial), Grade 2 (moderate difficulty but low severity), Grade 3 (serious situation), or Grade 4 (fatal outcome). They identified 13 severe (grade 3 or 4) anaphylactoid or anaphylactic reactions in 40,000 general anesthesia with NMBA (33 per 100,000).

A study conducted in France examined anaphylactic reactions occurring during anesthesia in 38 centers over the period from July 1994 to December 1996 [**15]**. There were 692 cases of anaphylaxis (i.e., characteristic clinical symptoms and positive allergy tests) and 611 anaphylactoid reactions (i.e., characteristic clinical symptoms and negative allergy tests) identified. The denominator of exposures was not known for the 38 centers. However, by applying a similar method since 1984 the Perioperative Anaphylactoid Reactions Study Group (GERAP) observed an average of about 200 annual cases of anaphylaxis related to NMBAs. The authors assume that this survey investigated half of the whole French anesthesia population and that the number of perianesthetic cases in France should therefore be doubled (i.e., 400). According to statistics provided by the French Society of Anesthesia

per year in France there are 2.5 million operations with general anesthesia that received NMBAs. Based on these assumptions relating the centers to the overall French population, the authors indirectly estimated a rate of 15 allergic anaphylaxis cases per 100,000 exposures in patients exposed to NMBAs. A similar study in France conducted from 1997 to 2004 reported a rate of 18.4 IgE-mediated anaphylaxis cases per 100,000 anesthetic procedures using NMBAs [**17]**. The rates in these French studies are lower than the Norwegian studies because the cases had to have positive allergy tests whereas the Norwegian studies included both allergic and non-allergic cases.

Cleveland Clinic Study

An epidemiological study **[16]** was sponsored by Merck at the Cleveland Clinic to better understand the incidence of perioperative anaphylaxis among patients exposed to NMBAs. This study aimed at assessing events occurring during general anesthesia up to entry into the Post Anesthesia Care Unit (PACU). This retrospective study included operations registered in the Cleveland Clinic Perioperative Health Documentation System (PHDS) between April 2005 and October 2011. Up to the first 10 operations for patients having multiple procedures during the study period were included in the analyses, with the exception that no operations having allergic reactions were excluded.

Based on modified Sampson's criteria **[1]** applicable in surgical setting and the information available in the PHDS, an electronic query was performed and yielded 4,008 candidate cases of anaphylaxis out of the 178,746 operations registered in the PHDS. An AC from the Cleveland Clinic composed of three anesthesiologists, who had the option to consult with an immunologist to gather additional insight before rendering a final decision, judged that 264 of these cases were true anaphylaxis. In 233 of the 264 operations (88%) in which anaphylaxis was experienced, the patient was exposed to NMBAs, whereas 73% of all operations were exposed to NMBAs.

The incidences of anaphylaxis per 100,000 operations exposed to NMBAs from the Cleveland Clinic Study are displayed in **Table 11**. These results show that a sensitive and systematic assessment of anaphylaxis cases yields incidence rates that are 3 to 10 times higher than reported in the French [**15**] and Norwegian surveys **[14; 13]**. However, nearly 85% of the cases were adjudicated as Grade 1 (trivial) or Grade 2 (low severity). When restricted to severe cases (grade 3 or higher), the incidence rate in the Cleveland Clinic study is 25 per 100,000 which is consistent with the 15-34 per 100,000 background rate reported by the French and Norwegian surveys for severe anaphylaxis.

Table 11 Results From the Cleveland Clinic Report on Incidence of Intra-Operative Anaphylaxis per 100,000 Operations Exposed to NMBAs

Anaphylaxis[a]	Cases/Total	Incidence per 100,000 Operations	95% CI
Regardless of severity grades[a]	233/131,137	178	156-202
Severe anaphylaxis (i.e., severity grades ≥ 3)[a]	33/131,137	25	18-35

CI = Confidence Interval; NMBA = Neuromuscular Blocking Agent

[a] Each case of anaphylaxis was assigned a severity grade as follow:

Grade 1 Trivial problem, easily dealt with and not affecting the patient's condition;

Grade 2 Moderate difficulty with some effect on the patient, but of a low severity;

Grade 3 Serious situation which is either very difficult to manage, or which causes a serious deterioration in the patient's state, and which may or may not have postoperative consequences;

Grade 4 Respiratory and/or cardiac arrest;

Grade 5 Death

Post-Marketing Reporting Rates of Anaphylaxis

Anaphylaxis is likely to be under-reported in post-marketing spontaneous reports. Systematic literature reviews indicate that only about 10% of all AEs are reported overall but reporting rates vary considerably depending on severity, setting, labeling, degree of monitoring, and other factors **[18; 19]**. Reporting rates for more serious events and events that are more specifically associated with an exposure are in the range of 23-50% **[18; 19]**. Therefore, in the Sponsor's assessments of post-marketing data, sensitivity analyses are provided over a range of 10% to 25% for reporting rates.

Post-marketing Experience

As of 31-Mar-2015, over 12.1 million vials of sugammadex have been sold worldwide according to sales data provided by Intercontinental Marketing Services (IMS) and from the Sponsor's internal distribution data from the Worldwide Financial Repository System (WFRS) database. As noted previously, the Sponsor estimates that approximately 95% of vials sold have been utilized, translating to approximately 11.5 million patients exposed to sugammadex since market introduction. Post-marketing data is reported spontaneously by clinicians and limited data is often available for reporting.

Post-marketing Data

The Sponsor's pharmacovigilance database was searched for post-marketing reports of anaphylaxis and serious hypersensitivity received from healthcare providers (HCPs) including non-interventional studies, cumulatively from market introduction through 22-Apr-2015 in patients administered sugammadex. Anaphylaxis reports were identified by querying the MedDRA version 18.0 narrow "Anaphylactic reaction" SMQ, along with narrow terms from the "Anaphylactic/anaphylactoid shock" sub-SMQ in the Shock SMQ. Serious hypersensitivity reports were identified by querying serious broad terms in the "Anaphylactic reaction" SMQ (excluding narrow terms) and serious narrow and broad terms in the "Hypersensitivity" SMQ (excluding narrow terms in the "Anaphylactic reaction" SMQ. These reports were included in the sensitivity analysis that follows. Note that the broad

Anaphylaxis SMQ includes many nonspecific terms that limit the interpretation of the reports resulting from the queries performed.

A total of 414 reports were identified in this query, of which 259 represented reports of anaphylaxis and 155 represented reports of serious hypersensitivity. For the purpose of consistency with the evaluation of clinical trial cases, all 259 reports with a term mapping to anaphylaxis were reviewed by an independent AC. This AC was composed of many of the same members used to adjudicate reports of anaphylaxis from the clinical trial data. The AC reviewed each report for signs and symptoms of anaphylaxis and/or hypersensitivity, using Sampson criterion 1 as the basis for adjudication. Cases were adjudicated either as anaphylaxis, hypersensitivity, neither, or as containing insufficient information for adjudication. The AC could not confirm that all 259 reports represented anaphylaxis. However, as anaphylaxis is the event of greatest clinical significance in the hypersensitivity spectrum, all 259 cases are included in the Sponsor's analysis as representing anaphylaxis, regardless of the AC evaluation. In addition, in order to ensure that as many anaphylaxis cases as possible were captured, all 155 reports containing a serious hypersensitivity term were evaluated by the same AC to determine whether any of them met criteria for anaphylaxis. Fourteen reports with serious hypersensitivity terms were determined by the AC to represent anaphylaxis; these have been added to the 259 anaphylaxis reports, for a total number of 273 anaphylaxis reports.

In the spontaneous reporting environment, under-reporting and difficulties estimating usage of product limit the precision with which the incidence of AEs can be estimated. A commonly accepted estimate is that approximately 10% of serious adverse events are reported, and reporting rates tend to be higher for events of greater clinical significance, and when the adverse reaction occurs in the presence of a healthcare professional **[18; 19]**. As noted previously, the Sponsor estimates that approximately 95% of doses sold were used, giving 11.5 million patient exposures.

Assuming 10% of the cases were reported and that 95% of the sold vials were used, the 273 total anaphylaxis cases reported yield a frequency of post-marketing reports of 23.7 per 100,000 operations [95% CI: 22.8; 24.6] or 0.024% (95% CI: 0.023-0.025%). This falls within the published range of background rates of 15 to 34 for cases of severe anaphylaxis (see Section 6.5.4 above). Thus, taken as a whole, the post-marketing surveillance data suggest that the additional risk for anaphylaxis associated with sugammadex beyond that already present in surgical patients is small.

Discussion and Conclusion of Post-marketing Data

Analysis of the post-marketing reports of anaphylaxis do not permit precise estimation of rates or attribution of causality, and must be considered with attention to the number of factors that limit interpretation of post-marketing data; but within these limits the results suggest that the sugammadex-associated increase in risk for anaphylaxis beyond that already present for surgical patients is small and unlikely to meaningfully change the overall safety profile for patients undergoing anesthesia with NMB.

The most commonly described clinical features in the 273 anaphylaxis reports were mucocutaneous manifestations and decreased blood pressure/hypotension, which were generally effectively managed with methods readily available in an operating room or post-operative care setting. Due to missing information, these reports cannot be formally classified according to severity; however, on inspection they encompass a range of severities, and most subjects recovered quickly with standard treatment. Most patients were treated with standard medical interventions for anaphylaxis, including epinephrine, antihistamines, corticosteroids, and vasopressors. The feature that appeared to be most closely associated with prolonged hospitalization is the need for enhanced ventilatory support (reintubation or prolonged intubation); this occurred in a small minority of patients. Finally, based on conservative assumptions about reporting and exposure, the incremental risk for anaphylaxis attributable to sugammadex in surgical patients appears limited.

With the exception of four fatalities, all patients in whom an outcome was reported recovered (n=241). In the four reports with fatal outcome, the patients died on postoperative days 3, 4 and 19 in three reports and in the fourth report, the patient died of circulatory failure of unknown etiology after successfully receiving two doses of sugammadex 200 mg on each of two consecutive days to reverse long term NMB given for mechanical ventilation and recurrence of NMB following cardiac arrest. It is important to note that analysis of individual cases for causality in the postmarketing setting, where case details are collected in a less structured manner, is difficult, and may give limited insight into the role of sugammadex in the patient outcome. Details of these four reports are as follows:

- Fatal report #1: 40 year-old male admitted after cardiopulmonary arrest due to myocardial infarction at another hospital. The patient was diagnosed with "circulatory collapse", a term in the Anaphylaxis SMQ. The patient was in a state of pulseless electrical activity (PEA), and percutaneous cardiac pulmonary support was begun. The patient was placed on long-term rocuronium for mechanical ventilation, and given 800 mg of sugammadex in 200 mg doses over an undefined period after 3 days of rocuronium administration; he died due to circulatory failure of primary cardiac etiology.

- Fatal report # 2: 70 year old male with celiac artery aneurysm and suspected extensive pancreatic necrosis underwent celiac artery aneurysm surgery. The patient was diagnosed with "distributive shock", a term in the Anaphylaxis SMQ. Access to the artery could not be obtained and surgery could not be completed. There was some difficulty in establishing hemostasis with subsequent decrease in hemoglobin, which the reporter attributed to the manipulation of the pancreas during surgery. The patient developed hypotension, tachycardia and decreased oxygen saturation and died on postoperative day #4 of distributive shock.

- Fatal report #3: 56 year-old female with extensive surgical procedure for ovarian cancer. Developed cardiac arrest after administration of sugammadex. The patient was diagnosed with anaphylactic shock. The patient had intra-aortic balloon pump placed, developed intraabdominal bleeding, cerebral edema, and renal failure and died 19 days post surgery of cerebral edema.

- Fatal report # 4: 68 year-old male with history of metastatic prostate cancer undergoing gastrectomy for gastric cancer. The patient developed shock and cardiac arrest after sugammadex administration. The patient was diagnosed with anaphylactoid shock. The patient developed disseminated intravascular coagulation (DIC), extensive bleeding requiring reoperation, and died on postoperative day #3 of multiorgan failure.

The first two patients described above with fatal outcomes had serious underlying diseases (primary cardiac disease with recent myocardial infarction, pancreatic necrosis) to which their deaths appear attributable. It is unlikely that sugammadex played a role in the outcome of these two patients.

The second two patients described above were diagnosed by the reporting physicians with anaphylaxis/anaphylactic shock. Given the timing of sugammadex administration and the subsequent sequence of events, it is not possible to completely exclude a relationship of these events to sugammadex; however, it is not possible, given the complexity of these four cases, to assign a single causal factor to the poor outcomes. The Adjudication Committee concluded that none of the four cases met the definition of anaphylaxis.

In summary, to the extent that anaphylaxis associated with sugammadex does occur, it presents in a setting where the tools needed to treat the condition rapidly and effectively are already in place, including highly trained medical staff that can respond to the situation without delay. Risks can be further mitigated by appropriate labeling and ensuring that physicians are aware of and are prepared to respond to the possibility of hypersensitivity with the use of sugammadex.

6.5.5 Summary and Conclusions for Hypersensitivity (Including Anaphylaxis)

- In conclusion, there are three sources of information concerning the incidence of hypersensitivity and anaphylaxis: the dedicated hypersensitivity Trial P101, the clinical trial database, and the post-marketing experience. The rates of anaphylaxis in these three settings differ and this likely reflects the different subject populations and the different methods by which cases were ascertained in these settings.

    - The observed event frequency of anaphylaxis in the dedicated Trial P101, 0.33% (1/299 subjects), is higher than in either the clinical trials database or the post-marketing safety database, based on a single case of anaphylaxis at the 16 mg/kg dose. This is most probably a reflection of the trial design in which events were collected in awake and alert healthy subjects receiving sugammadex alone using an intensive case-finding methodology (i.e., Targeted Hypersensitivity Assessment) that solicited events. This methodology was chosen because its high sensitivity best served the goal of characterizing the potential for sensitization by assessing progression from no or very mild events over repeated administration. However, it is quite different from the way that events are typically identified and assessed for clinical importance and to make decisions about risk and need for intervention in usual clinical practice.

- In the Pooled Phase 1 – 3 dataset [N=3519 unique subjects], which was primarily composed of surgical patients receiving anesthesia and/or NMBA together with sugammadex, no events of anaphylaxis were reported by investigators. As noted above, the absence of events provides evidence that the estimated risk for anaphylaxis in this population is ≤ 0.1%.

- Based on the post-marketing data from approximately 11.5 million patient exposures, the estimated rate of anaphylaxis is 24 in 100,000 or 0.024%. Since this rate is derived from reporting of anaphylaxis in a setting where multiple agents may be causative, a precise estimate of the rate attributable to sugammadex alone is not possible, but these post-marketing data suggest that the additional risk for anaphylaxis associated with sugammadex beyond that already present in surgical patients is small. These results are consistent with those from the Pooled Phase 1-3 database as noted above.

- Altogether the results from the work performed to characterize the risk for hypersensitivity including anaphylaxis after administration of sugammadex support the following conclusions:

  - The results of Trial P101 provide evidence that:
    - Sugammadex may induce immediate hypersensitivity reactions and anaphylaxis. No delayed reactions were observed.
    - The majority of hypersensitivity events were mild to moderate in severity, brief in duration, often lasting less than an hour, and resolved spontaneously.
    - Anaphylaxis was observed immediately after the first administration of sugammadex and only in the 16 mg/kg group.
    - Three events of hypersensitivity (all at the 16 mg/kg dose) were judged to require intervention, and all were effectively managed with usual treatment.
    - Neither the frequency nor severity of hypersensitivity increased after repeated dosing.
  - In the cumulative Phase 1-3 trial database, no cases of anaphylaxis were identified, which corresponds to an upper bound of the 95% confidence interval of 0.1%.
  - In post-marketing experience, anaphylaxis with serious clinical signs has been reported with an estimated frequency that suggests that the contribution to increased risk attributable to sugammadex is small. Review of the cases reported also provides evidence that anaphylaxis that occurs in the surgical setting in the presence of sugammadex is responsive to usual treatment.
  - As sugammadex is administered in an operating room setting where patients are monitored closely, are generally intubated, have venous access in place, and staff trained to handle such medical situations with the medications necessary to treat the event directly at hand, the dedicated hypersensitivity trial, the experience in the clinical trial database, and the analysis of events in the post-marketing database suggest that risks to patients are limited and treatable in the clinical setting of the intended use.

- Appropriate labeling will alert clinicians for hypersensitivity reactions including anaphylaxis.

6.6 Cardiac Safety

An analysis of cardiac arrhythmias after sugammadex administration was requested by the FDA. Specifically, the FDA requested further evaluation of the cardiovascular safety profile, particularly related to additional studies to assess whether sugammadex has effects on QT prolongation or is associated with cardiac arrhythmias. The following assessment is based on results from dedicated Phase 1 clinical studies characterizing the potential impact on QTc prolongation, the analysis of the vital signs and physician-reported cardiac AEs collected in Pooled Phase 1-3 clinical trials and Pooled Phase 1 trials and the analysis of ex-US Post-marketing AE reporting after an estimated 11.5 million patients exposed in over 50 countries. Together, these analyses support the overall cardiovascular safety of sugammadex within the intended indication, and provide evidence that sugammadex is without clinically significant effects on myocardial repolarization, heart rate or the incidence of cardiac arrhythmias. The only exception is rare cases of clinically significant bradycardia during anesthesia emergence shortly after sugammadex administration reported through post-marketing pharmacovigilance. These cases are readily detectable in the perioperative setting, and typically respond well to usual interventions. The Sponsor proposes to communicate this risk through appropriate labeling.

6.6.1 QT/Myocardial Repolarization

There were three dedicated studies (two Thorough QT/QTc studies and one QT/QTc interaction trial) evaluating the effect of sugammadex alone, in combination with NMBA (rocuronium or vecuronium), and in combination with anesthesia (sevoflurane or propofol). In none of these studies was there evidence of an effect of sugammadex on the QT interval. No cases of Torsade de Pointes were reported in the sugammadex development program.

Meta-Analysis of Sugammadex Clinical Trials to Characterize Effects on QTcF

A meta-analysis that incorporated all Phase 2-3 studies with at least one pre-specified post-dose ECG recording (N=452 on sugammadex) did not suggest evidence of QTcF prolongation at either two or 30 minutes after administration of sugammadex, when concentrations are high. The estimated mean placebo-adjusted QTcF changes from baseline were -0.5 milliseconds (95% CI: -4.8 to 3.7 milliseconds) and -0.1 milliseconds (95% CI: -4.8 to 4.7 milliseconds) at 2 and 30 minutes after sugammadex administration, respectively.

An analysis of QTc outliers using Fridericia's correction showed that the proportions of patients with outlying QTcF values were the same or smaller for sugammadex compared to placebo (**Table 12**).

Table 12 Number (%) of Subjects With QTcF >500 milliseconds or QTcF Change From Baseline >60 milliseconds (All Phase 2-3 ECG Trials)

Criterion	Protocol	Placebo			Sugammadex		
		N	n	%	N	n	%
QTcF >500 milliseconds	All Trials	77	4	5.2	452	10	2.2
	PBO-Cont Trials[a]	77	4	5.2	374	8	2.1
QTcF change from baseline >60 milliseconds	All Trials	76	1	1.3	448	5	1.1
	PBO-Cont Trials[a]	76	1	1.3	371	3	0.8
QTcF >500 milliseconds or QTcF change from baseline >60 milliseconds	All Trials	77	4	5.2	452	12	2.7
	PBO-Cont Trials[a]	77	4	5.2	374	8	2.1

PBO-Cont=Placebo-Controlled; QTcF=Fridericia-Corrected QT Interval; N= Number of Subjects; n=Number of Cases

[a] Totals for placebo-controlled trials only.

In summary, a meta-analysis of all Phase 2-3 studies with at least one pre-specified post-dose ECG did not demonstrate evidence of QT prolongation compared to placebo.

Reporting of QT-Related Adverse Events in Pooled Trials

In the Pooled Phase 1-3 trials, the combined incidence of the AEs for the SMQ 'Torsade de Pointes, shock-associated conditions' (*narrow search and broad search*) was low and comparable for the sugammadex and placebo groups (0.9% and 1.2%, 1.1% and 1.3%, respectively). When looking at the specific preferred terms constituting the SMQ 'Torsade de Pointes, shock−associated conditions' in the Pooled Phase 1-3 trials, most of the AEs were the result of physician observations of abnormal or prolonged QT interval without clinical symptoms, which were to be reported as serious AEs in trials performed at the time of the original submission. The incidence of 'QT prolonged' in the sugammadex group was similar to the placebo group (0.7% in each group for both narrow and broad searches). There were two (0.1%) reports of 'ventricular tachycardia' in the sugammadex group (none in the placebo group) found in this SMQ search: one was an SAE of non-sustained ventricular tachycardia which consisted of an episode <15 seconds in duration observed 5.5 hours after sugammadex administration in a patient with significant coronary heart and valve disease and considered as 'unrelated to sugammadex' by the investigator; the second AE of ventricular tachycardia was reported as an AE only and consisted of an episode of non-sustained ventricular tachycardia that was documented by cardiac telemetry only in a Phase 1 trial, approximately four hours after administration of 32 mg/kg sugammadex. Results for this SMQ search were similar for the sugammadex and placebo treatment groups in the Pooled Placebo-controlled trials: the *narrow search* and *broad search* showed overall similar incidences in the sugammadex group and the placebo group (1.8% and 1.9% for sugammadex, 1.1% and 1.3% for placebo, respectively). When looking at this SMQ using the *narrow* and *broad search* in the Pooled Neostigmine-controlled trials, there were similar AE incidences for the sugammadex and neostigmine groups (0.3% and 0.5% for sugammadex, 0.2% and 0.6% for neostigmine, respectively). The SMQ group various AEs that can induce shock like renal or respiratory failure but often are of less relevance to proarrhythmic events. No AEs with the preferred term of 'Torsade de Pointes' were observed

in any of the Phase 1-3 trials. These reported AEs including peri/postoperative renal and respiratory problems occurred at a low incidence (0.1%).

Overall, the evaluation of combined Phase 1-3 studies therefore did not suggest an increased incidence of QT-related AEs in subjects treated with sugammadex as compared to placebo.

6.6.2 Heart Rate Change

The potential effect of sugammadex on heart rate was assessed using the estimated difference in change from baseline (comparing mean heart rate effects) as well as shift analysis (to identify potential outliers).

Estimated Difference in Subjects in Pooled Phase 1 Trials (Who Received Sugammadex, but no NMBA nor General Anesthesia) and Pooled Phase 1-3 Trials

The analyses of Phase I data investigated the potential effect of sugammadex alone (as opposed to sugammadex given during anesthesia to reverse NMB). The results for the Pooled Phase 1 group with a minimal increase in heart rate did not suggest evidence of a decrease in heart rate after sugammadex administration as compared with placebo, and suggest that sugammadex, administered alone (to subjects with no anesthesia or NMBA), was not associated with a decrease in heart rate (**Table 13**).

The analyses for the Pooled Phase 1-3 group driven by results in patients on multiple background therapies showed a small reduction in mean heart rate (-1.5, 95% CI -2.4, -0.6) for the sugammadex group relative to placebo only observed at two minutes after dosing with sugammadex (**Table 13**). The heart rate effect in this analysis was transient with no differences (in the same subjects) at either five or 10 minutes after sugammadex.

Table 13 Model-based Estimated Difference in Change from Baseline of Heart Rate (BPM) of Sugammadex Versus Placebo in Pooled Phase 1 Trials and Pooled Phase 1-3 Trials by Time Point Based on Vital Sign Data

Time Point	Estimated (bpm) difference between sugammadex and placebo	95% CI
Phase 1†		
2 minutes	1.3	(0.7, 1.9)
5 minutes	1.4	(0.8, 2.0)
10 minutes	1.6	(1.0, 2.1)
Phase 1-3 Trials‡		
2 minutes	-1.5	(-2.4, -0.6)
5 minutes	-0.2	(-1.4, 0.9)
10 minutes	-0.1	(-1.3, 1.2)

BPM=Beats Per Minute; CI=Confidence Interval

As based on differences in least squares (LS) means from an ANCOVA model including factors for study and treatment and baseline heart rate as covariates. For sugammadex treatment all dosages were pooled.

†Estimates based on 1256 placebo subjects and 2014 sugammadex subjects with at least one post-baseline heart rate measurement ‡Estimates based on 467 placebo subjects and 3442 sugammadex subjects with at least one post-baseline heart rate measurement.

***Shift Analyses of Heart Rate Changes*:**

To identify potential outliers in heart rate response, a shift analyses with multiple cut-offs were performed. **Table 14** shows the proportion of subjects in each group in Pooled Phase 1-3 trials who had a clinically significant reduction (≥20 bpm) of the heart rate resulting in a heart rate of 50 bpm or lower following administration of study drug (similar results were seen for other heart rate cut points (5, 10, 15 or 25 bpm not presented here). The proportion of subjects meeting these criteria was small at all timepoints with slightly higher rates in the sugammadex group compared to placebo. The proportion was highest in subjects receiving 16 mg/kg. A statistical comparison is limited by the small sample size in this group.

Table 14 Number of Subjects with a Decrease ≥20 BPM Resulting in a Heart Rate ≤50 BPM for Exposures for Adult Subjects in Pooled Phase 1-3 Trials by Time Point

	Placebo (N=544)			2 mg/kg (N=895)			4 mg/kg (N=1921)			16 mg/kg (N=98)			Total Sugammadex[a] (N=3601)		
	n	m	%	n	m	%	n	m	%	n	m	%	n	m	%
2 min	464	1	0.2	865	1	0.1	1799	3	0.2	89	1	1.1	3229	6	0.2
5 min	422	0	0.0	754	2	0.3	1715	5	0.3	56	1	1.8	2957	8	0.3
10 min	466	0	0.0	861	5	0.6	1778	4	0.2	93	1	1.1	3386	10	0.3
Any timepoint	467	1	0.2	874	7	0.8	1819	8	0.4	94	3	3.2	3442	19	0.6

BPM=Beats Per Minute; N=number per treatment group; n=number of subjects with heart rate data at each time point
m=number of subjects at each timepoint with decrease ≥20 BPM Resulting in a Heart Rate ≤50 BPM
[a] Totals for sugammadex include all doses of sugammadex including ones not shown in the table.

6.6.3 Cardiac Arrhythmias

To determine the incidence of AEs related to cardiac arrhythmia in the clinical database, searches for AEs were conducted utilizing the vast variety of terms captured within the SMQ 'Cardiac Arrhythmia'.

Pooled Phase 1-3 Trials

Results from the SMQ search show that the overall incidence of arrhythmia-related AEs is comparable between subjects exposed to sugammadex (*narrow search* 1.7%, *broad search* 4.6%), and placebo (*narrow search* 1.8%, *broad search* 4.0%). The AE incidence for subjects exposed to neostigmine is higher than for those exposed to sugammadex (neostigmine *broad search* 8.4%, sugammadex *broad search* 4.6%). The AE incidence was also higher in the succinylcholine group *(broad search* 9.0%), a depolarizing NMBA agent with short duration of action currently used for rapid sequence induction, than in the sugammadex group.

The cumulative rates for cardiac arrhythmia AEs that occurred within the first 24 hours after study drug administration are shown as Kaplan–Meier curves in **Figure 11**, by treatment group. The rate at which cardiac events occurred in subjects exposed to sugammadex is comparable to those exposed to placebo and are lower than for events occurring with neostigmine or succinylcholine exposures.

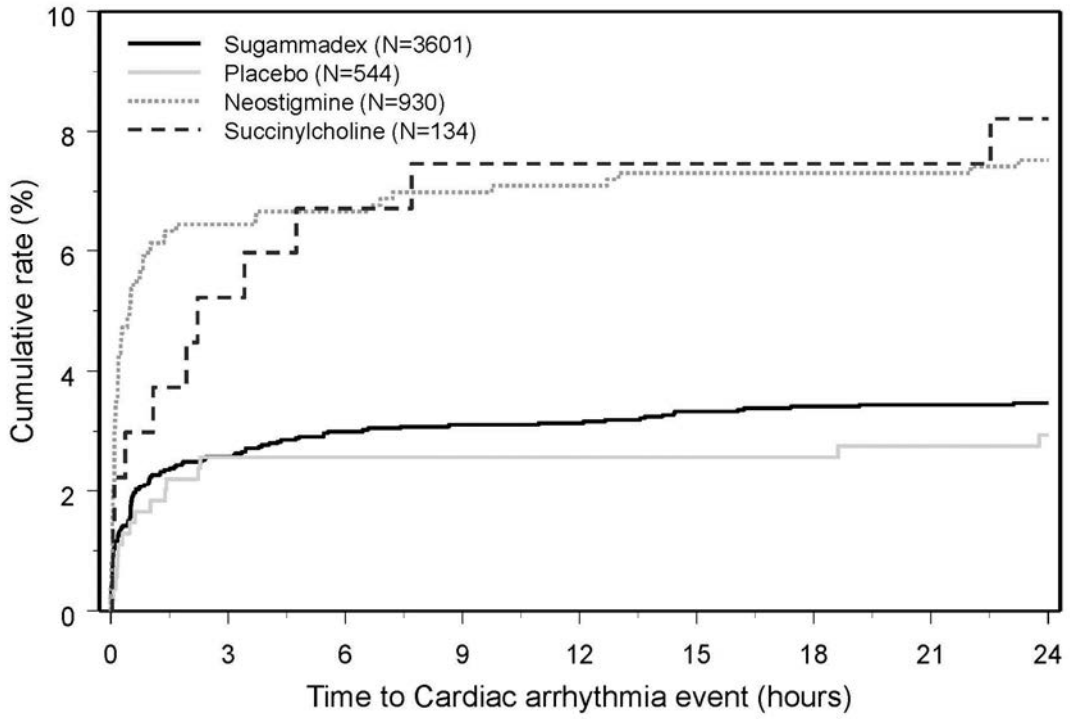


Figure 11 Kaplan-Meier Curve of Cumulative Rate of Cardiac Arrhythmias (*SMQ Cardiac Arrhythmias, Broad Search*) for Subjects Exposures by Treatment for the Pooled Phase 1-3 Trials with Anesthesia and/or NMBA

Table 15 depicts the specific preferred terms found in the Pooled Phase 1-3 database in association with the SMQ 'Arrhythmia related investigations signs and symptoms' SMQ; this SMQ is only comprised of broad category terms. Overall, the rates are low and comparable for subject exposures to sugammadex (3.2%) and placebo (2.2%). There was an overall higher incidence in the neostigmine and succinylcholine treatment groups (7.6% and 8.2%, respectively). The incidence of bradycardia was higher for subjects exposed to neostigmine and succinylcholine (4.5% in each treatment group) than for those exposed to sugammadex (1.0%). The majority of AEs captured by the SMQ 'Arrhythmia related investigations signs and symptoms' occurred at <1% and are similar between all treatment groups. A report of cardiac arrest was reported in this SMQ search for one subject in the sugammadex group. This subject was a 61 year old male who was scheduled for panendoscopy due to a tumor in the paranasal sinus. As part of the anaesthetic procedure the subject received 4.0 mg/kg sugammadex. Twelve minutes later the subject experienced a severe oculocardiac reflex, due to unintentional pressure on the eye bulbus during the surgical procedure resulting in asystole for one minute. The subject recovered after chest compression and atropine (0.25 mg). The investigator did not consider the event to be related to study drug.

Table 15 Number (%) of Subject Exposures with Adverse Events within SMQ Arrhythmia-Related Investigations in Pooled Phase 1-3 Trials

SMQ: Arrhythmia Related Investigations, Signs and Symptoms (B*road Search*) AE terms	Placebo	Sugammadex[b]	Neostigmine	Succinylcholine
	N=544	N=3601	N=930	N=134
Any of below named AE Terms (Total)	12 (2.2)	114 (3.2)	71(7.6)	11 (8.2)
Bradycardia	4 (0.7)	35 (1.0)	42 (4.5)	6 (4.5)
Cardiac arrest	0 (0.0)	1 (0.0)	0 (0.0) [a]	0 (0.0)
Electrocardiogram abnormal	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)
Heart rate decreased	1 (0.2)	7 (0.2)	1 (0.1)	0 (0.0)
Heart rate increased	0 (0.0)	5 (0.1)	4 (0.4)	0 (0.0)
Loss of consciousness	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Palpitations	1 (0.2)	8 (0.2)	4 (0.4)	0 (0.0)
Syncope	3 (0.6)	13 (0.4)	3 (0.3)	2 (1.5)
Tachycardia	4 (0.7)	49 (1.4)	22 (2.4)	3 (2.2s)

SMQ = Standardized MedDRA Query.

a One subject (Trial P07038, 302/100796) treated with neostigmine, died due to a cardiac arrest. The event, unlikely related to sugammadex according to the investigator, was reported and coded as 'death' which is not part of the SMQ, and the subject was therefore not counted in the table.

b. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

A review of the specific AE terms captured within the several other SMQ subcategories of ‘Cardiac Arrhythmias’ revealed other most frequent AEs in the Pooled Phase 1-3 group were atrial fibrillation, electrocardiogram QT prolonged, electrocardiogram QT interval abnormal, and sinus tachycardia, all of which occurred at similar rates and without clinically important differences between treatment groups.

Pooled Placebo-Controlled, Neostigmine-Controlled, and Pooled Phase 1 Trials

In addition to the pooled analysis of the overall data, ‘Cardiac Arrhythmias’ SMQ and ‘Arrhythmia related investigations signs and symptoms’ SMQ were compared in Pooled Placebo-controlled, Pooled Neostigmine-controlled, and pooled Phase 1 trials in subjects with no anesthesia and NMBA.

In the Pooled Placebo-controlled trials, the incidence of the SMQ ‘Cardiac Arrhythmias’ was similar in subjects exposed to sugammadex [*narrow search* 2.2%, *broad search* 5.2%,] and those exposed to placebo [*narrow search* 1.8%, *broad search* 4.0%]). In the Pooled Neostigmine-controlled trials, the incidence was lower for the sugammadex (*narrow search* 1.3%, *broad search* 3.8%) group than for the neostigmine (*narrow search* 1.1%, *broad search* 8.6%) group. In the Pooled Phase 1 trials, overall, the AE incidence in the total

sugammadex group was <1% for the narrow or broad SMQ searches for 'Cardiac Arrhythmias'.

The incidence of the SMQ for 'Arrhythmia related investigations signs and symptoms' (comprised of broad terms) in the Pooled Placebo-controlled trials was similar for sugammadex [3.2%] and for placebo [2.2%]) (**Table 16**). In the Pooled Neostigmine-controlled trials, there was a lower observed incidence of AEs for subject exposures to sugammadex [2.9%] than for neostigmine [7.8%] (**Table 17**). The incidence of bradycardia was also comparable in the Pooled Placebo-controlled trials (1.3% for the sugammadex and 0.7% for placebo treatment groups). In the Pooled Neostigmine-controlled trials, the incidence of bradycardia was higher after neostigmine (4.8%) than after sugammadex (0.5%). In the Pooled Phase 1 studies, there were no events of bradycardia reported in the sugammadex group at dose levels up to 96 mg/kg; 'tachycardia' was observed at 0.6% for the subjects exposed to sugammadex and at 0.1% for the placebo group.

Table 16 Number (%) of Subject Exposures with Adverse Events within SMQ Arrhythmia-Related Investigations in Pooled Phase 1-3 Placebo-controlled Trials

SMQ: Arrhythmia related investigations, signs and symptoms			
		Placebo	Sugammadex[a]
		N=544	N=1078
SMQ search	AE term		
Broad	Any of below named AE Terms (Total)	12 (2.2)	35 (3.2)
	Bradycardia	4 (0.7)	14 (1.3)
	Cardiac arrest	0 (0.0)	1 (0.1)
	Electrocardiogram abnormal	0 (0.0)	1 (0.1)
	Heart rate decreased	1 (0.2)	2 (0.2)
	Heart rate increased	0 (0.0)	3 (0.3)
	Palpitations	1 (0.2)	1 (0.1)
	Syncope	3 (0.6)	3 (0.3)
	Tachycardia	4 (0.7)	10 (0.9)

SMQ = Standardized MedDRA Query.

a. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

Table 17 Number (%) of Subject Exposures with Adverse Events within SMQ Arrhythmia-Related Investigations in Pooled Phase 1-3 Neostigmine-controlled Trials

SMQ: Arrhythmia related investigations, signs and symptoms			
		Sugammadex[a]	Neostigmine
		N=871	N=881
SMQ search	Preferred term		
Broad	** Any of below named Preferred Terms **	25 (2.9)	69 (7.8)
	Bradycardia	4 (0.5)	42 (4.8)
	Heart rate decreased	0 (0.0)	1 (0.1)
	Heart rate increased	0 (0.0)	4 (0.5)
	Palpitations	3 (0.3)	4 (0.5)
	Syncope	5 (0.6)	3 (0.3)
	Tachycardia	16 (1.8)	20 (2.3)

SMQ = Standardized MedDRA Query

a. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (2, 3 and 4 mg/kg).

In conclusion, based on the clinical trial experience, sugammadex is not associated with any increase in the incidence of arrhythmia-related AEs in healthy subjects and surgical patients when compared to placebo in an integrated analysis of AEs across the Phase 1-3 studies. The incidence of arrhythmia-related AEs with exposure to sugammadex is lower than with neostigmine or succinylcholine as the current standard-of-care.

Literature Review of Arrhythmia in Surgical Populations

Post-marketing reports can provide important information about the safety of drugs, but have important limitations, one of which is the difficulty in distinguishing whether events being reported are related to the expected consequences of the underlying illness and broad range of interventions, or are more specific to the particular drug of interest. To address this problem, it is helpful to establish estimates of background rates for the events of interest that can help provide a context for analysis. Establishing such estimates for cardiac arrhythmia and cardiac arrest in populations of patients undergoing surgery is complicated by differences in case definitions, surgical populations, anesthesia types, and observation periods. In addition, many arrhythmias during surgery under anesthesia go unreported since studies with continuous cardiac monitoring during surgery report an incidence of arrhythmias ranging from 14% to 22% **[20; 21; 22; 23]**. However, several studies are available that provide information about the expected range for these events that help provide a context for interpreting the frequency of cardiac arrhythmias and cardiac arrests reported in the sugammadex post-marketing database.

A Norwegian study however investigated serious intraoperative problems that were defined as "an event that requires one or more measures either to prevent further complications, or to treat a situation that is currently or potentially serious, and which does not routinely occur during the conduct of anesthesia" **[14]** and could therefore be used to put our post-marketing experience into perspective. This study conducted during the period 1996-2000 reported a rate of arrhythmia intraoperative AEs approximately between 0.003% and 0.02% in general anesthesia patients **[14]**. All of the arrhythmia cases in that study were cases of bradyarrhythmia.

A literature review published in 2008 reported that incidence of perioperative cardiac arrest (defined as requiring either internal or external cardiac massage) ranges between 0.046% and 0.19% surgeries and rates were higher for general anesthesia (0.055%) than for regional anesthesia (0.015%) **[24]**. In a Mayo Clinic study conducted from 1990-2000 of 376,082 surgeries under general anesthesia, six of 24 (25%) of the anesthesia-related cardiac arrests were associated with neuromuscular reversal agents given just before arrest and an additional three cases were associated with inadequate reversal of NMB **[25]**. Therefore, it is not unexpected that cardiac arrests will be reported in association with emergence from anesthesia.

Summary of Post-marketing Experience

The following describes the methodology for identifying cases of cardiac arrhythmia or cardiac arrest in the post-marketing database. The Sponsor's pharmacovigilance database was searched for post-marketing reports of cardiac arrhythmia received from HCPs including non-interventional studies, cumulatively from the first market introduction through 22-Apr-2015 in patients treated with sugammadex. As of 31-Mar-2015, this experience is based on an estimated 11.5 million patients exposed in over 50 countries. Overall, the estimated rate of arrhythmias based on postmarketing reports is consistent with estimates of the background rate as discussed below.

The SMQ search 'Cardiac Arrhythmia terms (including bradyarrhythmias and tachyarrhythmias)' in this time interval identified a total of 145 reports with a total of 180 events, with some patients having more than one arrhythmia-related event (see **Table 18**). These cases are highly heterogeneous. The individual reports were reviewed to identify potential patterns such as those discussed in the sections below. One hundred six (59%) of these 180 arrhythmia-related events were classified as 'serious'. The outcome was provided in 120 of the 145 reports. Of the 120 patients in whom outcome was reported, there were five deaths. Two of the fatalities were described in Section 6.5.4 under anaphylaxis (Fatal reports #3 and #4); each of these patients experienced cardiac arrest, and so are also mentioned here. There are an additional three fatalities associated with a cardiac arrhythmia term noted in this section. Additional details about these reports are found in **Appendix 5**.

- Fatal report #5 describes a 72 year-old male undergoing a pancreaticoduodenectomy who died the same day from acute myocardial infarction and cardiac arrest;
- Fatal report #6 describes a 90-year old patient with renal failure who underwent removal of a peritoneal catheter with uncomplicated use of sugammadex, and died on postoperative day #5 of myocardial ischemia leading to cardiac arrest;

- Fatal report #7 contained minimal information, and describes a patient with gastric cancer who underwent a thoracotomy to remove clots from a chest tube insertion, developed acute pulmonary edema and cardiac arrest and who died the same day.

Table 18 SMQ Arrhythmia-Related Events in Postmarketing Experience (25-Jul-2008 to22 Apr 2015)

Preferred Term	Number of Events† (serious)
Bradycardia	61 (21)
Cardiac arrest	30 (30)
Tachycardia	19 (13)
Heart rate increased	14 (7)
Heart rate decreased	8 (4)
Ventricular fibrillation	6 (6)
Cardio-respiratory arrest	5 (5)
Atrial fibrillation	4 (0)
Atrioventricular block	3 (2)
Atrioventricular block complete	3 (2)
Atrioventricular block second degree	3 (3)
Pulseless electrical activity	3 (3)
Supraventricular tachycardia	3 (2)
Ventricular tachycardia	3 (0)
Arrhythmia	2 (0)
Bradyarrhythmia	2 (1)
Sinus bradycardia	2 (2)
Sinus tachycardia	2 (2)
Supraventricular extrasystoles	2 (1)
Atrioventricular block first degree	1 (0)
Extrasystoles	1 (0)
Heart rate irregular	1 (1)
Ventricular arrhythmia	1 (1)
Ventricular extrasystoles	1 (0)
Total Events	180 (106)

***** The sum of events may be greater than the total number of distinct reports, as a report may have more than one event.

As shown in the table above, bradycardia-related arrhythmias, tachycardia-related-arrhythmias, and cardiac arrests comprise the majority (159/180) events and are discussed in the following subsections.

Reports of Bradycardia-Related Events (73 reports)

After an estimated 11.5 million patients exposed, 73 cases of bradycardia-related events (Preferred Terms ‘bradycardia’, ‘heart rate decreased’, ‘sinus bradycardia’, and ‘bradyarrhythmia’) have been received including one case of cardiac arrest in which the

report narrative describes "heart rate slowed" prior to cardiac arrest that was not specifically coded.

Thirty-two reports describe a distinct clinical pattern of bradyarrhythmia during anesthesia emergence within minutes of sugammadex administration in otherwise stable patients. This pattern was first described by the Sponsor in December 2012. Absent any other root cause, these cases were seen as potentially related to sugammadex. As a result, the product labeling for sugammadex was updated to include information regarding '*marked bradycardia'* in both the marketed products circulars and the risk language for the Investigators Brochure. All 32 patients recovered, including six reports in which cardiac arrest was reported together with a bradyarrhythmia. Recovery was spontaneous in seven reports; anticholinergic therapy alone was effective in 16 reports; cardiopulmonary resuscitation (CPR) alone was described in one report; various combinations of anticholinergics, vasopressors and/or CPR were utilized in eight reports.

The remaining 41 reports represent a heterogeneous grouping of bradyarrhythmias. Seven of these bradyarrhythmias were reported in the context of anaphylaxis. There was no consistent pattern in the other 34 reports. Six of these cases also reported cardiac arrest (including Fatal Reports #3 and #5 described previously):

- One patient had neostigmine administered before AE onset; intervention and outcome information was not provided, and the event was considered not related to sugammadex by the reporting physician;
- One patient recovered with a combination of epinephrine and CPR
- One patient recovered with an unspecified medication following a brief episode of bradycardia and cardiac arrest;
- A 58 year old male who had a complex medical and surgical history, and underwent surgery in the region of the brainstem (clipping of a basilar artery aneurysm). Five minutes after sugammadex administration, the patient had ST segment elevation, bradycardia, and hypotension leading to cardiac arrest. Two weeks after initial surgery, the patient underwent a tracheostomy; five minutes after sugammadex, the patient experienced ST segment depression, hypotension, and cardiac arrest. The patient was found to have coronary spastic angina on cardiac catheterization;

In summary, the Sponsor has received a total of 73 reports of clinically significant bradycardia events. Included in these are 32 reports that follow a particular clinical pattern that suggests a possible relationship to the administration of sugammadex. These events occur infrequently, are detectable and, where information is provided, appear to be manageable in the perioperative setting with standard medical management. Appropriate product labeling can inform prescribers about the rare bradycardia events observed during use of sugammadex.

Reports of Tachycardia-Related Events (44 reports)

Cumulatively through 22-Apr-2015, 44 reports with a tachycardia-related event have been received in patients treated with sugammadex. Preferred terms included were heart rate increased (14), sinus tachycardia (2), supraventricular tachycardia (3), tachycardia (19), ventricular fibrillation (6), and ventricular tachycardia (3). Seven of the 44 reports included additional arrhythmias other than tachyarrhythmias and are discussed as appropriate in those sections (i.e bradycardia, cardiac arrest, atrial fibrillation). Of the remaining 37 tachycardia-related events, a majority (29/37) were reported in the context of anaphylaxis or serious hypersensitivity. The management of these patients generally consisted of treating the primary event of hypersensitivity or anaphylaxis and the tachycardia-related events resolved without the need for any specific anti-arrhythmic therapy.

There were five patients with six events of ventricular fibrillation (one patient experienced two events). Because of the clinical significance of this arrhythmia, these patients are summarized briefly here, and are mentioned as well in the other sections in which they occur. Two of these patients are included in "Reports of Bradycardia-Related events", above.

- A medically compromised patient experienced bradycardia, hypotension and ST segment elevation unresponsive to vasopressors and anticholinergics, followed by two events of ventricular fibrillation leading to cardiac arrest 30 minutes after sugammadex administration, which was successfully treated with CPR and defibrillation;

- A medically compromised patient (Fatal report #5) who underwent a pancreaticoduodenectomy, experienced bradycardia and PEA leading to ventricular fibrillation, ST segment depression, cardiac arrest and subsequent death following multiple doses of epinephrine and defibrillation.

Three of these patients are included in "Reports of Cardiac Arrest-Related Events without Antecedent Bradycardia", below.

- One patient experienced ventricular tachycardia and ventricular fibrillation leading to cardiac arrest following sugammadex administration that was successfully treated with CPR, epinephrine and defibrillation;

- One patient experienced ventricular fibrillation, cardio-respiratory arrest and anaphylactoid reaction 10 minutes after sugammadex administration that was treated with CPR, an antiarrhythmic, epinephrine and defibrillation with recovery;

- One patient with coronary stenosis who underwent abdominal aortic aneurysm repair experienced ventricular fibrillation and cardiac arrest following sugammadex administration that was treated with CPR, defibrillation, epinephrine, anti-arrhythmics and corticosteroids with recovery. Anaphylactic shock was suspected.

Reports of Cardiac Arrest-Related Events without Antecedent Bradycardia (23 reports)

Beyond the 12 reports of cardiac arrest in the context of bradycardias (discussed above) , 23 reports with preferred terms of cardiac arrest, cardio-respiratory arrest, or pulseless electrical activity were reported in patients treated with sugammadex without antecedent bradycardia. Included in these 23 reports are Fatal Reports 4, 6 and 7, briefly described previously in this document. Three cases reported as 'cardiac arrest' describe events that might not meet a strict medical definition of cardiac arrest:

- One case describing a "momentary pause" that recovered spontaneously;
- Two patients recovered with limited intervention without any formal CPR measures (atropine alone or atropine and a precordial thump or chest pressure).

Eight cases described patients with reported anaphylactic reactions to sugammadex who had a reported cardiac arrest. The remaining cases represent a heterogeneous group of events typically seen in patients with complex medical comorbidities and surgical operations but without common clinical elements that would suggest a relationship to sugammadex.

Reports of Other Cardiac Arrhythmia Related Events (12 reports)

These 12 cases represent a small number of isolated cases during the emergence phase after anesthesia with no consistent pattern of cardiac arrhythmia or evidence to suggest an association with the administration of sugammadex. The cardiac arrhythmia events reported in these 12 cases include: Arrhythmia (two cases), Atrial fibrillation (one case), Atrial fibrillation and Heart rate increased (one case), Atrial fibrillation, Atrioventricular block and Atrioventricular block first degree (one case), Atrioventricular block complete (one case), Atrioventricular block second degree (two cases), Extrasystoles (one case), Heart rate irregular (one case), and Supraventricular extrasystoles (two cases).

Sensitivity Analysis using Post-marketing Reports

An estimate of the frequency of cardiac arrhythmias in patients receiving sugammadex in general use was derived as follows. As of 31-Mar-2015, a total of 12,106,246 vials of sugammadex had been sold. Assuming 95% of the these vials were actually administered to patients, and assuming that only 10% of cardiac arrhythmias are reported as AEs, the estimated post-marketing reporting rate of all cardiac arrhythmias in patients receiving sugammadex would be 0.015%, which is within the background rate of 0.003% to 0.02% in general anesthesia patients **[14]**. The 73 reports of bradycardia-related events correspond to a post-marketing reporting rate of 0.006%. For cardiac arrest regardless of preceding arrhythmia (35 cases), the estimated rate based on reporting rate is 0.003%. The rate of cardiac arrest reported in the literature is 0.003% for the emergence phase of general anesthesia and 0.046% to 0.19% for the entire perioperative period with general anesthesia **[24; 25]**. The post-marketing reporting rate of cardiac arrest in patients who receive sugammadex is not increased over expected background rates in a diverse perioperative population.

Summary and Conclusions for Cardiac Safety

- The evidence does not suggest QT/QTc prolongation when sugammadex is dosed alone, in combination with the NMBAs rocuronium or vecuronium, or in combination with the anesthetics sevoflurane or propofol, based on the results of dedicated ECG studies and available clinical trial data. There have been no reports of QT prolongation due to sugammadex based on post-marketing AE reporting. There have been no reports of Torsade de Pointes in either the clinical trial database or the post-marketing pharmacovigilance database reflecting an estimated 11.5 million patients exposed to sugammadex.
- Sugammadex did not show any increase in the incidence of arrhythmia-related AEs in healthy subjects and surgical patients when compared to placebo in an integrated analysis of AEs across the Phase 1-3 studies.
- In postmarketing data, infrequent cases of bradycardia requiring intervention and isolated cases of bradycardia with cardiac arrest during anesthesia emergence shortly after sugammadex administration have been reported. As cardiac function is closely monitored in the operative and peri-operative setting, bradycardia is readily detectable, and the available data provide evidence that when bradycardia does occur, it is manageable and responsive to usual interventions. Appropriate labeling around these events will provide information to physicians to assist in their identification and management.
- The overall number of reports of cardiac arrest is low (35) and consistent with expected background rates in a diverse perioperative population. While information from post-marketing reports is limited and often incomplete, examination of the cases without antecedent bradycardias does not identify a new cardiac safety concern.
- The evidence does not suggest an association of sugammadex with any cardiac rhythm disturbances other than bradycardia. The incidence of arrhythmias other than bradycardia in real world patients is low, in line with the expected rate, and upon a case-by-case review typically well explained through multiple comorbidities and often complicated perioperative conditions.

6.7 Additional Safety Findings

No clinically relevant effects of sugammadex were observed for hematology, biochemistry, or urinalysis analytes. No clinically important effects of sugammadex were observed on blood pressure, pulse rate, respiratory rate, body temperature, or body weight in Phase 1 subjects who were not anesthetized and who did not receive an NMBA. In subjects who received an NMBA in the Pooled Phase 1-3 trials, observed changes in vital signs were considered within the expected range and appropriate for a population of surgical subjects. No clinically relevant effects of sugammadex were observed on respiratory rate or body temperature.

6.8 Overall Safety Conclusions

– Sugammadex was found to be generally safe and well tolerated

- Sugammadex is associated with hypersensitivity, including anaphylaxis
    - The risk does not appear to increase with repeat doses
    - The incremental risk for anaphylaxis in surgical patients is small
    - Onset is within minutes, and occurs in a highly monitored setting where symptoms can be recognized quickly and treated effectively
- Sugammadex is rarely associated with bradycardia requiring intervention, which is readily detectable and manageable in the highly monitored setting in which it is used

7 BENEFITS-RISK ASSESSMENT

Sugammadex (MK-8616, Org 25969, SCH 900616), a modified γ-cyclodextrin, is a NMB reversal agent with a novel mechanism of action, capable of reversing any depth of NMB with the non-depolarizing NMBAs rocuronium or vecuronium. The reversal of a rocuronium- or vecuronium-induced NMB by sugammadex is based on its unique ability to form an inclusion complex with the NMBA, preventing NMBA binding to nicotinic receptors in the neuromuscular junction. This unique mechanism of action distinguishes sugammadex from reversal agents based on the inhibition of acetylcholine esterase, having no effect on cholinergic neurotransmitters or receptors. Furthermore, due to the removal of the muscle relaxant from its site of action by forming tightly bound molecular complexes, sugammadex is able to reverse any depth of NMB including a deep NMB. Sugammadex thus represents a fundamentally different approach to the reversal of NMB compared with currently available options.

Unmet Medical Need

Neuromuscular junction blockade, an integral component of modern general anesthesia, is achieved by the IV administration of NMBAs for the duration of surgical procedures. In order to reverse NMB, the anesthesiologist in current practice typically attempts to time the administration of NMBA such that spontaneous recovery coincides with the end of surgery. The spontaneous recovery approach has several important drawbacks:

- Spontaneous recovery requires coordination by the anesthesiologist and the surgeon to ensure that recovery from NMB coincides with the end of surgery. This requires qualitative judgments by which the anesthesiologist maintains sufficient depth of blockade to enable the surgery while allowing the NMB to wear off by the time the surgery finishes. If the anesthesiologist ‘undershoots,’ then involuntary movements or excessive muscle tone can create a sub-optimal operative field. Indeed, in some cases, irreparable organ damage can occur, as with sudden movement during inner ear surgery. If the anesthesiologist 'overshoots', the patient will remain paralyzed past the end of the procedure, unnecessarily lengthening the time exposed to general anesthetic agents. Furthermore, this approach fails for procedures in which deep NMB is required throughout the procedure, such as laryngoscopy and bronchoscopy. The spontaneous recovery paradigm suffers when unforeseen circumstances arise that require urgent or emergent NMBA supplementation, leading to prolonged exposure to general anesthetics at the end of surgery.

- After completion of surgery, spontaneous recovery without reversal of residual blockade increases the risk of patients being extubated before the effect of NMBA is fully reversed (residual NMB) with the attendant risk of respiratory complications, as well as the risk that recurrence of NMBA effects results in respiratory complications including, at the extreme, a need for emergency reintubation **[2]** and **[26]**.

The alternative to spontaneous recovery involves administration of an anti-cholinesterase agent, flooding the neuromuscular junction with acetylcholine so that by the law of mass action, NMBA molecules are less likely to engage the post-junctional receptors. This approach also has several limitations:

- Anti-cholinesterase agents result in flooding of autonomic sites with acetylcholine, causing unwanted autonomic nervous system side effects, such as bradycardia. To counteract the reversal agent associated autonomic muscarinic effects, in clinical practice anti-muscarinic drugs such as atropine or glycopyrrolate are almost always administered concomitantly.
- Available compounds can only reverse moderate depth NMB; they are ineffective for reversal of deep NMB, and ineffective for urgent or emergent reversal of NMB in instances when the need for rapid reversal of NMB arises shortly after NMBA administration.
- Importantly, in part because of the limitations of currently available reversal agents, studies have shown that in clinical practice a significant proportion of patients experience a recurrence of NMB **[2]** and **[26]** or do not reach full recovery from NMB at the time of extubation (residual NMB). Recent evidence in 18,579 surgical patients who received an intermediate acting NMBA during surgery and 18,579 control patients who did not receive such agents shows that the use of an intermediate acting NMBA carries an increased risk of postoperative hypoxemia (oxygen desaturations to less than 90%) after extubation (odds ratio 1.36, 95% confidence interval 1.23 to 1.51) and reintubations, increasing the risk for unplanned admission to an intensive care unit (1.40, 1.09 to 1.80). Qualitative monitoring of neuromuscular transmission did not decrease this risk, and neostigmine reversal increased the risk of hypoxemia (1.32, 1.20 to 1.46) **[27]**. These data highlight the risk of clinically meaningful respiratory complications in current clinical practice with NMBA and available reversal strategies.

In summary, current clinical practice with NMBAs and available reversal agents is associated with the need, during many procedures, to reverse NMB earlier than would optimally be desired, creating a risk for unwanted movement and associated safety concerns, as well as a significant risk of residual NMB, which can translate into clinically meaningful respiratory complications **[28]**. No agent in current U.S. clinical practice is available to reverse deep NMB reliably at any time during surgery, nor is there a reversal agent for the urgent or emergent reversal of NMB when clinically needed.

Clinical Benefit

The efficacy and safety of sugammadex has been studied in a total of 56 clinical trials to date, with 4453 unique subjects exposed to IV sugammadex. Evidence from the pivotal trials and pooled efficacy analyses for the proposed indication outlined in this document establishes that sugammadex reliably, effectively, and completely reverses any level of rocuronium- or vecuronium-induced NMB currently used in clinical practice. Reversal of NMB with sugammadex will lead to a higher proportion of fully recovered patients, based on a TOF of ≥ 0.9, faster than with existing treatments such as neostigmine.

For the reversal of deep NMB and for urgent or emergent situations, no alternative reversal agents are currently available. Sugammadex provides anesthesiologists with the ability to rapidly reverse rocuronium-induced NMB in urgent or emergent situations, which in some situations is potentially life-saving and not currently available in U.S. anesthesia practice. This unique benefit of sugammadex makes complicated timing assessments obsolete and allows surgeons to operate with any required degree of NMB at any point during the surgery, which has the potential to improve the surgical operating conditions and to reduce the risk of injury related to patient movement.

Sugammadex use avoids side effects associated with neostigmine and required concomitant anti-muscarinic drugs.

Lastly, the use of sugammadex at the recommended doses at the different depths of NMB is associated with a low risk of residual NMB as compared to usual care treatment with neostigmine and recurrence of NMB, thereby reducing the risk of anesthesia-related and perioperative pulmonary complications, including the need for reintubation.

In summary, the efficacy of sugammadex for routine and for urgent or emergent reversal of NMB has been systematically studied, and is shown to provide clinically meaningful differences from the current standard of care. Sugammadex offers a novel means for reversing rocuronium- and vecuronium-induced NMB quickly and reliably, providing advantages both during surgical procedures and in the post-operative recovery period.

Risks

Based on a large clinical trials database and post-marketing experience in approximately 11,500,000 patients, the use of sugammadex has been demonstrated to be generally safe and well tolerated. In placebo-controlled trials of subjects treated with NMBA and general anesthesia, the incidence of reported AEs was 74% with sugammadex and compares favorably with that of 82% for placebo. For the vast majority of the SOCs, in which the AEs were grouped according to the MedDRA version 17.0, similar or lower incidences of AEs were reported with sugammadex as compared with placebo. There were few AEs reported at a higher incidence in the sugammadex group than placebo; most were reported with an incidence of less than 4%, and many of these events are related to the applied surgical procedures and/or general anesthesia, which are routinely monitored and managed within the perioperative setting and do not suggest a serious safety concern. The following summarizes other the key questions that have arisen and been addressed in the safety database.

Hypersensitivity

The risks of hypersensitivity and/or anaphylaxis after sugammadex administration were thoroughly investigated. In a dedicated hypersensitivity trial (Trial P101) in healthy subjects, the incidence of hypersensitivity reactions with repeat administration of sugammadex has been estimated, with the numerically highest incidence of 9.5% at 16 mg/kg, and lower incidence of 6.6% at 4 mg/kg compared to 1.3% in placebo. A risk for anaphylaxis was identified, with the greatest risk for anaphylaxis being associated with the 16 mg/kg dose, which is proposed for use only when there is an urgent or emergent need for reversal where the benefit is likely to be lifesaving.

The vast majority of clinical events of hypersensitivity and/or anaphylaxis occurred shortly after sugammadex administration (most of them within minutes). The events generally resolved quickly and spontaneously, and in the remaining cases responded to usual symptomatic treatments with antihistamines, corticosteroids and epinephrine. Importantly, there was no indication that the frequency or severity of hypersensitivity increased after repeated dosing of sugammadex, and there was no biochemical evidence for mast cell degranulation or IgE antibodies to sugammadex. This provides evidence that sensitization to sugammadex does not occur, and that hypersensitivity reactions to sugammadex are unlikely to be Type I immune-mediated phenomena.

Retrospective and prospective adjudication of suspected hypersensitivity and anaphylactic events from the Pooled Phase 1-3 dataset, which included 3519 subjects exposed to sugammadex, did not identify any events of anaphylaxis. In the dedicated hypersensitivity trial anaphylaxis was reported, only after the 16 mg/kg dose. In the cumulative postmarketing worldwide safety experience, anaphylaxis spontaneous reports provides evidence that any incremental risk for anaphylaxis attributable to sugammadex is small, and that episodes that do occur are manageable with usual treatment. Overall, the weight of evidence from all sources suggests that the risk of serious anaphylaxis related to sugammadex administration is limited and does not meaningfully change the overall safety profile for patients undergoing anesthesia with NMB. Anaphylaxis related to sugammadex occurs very soon after exposure, and these events can be effectively managed in the perioperative setting in which sugammadex is intended to be used by highly trained medical staff. The risk can be further mitigated by ensuring that physicians are aware of and are prepared to respond to the possibility of hypersensitivity with the use of sugammadex.

Cardiovascular Effects

Based on dedicated clinical studies, the overall clinical development experience and the post-marketing experience outside of the US, there is no evidence that suggests association with sugammadex and QTc prolongation or cardiac arrhythmias. The reported incidence of cardiac arrhythmias within the clinical development program is low, comparable to placebo and lower than in neostigmine treated patients. The comprehensive analysis of spontaneous post-marketing safety reports supports this conclusion without the suggestion of an arrhythmogenic or QTc-prolonging effect of sugammadex. A small and transient effect on heart rate observed in surgical subjects treated with anesthesia and/or NMBA (not observed in subjects without NMBA) has been hypothesized to be related to the vagolytic effects of

underlying NMBA. While no clinically concerning bradycardia was observed in the clinical trials, a small number of post-marketing reports suggest that bradycardia of clinical concern can occur shortly after sugammadex reversal of NMB. Those cases were generally managed effectively with atropine or other usual anticholinergic treatments that would be available to the anesthesiologist as part of standard care.

In summary, the data provided support the conclusion that the risks associated with sugammadex are limited and well-characterized. The clinical experience to date in 5999 subject exposures to IV sugammadex indicates that AEs will generally occur infrequently and in the perioperative setting, very soon after sugammadex exposure, when patients undergo close monitoring and where untoward sequelae can be rapidly identified and effectively managed with routine treatments and interventions. In addition to the totality of the exposure experience with sugammadex in clinical trials, the exposure experience in clinical practice since the first global approval in 2008 and approved and marketed today in more than 50 countries worldwide, with approximately 11.5 million patients exposed, provides substantial reassurance regarding the risks associated with sugammadex use. In terms of risk mitigation, it is concluded that the identified risks can be managed with appropriate labeling and routine pharmacovigilance.

Benefit-Risk Conclusions

Sugammadex is a novel agent for reversal of NMB with a mechanism of action different from any currently available treatment. The available data provide strong, replicable evidence that sugammadex is highly efficacious for reversal of moderate and deep NMB. Reversal of deep NMB is a unique benefit of sugammadex unavailable with current treatments, and as such, provides opportunity for maintenance of deep block throughout surgery. This offers the potential to facilitate intubation, decrease patient movement, and improve surgical conditions (by decreasing abdominal wall tension, increasing surgical exposure, etc.) until the end of the procedure, creating a safer surgical environment. Sugammadex is a potentially important option in urgent or emergent situations that require rapid reversal of NMB following administration of rocuronium; again, this benefit is unique to sugammadex. Case reports have documented that used in this way, sugammadex can prevent serious morbidity or even death **[3]**. Finally, sugammadex has been shown to be superior (faster and effective in a higher proportion of treated subjects) to both placebo and neostigmine, minimizing the time required to reverse NMB in surgical patients as compared with current standard of care. Because of this advantage, the use of sugammadex is associated with a low risk of residual NMB or recurrence of NMB compared with current treatment when used at the recommended doses; this may provide a safety advantage compared with current practice with respect to post-operative complications related to clinical issues such as the need for re-intubation, or complications related to extubation performed prior to adequate recovery of function in muscles important for respiration and swallowing. From a risk perspective, sugammadex has been shown to be generally safe and well tolerated. Identified risks associated with sugammadex use are few, occur infrequently, and can be safely managed with the proposed risk-mitigation strategies, including appropriate labeling and clinical management with established perioperative practices in the setting where sugammadex will be used. The clinical trial data (with 5999 subject exposures to IV sugammadex) are also consistent with and supported by post-marketing data from the large

number of patients already treated in clinical practice (based on an estimated 11.5 million patients exposed); sugammadex is used clinically in more than 50 countries worldwide.

In conclusion, the benefits of sugammadex markedly outweigh its risks, and sugammadex represents an important addition to the pharmacologic interventions available for patients undergoing anesthesia with NMB in the surgical setting.

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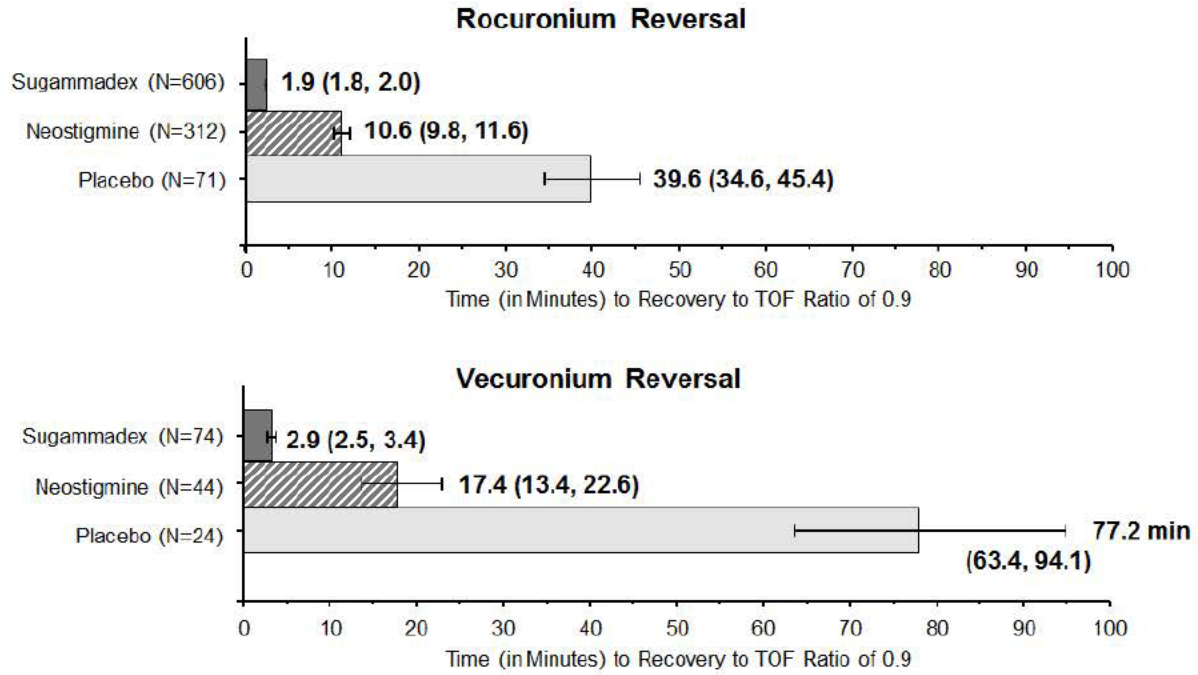
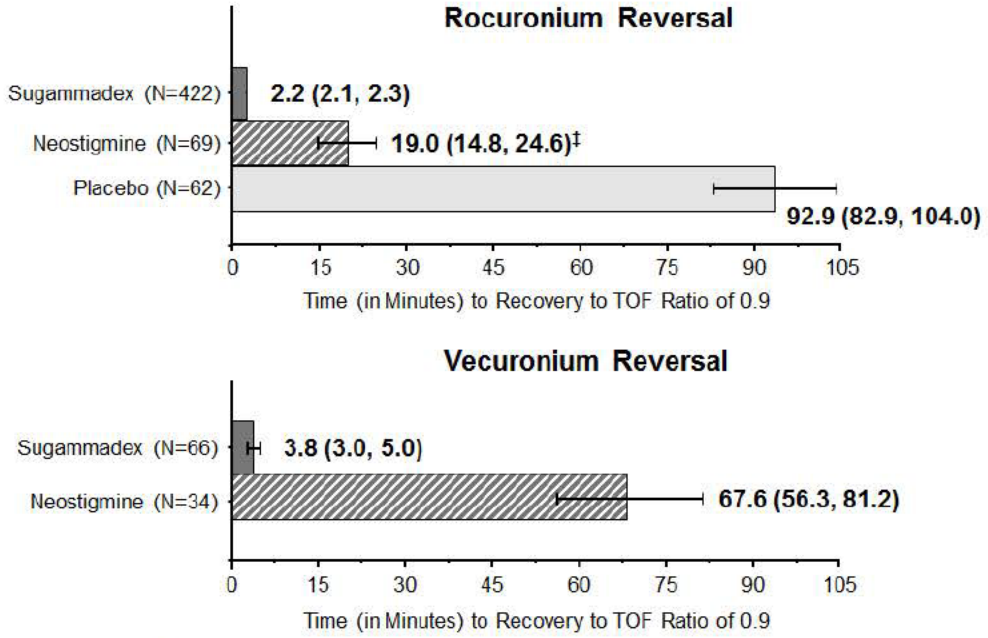
Appendix 1 Sugammadex 2 mg/kg Superior to Neostigmine in Reversal of Moderate Blockade (Pooled Efficacy Trials†, Intent-to-Treat Analysis)



Results presented as Geometric Mean (95% CI). † Represents 16 trials.

Appendix 2 Sugammadex 4 mg/kg Superior to Neostigmine in Reversal of Deep Blockade (Pooled Efficacy Trials†, Intent-to-Treat Analysis)



Results presented as Geometric Mean (95% CI).
† Represents 9 trials.
‡ In some trials, neostigmine was used as per usual care (moderate NMB).

Appendix 3 Subjects (%) With Adverse Events by Dose for Pooled Phase 1-3 Trials Incidence ≥2% in Total Sugammadex or Placebo

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total sugammadex[a]
		(N=544)	(N=895)	(N=1921)	(N=98)	(N=3601)
		n (%)	n (%)	n (%)	n (%)	n (%)
At least one AE	Total	447 (82.2)	693 (77.4)	1623 (84.5)	79 (80.6)	2849 (79.1)
Injury, poisoning and procedural complications	Total	280 (51.5)	474 (53.0)	1161 (60.4)	54 (55.1)	1904 (52.9)
	Procedural pain	191 (35.1)	391 (43.7)	878 (45.7)	32 (32.7)	1433 (39.8)
	Incision site pain	6 (1.1)	58 (6.5)	106 (5.5)	4 (4.1)	191 (5.3)
	Wound complication	32 (5.9)	34 (3.8)	71 (3.7)	0 (0.0)	182 (5.1)
	Procedural nausea	31 (5.7)	34 (3.8)	74 (3.9)	1 (1.0)	113 (3.1)
	Procedural hypotension	9 (1.7)	20 (2.2)	63 (3.3)	10 (10.2)	110 (3.1)
	Procedural hypertension	22 (4.0)	33 (3.7)	46 (2.4)	7 (7.1)	97 (2.7)
	Anaemia postoperative	51 (9.4)	7 (0.8)	66 (3.4)	0 (0.0)	73 (2.0)
	Post procedural complication	24 (4.4)	13 (1.5)	43 (2.2)	3 (3.1)	65 (1.8)
	Procedural vomiting	14 (2.6)	14 (1.6)	36 (1.9)	0 (0.0)	53 (1.5)
	Wound secretion	19 (3.5)	1 (0.1)	27 (1.4)	0 (0.0)	30 (0.8)
Gastrointestinal disorders	Total	195 (35.8)	301 (33.6)	748 (38.9)	33 (33.7)	1257 (34.9)
	Nausea	96 (17.6)	174 (19.4)	429 (22.3)	22 (22.4)	730 (20.3)
	Vomiting	43 (7.9)	84 (9.4)	200 (10.4)	15 (15.3)	361 (10.0)
	Constipation	73 (13.4)	38 (4.2)	206 (10.7)	3 (3.1)	264 (7.3)
	Diarrhoea	22 (4.0)	19 (2.1)	53 (2.8)	0 (0.0)	84 (2.3)
	Abdominal pain	8 (1.5)	29 (3.2)	41 (2.1)	2 (2.0)	82 (2.3)
General disorders and administration site conditions	Total	117 (21.5)	192 (21.5)	403 (21.0)	14 (14.3)	755 (21.0)
	Pyrexia	17 (3.1)	77 (8.6)	109 (5.7)	5 (5.1)	228 (6.3)
	Pain	16 (2.9)	43 (4.8)	115 (6.0)	3 (3.1)	187 (5.2)
	Chills	27 (5.0)	30 (3.4)	61 (3.2)	7 (7.1)	117 (3.2)
	Oedema peripheral	23 (4.2)	14 (1.6)	66 (3.4)	1 (1.0)	90 (2.5)
Nervous system disorders	Total	87 (16.0)	136 (15.2)	243 (12.6)	17 (17.3)	503 (14.0)
	Headache	42 (7.7)	61 (6.8)	99 (5.2)	10 (10.2)	202 (5.6)
	Dizziness	13 (2.4)	44 (4.9)	67 (3.5)	6 (6.1)	137 (3.8)

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total sugammadex[a]
		(N=544)	(N=895)	(N=1921)	(N=98)	(N=3601)
		n (%)	n (%)	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	Total	51 (9.4)	102 (11.4)	216 (11.2)	15 (15.3)	419 (11.6)
	Oropharyngeal pain	27 (5.0)	42 (4.7)	66 (3.4)	5 (5.1)	130 (3.6)
	Cough	11 (2.0)	13 (1.5)	49 (2.6)	8 (8.2)	99 (2.7)
Musculoskeletal and connective tissue disorders	Total	103 (18.9)	75 (8.4)	269 (14.0)	15 (15.3)	398 (11.1)
	Back pain	22 (4.0)	28 (3.1)	67 (3.5)	3 (3.1)	114 (3.2)
	Arthralgia	42 (7.7)	4 (0.4)	65 (3.4)	3 (3.1)	74 (2.1)
	Pain in extremity	15 (2.8)	13 (1.5)	35 (1.8)	6 (6.1)	58 (1.6)
	Joint swelling	12 (2.2)	1 (0.1)	15 (0.8)	0 (0.0)	17 (0.5)
Psychiatric disorders	Total	89 (16.4)	60 (6.7)	275 (14.3)	10 (10.2)	371 (10.3)
	Insomnia	22 (4.0)	20 (2.2)	103 (5.4)	5 (5.1)	141 (3.9)
	Sleep disorder	56 (10.3)	9 (1.0)	107 (5.6)	0 (0.0)	120 (3.3)
Investigations	Total	33 (6.1)	96 (10.7)	166 (8.6)	9 (9.2)	331 (9.2)
Vascular disorders	Total	60 (11.0)	36 (4.0)	170 (8.8)	4 (4.1)	248 (6.9)
	Hypertension	14 (2.6)	15 (1.7)	48 (2.5)	1 (1.0)	79 (2.2)
	Haematoma	26 (4.8)	2 (0.2)	61 (3.2)	0 (0.0)	67 (1.9)
	Hypotension	11 (2.0)	11 (1.2)	38 (2.0)	3 (3.1)	62 (1.7)
Skin and subcutaneous tissue disorders	Total	38 (7.0)	52 (5.8)	149 (7.8)	6 (6.1)	235 (6.5)
	Pruritus	9 (1.7)	17 (1.9)	50 (2.6)	2 (2.0)	76 (2.1)
Renal and urinary disorders	Total	40 (7.4)	53 (5.9)	114 (5.9)	3 (3.1)	194 (5.4)
	Urinary retention	13 (2.4)	13 (1.5)	23 (1.2)	2 (2.0)	49 (1.4)
Metabolism and nutrition disorders	Total	39 (7.2)	50 (5.6)	107 (5.6)	2 (2.0)	176 (4.9)
	Hypokalaemia	27 (5.0)	17 (1.9)	49 (2.6)	1 (1.0)	68 (1.9)
Infections and infestations	Total	37 (6.8)	30 (3.4)	123 (6.4)	0 (0.0)	169 (4.7)
	Urinary tract infection	11 (2.0)	7 (0.8)	27 (1.4)	0 (0.0)	35 (1.0)
Blood and lymphatic system disorders	Total	54 (9.9)	26 (2.9)	113 (5.9)	4 (4.1)	152 (4.2)
	Anaemia	50 (9.2)	21 (2.3)	95 (4.9)	3 (3.1)	124 (3.4)

		0 mg/kg (Placebo)	2 mg/kg	4 mg/kg	16 mg/kg	Total sugammadex[a]
		(N=544)	(N=895)	(N=1921)	(N=98)	(N=3601)
		n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac disorders	Total	27 (5.0)	39 (4.4)	75 (3.9)	7 (7.1)	135 (3.7)
Ear and labyrinth disorders	Total	11 (2.0)	9 (1.0)	38 (2.0)	1 (1.0)	59 (1.6)

a. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

Appendix 4 Subjects (%) With Adverse Events in Pooled Placebo-Controlled Trials (Incidence ≥2% in Either Treatment Group)

		Placebo	Sugammadex[a]
		(N=544)	(N=1078)
		n (%)	n (%)
At least one AE	Total	447 (82.2)	793 (73.6)
Injury, poisoning and procedural complications	Total	280 (51.5)	455 (42.2)
	Procedural pain	191 (35.1)	268 (24.9)
	Wound complication	32 (5.9)	71 (6.6)
	Anaemia postoperative	51 (9.4)	54 (5.0)
	Airway complication of anaesthesia	0 (0.0)	42 (3.9)
	Anaesthetic complication	1 (0.2)	37 (3.4)
	Procedural hypotension	9 (1.7)	36 (3.3)
	Post procedural complication	24 (4.4)	32 (3.0)
	Procedural hypertension	22 (4.0)	25 (2.3)
	Procedural complication	3 (0.6)	22 (2.0)
	Procedural vomiting	14 (2.6)	22 (2.0)
	Wound secretion	19 (3.5)	22 (2.0)
	Procedural nausea	31 (5.7)	21 (1.9)
Gastrointestinal disorders	Total	195 (35.8)	310 (28.8)
	Nausea	96 (17.6)	169 (15.7)
	Vomiting	43 (7.9)	100 (9.3)
	Constipation	73 (13.4)	74 (6.9)
	Diarrhoea	22 (4.0)	23 (2.1)
General disorders and administration site conditions	Total	117 (21.5)	216 (20.0)
	Pain	16 (2.9)	51 (4.7)
	Pyrexia	17 (3.1)	44 (4.1)
	Chills	27 (5.0)	41 (3.8)
	Oedema peripheral	23 (4.2)	36 (3.3)
Musculoskeletal and connective tissue disorders	Total	103 (18.9)	143 (13.3)
	Arthralgia	42 (7.7)	47 (4.4)
	Back pain	22 (4.0)	34 (3.2)
	Pain in extremity	15 (2.8)	13 (1.2)
	Joint swelling	12 (2.2)	5 (0.5)

		Placebo	Sugammadex[a]
		(N=544)	(N=1078)
		n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	Total	51 (9.4)	130 (12.1)
	Cough	11 (2.0)	51 (4.7)
	Oropharyngeal pain	27 (5.0)	38 (3.5)
Nervous system disorders	Total	87 (16.0)	122 (11.3)
	Headache	42 (7.7)	53 (4.9)
	Dizziness	13 (2.4)	21 (1.9)
Investigations	Total	33 (6.1)	112 (10.4)
Psychiatric disorders	Total	89 (16.4)	100 (9.3)
	Sleep disorder	56 (10.3)	45 (4.2)
	Insomnia	22 (4.0)	36 (3.3)
Vascular disorders	Total	60 (11.0)	88 (8.2)
	Haematoma	26 (4.8)	28 (2.6)
	Hypotension	11 (2.0)	26 (2.4)
	Hypertension	14 (2.6)	21 (1.9)
Renal and urinary disorders	Total	40 (7.4)	62 (5.8)
	Urinary retention	13 (2.4)	20 (1.9)
Blood and lymphatic system disorders	Total	54 (9.9)	58 (5.4)
	Anaemia	50 (9.2)	47 (4.4)
Metabolism and nutrition disorders	Total	39 (7.2)	56 (5.2)
	Hypokalaemia	27 (5.0)	20 (1.9)
Skin and subcutaneous tissue disorders	Total	38 (7.0)	55 (5.1)
Infections and infestations	Total	37 (6.8)	52 (4.8)
	Urinary tract infection	11 (2.0)	14 (1.3)
Cardiac disorders	Total	27 (5.0)	40 (3.7)
Ear and labyrinth disorders	Total	11 (2.0)	25 (2.3)

a. The sugammadex column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg).

Appendix 5 Postmarketing Reports of Fatal Outcome 25-Jul-2008 through 22-Apr-2015

Fatal Case #	Age/Sex	Dose of sugammadex	Concurrent Conditions/Surgery/Other Information	Time of Death
1	40/M	Multiple 200 mg doses over 24 hours	Acute myocardial infarction, cardiogenic shock, cardiac failure and pulmonary edema, admitted after cardio-respiratory arrest at another hospital; underwent percutaneous coronary intervention and was administered rocuronium over 3 days for mechanical ventilation, during which time renal and hepatic failure developed. Successfully given multiple doses of sugammadex for NMB reversal over 2 days but had subsequent recurrences of NMB. Developed circulatory failure of primary cardiac etiology and died 4 days after admission after receiving multiple doses of sugammadex on days 3 and 4	Died 4 days after admission
2	70/M	NR	Celiac artery aneurysm, suspected extensive pancreatic necrosis and hypertension; underwent celiac artery aneurysm surgery complicated by difficulty in obtaining hemostasis, resulting in decreased hemoglobin values which the reporter attributed to the manipulation of the pancreas during surgery. Developed hypotension, tachycardia, and decreased oxygen saturation 2-3 minutes after sugammadex with subsequent lactic acidosis and treatment resistant distributive shock.	Died 4 days after surgery
3	56/F	2.9 mg/kg	Ovarian cancer; underwent total abdominal hysterectomy, salpingo-oophorectomy, lymph node excision and omenectomy. Developed bradycardia and cardiac arrest 1 minute after sugammadex, diagnosed as anaphylactic shock. Patient resuscitated with CPR, epinephrine, atropine and nifekalant; balloon pump placed, developed shock from bleeding from weakened aortic wall from lymph node dissection. Died of renal failure, DIC, and cerebral ischemia.	Died 19 days after surgery
4	68/M	2 mg/kg	Prostate cancer with metastasis to femur and gastric cancer; underwent total gastrectomy and sub-total colectomy. Developed anaphylactoid shock (hypotension, flushing) and cardiac arrest 2 minutes after sugammadex that improved with CPR, epinephrine, vasopressors and defibrillation. Subsequently developed dissecting aortic aneurysm, DIC, intra-abdominal hemorrhage and multi-organ failure. Blood pressure stabilized, but then patient underwent reoperation for hemostasis and colectomy for intestinal ischemia. Multi-organ failure progressed.	Died 3 days after initial surgery
5	72/M	2.3 mg/kg	Cancer of duodenal papilla, cerebral infarction, arteriosclerosis, and liver disorder; underwent pancreaticoduodenectomy. Developed hypertension, then hypotension, bradycardia, ventricular fibrillation, and cardiac arrest 74 minutes after sugammadex administration; ECG revealed marked ST segment depression. Postmortem computerized tomography showed severe coronary artery sclerosis; diagnosed as acute myocardial infarction.	Died 3 hours after surgery
6	90/F	4 mg/kg	Minimal information. Patient with dialysis- dependent renal failure and sepsis due to peritonitis; underwent removal of peritoneal catheter with uncomplicated use of sugammadex. Cardiac arrest associated with myocardial infarction occurred 5 days after surgery.	5 days after surgery

Fatal Case #	Age/Sex	Dose of sugammadex	Concurrent Conditions/Surgery/Other Information	Time of Death
7	76/M	3.3 mg/kg	Minimal information. Patient with gastric cancer; underwent evacuation of clots from chest tube insertion (reason for chest tube unknown). Developed cardiac arrest and pulmonary edema 2 minutes after sugammadex.	Died day of surgery
8	78/F	100 mg	Aortic valve stenosis and diabetes mellitus; underwent surgery for aortic valve stenosis. Developed hypotension and cardiac arrest shortly after sugammadex. Recovered with epinephrine and percutaneous cardiopulmonary support. Died from complications of underlying aortic valve stenosis.	Died 5 days after surgery
9	60/M	3.2 mg/kg	Hepatitis B and hepatocellular carcinoma; underwent microwave coagulo-necrotic (MCN) therapy and uncomplicated use of sugammadex for NMB reversal. Jaundice and hepatic function disorder were observed the day after surgery. Subsequently died of hepatic failure.	Died 3 months after surgery
10	79/F	1.5 mg/kg	Renal failure, aortic valve insufficiency, and craniopharyngioma; underwent unspecified surgery and experienced 2 episodes of decreased blood pressure, one 15 minutes after sugammadex that resolved with vasopressors and intravenous fluids, and one 2-3 hours later that resolved spontaneously. Developed multi-organ failure 30 hours after surgery.	Died 7 days after surgery.
11	78/M	2 mg/kg	Lung cancer with intermittent hemoptysis; underwent lumbar cord tumor removal with uncomplicated use of sugammadex. Four days post-operatively, developed increased hemoptysis, pneumonia and pulmonary edema and subsequently died.	Died 11 days after surgery
12	70/M	2 mg/kg	Bladder cancer, and cardiovascular disorder; underwent two surgeries 5 days apart (transurethral resection (TUR) and cystectomy) with uncomplicated use of sugammadex after the TUR. Received radiation therapy and died due to an unspecified respiratory complication	Died 2 months after surgery
13	NR/F	NR	Inoperable tracheal and esophageal carcinoma with tracheal narrowing and difficulty breathing; underwent tracheal stenting and was administered sugammadex. Developed grave ST segment depression enroute to the recovery room that was managed with nitroglycerine and a beta blocker. Trans-thoracic ultrasound revealed poor left ventricular function and "Takotsubo-type ultrasound findings" (stress cardiomyopathy). Subsequently developed pulmonary edema and died day of surgery	Died day of surgery

NR= Not reported; CPR= cardiopulmonary resuscitation; DIC= dissenminated intravascular coagulation