

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022225Orig1s000

MEDICAL REVIEW(S)

Summary Basis for Regulatory Action

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| Date | April 22, 2015 |
| From | Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II |
| Subject | Summary Review |
| NDA/BLA # Supp # | 22-225 |
| Applicant | Merck/Organon USA |
| Proprietary / Established (USAN) Names | (b) (4) Sugammadex Sodium |
| Dosage Forms / Strength | Sterile solution, injectable 100 mg/mL |
| Proposed Indication(s) | 1. Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium 2. Immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Action: | <i>Complete Response</i> |

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding sugammadex, and I refer the reader to the reviews in the action package for a more detailed discussion. This is a review (3rd cycle) of the Complete Response (CR) to the Complete Response Action that was taken on September 20, 2013 (2nd cycle). The action taken on September 20, 2013 was in response to the CR submission to address the deficiencies identified in the Not Approvable action that was taken on July 31, 2008 (1st cycle).

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex was designed so that the negatively charged sugar groups within its center would attract the positively charged ammonium groups of rocuronium bromide (RCB) and vecuronium bromide (VCB) and sequester these neuromuscular blocking agents within its core by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of RCB and VCB within sugammadex renders them inactive and thereby reverses paralysis that otherwise would have occurred due to their activity at the neuromuscular junction.

This application was not approved on the first cycle due to safety concerns observed during clinical development related to hypersensitivity/anaphylaxis reactions and the effects of the product on coagulation and bleeding. During the first cycle review, this application was granted a priority review and was presented at a meeting of the Anesthesia and Life Support

Drugs Advisory Committee (ALSDAC)¹ on March 11, 2008. The anaphylaxis concern was noted late in the review, just before the advisory committee (AC) meeting, and did not benefit from a full analysis prior to the AC meeting. Therefore, committee members (mainly anesthesiologists or pain experts) had minimal information regarding the anaphylactic potential of sugammadex² to use in safety considerations when advising about marketability. While the Committee voted for approval they did not have access to all the relevant safety information and allergy expertise was not available to enrich the discussion regarding conclusions and marketability. Therefore, a Not Approvable action was taken.

The CR that led to the CR action on September 20, 2013, included several new studies and trials, the most relevant being Trial P06042. This trial was a repeat administration of the mid (4 mg/kg) and high dose (16 mg/kg) of sugammadex designed to be conducted in a blinded fashion to obtain further information on anaphylaxis with sugammadex use regarding the incidence, time course and risks associated with re-exposure. However, during the course of inspection of site #2 the Office of Scientific Investigation (OSI) investigators found that there had been unblinding, calling into question the integrity of the data from that site (see details from my review of September 20, 2013). The Applicant notified us that there were protocol violations at the remaining three sites as well where study staff administered the study medication and also performed the safety evaluations. This called into question data integrity from all the sites where the study was conducting leading to cancellation of the AC meeting and subsequent CR action.

With this submission, the sponsor has conducted Trial P101 which is a repeat dose trial similar to Trial P06042. However, an OSI inspection identified possible data integrity issues from this trial as well. The first issue is with the data management at Merck. The statistical staff at Merck, upon extracting SAS data sets from the Clinical Data Repository (CDR), noted that one column was not properly blinded. This could lead to full un-blinding of the trial. Access and realization of un-blinding potential occurred in early March of 2014, when all randomized subjects had received at least one dose of assigned treatment, but before anyone had received a third dose. Merck stated that 11 people had access to these data and that they took action to correct this problem and received signed attestations from all employees involved that they did not contact study sites or unblinded investigators to treatment. However the 11 people that had access have since been terminated from employment at Merck and are not available for further interview. Merck deleted all records of the unblinded data from the local server and individual computers and the data system they used for this work does not have an audit trail.

The second issue is that when OSI inspected two of the six study sites, one had a protocol violation where the assessor of adverse events was also giving dosing. This occurred in the first six subjects. The protocol requires different people administer the drug and do the adverse event assessments. This was a major protocol violation, the same issue that made the first trial invalid, and raises concerns about what may have happened at the four sites that have not been inspected.

¹ The ALSDAC has since been renamed the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC).

² There was not any repeat-dose data available.

2. Conclusions and Recommendations

While it seems unlikely that there was systematic un-blinding related to the central event, there is still residual concern about potential un-blinding at the study sites, which is important given the subjective nature of the adverse event assessment.

One could question if this trial has the relevance that it did when first requested years ago. At that time, the sponsor was denying that sugammadex had anaphylaxis potential. Therefore it was important, given that this drug may be used in millions of patients, to try to define this aspect better. However, it is now recognized that anaphylaxis occurs, and there is a great deal of foreign post-marketing experience upon which to draw safety information. However, what we are still missing is a rate estimate and whether re-exposure may increase the rate due to sensitization.

Internal discussions have led to the conclusion that if the remaining four sites do not have major protocol violations, then we can rely upon the data from Trial P101 for regulatory purposes. We can also do some sensitivity analyses to assure ourselves that there was not systematic un-blinding related to the central event. If both of these procedures provide reassurance, then we will be able to present the results of Trial P101 to an advisory committee meeting.

Therefore, for the current time I recommend a CR action with the remediation to include those things discussed above.

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/s/

CURTIS J ROSEBRAUGH
04/22/2015



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Ave.
 Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

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| Date | April 21, 2015 |
| From | Rigoberto Roca, M.D. |
| Subject | Deputy Division Director Summary Review |
| NDA/Supplement No. | 022225/099 |
| Applicant Name | Organon USA, Inc. / Merck & Co. |
| Date of Original Submission | October 31, 2007 Complete Response letter issued July 31, 2008 |
| Date of First Complete Response Submission | December 21, 2012 Complete Response letter issued September 20, 2013 (includes a 3-month clock extension) |
| Date of Second Complete Response Submission | October 22, 2014 |
| PDUFA Goal Date | April 22, 2015 |
| Proprietary Name / Established (USAN) Name | Bridion / sugammadex sodium |
| Dosage Forms / Strength | Solution for intravenous injection / 100 mg/mL |
| Proposed Indication | Reversal of moderate or deep muscular blockade by rocuronium or vecuronium. |
| Recommended Action | Complete Response |

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| Material Reviewed/Consulted | |
| OND Action Package, including reviews by: | |
| Medical Officer | Arthur Simone, MD, PhD |
| Pharmacology Toxicology | Alex Xu, PhD; Jay Chang, PhD; Dan Mellon, PhD; |
| OPQ/ONDP | Yong Hu, PhD; Julia Pinto, PhD |
| OPQ/DMA | Vinayak Pawar, PhD; Stephen Langille, PhD |
| OMPQ/DGMPA/NDMAB | Juandria Williams, PhD / Mahesh Ramanadham |
| OPQ/OBP/DBRR IV | Frederick Mills, PhD; Gerald Feldman, PhD |
| OCP/DCP II | Srikanth Nallani, PhD; Yun Xu, PhD |
| OCP/ Division of Pharmacometrics | Atul Bhattaram, PhD; Kevin Krudys, PhD |
| OSE/OMEPRM/DMEPA | James Schlick, MBA, RPh; Vicky Borders-Hemphill, PharmD |
| OSE/OPE/DPV II | Martin Pollock, PharmD; Sara Camilli, PharmD; Scott Proestel, MD |
| OSE/OMEPRM/DRISK | Leah Hart-Banks, PharmD; Kim Lehrfeld, PharmD; Reema Mehta, PharmD |
| OSI/DCCE/GCPAB | Cynthia Kleppinger, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH |
| Project Management Staff | Diana Walker, PhD; Parinda Jani |
| OND/ODE II/ DPARP | Erika Torjusen, MD; Banu Karimi-Shah, MD; Badrul Chowdhury, MD, PhD |
| DPMH | Carol Kasten, MD |

DBRR IV = Division of Biotechnology Review and Research IV
 DCCE = Division of Clinical Compliance Evaluation
 DCP II = Division of Clinical Pharmacology II
 DGCPC = Division of Good Clinical Practice Compliance
 DGMPA = Division of GMP Assessment
 DMA = Division of Microbiology Assessment
 DMEPA = Division of Medication Error Prevention and Analysis
 DPARP = Division of Pulmonary, Allergy, and Rheumatology Products
 DPMH = Division of Pediatrics and Maternal Health
 DRISK = Division of Risk Management
 DPV II = Division of Pharmacovigilance II
 GCPAB = Good Clinical Practice Assessment Branch
 NDMAB = New Drug Manufacturing Assessment Branch

OBP = Office of Biotechnology Products
 OCP = Office of Clinical Pharmacology
 ODE II = Office of Drug Evaluation II
 OMEPRM = Office of Medication Error Prevention and Risk Management
 OMP = Office of Medical Policy
 OMPQ = Office of Manufacturing and Product Quality
 ONDP = Office of New Drug Products
 OPE = Office of Pharmacovigilance and Epidemiology
 OPQ = Office of Pharmaceutical Quality
 OPDP = Office of Professional Drug Promotion
 OSE = Office of Surveillance and Epidemiology
 OSI = Office of Scientific Investigations

1. Introduction

The Applicant, Organon, Pharm, a subsidiary of Merck, Inc., has submitted a complete response to the Complete Response letter issued on September 20, 2013. This is the third review cycle for this application, as it received a Non-approval letter on July 31, 2008.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

2. Background

Sugammadex, also known as Org25969, is a new molecular entity of the γ -cyclodextrin class. It was designed, by selective addition of functional groups around the structure, to bind rocuronium and vecuronium. It consists of ring-like structure with a lipophilic core and a hydrophilic outer surface. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center, and then held in place by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of the neuromuscular blocking agent from the neuromuscular junction will in effect reverse the paralysis. The initial submission of this application requested the following indication: for routine reversal of "shallow" and "profound neuromuscular blockade induced by rocuronium and vecuronium, and "immediate reversal" of neuromuscular blockade at 3 minutes after administration of rocuronium.

At this time, the Applicant has modified the indication to read as follows:

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

In addition, the following language is being proposed for the Dosage and Administration section:

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- 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.
- 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.
- 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

The regulatory history of this application is well-detailed in Dr. Simone's review, and will only be briefly summarized here.

- July 31, 2008 – the Agency issued a Not Approvable letter, citing two deficiencies:
 - Inadequate characterization of the hypersensitivity and anaphylactic reactions noted in the clinical trials, particularly with regard to the safety of repeat exposure to sugammadex.
 - Inadequate evaluation of the effects of sugammadex on coagulation.
- December 20, 2012 – the Applicant submitted a complete response to the letter, including the results of a clinical study, P06042, intended to evaluate the risk of hypersensitivity and anaphylactic reactions.
- September 20, 2013 – the Agency issued a Complete Response letter, because the routine inspection of the clinical sites involved in Study P06042 identified several protocol deviations that could impact the validity, reliability, and integrity of the data. Therefore, the deficiency related to the hypersensitivity and anaphylaxis reactions remained unresolved.
- November 21, 2013 – a meeting was held with the Applicant to discuss their plans to address the deficiency and, specifically, the key elements that should be incorporated into the new trial.
- October 22, 2014 – date of submission currently under review.

In this submission, the Applicant included the results from Study P101, a study conducted to characterize the hypersensitivity and anaphylactic reactions, because the results from Study P06042 had been deemed to be unreliable. The assessment and conclusions by the review team are discussed further in Section 8 (Safety) of this review.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The drug substance (Org 25969), a modified γ -cyclodextrin, is an octasodium salt. The mode of action is based on the formation of 1:1 complex with rocuronium or vecuronium. The drug substance contains (b) (4), Org 48302, which has an activity and pharmacological profile similar to Org 25969; therefore, it is considered an active entity. Org 48302 is typically present at levels of (b) (4)% in the representative drug substance batches. The drug substance is highly soluble in water; its hygroscopicity is managed by controlling manufacturing and storage conditions.

The drug product, a sterile parenteral solution for intravenous administration, is prepared by (b) (4)

(b) (4) The target concentration of the active ingredients is 100 mg/mL (expressed as the free acid). The container closure system is a type I glass vial with a latex-free (b) (4) rubber closure and an aluminum flip off cap.

The product quality reviewer indicated in his review that critical process steps for the manufacture of the drug product include the following: pH adjustment, adjustment to final volume, (b) (4)

of vials and visual inspection. The drug product is sensitive to light, especially under severe stress conditions. The Applicant proposes that the primary container be exposed to light no longer than 5 days, (b) (4)

Dr. Hu's review indicated that the photostability data submitted in the application support the 5-day maximum limit on exposure to normal indoor lighting, (b) (4)

Specific Issues Identified in the Course of this Review Cycle

The assessments and conclusions of the review team for the two previous review cycles were that there were no product quality issues that precluded approval. In this submission, the Applicant changed the commercial manufacturing site for the drug product and modified certain aspects of the sterilization process.

The review team concluded that the Applicant provided adequate batch analysis data and additional stability data to support the proposed process change at the new site.

The product quality microbiology reviewer, Dr. Pawar, noted in his review that the product is manufactured (b) (4). No deficiencies were noted with respect to the product quality microbiology requirements for a sterile product.

The facilities inspection did not identify any issues or concerns that would preclude approval.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the product quality reviewers that there are no manufacturing issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

There had not been any nonclinical issues identified during the first two review cycles that would have precluded approval. The Applicant did not submit any new nonclinical data submitted during this review cycle.

However, the changes to the package insert that had been recommended during the first two cycles had not been communicated to the Applicant yet, so the review team focused on whether the recommendations were unchanged and the conversion sections of the insert to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Outstanding or Unresolved Issues

There were no outstanding or unresolved pharmacology/toxicology issues that precluded approval during the first review cycle, and there are none during this review cycle.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology issues that precluded approval during either of the two previous review cycles. The Applicant included in this submission the study report of a study conducted to assess the pharmacokinetics of sugammadex in patients with renal impairment.

The details of the study design are well-described in Dr. Nallani's review. The description of the study and his assessment of the results are reproduced below:

This study (P105) was a 2-center, 2-part, open-label, single-dose (sugammadex 4 mg/kg) study evaluating the effect of chronic renal impairment on sugammadex PK in subjects with severe or moderate renal impairment compared to healthy matched control subjects. Part 1 (n=24) of this study included eight (8) subjects with severe (CLcr <30 mL/min), eight (8) subjects with moderate (CLcr 30 - <50 mL/min) renal impairment and eight (8) healthy control subjects (CLcr ≥80 mL/min). The sponsor [sic] utilized previously established (and reviewed) bioanalytical methodology for assessing sugammadex plasma levels. The sponsor indicated that a preliminary review of the sugammadex concentration data from Part 1 of the study combined with dosing irregularities reported from the clinical research units indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue. Substantial delays in Tmax (range: 1 to 4 hours) and an apparent absorption phase in the pharmacokinetic (concentration-time) profiles provided additional evidence of dosing issues. Given the apparent dosing irregularities in Part 1, the pharmacokinetic data from Part 1 are considered to be uninterpretable; therefore, the study was subsequently amended to include a Part 2 in order to achieve the original pharmacokinetic objectives of the study. Part 2 provided clarification on the dosing procedures in order to ensure that bolus IV administration was achieved (a direct stick method of administration through a fixed needle was used in Part 1) and the duration of pharmacokinetic collection was reduced to 10 days postdose in subjects with moderate and severe renal impairment with flexibility to extend the pharmacokinetic collection in subjects with severe renal impairment, if warranted. This reduction in collection time was based on Part 1 data indicating that, despite the dosing irregularities, none of the subjects with severe or moderate renal impairment had measurable sugammadex concentrations (all were < lower limit of quantitation [LLOQ]) on Day 7 (144 hours) and Day 4 (72 hours), respectively. In Part 2 (n=18) of this study, six (6) subjects with severe (CLcr <30 mL/min), six (6) subjects with moderate (CLcr 30 - < 50 mL/min) renal impairment and six (6) healthy control subjects (CLcr > 80 mL/min) received single doses of IV sugammadex (4 mg/kg). The total enrollment in this study was N=33. Eligible subjects from Part 1 could enroll in Part 2 (n=9 subjects participated in both parts).

Results and Conclusions: As a result of the dosing issues in Part 1, the final pharmacokinetic and subsequent statistical analyses were not conducted for Part 1 of the study. Based on data from Part 2, sugammadex exposure (AUC_{0-∞}) was higher in subjects with moderate and severe renal impairment compared to healthy control subjects. Specifically, the GMR (90% CI) of AUC_{0-∞} in subjects with moderate and severe renal impairment compared to healthy subjects was 2.42 (1.84, 3.17) and 5.42 (4.12, 7.11), respectively. By comparison, the GMR (90% CI) of C_{max} in subjects with moderate and severe renal impairment compared to healthy subjects was 0.92 (0.72, 1.18) and 0.94 (0.73, 1.21), respectively. Clearance progressively decreased and apparent half-life (t_{1/2}) was progressively prolonged with increased levels of renal dysfunction.

Dr. Nallani's final assessment was that the findings from the analyses were similar to those from the previous review cycles, and could be incorporated into the label.

Outstanding or Unresolved Issues

There were no outstanding or unresolved clinical pharmacology issues that precluded approval during the first review cycle, and there are none during this review cycle.

6. Clinical Microbiology

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

7. Clinical/Statistical – Efficacy

As noted by Dr. Simone, adequate data were submitted in the original application to support the efficacy of sugammadex in reversing neuromuscular blockade induced by rocuronium or vecuronium. The following table, reproduced from my review of July 18, 2008, summarizes certain key features of the pivotal studies that supported the efficacy of sugammadex.

| | Study 301 | Study 302 | Study 310 | Study 303 |
|---------------------------|---|---|--|---|
| Location | Europe | United States | Europe | United States and Canada |
| Study period | November 2005 to March 2006 | November 2005 to November 2006 | November 2005 to May 2006 | February 2006 to August 2006 |
| Clinical scenario | “shallow” neuromuscular block, defined as the return of T ₂ (the second twitch in a train-of-four stimulation) | “profound” neuromuscular block, defined as 1-2 post tetanic counts | “shallow” neuromuscular block, defined as the return of T ₂ | “Immediate” reversal (defined as 3 minutes following rocuronium administration) |
| Dose of sugammadex | 2 mg/kg | 4 mg/kg | 2 mg/kg | 16 mg/kg |
| Treatment groups | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Cis-atricurium/neostigmine | a. Rocuronium/Org25969 b. Succinylcholine/no reversal agent |
| Number of patients | 196 randomized | 182 randomized | 84 randomized | 115 randomized |
| Primary efficacy endpoint | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₁ = 0.1 |

The efficacy results from the four studies are summarized in the following table, reproduced from my review of July 18, 2008.

| Study # | Scenario | Time (in minutes) | | p-value |
|---------|-------------|-------------------|------------|---------|
| | | Sugammadex | Comparator | |
| 301 | Routine | 1:29 (R) | 18:30 | <0.0001 |
| | Shallow | 2:48 (V) | 16:48 | |
| 302 | Routine | 2:52 (R) | 50:22 | <0.0001 |
| | Profound | 4:28 (V) | 66:12 | |
| 303 | “Immediate” | 4:22 | 7:04 | <0.0001 |
| 310 | Routine | 2:02 | 8:46 | <0.0001 |
| | Shallow | | | |

The following paragraphs are reproduced from the Efficacy Summary in Dr. Simone’s review.

Based on the clinical trials reported in the original NDA submission, sugammadex was found to

be effective for reversing rocuronium- and vecuronium-induced neuromuscular blockade when administered under two clinical conditions:

1. With the spontaneous return of the second twitch (T2) of the abductor pollicis muscle, when a train-of-four (TOF) electrical stimulus is applied to the ulnar nerve.
2. With the presence of one to two post-tetanic contractions of the adductor pollicis longus muscle, when a TOF stimulus is applied following a tetanic electrical stimulus to the ulnar nerve.

Sugammadex was also found to be effective for reversing the neuromuscular blockade when it is given at three minutes following a rapid sequence induction (RSI) dose of rocuronium (1.2 mg/kg) rocuronium. This reversal occurs at the time when the maximal pharmacodynamic effect of rocuronium is expected.

For the first two clinical scenarios above, sugammadex provided a more rapid return of the ratio of the intensity of the fourth twitch (T4) in a TOF stimulus to that of the first twitch (T1) to 90% ($T4/T1 = 0.9$) compared to placebo or neostigmine, the anticholinesterase agent most commonly used in clinical practice for the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

For the third clinical scenario, sugammadex was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied in this scenario was the return of T1 in a TOF stimulus to 10% of its baseline value. Sugammadex reversed the neuromuscular blockade induced by rocuronium in less time than it took for the effects of succinylcholine to spontaneously resolve to the same point, 4.3 minutes versus 7.2 minutes on average, respectively. However, the clinical relevance of this level of recovery was not demonstrated in the clinical study and not otherwise provided by the Applicant.

The Applicant also evaluated the time to $T4/T1 = 0.9$ for the rocuronium/sugammadex treatment group as a secondary endpoint and the time for T1 to return to 90% of its baseline level following treatment with succinylcholine. These recovery points are likely to be more clinically relevant. For these endpoints, sugammadex induced recovery took an average of 5.4 minutes compared to the spontaneous succinylcholine recover which took an average of 10.9 minutes.

The Applicant indicated in the original NDA submission that the ability to reverse the highest labeled dose of rocuronium at the time of its maximum effect has the potential to reduce the morbidity and mortality that are associated with the inability to intubate or ventilate a paralyzed patient. However, they provided no evidence that such a claim is valid, and in the current submission, they have changed this use of sugammadex from “[i]f there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg BRIDION™ is recommended” to “16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.” The revised use implies that the high dose of sugammadex (b) (4)

when the need is urgent; however, there is no evidence (b) (4)

The revised labeling (b) (4)

Therefore, the label needs to be revised to reflect the conditions under which the three doses of sugammadex were found to be effective and (b) (4)

In the first resubmission, there was one new study that warrants special note especially as it relates to a study in the current submission. Study P05774 evaluated the T4/T1 values for subjects, at the time of extubation, after sugammadex was administered per proposed labeling at 1-2 PTCs and

after neostigmine was administered per standard of care. Twitch monitoring was not used following administration of study drug to assess the level of recovery from neuromuscular blockade as part of overall evaluation of a patient's readiness to be extubated. The study showed that more subjects were extubated with $T4/T1 < 0.9$ when treated with neostigmine than with sugammadex. (b) (4)

The current submission contains the final study report for clinical trial P07981 in which the Applicant evaluated the extent of residual paralysis that occurred in the Post-Anesthesia Care Unit (PACU) following treatment with either sugammadex or neostigmine. The results indicated that there was no residual paralysis, measured as $T4/T1 \geq 0.9$, with sugammadex treatment; however, more than 50% of subjects had residual paralysis with neostigmine treatment. The trial also evaluated various time intervals relative to study drug administration, e.g., time to extubation, time to discharge from the operating room, and time to discharge from PACU, grip strength and pulmonary function testing were also performed on admission to PACU and when subjects were more awake. Despite the differences in residual paralysis, the only significant differences for the other endpoints were a 4 minute earlier time to extubation and discharge from the operating room for sugammadex-treated subjects. There was no difference for any other time interval assessed and no difference for either grip strength or any pulmonary function tests that were performed either on entry to the PACU or when the subjects were more fully awake. The trial and its findings are described in detail in Section 9.4. (b) (4)

In summary, the efficacy studies conducted over the entire development program support the finding that sugammadex is superior to neostigmine for reversing rocuronium and vecuronium when administered as proposed. The additional studies of the 16 mg/kg dose of sugammadex demonstrated that it is effective at reversing doses of rocuronium up to 1.2 mg/kg after 3 minutes. The studies showed that there was less residual paralysis following sugammadex treatment than neostigmine treatment; however, the residual paralysis was not associated with any differences in grip strengths, pulmonary function tests, or discharge from the PACU. The studies did not show the need for dose adjustments of sugammadex based on age, gender, race, renal impairment, or hepatic impairment.

Outstanding or Unresolved Issues

I concur with Dr. Simone that there are no outstanding issues or concerns regarding the efficacy of sugammadex that would preclude approval.

8. Safety

Study P101

The Applicant conducted Study P101, to address the deficiency identified in the Complete Response letter issued by the Agency on September 20, 2013. It was titled "A randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex (MK- 8616) in healthy subjects." It had the following primary objective: to determine the number and percentage of

subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo. It also had several secondary objectives and exploratory objectives, as noted below.

Secondary Objectives:

- To determine the number and percentage of subjects with adjudicated anaphylaxis according to the definition of Sampson (Criterion 1) for each dose group of sugammadex and placebo.
- To investigate the change over time in frequency and severity of adjudicated hypersensitivity symptoms for each dose group of sugammadex and placebo.
- To evaluate the safety and tolerability of administration of repeated single doses of sugammadex in healthy subjects.

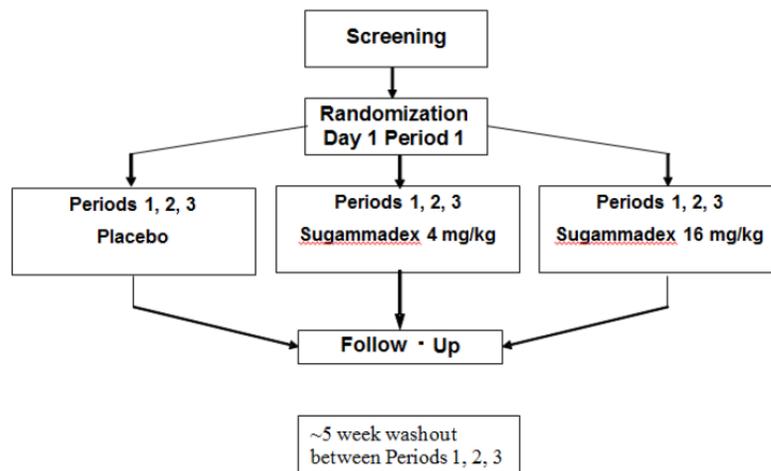
Exploratory Objectives:

- To measure levels of anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of hypersensitivity and in a subset of subjects without adjudicated symptoms of hypersensitivity.
- To measure mast cell tryptase levels in subjects referred for adjudication of Potential Hypersensitivity.
- To collect samples for potential hypersensitivity research.

The design of the study is well-described in Dr. Simone's review, as well as in Dr. Erika Torjusen's consultative review (from the Division of Pulmonary, Allergy, and Rheumatology Products [DPARP]). Briefly, subjects were randomized to one of three treatments:

1. Treatment Arm A: Sugammadex 4 mg/kg single intravenous bolus injection in each of 3 periods
2. Treatment Arm B: Sugammadex 16 mg/kg single intravenous bolus injection in each of 3 periods
3. Treatment Arm C: Placebo single intravenous bolus injection in each of 3 periods

A schematic for the protocol is depicted below:



A total of 375 subjects were randomized and received at least one dose in the study. This was considered the All-Subjects-as Treated (ASaT) population. The subjects' disposition is summarized in the following table, reproduced from Dr. Torjusen's review.

| Table 1: Patient Disposition - Study P101 | | | |
|---|-------------------------|---|--|
| | Placebo N=76 | Sugammadex 4 mg/kg N=151 | Sugammadex 16 mg/kg N=148 |
| | n (%) | | |
| Patients who completed the study | 64 (84.2) | 136 (90.1) | 134 (90.5) |
| Patients who discontinued | 12 (15.8) | 15 (9.9) | 14 (9.5) |
| Reasons for discontinuation | | | |
| <i>Adverse Events</i> | 3 (3.9) | 3 (2.0) | 5 (3.4) |
| <i>Lost to Follow Up</i> | 2 (2.6) | 4 (2.6) | 6 (4.1) |
| <i>Physician Decision</i> | 1 (1.3) | 0 | 0 |
| <i>Protocol Violation</i> | 1 (1.3) | 4 (2.6) | 0 |
| <i>Withdrawal by Subject</i> | 5 (6.6) | 4 (2.6) | 3 (2.0) |
| <i>Hypersensitivity-Related†</i> | 1 (1.3) | 1 (0.7) | 5 (3.4) |
| <i>Adverse Events</i> | 0 | 1 (0.7) | 4 (2.7) |
| <i>Lost to Follow Up</i> | 0 | 0 | 1 (0.7) |
| <i>Withdrawal</i> | 1 (1.3) | 0 | 0 |
| † Subjects with suspected hypersensitivity reactions after one randomized dose Source: Clinical Study Report P101 Module 5.3.5.4, Table 2, page 5, Clinical Study Report P101 Module 5.3.5.4, Section 16.2.1, p. 2-6 | | | |

Dr. Torjusen noted in her review that adverse events were the most common reason for discontinuation among subjects in the 16 mg/kg group compared to the 4 mg/kg group. Furthermore, this relationship was even more pronounced among the patients experiencing a hypersensitivity adverse event, and there was the suggestion of a dose-response relationship.

Dr. Torjusen's review provides more details regarding the adverse events and the specific symptoms that were reported by the subjects. In conclusion, Dr. Torjusen's review noted the following:

In this submission, the Applicant provided the results of a second dedicated hypersensitivity study, P101, a randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex in healthy subjects.

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2) and a targeted hypersensitivity assessment (see Appendix 3), the Applicant identified 137 cases of suspected hypersensitivity in 94 subjects, and 1 case of anaphylaxis. Using NIAID/FAAN criterion #1, DPARP agreed with the Applicant's single case identification of anaphylaxis. Study P101 consisted of 299 unique healthy volunteer subjects who received sugammadex. As a result, the frequency of anaphylaxis was 0.33% (1/299) in this study. It is of note that the case of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

Among the hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, pruritus, and urticaria. Several hypersensitivity symptoms, including erythema, eye disorders, nausea, sneezing, urticaria, and vomiting showed a dose-response, more frequently occurring in the high-dose group when compared to the low-dose group and placebo. Hypersensitivity reactions were more frequently noted in the 16 mg/kg dose group, occurring ≤ 35 minutes of dosing, and with the first dose of sugammadex.

Review of post-marketing reports, in the context of the data from controlled clinical trials, reveals the presence of a consistent constellation of symptoms including rash, erythema, urticaria, hypotension, and response to standard treatment for anaphylaxis/hypersensitivity reactions.

Mechanistic data submitted do not elucidate a clear causal mechanism leading to anaphylaxis and hypersensitivity. While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available mechanistic and clinical data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.

DPARP concludes that sugammadex causes anaphylaxis and hypersensitivity events. This risk appears to increase with higher doses and does not appear to increase with repeated exposure. Whether this risk is greater than the risk for other drug products commonly used in the perioperative setting is difficult to determine. The incidence of anaphylaxis during general anesthesia reported in the literature covers a wide range, with estimates from 1:3500 to 1:25,000.^{2,3} Given changes in medical and surgical practices over time, such as the decreased use of latex and utilization of new measures to prevent medical errors, obtaining an accurate estimate of the frequency of peri-operative anaphylaxis in the context of current standards of care is challenging. For this reason, there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-benefit assessment for sugammadex depends primarily on the efficacy and safety data specific to sugammadex and its expected use in a real-world setting.

Additional Safety Data

As noted in Dr. Simone's review, the Applicant has conducted 24 additional clinical trials since the submission of the original application, increasing the size of the safety database to 6,050 subject exposures in 4,428 individuals. The Applicant indicates in the submission that sugammadex is currently approved in 75 countries, and marketed in more than 50 countries worldwide.

Dr. Simone's conclusions regarding the safety database were as follows:

Regarding the updated safety database from the clinical development program, the analyses of common adverse events demonstrated that sugammadex had a safety profile that, in general, posed only minimal additional risk compared to placebo and a level of risk that appeared to be no worse than that of neostigmine. The most common adverse events were nausea, vomiting, and pain. Only dysgeusia, nausea, nasopharyngitis, and possibly headache, appeared to be sugammadex-dose related. Similarly, the analysis of SAEs reported in the clinical trials indicated that, overall, the safety profile for sugammadex was not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm related adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it was only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appeared to differ substantially from placebo and neostigmine. Review of the postmarketing data produced similar findings; although, it was noted that many of the cardiovascular reactions occurred in the setting of hypersensitivity and anaphylactic reactions.

The review of the updated safety database indicated that there were no subpopulations at greater risk from sugammadex or for whom the dose of sugammadex needed to be adjusted.

Regarding the postmarketing adverse reaction database, the review of the data indicated that anaphylactic reactions were the most frequently reported adverse events followed by changes in heart rate and blood pressure. There was no indication of a new safety signal in the database.

In summary, the safety profile for sugammadex has been adequately characterized to perform a benefit-risk analysis, provided the OSI inspections for Study P101 raise no concerns over data integrity. The overall safety of sugammadex did not differ substantially from placebo in the clinical trials, and sugammadex appears to pose no greater risk than neostigmine, with the exception of hypersensitivity and anaphylactic reactions that have been generally mild to moderate in severity, readily diagnosed with standard patient monitoring, and successfully treated, when intervention was needed.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding safety issues that would preclude approval.

9. Advisory Committee Meeting

An advisory committee meeting that was scheduled for March 18, 2014 was canceled pending resolution of concerns about potential data integrity issues. These concerns are further described below in Section 11 of this review.

10. Pediatrics

The Applicant had previously conducted one trial which included pediatric patients (Trial 19.4.306). It was not conducted under an IND and included only foreign clinical sites (Germany, Finland, France, and the UK). The following description and summary of results are from the Applicant's submission:

Summary of Pediatric Trial 19.4.306

Trial 19.4.306 was designed as a dose-finding trial investigating 4 doses of sugammadex (0.5, 1.0., 2.0 and 4.0 mg/kg) and placebo for the reversal of rocuronium induced moderate NMB ("at the reappearance of T2") at different age groups of pediatric subjects. The trial also investigated a cohort of adult subjects. The full CSR for this trial was included in Module 5.3.4.2 of the original NDA for sugammadex. Table 1 summarizes the efficacy data by dose and age group and also presents an overview of the number of evaluated pediatric and adult subjects in Trial 19.4.306.

Table 1 Summary of the recovery times (min:sec) from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 by dose and age group (PP group)

| Age class | Statistic | Dose group | | | | |
|-----------|-----------|------------|------------------------|------------------------|------------------------|------------------------|
| | | Placebo | 0.5 mg/kg Org 25969 | 1.0 mg/kg Org 25969 | 2.0 mg/kg Org 25969 | 4.0 mg/kg Org 25969 |



At present, the Applicant’s proposed pediatric plan (b) (4)

 The Applicant intends to do a trial that will study sugammadex in all the pediatric age groups, in a staggered approach, for reversal of moderate and deep neuromuscular blockade induced by rocuronium or vecuronium.

The Applicant’s plan was discussed at the Pediatric Review Committee (PeRC) meeting of March 4, 2015. The committee concurred that the application triggered the requirements under the Pediatric Research Act (PREA) of 2003, and that studies for all pediatric patients could be deferred because adult studies have been completed and the application appeared ready for approval. The committee did note that, if the application does get approved, the timeline for the completion of the studies should be advanced significantly.

11. Other Relevant Regulatory Issues

The Division of Good Manufacturing Practice Assessment (DGMPA) conducted inspections as part of the routine PDUFA pre-approval clinical investigation data validation in support of an NDA. In addition to the Applicant’s central site, two clinical sites inspected.

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Dr. Kleppinger noted the following in her overall assessment of findings and recommendations:

Dr. Gartner was issued a Form FDA-483, citing inspectional observations and the classification for this clinical site inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.

Dr. Hernandez-Illas was not issued a Form FDA 483; the classification of this clinical site inspection is NAI (No Action Indicated). Data from this site is considered reliable based on the available information.

Merck was issued a Form FDA-483, citing inspectional observations and the recommended classification by the FDA ORA investigator for this Sponsor inspection is OAI (Official Action Indicated). As noted above, the potential unblinding of all subjects prior to database lock could impact the validity and reliability of the submitted data to determine the primary safety and efficacy analyses. Because of the potential unblinding of all subjects prior to database lock, it is recommended that the review team consider doing sensitivity analyses with a set of plausible possibilities, including analyses of the data for the time period before and after March 11, 2014. In addition, although no significant issues were noted at the two clinical sites inspected, it is recommended that the additional four clinical sites be inspected to evaluate adequacy of conduct of the study and determine whether there is any evidence of unblinding at site level.

The findings from the inspections were discussed with the Applicant at a face-to-face meeting held on March 4, 2015. The Applicant submitted a briefing package and made a presentation at the meeting, describing the protocol violations, the genesis for the evaluations, the actions that they took upon becoming aware of the violations and their assessment of the potential impact the violations had on the results of the study. The Applicant indicated at the meeting that sensitivity analyses had not yet been conducted to assess the impact of the affected data on the overall results of the study.

Internal discussions were held after the meeting between the review division, and representatives from ODE II and OND. The outcome of the discussions was that, even though the observed protocol violations had a low probability of having a significant impact on the results of Study P101, the sequence of events that resulted in the protocol violations made it necessary to inspect the remaining clinical sites. Because these inspections could not be conducted prior to the already-scheduled advisory committee, the meeting had to be canceled.

Outstanding or Unresolved Issues

The issue of the risk of hypersensitivity and anaphylaxis, particularly after repeated exposure, appears to have been adequately addressed by the results from Study P101. However, due to the concerns identified by the routine inspections, it is not clear whether the results from this study

are valid or reliable. It will be necessary to inspect the remaining clinical sites before a final conclusion can be made regarding Study P101.

12. Labeling

The review team continued internal discussions regarding the package insert, in anticipation of sharing the modifications with the Applicant during the next review cycle. The Division of Medication Error Prevention and Analysis (DMEPA) provided recommendations for modifications to the package insert, container labels, and carton labeling during the previous review cycles.

Although the final wording in the package insert is still to be determined, the review team has identified the following aspects will need to be addressed:

- **Indications and Usage section:**
The terms (b) (4) are relative terms and can mean different things to different people. The level of blockade, using descriptors observed during peripheral nerve stimulation would be more direct and objective.
- **Dosage and Administration section:**
The clinical situations where the high dose (16 mg/kg) should be used will need to be clarified.
- **Warnings and Precautions section:**
Several subsections within this section will need clarification.
- **Clinical Trial Experience section:**
The adverse event experience observed in the clinical trials needs to be clarified.
- **Postmarketing Experience section:**
The section currently includes cardiac disorders, but also needs to include other events observed, such as anaphylaxis and events where the product was reported as being ineffective.
- **Overdosage section:**
The wording needs to be modified (b) (4) than what is noted in the Dosage and Administration Section.
- **Controlled Clinical Studies section:**
(b) (4)

As mentioned above, the review team also reviewed the package insert to assess what modifications were needed in order for it to be in compliance with the Pregnancy and Lactation Labeling Rule. This included a consultation with the Division of Pediatric and Maternal Health.

The Office of Prescription Drug Products (OPDP) deferred any review the label until the next review cycle.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

Risk:Benefit Assessment

The Applicant has submitted adequate information to support the safety and efficacy of sugammadex when used as proposed by the Applicant. However, the observations from the routine inspections indicated several protocol violations that raised questions about the integrity and reliability of the data generated from Study P101, the key study intended to address the remaining deficiency. Although review of the violations at one of the two clinical sites inspected and the unblinding of subjects prior to database lock at the Applicant's central site had a low probability of having a significant impact on the results of the study, inspection of the remaining clinical sites was deemed to be necessary in order to establish whether there were other protocol violations that would further impact the validity and integrity of the data. Since these inspections could not logistically be carried out prior the already-scheduled advisory committee meeting, the meeting was canceled. Subsequently, my recommendation is that this application be given a Complete Response at this time.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

This application is subject to the postmarketing requirements of the Pediatric Research Equity Act. As described in Section 10, the submission of pediatric data is currently deferred, and the Applicant intends to pursue a clinical trial (b) (4) to the pediatric population.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RIGOBERTO A ROCA
04/21/2015

CLINICAL REVIEW

| | |
|--|---|
| Application Type | NDA - Complete Response |
| Application Number(s) | 022225 |
| Priority or Standard | Standard |
| 3 rd Cycle Submit Date(s) | October 22, 2014 |
| 3 rd Cycle Received Date(s) | October 22, 2014 |
| 3 rd Cycle PDUFA Goal Date | April 22, 2015 |
| Division / Office | DAAAP/ODE 2 |
| Reviewer Name(s) | Arthur Simone, MD, PhD |
| Review Completion Date | April 3, 2015 |
| Established Name | Sugammadex sodium |
| (Proposed) Trade Name | Bridion |
| Therapeutic Class | Neuromuscular blockade reversal agent |
| Applicant | Organon USA Inc. |
| Formulation(s) | Injectable |
| Dosing Regimen | Single-dose |
| (Proposed) Indication(s) | Routine reversal of moderate or deep NMB by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Intended Population(s) | Adults |
| Application Type | NDA - Complete Response |

Table of Contents

| | | |
|----------|---|-----------|
| 1 | RECOMMENDATIONS/RISK BENEFIT ASSESSMENT | 9 |
| 1.1 | Recommendation on Regulatory Action | 9 |
| 1.2 | Risk Benefit Assessment..... | 10 |
| 1.3 | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . | 11 |
| 1.4 | Recommendations for Postmarket Requirements and Commitments | 11 |
| 2 | INTRODUCTION AND REGULATORY BACKGROUND | 12 |
| 2.1 | Product Information | 12 |
| 2.2 | Currently Available Treatments for Proposed Indications..... | 13 |
| 2.3 | Availability of Proposed Active Ingredient in the United States | 13 |
| 2.4 | Important Safety Issues with Consideration to Related Drugs..... | 13 |
| 2.5 | Summary of Presubmission Regulatory Activity Related to Submission | 13 |
| 2.6 | Other Relevant Background Information | 15 |
| 3 | ETHICS AND GOOD CLINICAL PRACTICES..... | 16 |
| 3.1 | Submission Quality and Integrity | 16 |
| 3.2 | Compliance with Good Clinical Practices | 16 |
| 3.3 | Financial Disclosures..... | 17 |
| 4 | SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES | 18 |
| 4.1 | Chemistry Manufacturing and Controls | 18 |
| 4.2 | Clinical Microbiology..... | 18 |
| 4.3 | Preclinical Pharmacology/Toxicology | 18 |
| 4.4 | Clinical Pharmacology | 18 |
| 4.4.1 | Mechanism of Action..... | 18 |
| 4.4.2 | Pharmacodynamics..... | 19 |
| 4.4.3 | Pharmacokinetics..... | 19 |
| 5 | SOURCES OF CLINICAL DATA..... | 20 |
| 5.1 | Tables of Studies/Clinical Trials | 20 |
| 5.2 | Review Strategy | 21 |
| 5.3 | Discussion of Individual Studies and Clinical Trials..... | 21 |
| 6 | REVIEW OF EFFICACY | 23 |
| | Efficacy Summary..... | 23 |
| 6.1 | Indication | 25 |
| 6.1.1 | Methods | 26 |
| 6.1.2 | Demographics | 31 |
| 6.1.3 | Subject Disposition..... | 34 |
| 6.1.4 | Analysis of Primary Endpoint(s) | 34 |
| 6.1.5 | Analysis of Secondary Endpoints(s) | 41 |

| | | |
|----------|--|-----------|
| 6.1.6 | Other Endpoints | 43 |
| 6.1.7 | Subpopulations | 43 |
| 6.1.8 | Analysis of Clinical Information Relevant to Dosing Recommendations ... | 44 |
| 6.1.9 | Discussion of Persistence of Efficacy and/or Tolerance Effects..... | 44 |
| 6.1.10 | Additional Efficacy Issues/Analyses | 44 |
| 7 | REVIEW OF SAFETY..... | 45 |
| | Safety Summary | 45 |
| 7.1 | Methods..... | 49 |
| 7.1.1 | Studies and Clinical Trials Used to Evaluate Safety | 49 |
| 7.1.2 | Categorization of Adverse Events | 53 |
| 7.1.3 | Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence..... | 53 |
| 7.2 | Adequacy of Safety Assessments | 55 |
| 7.2.1 | Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations | 55 |
| 7.2.2 | Explorations for Dose Response..... | 56 |
| 7.2.3 | Special Animal and/or In Vitro Testing | 58 |
| 7.2.4 | Routine Clinical Testing | 58 |
| 7.2.5 | Metabolic, Clearance, and Interaction Workup | 59 |
| 7.2.6 | Evaluation for Potential Adverse Events for Similar Drugs in Drug Class .. | 59 |
| 7.3 | Major Safety Results | 60 |
| 7.3.1 | Deaths..... | 60 |
| 7.3.2 | Nonfatal Serious Adverse Events | 63 |
| 7.3.3 | Dropouts and/or Discontinuations | 66 |
| 7.3.4 | Significant Adverse Events | 66 |
| 7.3.5 | Submission Specific Primary Safety Concerns | 68 |
| 7.4 | Supportive Safety Results | 105 |
| 7.4.1 | Common Adverse Events | 105 |
| 7.4.2 | Laboratory Findings | 109 |
| 7.4.3 | Vital Signs | 117 |
| 7.4.4 | Electrocardiograms (ECGs) | 124 |
| 7.4.5 | Special Safety Studies/Clinical Trials | 124 |
| 7.4.6 | Immunogenicity | 124 |
| 7.5 | Other Safety Explorations..... | 125 |
| 7.5.1 | Dose Dependency for Adverse Events | 125 |
| 7.5.2 | Time Dependency for Adverse Events..... | 125 |
| 7.5.3 | Drug-Demographic Interactions | 125 |
| 7.5.4 | Drug-Disease Interactions..... | 126 |
| 7.5.5 | Drug-Drug Interactions..... | 127 |
| 7.6 | Additional Safety Evaluations | 128 |
| 7.6.1 | Human Carcinogenicity | 128 |
| 7.6.2 | Human Reproduction and Pregnancy Data..... | 128 |
| 7.6.3 | Pediatrics and Assessment of Effects on Growth | 128 |

| | | |
|----------|--|------------|
| 7.6.4 | Overdose, Drug Abuse Potential, Withdrawal and Rebound..... | 128 |
| 7.7 | Additional Submissions and Safety Issues | 129 |
| 8 | POSTMARKET EXPERIENCE..... | 130 |
| 9 | APPENDICES | 140 |
| 9.1 | Literature Review/References | 140 |
| 9.2 | Labeling Recommendations | 140 |
| 9.3 | Advisory Committee Meeting..... | 142 |
| 9.4 | Review of Clinical Studies Conducted Since the Last NDA Submission | 143 |
| 9.4.1 | Study P07981 | 143 |
| 9.4.2 | Study P07982 | 158 |
| 9.4.3 | Study P105 | 169 |
| 9.4.4 | Study P101 | 182 |

Table of Tables

| | |
|---|----|
| Table 1. Clinical studies conducted to date not included in the original NDA submission | 20 |
| Table 2. Study 301 treatment groups | 26 |
| Table 3. Demographics for subjects in the original submission integrated summary of efficacy database | 33 |
| Table 4. Subject disposition for efficacy studies of the proposed indication. (Based on data from Table 2-2.1 on p. 323, Table 2-2.1 on p. 335, and Table 2-3.1 on p. 346 of Section 2.5 in the second NDA resubmission) | 34 |
| Table 5. Summary of results from Studies 301 and 302..... | 37 |
| Table 6. Summary of the results from Study 303 | 40 |
| Table 7. (b) (4) | 41 |
| Table 8. Comparisons of the findings for Studies 301, 302 and 303 for reversal of rocuronium | 42 |
| Table 9. Clinical trials used for the evaluation of safety..... | 49 |
| Table 10. Subject counts and treatment exposures for the entire clinical development program..... | 55 |
| Table 11. Numbers of subjects and exposures for all intravenous treatments | 57 |
| Table 12. Serious adverse events alphabetically by system organ class, treatment, and dose | 64 |
| Table 13. Distribution of severe adverse events across treatment arms..... | 67 |
| Table 14. Distribution of adverse events and serious adverse events across treatments and doses..... | 67 |
| Table 15. Applicant findings of anaphylaxis and hypersensitivity in the Pooled Phase 1-3 trials (based on Table 46, p. 146 of the ISS)..... | 73 |
| Table 16. Applicant findings of anaphylaxis and hypersensitivity in the Placebo-Controlled trials (based on Table 47, p. 147 of the ISS)..... | 74 |
| Table 17. Summary of cardiac arrhythmia adverse events from the original NDA safety database occurring within 72 hours of study drug administration [2007 safety database (original submission)]..... | 84 |
| Table 18. Summary of cardiac arrhythmia and acute myocardial infarction SAE data from the original NDA safety database..... | 85 |
| Table 19. Number (%) of subject exposures with AEs within Cardiac Arrhythmias related SMQs during the treatment period (combined data from Tables 69 and 70 on pp. 197-198 and 200-201 in Section 5.3.5.3 of the 2012 resubmission) | 89 |
| Table 20. Arrhythmia-related Investigations (signs and symptoms) (Broad SMQ) in pooled Phase 1-3 placebo-controlled studies (Table 67 on p. 193 of Section 5.3.5.3 of the 2012 resubmission) | 91 |
| Table 21. Markedly Abnormal pulse rates at any In-Treatment post-baseline timepoint in pooled Phase 1-3 placebo-controlled studies (Table 113 on p. 300 of Section 5.3.5.3 of the 2012 NDA resubmission)..... | 92 |

| | |
|---|-----|
| Table 22. Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 112 on p. 299 of Section 5.3.5.3 in the 2012 NDA resubmission)..... | 92 |
| Table 23. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled placebo-controlled trials in order of decreasing incidence in the total sugammadex group (Table 114 on p. 300 in Section 5.3.5.3 of the 2012 NDA resubmission)..... | 93 |
| Table 24. Number (%) of subject exposures with heart rate \geq 50 bpm at baseline and heart rate $<$ 50 bpm after baseline for exposures in pooled Phase 1-3 studies by time point (Table 77 on p. 208 of Section 5.3.5.3 of the 20121 resubmission)..... | 94 |
| Table 25. Number (%) of subject exposures for subjects with a decrease \geq 20 bpm resulting in a heart rate \leq 50 bpm for exposures pooled Phase 1-3 trials by time point (Table 78 on p. 210 of Section 5.3.5.3 of the 2012 resubmission) | 94 |
| Table 26. Number of exposures for adult subjects who received NMBA and placebo or sugammadex in pooled Phase 2-3 studies who were administered atropine within one hour after study drug, by NMBA (Table 79 on p. 212 of Section 5.3.5.3 of the 2012 resubmission) | 95 |
| Table 27. Summary of serious adverse events related to cardiac arrhythmia and acute myocardial infarction in the 2012 resubmission safety database | 98 |
| Table 28. Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the 2012 resubmission safety database | 100 |
| Table 29. Cardiac AEs occurring within 24 hours of study drug administration [2014 safety database (current submission)] | 102 |
| Table 30. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13) | 103 |
| Table 31. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13) | 103 |
| Table 32. Summary of adverse events by system organ class in descending rates for sugammadex treatments..... | 106 |
| Table 33. Summary of adverse events by system organ class in descending rates for sugammadex treatments..... | 108 |
| Table 34. Notable shift categories (Table 84 on p. 251 in Section 5.3.5.3 of the NDA resubmission)..... | 111 |
| Table 35. Absolute value cutoffs and changes for blood pressure and heart rate that were used to determine “markedly abnormal values” (from Table 138 on p. 4317 in Appendix A of Section 5.3.5.3 in the NDA resubmission)..... | 118 |
| Table 36. Postmarketing adverse event counts in decreasing order by System Organ Class | 130 |
| Table 37. Postmarketing cardiac rhythm-related adverse events by decreasing frequency | 136 |
| Table 38. Cardiac reactions occurring in patients who had an anaphylactic or hypersensitivity reaction | 137 |

| | |
|---|-----|
| Table 39. Results for primary endpoint measurements (based on Table 11-3, p. 89 of the final study report) | 153 |
| Table 40. Distribution of T ₄ /T ₁ ratios for the neostigmine-treated subjects (based on Table 11-2, p. 87 of the final study report) | 154 |
| Table 41. Results for secondary time-interval measurements (based on Table 11-4, p. 91 of the final study report)..... | 154 |
| Table 42. Results of grip strength testing (based on Table 11-6, p. 95 of final study report) | 155 |
| Table 43. Results of pulmonary function testing (based on Tables 11-7 and 11-8, pp. 96-97 of the final study report) | 156 |
| Table 44. (based on Table, pp. 9-10 of protocol in Appendix 16.1.1 of the final study report) | 163 |
| Table 45. Subject disposition (based on Table on p. 5 of final study report) | 166 |
| Table 46. Schedule of assessments (based on Table 9-2, p. 42 of the final study report) | 176 |
| Table 47. Summary of pharmacokinetic findings for Part 2 (Table 11-1, p. 85 of the final study report) | 179 |
| Table 48. Schedule for Study P101 (Table 9-1, pp.48-50 | 191 |
| Table 49. Disposition of subjects in P101 (based on Table 2, p. 5 of the final study report) | 197 |
| Table 50. Applicant-reported findings for hypersensitivity and anaphylaxis (based on Table 4, p. 7 of the final study report)..... | 198 |
| Table 51. Severity of hypersensitivity reactions in P101 (based on Table 5, p. 10 of the final study report) | 199 |

Table of Figures

| | |
|--|-----|
| Figure 1. Structural formula of sugammadex (Figure 1, p.2 of Module 2.2 in original NDA) | 12 |
| Figure 2. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at the reappearance of T_2 by treatment group and NMBA (Figure 5 on p. 44 of Section 2.5 of the second NDA resubmission)..... | 38 |
| Figure 3. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at 1-2 PTCs by treatment group and NMBA (Figure 8 on p. 48 of Section 2.5 of the second NDA resubmission)..... | 39 |
| Figure 4. Trial design schematic (Figure 2.1, p. 5 of protocol in Appendix 16.1.1 of the final study report) | 162 |
| Figure 5. Schematic of the protocol for study P101 (Figure 9-1, p. 44 of the final study report) | 190 |

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A Complete Response action is recommended.

In the Not Approvable letter issued on July 31, 2008, and the Complete Response (CR) letter issued on September 20, 2013, the Applicant was required to determine the risk of hypersensitivity and anaphylactic reactions, particularly with repeat exposure to the product. In the first complete response, Study P06042 was designed and conducted to address this deficiency. However, the audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from the study such that the deficiency remained unresolved. In the current submission, Study P101 was designed and conducted to address the deficiency. However, the audit conducted during the OSI inspection found that substantial protocol deviations occurred at one of the two clinical sites inspected and that there were issues with the data being unblinded to the statisticians at the site where the data were stored and analyzed. A number of other findings made at the time of the inspection brought into question, once again, the validity, reliability, and integrity of the data. Although the Applicant provided a reasonable explanation for how the integrity of the data was maintained despite the multiple shortcomings and missteps that occurred centrally and at one of the inspected sites, the poor conduct of the study during this cycle in conjunction with the poor conduct of Study P06042, warrant that the Agency inspect the remaining clinical sites to assure that there are no other issues that would preclude the use of the data from Study P101 to address the deficiency in the CR letter. In addition, the Applicant should conduct sensitivity analyses to determine whether the study results are impacted by removing the data from subjects whose hypersensitivity assessments were not made per protocol or by removing the data from subjects that were unblinded to the statisticians. These analyses will provide further assurance that the integrity of the data was not compromised.

Without the support of the findings in Study P101, it is still not possible to determine the risk of anaphylaxis occurring with repeat exposure to sugammadex, and it is, therefore, still not possible to determine whether the benefits of faster recovery from neuromuscular blockade at the end of surgery outweigh the risk of a potentially life-threatening reaction in a substantial segment of the population that presents for multiple surgical procedures over the course of a lifetime. To address this outstanding deficiency, the Applicant should be required to do one of the following:

1. For Study P101, identify all subjects with a major protocol violation, including those for whom the investigators did not follow the protocol regarding the

administration of the study drug and assessments of hypersensitivity and anaphylactic reactions. Evaluate whether there is a difference in the nature, frequency, and severity of the signs and symptoms of hypersensitivity and anaphylaxis between the violation group and the per protocol groups for each of the treatments. Perform sensitivity analyses on the primary and key secondary endpoints with the data from the per protocol subjects. In addition, identify the subjects whose data were unblinded to the statisticians and perform a sensitivity analysis comparing the findings from the appropriately treatment-blinded subjects to those for whom the treatment was unblinded. For both sensitivity analyses, provide a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the findings, thereby allowing the study to address the deficiency cited above. Submit the source documents utilized to support the inclusion of the remaining subjects incorporated in the reanalyses.

Or

2. Repeat Study P101 and submit the clinical study report to the Agency.

1.2 Risk Benefit Assessment

The studies conducted to assess the efficacy of sugammadex have consistently shown it to be superior to neostigmine reducing recovery times, based on peripheral nerve stimulation, from rocuronium by 15 to 45 minutes when administered after spontaneous recovery has begun, i.e., at the reappearance of the second twitch (T_2) and at 1-2 post-tetanic contractions (PTCs), in response to a train-of-four electrical stimuli at a peripheral nerve, respectively, and from vecuronium by 10 to 60 minutes when administered at the same timepoints into spontaneous recovery. Sugammadex has also been shown to be effective at reversing the maximum labeled dose of rocuronium at three minutes following its administration when its neuromuscular blocking effects are at their peak. Lastly, in the current cycle, the Applicant has demonstrated that the use of sugammadex is associated with less residual paralysis, compared to neostigmine, when patients are in the Post Anesthesia Care Unit (PACU).

In the clinical trial assessing residual paralysis in the PACU (P07981), the Applicant evaluated a number of pertinent time intervals and assessments of neuromuscular function in an effort to demonstrate a clinical benefit of sugammadex beyond the reductions in reversal times. The results of the trial indicated that the use of sugammadex, on average, reduced the time to extubation of the trachea and the time to discharge from the operating room by 4 minutes each compared to neostigmine. The trial results indicated that, despite the residual paralysis that occurred in the PACU with

neostigmine treatment, there was no significant difference between the two reversal agents for:

- Time to discharge from the PACU
- Grip strength in either the dominant or non-dominant hand
- Pulmonary function test results

At this time, the risks associated with sugammadex have not been fully characterized. With the exception of anaphylaxis, the risks are generally no worse than those for neostigmine, and often less. The risks with the greatest potential for morbidity and mortality, i.e., bradycardia, hemodynamic changes, and anaphylaxis generally occurred shortly after the administration of sugammadex, while patients are in a clinical setting where they are continuously monitored for such events and the staff and facilities needed to treat them are readily available. Although the anaphylactic events were typically reported as mild to moderate in severity, the frequency with which they have been observed, up to 1% in two clinical trials, raises the concern over the possibility of increased risk with repeat exposure, which would likely occur in a large segment of the population. Therefore, to be able to complete the benefit-risk assessment, it is imperative that the issues surrounding the repeat-dose anaphylaxis study be resolved as discussed in Section 1.1.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At present there is no need for any postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant should be required to conduct studies to assess safety, efficacy, and appropriate dosing regimens for sugammadex in pediatric patients. The pediatric studies should include each of the three timepoints for administration of sugammadex labeled for the adult population, i.e., at the reappearance of T_2 , at 1-2 PTCs, and at three minutes after the rapid-sequence-induction dose (1.2 mg/kg) of rocuronium. The studies should also evaluate safety and efficacy and appropriate dosing regimens for vecuronium as well as rocuronium for the first two timepoints of administration, i.e., at the reappearance of T_2 and at 1-2 PTCs. The pediatric studies should not be started until the remaining safety issues for the adult population have been fully vetted by the Agency.

2 Introduction and Regulatory Background

2.1 Product Information

Sugammadex, Org 25969, is a modified γ -cyclodextran in which all eight primary alcohols have been substituted by thiopropionate groups, as shown in Figure 1 below. The drug product contains (b) (4) Org 48302, which is also a modified γ -cyclodextran, (b) (4) Org 48302 is (b) (4) (b) (4) It can comprise up to (4)% of the drug substance, and it has pharmacological activity and a pharmacokinetic profile that are similar to those of Org 25969. For the purposes of this review, sugammadex is used refer to the final drug product, i.e., both the Org 25969 and (b) (4) , Org 48302.

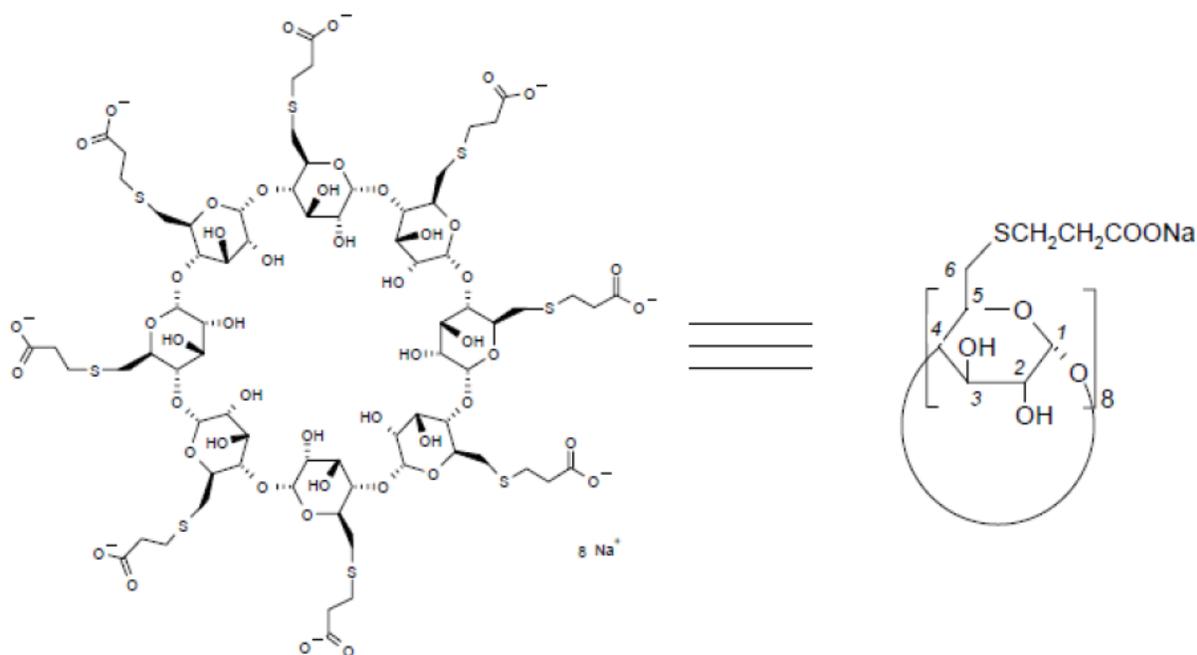


Figure 1. Structural formula of sugammadex (Figure 1, p.2 of Module 2.2 in original NDA)

2.2 Currently Available Treatments for Proposed Indications

Three anticholinesterase products, pyridostigmine (NDA 17-398), edrophonium (NDA 7-959), and neostigmine (NDA 204078) are approved as reversal agents for the neuromuscular blocking effects of all available nondepolarizing muscle relaxants. In the United States, neostigmine is the most commonly used reversal agent; it is preferred in clinical practice because of its more rapid onset of action and longer duration of action. An anticholinergic agent, e.g., atropine or glycopyrrolate, is frequently co-administered with the anticholinesterase to counter the cholinergic effects of these agents. One formulation of edrophonium, Enlon-Plus (NDA 19-678), is a combination product containing atropine as the anticholinergic.

2.3 Availability of Proposed Active Ingredient in the United States

Sugammadex is a new molecular entity not currently marketed in the United States. Sugammadex was approved in the European Union on July 25, 2008, for use in adults as well as children and adolescents 2 through 17 years of age. As of April, 2014, sugammadex has been approved for use in 48 countries. The Applicant reports the distribution of over [REDACTED]^{(b) (4)} vials for use in adult and pediatric patients through April, 2014. The Applicant has not reported any problems with obtaining a sufficient amount of the active ingredient to meet the current demand and has not indicated that a problem may exist with supplying the United States' market with product, if the NDA were to be approved at the end of this review cycle.

2.4 Important Safety Issues with Consideration to Related Drugs

Sugammadex is a new molecular entity and the first in its class as a new type of reversal agent for the neuromuscular blocking agents rocuronium and vecuronium. Therefore, there are no related drugs and no known safety issues to consider in this context.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On July 31, 2008, the Agency issued an NDA Not Approvable letter identifying two clinical deficiencies that needed to be addressed before the product could again be considered for approval:

1. The sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with

sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug. Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure. As widespread use of sugammadex sodium is expected, an individual patient may be exposed to the drug multiple times. This expected pattern of use is of concern because the risk of Type I hypersensitivity, including anaphylaxis, is likely to increase on repeat exposure.

2. The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program. The in vitro assessment indicated that sugammadex increased activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and the International Normalized Ratio (INR). In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol-specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined. The mechanism and the clinical significance of the effects of sugammadex on coagulation are not known.

In the NDA resubmission dated December 20, 2012, the Applicant addressed the two deficiencies identified in the Not Approvable letter. However, an audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) indicated that, for Study P06042, there were a number of protocol deviations and other findings that could impact the validity, reliability, and integrity of the data. Therefore, the deficiency related to anaphylaxis remained unresolved. A Complete Response letter was issued on September 20, 2013, with the following requirements to address the deficiency:

1. For Study P06042, identify all subjects with a major protocol violation, including those for whom treatment and adverse event evaluations could potentially be unblinded by the investigators and those whose data were potentially compromised because the site used an inadequate case report form that did not capture all adverse event data elements. Perform sensitivity analyses on the primary and key secondary endpoints with the data from the remaining subjects. Provide a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the findings, thereby allowing the study to address the deficiency cited above. Submit the source documents utilized to support the inclusion of the remaining subjects incorporated in the reanalyses.

OR

2. Repeat or conduct a trial similar to Study P06042 and submit the clinical study report to the Agency. If you choose to pursue this pathway, please discuss the trial protocol with the Agency prior to initiation.

A meeting was held with the Applicant on November 21, 2013, to provide input and try to come to an agreement on the Applicant's plan to address the deficiency, specifically, the key elements of the proposed trial, in addition to determining a proposed cut-off date for the Safety Update, and discussion of the Applicant's plans to present new clinical and post-marketing data in the Safety Update. The key points made at that meeting included:

1. The Applicant needed to include the 16 mg/kg dose group in the newly proposed study, in addition to the 4 mg/kg and placebo groups.
2. Due to the serious data integrity concerns, no qualitative or quantitative inferences could be made from Study P06042. Therefore, data regarding the 16 mg/kg dose needed to be generated in the new study for inclusion in the product label.
3. The protocol needed to ensure that administration (i.e., the method and duration of infusion) of the drug was standardized and consistent with the intended labeled use of the product.
4. The integrated clinical safety data set and its analyses needed to be updated and included in the Complete Response.
5. Data from all clinical studies completed at the time of the submission will need to be incorporated into the database and the analyses.
6. A 6-month cut-off date was acceptable, as was the submission of the new CIOMS forms.
7. All post-marketing reports, from product launch to the cut-off date, needed to be incorporated into a searchable database.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was organized and complete in terms of locating the clinical information necessary to complete this review. There were issues related to the safety databases that required multiple interactions with the Applicant before the issues were addressed and the safety analysis could begin. Specifically, the dosing dataset had to be revised to include only one row per subject, per dose administered and the route of administration of placebo treatments needed to be specified in the datasets. There was confusion regarding the number of unique subjects incorporated into the database; however, that issue was resolved once the dosing issues were addressed.

An inspection by the Office of Scientific Investigations (OSI) revealed a number of protocol violations at the Applicant's central site for gathering and analyzing the study data as well as at one of six sites responsible for performing the study to address the anaphylaxis related deficiency in the Complete Response letter. The Applicant met with the Agency to describe how unblinding by the statisticians at their central site did not impact the integrity of the data and to explain how some of the major protocol deviations occurred and provide a rationale for why they would not impact the findings of the study. Internal discussions at the Agency led to the conclusion that the likelihood of data being altered at the central site was very low, as was the likelihood that there any interaction between treatment-unblinded statisticians and clinical site investigators. However, in light of the protocol deviations that occurred with P06042 leading to concerns over data integrity and a Complete Response, and the importance of the anaphylaxis findings from P101 in assuring that the safety profile of sugammadex is adequately characterized prior to an approval action, it was determined that all of the clinical study sites needed to be inspected due the number and types of protocol deviations observed thus far. These inspections, as part of due diligence, will provide a better basis for determining whether the data integrity of P101 has been maintained and it is reasonable to rely on the study findings to address the remaining deficiency precluding approval.

3.2 Compliance with Good Clinical Practices

The Applicant has stated that all clinical trials, provided in this submission as well as the previous submissions, were conducted in compliance with Good Clinical Practices.

3.3 Financial Disclosures

In the original NDA submission, the Financial Certification and Disclosure document indicated that two investigators received significant payments:

1. [REDACTED] (b) (6) served on the adjudication committee, acted as a consultant, and received an institutional grant. He was an investigator in Study [REDACTED] (b) (6).
2. [REDACTED] (b) (6) received an educational grant and served as an investigator for Studies [REDACTED] (b) (6).

In the first resubmission, the Applicant made the following disclosures:

1. [REDACTED] (b) (6), disclosed that he received an unrestricted educational grant for 100,000.00 €. [REDACTED] (b) (6) received (part of) this grant, for his contribution as a Scientific Advisory Committee member for a study that is not the subject of this application.

The Applicant otherwise certified that, for those submissions, none of the clinical investigators, from whom information was obtainable, disclosed a proprietary interest in the product or a significant equity in the sponsor. The Applicant further certified none of the investigators was the recipient of significant payments of other sorts. Some of the financial disclosure information under Schering Plough's ownership of the product was listed as "not available" primarily for study P05768 (>30) and P055775 (>20), but some were also listed this way in studies P05769, P05773, and P06101. In each of these cases, disclosure information was listed as "available" under Merck's ownership.

Based on the blinded design of the key clinical studies, the limited number of disclosures reported, and the availability of all disclosures during Merck ownership of the NDA, the missing disclosures under Schering Plough's ownership is not expected to have a significant impact on the overall assessment of safety or efficacy.

In this resubmission, the Applicant indicated that there were no financial disclosures to be made.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The review team included Drs. Yong Hu, Luz Rivera, and Julia Pinto. They have not identified any issues that would preclude approval of sugammadex at this time.

4.2 Clinical Microbiology

A Clinical Microbiology review not required for this NDA.

4.3 Preclinical Pharmacology/Toxicology

The review team included Drs. Alex Xu, Jay Chang, and Dan Mellon. They have not identified any issues that would preclude approval of sugammadex at this time.

4.4 Clinical Pharmacology

The review team included Drs. Srikanth Nallani and Yun Xu. They have reviewed the final report for the single pharmacokinetic study in renally impaired subjects that was contained in the current submission and determined that the findings were similar to a previously reported study. They concluded there were no significant changes to be made to their recommendations for product labeling and that they had not identified any issues that would preclude approval of sugammadex at this time.

4.4.1 Mechanism of Action

Sugammadex works by forming inclusion complexes with various drug molecules. With its lipophilic core it attracts the lipophilic steroidal parts of the neuromuscular blocking agents (NMBAs) rocuronium and vecuronium. These two NMBAs are then retained in the core of the sugammadex molecule by the 8 side-chains connected to it, each with a

negatively charged group on its end that are attracted to the positively charged ammonium group on rocuronium and vecuronium.

While sugammadex is especially able to bind rocuronium and, to a lesser degree, vecuronium, (b) (4)

4.4.2 Pharmacodynamics

The pharmacodynamic effects of sugammadex were previously evaluated in Phase 2 and 3. The drug appears to have no other effect except binding rocuronium and vecuronium. As the NMBAs are bound to the sugammadex molecules, the amount of NMBA available to bind to receptors in the neuromuscular junction is reduced, resulting in the reversal of the blockade. The rate at which reversal of neuromuscular blockade occurs has been demonstrated to be dependent on the extent to which receptors at the neuromuscular junction bind the NMBA and the amount of sugammadex administered.

4.4.3 Pharmacokinetics

Key pharmacokinetic data for sugammadex in adults include:

1. The volume of distribution is 12-15 liters.
2. The terminal half-life is 1-4 hours.
3. The drug is not appreciably metabolized but is renally excreted unchanged.
4. The clearance rate of sugammadex is similar to the glomerular filtration rate in healthy humans.
5. PK parameters did not vary by gender, race (Caucasian versus Asian), or under general anesthesia.
6. Severe renal impairment increases exposure 8 fold and terminal half-life by up the 13-fold compared to normal controls.
7. Using high-flux dialysis filter, compared to low-flux filter, results in a more efficient clearance of sugammadex and the sugammadex-rocuronium complex from plasma.
8. The product is dose proportional within the planned dose range.
9. Pharmacokinetic modeling was used to predict the behavior of the drug in hepatically impaired patients
10. Sugammadex has no effect of 4 mg/kg of platelet aggregation effects of aspirin.
11. Sugammadex has no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 provides a list of all the studies completed up to the time of this resubmission. To the extent possible, the Applicant was to have incorporated the safety data from these studies into an updated safety database and reassess safety. The same was to have been done with the efficacy data generated by these studies.

Table 1. Clinical studies conducted to date not included in the original NDA submission

| Study Number | Type of |
|------------------|--|
| 19.4.110/P05854* | Skin prick and intradermal skin testing in volunteers not previously exposed to sugammadex; to investigate hypersensitivity |
| 19.4.112/P05860* | To assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by diflofenac or flucloxacillin 5 minutes after reversal of NMB by sugammadex |
| 19.4.113/P05861* | Assess the safety of re-use of rocuronium and vecuronium after reversal of NMB by sugammadex |
| 19.4.114/P05997* | Safety, PK in Chinese volunteers |
| 19.4.115/P05810* | Investigate the effect of sugammadex on hemostasis parameters |
| 19.4.116/P06315* | To evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers |
| 19.4.117/P06042* | Evaluate the incidence of hypersensitivity for each dose of sugammadex and placebo |
| 19.4.313/P05698* | To compare the T4/T1 ratio measured by the TOF-Watch® with the reappearance of T4 measured by a peripheral nerve stimulator within a subject |
| 19.4.316/P05767* | To demonstrate faster recovery from profound NMB with Org 25696 compared to placebo |
| 19.4.318/P05699* | To compare recovery from NMB by sugammadex and neostigmine |
| 19.4.324/P05768* | To show the recovery time from NMB induced by rocuronium after reversal by sugammadex is faster than by neostigmine |
| 19.4.326/P06101* | To compare recovery from NMB between sugammadex and neostigmine in Korean subjects |
| 19.4.328/P05769* | To show equivalent efficacy of sugammadex in subjects with normal or severely impaired renal function |
| 19.4.333/P05773* | To evaluate the dialysability of the sugammadex-rocuronium complex in vivo in subjects with renal impairment |
| 19.4.335/P05775* | To show the recovery time from NMB induced by rocuronium after reversal at a target depth of blockade of 1-2 PTCs by sugammadex is within 10 minutes in 95% of Caucasian subjects; and to show equivalence in the time to recovery in Chinese and Caucasian subjects |
| P07025* | To investigate the potential of an interaction between sugammadex and aspirin on platelet aggregation |

| Study Number | Type of |
|---------------------------------------|---|
| P07044* | To evaluate the potential interaction effect between sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity |
| P07038* | To assess the effect of reversal of NMB with sugammadex compared with reversal according to usual care |
| INT00103441* (Heuman et al., 2009) | Assessment of possible effect of Org 25969 on the incidence of bleeding complications in patients; an analysis of adverse events |
| 19.4.319/P05700* | To evaluate changes in plasma potassium levels after treatment with rocuronium followed by sugammadex or succinylcholine |
| 19.4.334/P05774* | To compare the incidence of residual NMB at time of tracheal extubation with sugammadex and neostigmine |
| P105-02/P105 [#] | A second assessment of the pharmacokinetics of MK-8616 in subjects with moderate and severe renal insufficiency |
| P07982/P076 [#] | To compare the use of deep or standard NMB in combination with low (starting at 8 mm Hg) or standard (starting at 12 mm Hg) insufflation pressure in patients undergoing laparoscopic cholecystectomy |
| P07981/P064 [#] | To assess the incidence of residual paralysis in the PACU and its effects on grip strength and pulmonary function |
| P101 [#] | To evaluate the incidence of hypersensitivity after repeated intravenous single dose administration of sugammadex (MK-8616) in healthy subjects |

* Studies submitted with the second submission

Studies submitted with the third (current) submission

5.2 Review Strategy

The focus of this review was on the following issues:

1. Findings of the trial conducted to address the remaining clinical deficiency, i.e., determination of the risk of anaphylaxis with repeat administration of sugammadex
2. Postmarketing safety data particularly as they relate to anaphylaxis/hypersensitivity, cardiac arrhythmias, postoperative bleeding
3. New study data related to residual paralysis in patients in the PACU and its safety implications
4. Reanalysis of the updated safety database to determine whether any new safety signals exist in light of the data obtained from the studies completed since the last review.

5.3 Discussion of Individual Studies and Clinical Trials

The study conducted by the Applicant to address the deficiency in the Complete Response letter is discussed in Section 7.4.5 and described in detail in Section 9.4.2

and the consultation from the Division of Pulmonary, Allergy and Rheumatology Products, which is included in the appendices of this review.

The other three trials which were completed since the last resubmission are also described in Section 9.4 and discussed as appropriate in the sections below.

6 Review of Efficacy

Efficacy Summary

Based on the clinical trials reported in the original NDA submission, sugammadex was found to be effective for reversing rocuronium- and vecuronium-induced neuromuscular blockade when administered under two clinical conditions:

1. With the spontaneous return of the second twitch (T_2) of the abductor pollicis muscle, when a train-of-four (TOF) electrical stimulus is applied to the ulnar nerve.
2. With the presence of one to two post-tetanic contractions of the adductor pollicis longus muscle, when a TOF stimulus is applied following a tetanic electrical stimulus to the ulnar nerve.

Sugammadex was also found to be effective for reversing the neuromuscular blockade when it is given at three minutes following a rapid sequence induction (RSI) dose of rocuronium (1.2 mg/kg) rocuronium. This reversal occurs at the time when the maximal pharmacodynamic effect of rocuronium is expected.

For the first two clinical scenarios above, sugammadex provided a more rapid return of the ratio of the intensity of the fourth twitch (T_4) in a TOF stimulus to that of the first twitch (T_1) to 90% ($T_4/T_1 = 0.9$) compared to placebo or neostigmine, the anticholinesterase agent most commonly used in clinical practice for the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

For the third clinical scenario, sugammadex was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied in this scenario was the return of T_1 in a TOF stimulus to 10% of its baseline value. Sugammadex reversed the neuromuscular blockade induced by rocuronium in less time than it took for the effects of succinylcholine to spontaneously resolve to the same point, 4.3 minutes versus 7.2 minutes on average, respectively. However, the clinical relevance of this level of recovery was not demonstrated in the clinical study and not otherwise provided by the Applicant.

The Applicant also evaluated the time to $T_4/T_1 = 0.9$ for the rocuronium/sugammadex treatment group as a secondary endpoint and the time for T_1 to return to 90% of its baseline level following treatment with succinylcholine. These recovery points are likely to be more clinically relevant. For these endpoints, sugammadex induced recovery took an average of 5.4 minutes compared to the spontaneous succinylcholine recover which took an average of 10.9 minutes.

The Applicant indicated in the original NDA submission that the ability to reverse the highest labeled dose of rocuronium at the time of its maximum effect has the potential to

reduce the morbidity and mortality that are associated with the inability to intubate or ventilate a paralyzed patient. However, they provided no evidence that such a claim is valid, and in the current submission, they have changed this use of sugammadex from “[i]f there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg BRIDION™ is recommended” to “16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.” The revised use implies that the high dose of sugammadex (b) (4) when the need is urgent; (b) (4)

The revised labeling (b) (4)

Therefore, the label needs to be revised to reflect the conditions under which the three doses of sugammadex were found to be effective and (b) (4)

In the first resubmission, there was one new study that warrants special note especially as it relates to a study in the current submission. Study P05774 evaluated the T_4/T_1 values for subjects, at the time of extubation, after sugammadex was administered per proposed labeling at 1-2 PTCs and after neostigmine was administered per standard of care. Twitch monitoring was not used following administration of study drug to assess the level of recovery from neuromuscular blockade as part of overall evaluation of a patient’s readiness to be extubated. The study showed that more subjects were extubated with $T_4/T_1 < 0.9$ when treated with neostigmine than with sugammadex. (b) (4)

The current submission contains the final study report for clinical trial P07981 in which the Applicant evaluated the extent of residual paralysis that occurred in the Post-Anesthesia Care Unit (PACU) following treatment with either sugammadex or neostigmine. The results indicated that there was no residual paralysis, measured as $T_4/T_1 \geq 0.9$, with sugammadex treatment; however, more than 50% of subjects had residual paralysis with neostigmine treatment. The trial also evaluated various time intervals relative to study drug administration, e.g., time to extubation, time to discharge from the operating room, and time to discharge from PACU, grip strength and pulmonary function testing were also performed on admission to PACU and when subjects were more awake. Despite the differences in residual paralysis, the only significant differences for the other endpoints were a 4 minute earlier time to extubation

and discharge from the operating room for sugammadex-treated subjects. There was no difference for any other time interval assessed and no difference for either grip strength or any pulmonary function tests that were performed either on entry to the PACU or when the subjects were more fully awake. The trial and its findings are described in detail in Section 9.4. (b) (4)

[REDACTED]

In summary, the efficacy studies conducted over the entire development program support the finding that sugammadex is superior to neostigmine for reversing rocuronium and vecuronium when administered as proposed. The additional studies of the 16 mg/kg dose of sugammadex demonstrated that it is effective at reversing doses of rocuronium up to 1.2 mg/kg after 3 minutes. The studies showed that there was less residual paralysis following sugammadex treatment than neostigmine treatment; however, the residual paralysis was not associated with any differences in grip strengths, pulmonary function tests, or discharge from the PACU. The studies did not show the need for dose adjustments of sugammadex based on age, gender, race, renal impairment, or hepatic impairment.

[N.B.: In the sections that follow, the tables, interpretations of the data, and comments contained therein are those of this reviewer unless they are specifically attributed to the Applicant or other entity.]

6.1 Indication

The Applicant currently proposes the following indication for sugammadex: [TRADENAME] is a selective relaxant binding agent indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

The following information in the Dosing and Administration section further modified the indication:

- Should be administered by trained healthcare providers.
- Administered as a single bolus injection.
- 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.

- 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T₂ (moderate blockade) following rocuronium- or vecuronium-induced blockade.
- 16 mg/kg is only recommended if there is an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium.

6.1.1 Methods

In the original NDA submission, the Applicant submitted data from 23 clinical trials evaluating the efficacy of sugammadex four of which they considered to be pivotal. These were reviewed by Dr. Robert Shibuya in the first review cycle and are summarized here.

Three of the pivotal trials were similar in design and evaluated the efficacy of sugammadex when used for, what the Applicant termed, “routine reversal.” These included Studies 19.4.301 (Study 301), 19.4.302 (Study 302), and 19.4.310 (Study 310) each of which is described briefly below.

Study 301

In this study, subjects included healthy adults without renal disease [American Society of Anesthesiologists – Physical Status (ASA-PS) 1-3] who were scheduled for surgery requiring general anesthesia in the supine position. Following screening, patients were randomized 1:1:1:1 to one of the treatment groups in Table 2.

Table 2. Study 301 treatment groups

| GroupNumber | Neuromuscular Blocking Agent (NMBA) | Reversal Agent |
|-------------|-------------------------------------|----------------|
| 1 | Rocuronium | sugammadex |
| 2 | Rocuronium | neostigmine |
| 3 | Vecuronium | sugammadex |
| 4 | Vecuronium | neostigmine |

General anesthesia was induced with a standardized intravenous sequence followed by paralysis with the specified NMBA. Anesthesia was maintained with sevoflurane and parenteral agents, and the level of neuromuscular blockade was monitored with a Train-Of-Four (TOF) nerve stimulator. At the return of the second twitch response to a train-of-four stimulation, T₂, the reversal agent was administered. This level of blockade was referred to as “shallow” blockade by the Applicant. The dose of sugammadex was 2 mg/kg; the dose of neostigmine was 50 mcg/kg.

The primary endpoint was the elapsed time between the start of administration of the reversal agent and the recovery of the T_4/T_1 ratio to 0.9, as measured by acceleromyography. Other clinical measures of recovery included a 5-second head lift and an assessment of general weakness. Safety was assessed from the induction of anesthesia through recovery by a safety assessor who was blinded to the treatment used.

Study 302

This study was similar in design to Study 301 but differed in two key aspects:

1. The reversal agent was administered when 1-2 twitches were detected following a tetanic stimulation, i.e., at 1-2 Post-Tetanic-Counts (PTCs). This level of blockade was referred to by the Applicant as “profound” blockade.
2. The dose of sugammadex was 4 mg/kg and the dose of neostigmine was 70 mcg/kg.

Study 310

This study differed from Study 301 and 302 in that there were two treatment groups:

1. Rocuronium reversed with sugammadex
2. Cisatracurium reversed with neostigmine

This study was not properly designed to evaluate efficacy because there was no constant between treatment arms to allow a comparison, i.e., there were different NMBAs and different reversal agents. The study was, therefore, considered to be supportive rather than pivotal.

Study 303

This study was designed to assess the efficacy of sugammadex when used for “immediate reversal” of rocuronium. The Applicant considered this use of sugammadex as having the potential to reduce morbidity and mortality in the clinical situation where an unconscious, paralyzed patient can neither be ventilated nor intubated and a rapid return to spontaneous ventilation desirable. Currently, in anesthesia practice, the shortest acting NMBA is succinylcholine, a depolarizing NMBA whose effect diminishes as the drug diffuses away from the neuromuscular junction and is broken down by plasma cholinesterase; at present, it cannot be reversed pharmacologically. The Applicant chose to compare the reversal of rocuronium, which has an onset of action similar to succinylcholine when a 1.2 mg/kg dose is administered, with sugammadex to the spontaneous recovery from succinylcholine to evaluate the possibility of a more rapid return to normal neuromuscular function. Thus, Study 303 differed substantially from Studies 301, 302, and 310. The following were the key differences:

1. Patient population
 - a. Subjects were healthier, i.e., only ASA-PS 1 and 2 patients were enrolled.

- b. Subjects had to be undergoing surgical procedures for which a short period of neuromuscular blockade was appropriate.
 2. Treatment arms
 - a. Rocuronium (1.2 mg/kg dose) followed by sugammadex (16 mg/kg dose) after three minutes had elapsed (the time point of maximal blockade)
 - b. Succinylcholine (1 mg/kg)
 3. Primary endpoint

Since patients treated with succinylcholine do not demonstrate fade on TOF stimulation, and therefore, T_4/T_1 does not vary with recovery, the primary efficacy endpoint was the elapsed time from the injection of NBMA to recovery of T_1 to 10% of the baseline value.

In the first NDA resubmission, the Applicant included the study reports for 10 additional efficacy trials, none of which they classified as pivotal. These studies are listed below with a brief description of their efficacy assessments. Only the first four of the studies were randomized, controlled, had a single method for administering the study drugs, and had a primary endpoint that assessed the efficacy of sugammadex as a reversal agent for neuromuscular blockade (versus assessed the level of neuromuscular blockade at the time of extubation). The other studies provided efficacy data for patients with renal impairment and for assessing recovery using accelerometry versus manual evaluation of TOF twitch responses.

1. Phase 3 Studies with sugammadex administered at the reappearance of T_2
 - a. P05768 (19.4.324): This was a randomized, active, parallel-group, multisite, safety-assessor-blinded trial of sugammadex of 291 adult, ASA-PS 1-3, Chinese and Caucasian subjects undergoing elective surgery under propofol anesthesia. It compared the recovery from rocuronium using either sugammadex (2 mg/kg) or neostigmine (50 mcg/kg) administered at the reappearance of T_2 . Neuromuscular functioning was monitored using a TOF-Watch® SX at the adductor pollicis. The primary efficacy endpoint was the time from study drug administration to recovery of the T_4/T_1 ratio to 0.9.
 - b. P06101 (19.4.326): This was a randomized, active-controlled, parallel-group, multi-site, safety-assessor-blinded study of 128 adult, ASA-PS 1-3, Korean subjects undergoing elective surgical procedures under general anesthesia requiring the administration of rocuronium and requiring reversal of neuromuscular blockade. Subjects were randomly assigned to sugammadex (2 mg/kg) or neostigmine (50 mcg/kg) administered at the reappearance of T_2 . Neuromuscular functioning was monitored using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was the time to recovery of the T_4/T_1 ratio to 0.9.
2. Phase 3 studies with sugammadex administered at 1-2 PTCs

- a. P05767 (19.4.316): This was a multi-center, randomized, parallel-group, comparative, placebo-controlled, safety-assessor blinded trial of 4.0 mg/kg sugammadex in 140, adult, ASA-PS 1-3 subjects undergoing profound neuromuscular blockade. Sugammadex or placebo was administered as a single bolus dose at the end of surgery when 1-2 PTCs were detected. Neuromuscular functioning was monitored with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was time to return of the T_4/T_1 ratio to 0.9.
 - b. P05699 (19.4.318): This was a multi-center, randomized, parallel-group, active-controlled, safety-assessor blinded trial of 133 adult ASA-PS 1-3 subjects scheduled to undergo a laparoscopic cholecystectomy or appendectomy under general anesthesia requiring neuromuscular relaxation with rocuronium. Subjects were randomized to either sugammadex (4 mg/kg) or neostigmine (50 mcg/kg) administered as a single bolus dose at the end of surgery when 1-2 PTCs were detected. Neuromuscular functioning was monitored with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. The primary efficacy endpoint for the study was the time from administration of study drug to the recovery of the T_4/T_1 ratio to 0.9.
 - c. P05774 (19.4.334): This was a multi-center, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded, anesthesiologist-TOF-Watch® SX-blinded trial of 100 adult, ASA-PS 1-3 subjects scheduled to undergo an elective, open-abdominal, surgical procedure expected to last \leq 4 hours under general anesthesia requiring reversal of neuromuscular blockade. Neuromuscular functioning was monitored continuously with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. Study drugs included sugammadex (4 mg/kg) administered when 1-2 PTCs, or better, were detected and neostigmine (50 mcg/kg), which was administered “per standard of care” knowing whether spontaneous recover had already reached 1-2 PTCs or better. The primary efficacy endpoint was the T_4/T_1 ratio at the time of tracheal extubation.
3. Special populations
- a. P05769 (19.4.328): This was an open-label, multicenter, parallel-group, comparative study in 68 adult, ASA-PS 1-3 subjects with normal and severely impaired renal function scheduled for a surgical procedure in the supine position under general anesthesia with propofol requiring neuromuscular relaxation with the use of rocuronium. Subjects received a single bolus dose of 4.0 mg/kg of sugammadex at a target depth of neuromuscular blockade of 1-2 PTCs. Neuromuscular monitoring was performed using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9.

- b. P05773 (19.4.333): This was a single center, exploratory, open label trial. It was designed to evaluate the dialysability of the sugammadex-rocuronium complex in vivo in 6 ASA-PS 1-4 subjects with severe renal impairment (creatinine clearance < 30 mL/min and a clinical indication for dialysis) who were hospitalized in an ICU scheduled for a surgical procedure in the supine position under general anesthesia requiring neuromuscular relaxation with the use of rocuronium. Subjects received a single 4 mg/kg dose of sugammadex at 15 minutes after administration of rocuronium after which, the dialysability of the sugammadex-rocuronium complex was evaluated for dialysis using the Fresenius 4008H hemodialyzer, with a hemodiafilter standard helixone membrane FX 600. Neuromuscular monitoring was performed using a TOF-Watch® SX at the adductor pollicis muscle. The primary efficacy endpoints for the trial were the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9, 0.8, and 0.7.
4. Other
- a. P05698 (19.4.313): This was a multi-center, randomized, peripheral nerve stimulator (PNS)-assessor-blinded, parallel-group, active, within-subject controlled trial of 91 adult, ASA-PS 1-3 subjects scheduled for a surgical procedure in the supine position under general anesthesia requiring neuromuscular relaxation with the use of rocuronium. Subjects were randomly allocated in a 1:2 ratio to receive either a single dose of 1.0 or 4.0 mg/kg sugammadex, respectively, and in a 1:1 ratio to having the TOF-Watch® SX affixed to either the dominant or the non-dominant forearm. The study drug was administered at 15 minutes after the last dose of rocuronium. The primary endpoints were the time from start administration of 4.0 mg/kg of sugammadex to recovery of the T_4/T_1 ratio to 0.9 for TOF-Watch® SX monitoring and the time from start administration of 4.0 mg/kg of sugammadex to reappearance of T4 as detected manually with PNS monitoring.
- b. P05700 (19.4.319): This was a multicenter, randomized, safety-assessor blinded, parallel group, active-controlled, comparative trial in 161 adult, ASA-PS 1-3 subjects scheduled for short (≤ 1.5 hours) surgical procedures in out-patient surgicenters. Subjects were randomly assigned to receive either rocuronium followed by a 4 mg/kg bolus dose of sugammadex for reversal at a target depth of blockade of 1-2 PTCs, or a 1 mg/kg bolus dose of succinylcholine followed by spontaneous recovery. Neuromuscular functioning was monitored using a TOF-Watch® SX device at the adductor pollicis muscle. The primary efficacy endpoint was the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9. The time from start of administration of succinylcholine to T_1 reaching 90% of baseline was a secondary endpoint.

- c. P05775 (19.4.335): This was an open-label, single-dose, multi-site trial to evaluate the time to recovery following administration of 4.0 mg/kg sugammadex at a target depth of 1-2 PTCs following rocuronium-induced neuromuscular blockade in 115 Chinese Asians living in China and 36 European Caucasians living in Europe. The subjects were ASA-PS 1-3 adults undergoing elective surgery under general anesthesia with rocuronium. Neuromuscular functioning was monitored using a TOFWatch® SX at the adductor pollicis muscle. After the last dose of rocuronium, at a target depth of blockade of 1-2 PTCs, a single 4.0 mg/kg dose of sugammadex was administered. The primary efficacy endpoint is the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9.

In the current submission, there were two additional studies that involved assessments of efficacy:

1. Study P07981: This study evaluated the use of sugammadex compared with neostigmine for reversal of neuromuscular blockade induced by rocuronium on incidence of residual blockade at PACU entry. The study also evaluated a number of time intervals, relative to the administration of study drug, as well as grip strength and pulmonary function test result in the two treatment groups. The primary endpoint was the percentage of subjects who had a T_4/T_1 ratio of 0.9 on admission to the PACU.
2. Study P076/P07982: This was a randomized, controlled, parallel group, blinded (subject, surgeon, and safety-assessors blinded to treatment) multi-site pilot trial to compare the use of deep or standard neuromuscular blockade (NMB) in combination with low (starting at 8 mm Hg) or standard (starting at 12 mm Hg) insufflation pressure using a 2x2 factorial design in subjects of both sexes undergoing laparoscopic cholecystectomy. The primary objective was to assess the benefit of deep neuromuscular blockade in surgical conditions compared to standard levels of neuromuscular blockade. The key secondary trial objective was to assess whether the use of low insufflation pressure improves the overall patient's pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as compared to standard insufflation pressure, based on a standard pain scale following a laparoscopic cholecystectomy.

Both of these new studies are described in greater detail in Section 9.4 below

6.1.2 Demographics

Table 3 provides summary demographic information for the original efficacy population. The Applicant was not required to, and therefore, has not provided an updated efficacy

database that would permit an update of original one. As the original submission included studies that were adequate to demonstrate the efficacy of sugammadex and there is no reason, based on its mechanism of action, to suspect that sugammadex would have a different efficacy profile based on demographic parameters, there was no need to update this table.

Table 3. Demographics for subjects in the original submission integrated summary of efficacy database

| Parameter | Placebo | Sugammadex (mg/kg) | | | | | | | | | | | Neostigmine (mcg/kg) | | Succinylcholine (Spontaneous Recovery)) |
|------------|---------|--------------------|-----|-----|----|------|-----|-----|----|----|-----|-----|----------------------|----|---|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 50 | 70 | |
| N | 479 | 132 | 184 | 824 | 12 | 1723 | 29 | 122 | 39 | 93 | 2 | 1 | 801 | 42 | 134 |
| Gender (%) | | | | | | | | | | | | | | | |
| F | 48 | 48 | 42 | 51 | 25 | 55 | 10 | 41 | 38 | 61 | 100 | 0 | 60 | 60 | 63 |
| M | 52 | 52 | 58 | 49 | 75 | 45 | 90 | 59 | 62 | 39 | 0 | 100 | 40 | 40 | 37 |
| | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Race (%) | | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 5 | 30 | 21 | 27 | 8 | 10 | 0 | 16 | 0 | 4 | 0 | 0 | 22 | 12 | 3 |
| Black | 0 | 0 | 0 | 4 | 0 | 3 | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 2 | 10 |
| Caucasian | 9 | 70 | 79 | 68 | 92 | 86 | 100 | 84 | 95 | 83 | 100 | 100 | 77 | 86 | 84 |
| Other | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 3 |
| | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ASA-PS (%) | | 0 | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 20 | 59 | 59 | 43 | 58 | 26 | 72 | 53 | 49 | 42 | 50 | 100 | 34 | 12 | 32 |
| 2 | 62 | 39 | 36 | 41 | 42 | 59 | 24 | 43 | 38 | 53 | 50 | 0 | 55 | 69 | 62 |
| 3 | 18 | 2 | 4 | 16 | 0 | 15 | 3 | 3 | 13 | 5 | 0 | 0 | 11 | 19 | 6 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Age (%) | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ≤ 65 y | 61 | 92 | 97 | 77 | 83 | 70 | 83 | 95 | 85 | 91 | 50 | 100 | 72 | 76 | 94 |
| > 65 y | 39 | 58 | 3 | 23 | 17 | 30 | 17 | 5 | 15 | 9 | 50 | 0 | 28 | 24 | 6 |

6.1.3 Subject Disposition

With a single administration of study drug in a confined setting such as the operating room, it would be expected that most subjects treated would complete the study. This was the situation that occurred with the sugammadex trials related to the proposed methods of dosing and administration as shown in Table 4. For each method of administering sugammadex, more than 90% of subjects randomized received the study drug, and 99% of treated subjects completed the study.

Table 4. Subject disposition for efficacy studies of the proposed indication. (Based on data from Table 2-2.1 on p. 323, Table 2-2.1 on p. 335, and Table 2-3.1 on p. 346 of Section 2.5 in the second NDA resubmission)

| Timing of Treatment | Randomized n | Treated ^A n (%) | Completed ^B n (%) | ITT ^C N (%) |
|--------------------------------|-----------------|-------------------------------|---------------------------------|---------------------------|
| Reappearance of T ₂ | 1577 | 1494 (95) | 1479 (99) | 1471 (93) |
| 1-2 PTCs | 953 | 885 (93) | 873 (99) | 845 (89) |
| 3 min. after rocuronium | 233 | 228 (98) | 226 (99) | 227 (97) |

^A Percent of randomized subjects who received study drug

^B Percent of treated subjects who completed the trial

^C Percent of randomized subjects

The same was found to be true in the studies submitted in the second and the current cycles.

6.1.4 Analysis of Primary Endpoint(s)

In general, the goal in reversing a neuromuscular blocking agent (NMBA) is to expedite and assure the return of neuromuscular function to the extent that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. In the clinical practice of anesthesia, a number of assessments may be made to evaluate a patient's ability to carry out both of these functions. These assessments include:

- Mechanical responses of muscles to electrical stimulation of the motor nerves supplying them
- Grip strength, which requires a level of consciousness that permits the patient to follow commands
- Sustained head lift, for 5 or more seconds, which requires a level of consciousness that either allows the patient to follow commands or is associated with a return of the gag reflex
- Spontaneous ventilation parameters, such as
 - a. Negative inspiratory force > -20 cm H₂O

- b. Tidal volume > 5 mL/kg
- c. Vital capacity > 10 mL/kg
- d. Respiratory rate < 30 breaths/min
- e. Appropriate oxygen saturation and end-tidal CO₂ levels

Often, the decision whether a patient is adequately recovered from the NMBA is based on a combination of these assessments; however, the standard of care includes the use of a peripheral nerve stimulator (PNS) to apply electric stimuli to an accessible peripheral nerve and permit an assessment of motor response.

The peripheral nerve stimulator has been used in clinical research as part of the development program for NMBAs, specifically, to characterize their pharmacodynamics and to support the efficacy findings and dosing requirements. In addition, and more apropos to this NDA, the device has been used to generate pharmacodynamic and dosing and administration data for Enlon (edrophonium), Enlon-Plus (edrophonium and atropine), and Neoversa (neostigmine) which are approved for the same indication sought for sugammadex, i.e. reversal of NMBAs. In this regard, the technology is used to determine whether use of a reversal agent is appropriate, the dose of the agent and extent of recovery of neuromuscular function following administration of the reversal agent. This method of monitoring the level of neuromuscular blockade most often involves evaluating the responses of the abductor pollicis longus to varying types of electrical stimulation applied to the ulnar nerve. It should be noted that there is no evidence-based support that distinguishes a particular type of electrical stimulus as the most predictive of full recovery of neuromuscular function or that identifies a specific response to electrical stimulation as indicative that normal function has been fully restored. The types of electrical stimulation patterns used by the Applicant are those typically used in clinical practice and clinical research:

1. Train-of-Four (TOF) ratio – Four electrical impulses of equal amplitude and duration (between 0.1 and 0.5 msec) are applied at 2 Hz (i.e., 0.5 sec intervals); the ratio of the twitch response to the fourth impulse (T₄) to that of the first impulse (T₁) defines the TOF ratio. Prior to administration of an NMBA, all four twitch responses are (ideally) identical and the TOF ratio is 1.0. With increasing nondepolarizing blockade, the ratio decreases (fades) and the TOF ratio is < 1.0; with recovery, the TOF ratio increases until it returns to 1.0.
2. Post-tetanic stimulation – A tetanic stimulation at 50 Hz for five seconds is applied followed 3 sec later by single twitch stimulation at 1 Hz. The number of evoked post tetanic twitches detected is called the post tetanic count (PTC). This method is useful when there is no response to single twitch, TOF or tetanic stimulations. A PTC of ≥ 8 generally indicates the imminent return of TOF responses.

While the method of stimulating nerves to elicit a response has been well established in anesthesia practice, the methods for assessing the responses have not and range from manual evaluation of twitch strength to mechanomyography, which measures the force

of contraction, and acceleromyography, which measures the acceleration of muscle contraction that in turn is proportional to the force. Early in the clinical development program, the Applicant argued that mechanomyography, the gold standard to quantitate the strength of contraction of the adductor pollicis, was not feasible because the equipment is no longer manufactured and the technique is too complex. They instead proposed the use of an acceleromyograph. The Division concurred with the proposal.

For Studies 301, 302, and 310, the applicant selected the return of the T_4 to T_1 ratio (T_4/T_1) to 0.9 as the primary endpoint. There is a substantial body of evidence in the literature that supports $T_4/T_1 = 0.9$ as an indication that sufficient neuromuscular function has returned for the patient to maintain a patent airway ventilate adequately without assistance. While this is the current standard, data in the literature up until the mid-1970s suggested that a $T_4/T_1 = 0.7$ was associated with clinically acceptable values for vital capacity, inspiratory force, and peak expiratory flow rates making this value often used as the standard cut-off point for adequate reversal of an NMBA. It should also be noted that other factors play a role in adequate ventilation in the immediate postoperative period, e.g., diminished respiratory drive due to sedatives and narcotics and muscle weakness related to inhaled anesthetics, which cannot be monitored with PNS.

For Study 303, the “immediate” reversal study, the Applicant selected an endpoint of $T_1 = 0.1$ of baseline. The justification for not using the more established T_4/T_1 ratio was that the comparator was succinylcholine, which is a depolarizing NMBA, and therefore, does not produce fade in twitch responses to the TOF stimulus. The Applicant did not provide any references to support the clinical significance of the cutoff, i.e., 0.1, for this endpoint, but clearly states that for recovery from rocuronium to $T_1 = 0.1$ will not be sufficient for a patient to either maintain a patent airway or adequately ventilate without assistance. Therefore, while the return of some strength is considered evidence of reversal of blockade or offset of action, for both succinylcholine and rocuronium, the clinical significance of this particular endpoint is subject to debate.

In this section, the efficacy studies will be considered based on their design, and therefore, the portion of the indication they support. For the pivotal studies, 301 and 302, the results are summarized in Table 5. The recovery from neuromuscular blockade induced with either rocuronium or vecuronium was markedly reduced with sugammadex compared to neostigmine. The differences were not only statistically significant, but likely to be clinically relevant as well. The reductions in recovery time, from 15 to 60 minutes, have important safety implications for patients in that it can reduce their exposure to and the risks from anesthetic agents and mechanical ventilation. The substantial reductions in recovery times also indicate that it is possible to maintain the paralysis to the end of the surgical procedure, thereby minimizing the risk of a surgical complication secondary to patient movement, without delaying recovery from the anesthetic and tracheal extubation, or alternatively, without beginning the recovery from the anesthetic and NMBA while the surgical procedure is still in

progress in order to minimize the time to tracheal extubation once the procedure has ended. These potential benefits would need to be demonstrated in clinical outcome studies for the purposes of making a claim; however, the incidence of adverse events related to intraoperative patient movement, exposures to anesthetic agents for periods up to an hour, and mechanical ventilation for an hour are low and would make a clinical study difficult due to the number of subjects needed.

Table 5. Summary of results from Studies 301 and 302

| Study # | Sugammadex/ Neostigmine Dose | Timing of Administration | N | Geometric Mean Time to $T_4/T_1 = 0.9$ (mm:ss) | | p-value |
|---------|------------------------------------|-----------------------------|----|--|-------------|---------|
| | | | | Sugammadex | Neostigmine | |
| 301 | 2 mg/kg 50 mcg/kg | Reappearance of T_2 | 96 | 01:29 (R) | 18:30 | <0.0001 |
| | | | 93 | 02:48 (V) | 16:48 | |
| 302 | 4 mg/kg 70 mcg/kg | 1-2 PTCs | 74 | 02:52 (R) | 50:22 | <0.0001 |
| | | | 83 | 04:28 (V) | 66:12 | |

R = rocuronium
 V = vecuronium

Although sugammadex has been clearly demonstrated to be superior to neostigmine for reversing rocuronium and vecuronium at the two time points of spontaneous recovery used in studies 301 and 302, there are two issues that need to be considered when weighing the product's benefits. First, some patients required substantially longer, than the mean value, to recover. For sugammadex, these outliers recovered sooner than the outliers associated with neostigmine treatment. This occurred for reversal administered at the reappearance of T_2 and at 1-2 PTCs. The Kaplan-Meier curves in Figure 2 and Figure 3 demonstrate this issue. The figures below were taken from the NDA submission and combine the efficacy data from all the trials (not Studies 301 and 302 alone) where study drug was administered at these time points in recovery. This finding indicates that not all patients are going to respond similarly to sugammadex, just as they do not respond similarly to neostigmine, and therefore, it is imperative that patients be monitored until full reversal is assured. This segues to the second issue that needs to be considered. The T_4/T_1 ratio is only an indicator of recovery from neuromuscular blockade, it does not indicate that a patient is able to maintain a patent airway or ventilate adequately without assistance. Therefore, it is important that clinicians take appropriate precautions in assessing patients prior to and after discontinuation of mechanical ventilation and tracheal extubation, as they have done in the past. The two figures also indicate that the data from the studies submitted in the second submission support the initial findings in the pivotal studies, 301 and 302, in that the Kaplan-Meier curves from those studies, not shown here but contained in Dr. Shibuya's review, are almost superimposable on the updated curves.

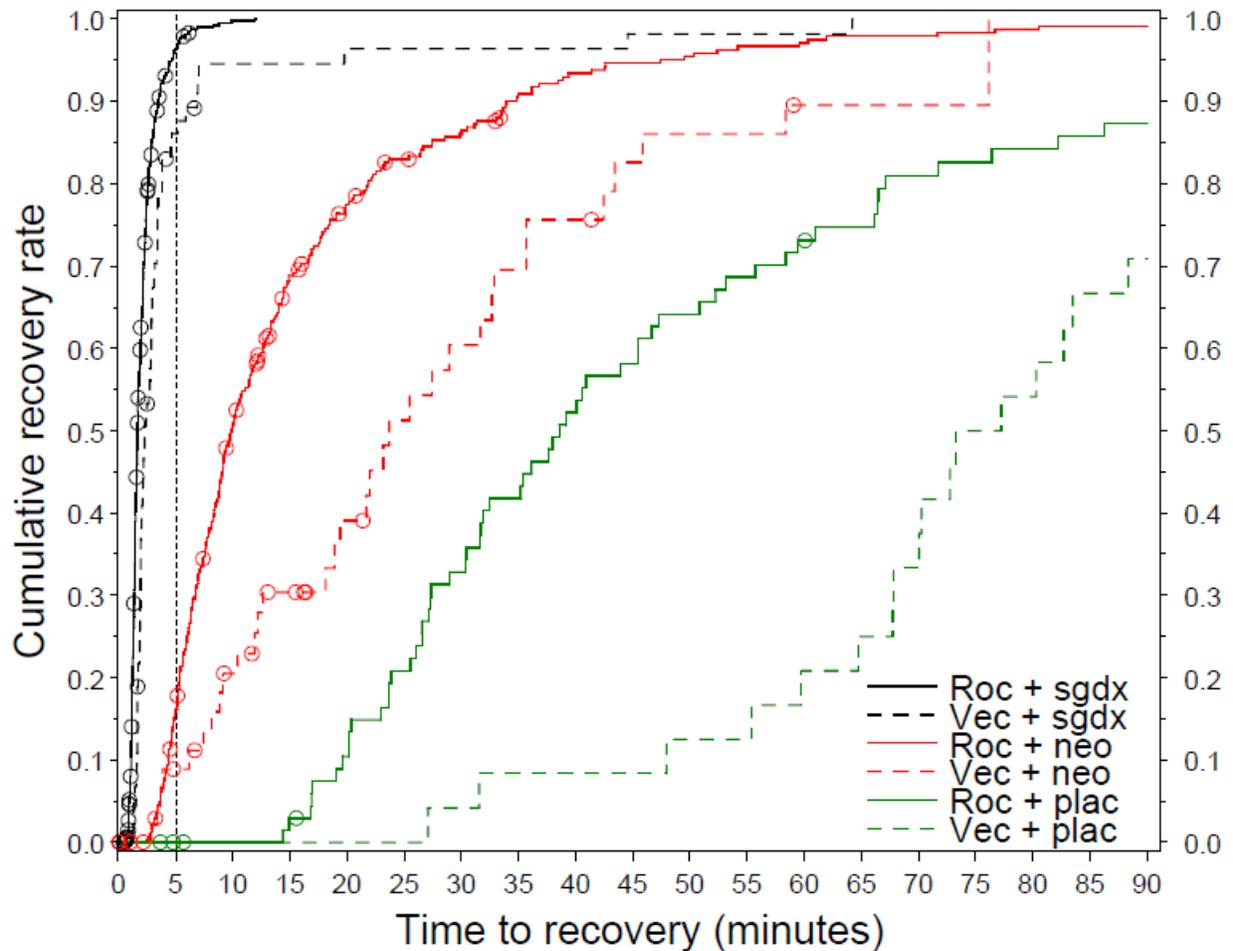


Figure 2. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at the reappearance of T_2 by treatment group and NMBA (Figure 5 on p. 44 of Section 2.5 of the second NDA resubmission)

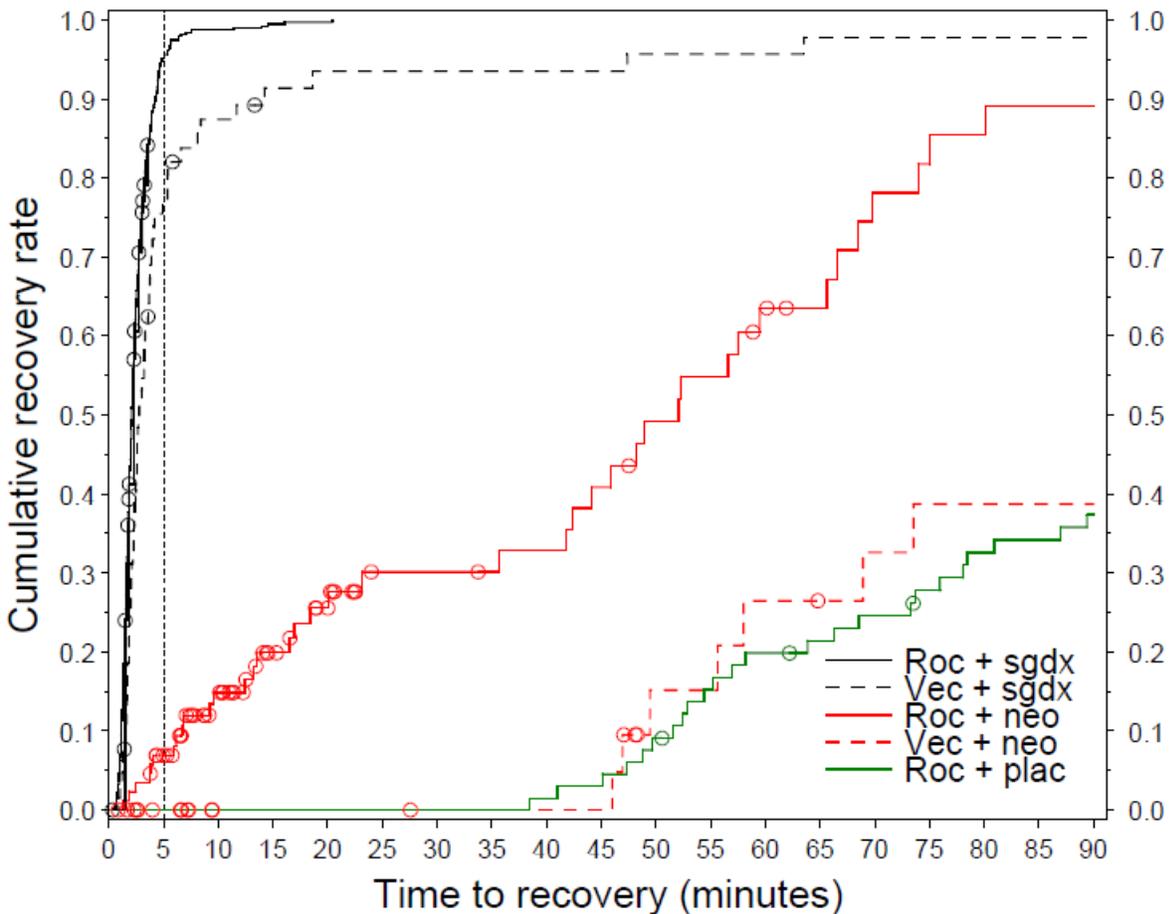


Figure 3. Kaplan-Meier curves for recovery times to T4/T1 = 0.9 with reversal administered at 1-2 PTCs by treatment group and NMBA (Figure 8 on p. 48 of Section 2.5 of the second NDA resubmission)

The results for the primary endpoint in Study 303 are summarized in Table 6. In this study, recovery with sugammadex was significantly faster than spontaneous recovery from succinylcholine – at least to the point where $T_1 = 0.1$. The Applicant has not provided any evidence that sugammadex would provide a faster recovery to the point that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. Nonetheless, the level of recovery observed with sugammadex at this timepoint is remarkable for three reasons:

1. This is the same point following rocuronium administration that the NMBA would be expected to have its maximal effect.
2. The maximum recommended dose of rocuronium was used, and sugammadex reliably reversed its effect.
3. None of the approved reversal agents would likely have any efficacy when administered at this time point. Although none were used as comparators, the

extent of recovery with neostigmine in Studies 301 and 302, and the superiority of sugammadex in those studies, strongly suggest the sugammadex would be superior when administered in this setting as well.

Table 6. Summary of the results from Study 303

| Statistical Parameter | Recovery Time for T ₁ = 0.1 [complete cases only] (mm:ss) | |
|-----------------------|--|---------------------------|
| | Rocuronium + Sugammadex (N=54) | Succinylcholine (N=53) |
| Mean (SD) | 4:21 (0:43) | 7:09 (1:33) |
| Median | 4:11 | 7:11 |
| Min. – Max. | 3:28 – 7:43 | 3:45 – 10:28 |

The precautionary comments made above regarding the use of sugammadex for reversal at reoccurrence of T₂ and at 1-2 PTCs apply in this setting as well. The Applicant had suggested, with the original NDA submission, (b) (4)

The Applicant has not conducted any new studies of the reversal of rocuronium at 3 minutes following its administration. Now however, they propose labeling that states: (b) (4)

This wording does away with the previous concerns that the product may be marketed for use with high-dose rocuronium as a substitute for succinylcholine during rapid sequence inductions. It also eliminates concerns regarding the use of the words “immediate reversal.”

However, the wording raises new issues:

1. There is no definition as to what constitutes an “urgent or emergent” need for reversal.
2. The wording suggests that this use of the product may expedite reversal at 1-2 post-tetanic contractions and the reappearance of T₂ compared to the normally recommended dose of sugammadex; however, such comparisons have not been studied.

Although it was not a pivotal study, (b) (4)

Although the findings may be accurate and the study appropriately designed to assess the primary

endpoint, the study does not demonstrate the efficacy of sugammadex. The study does appear to show that when patients are not monitored with PNS following administration of a reversal agent they are more likely to extubate a patient at a $T_4/T_1 = 0.9$ with sugammadex than neostigmine. The implication is that patients are “more” reversed with sugammadex than neostigmine and therefore, less likely to risk morbidity associated with inadequate reversal. However, the study was not designed to demonstrate such a benefit, and the exclusion of PNS monitoring from the assessments made prior to determining whether it was safe to extubate a patient is inconsistent with the current standard of care. (b) (4)

Table 7. T_4/T_1 ratios at the time of extubation (Table 7 on p. 24 of the proposed PI in the second NDA submission)

| T ₄ /T ₁ Ratio at Tracheal Extubation | Treatment Group | |
|---|-------------------------------|---------------------------------|
| | [TRADENAME] (4 mg/kg) N=43 | Neostigmine (50 mcg/kg) N=38 |
| T_4/T_1 Ratio ≤ 0.6 | 1 (2.3) | 10 (26.3) |
| $0.6 < T_4/T_1$ Ratio ≤ 0.7 | 0 (0.0) | 5 (13.2) |
| $0.7 < T_4/T_1$ Ratio ≤ 0.8 | 0 (0.0) | 5 (13.2) |
| $0.8 < T_4/T_1$ Ratio < 0.9 | 1 (2.3) | 6 (15.8) |
| $0.9 \geq T_4/T_1$ Ratio | 41 (95.4) | 12 (31.6) |

Lastly, the Applicant conducted Study P07981 to evaluate the occurrence of residual paralysis in the PACU following abdominal surgical procedures and reversal of NMB with sugammadex or neostigmine. As described in more detail in Section 9.4.1, there was no residual NMB in patients treated with sugammadex, as determined by a $T_4/T_1 \geq 0.9$, but in patients treated with neostigmine, only 43% had no residual blockade. Despite the discrepancy between treatment groups for residual paralysis, and the considerable percentages of neostigmine treated subjects with $T_4/T_1 \leq 0.7$, there was no difference between treatment groups for grip strength in either the dominant or nondominant hand or for pulmonary function test results with testing done on admission to the PACU when patients were awake enough to answer basic demographic questions and when they achieved Richmond Agitation Sedation Scale scores of 0 ± 1 . Considering the recent press given to residual paralysis, (b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

Generally, the secondary endpoints in the majority of the efficacy studies were the time to reaching a T_4/T_1 of 0.8 and 0.7. The findings for the secondary endpoints were

consistent with the findings for the primary endpoint. For pivotal Study 303, recovery to $T_4/T_1 = 0.9$ for sugammadex (16 mg/kg) was evaluated as a secondary endpoint, but was not compared to any other assessments in the study. However, comparing Study 303 to Studies 301 and 302, it is noted that:

1. The populations were similar.
2. The neostigmine treatments were administered after spontaneous recovery had begun – giving them an advantage over the sugammadex treatment in Study 303.
 - The 70 mcg/kg dose of neostigmine is the highest labeled dose (by weight) for that product.

Therefore, it may be possible to compare the recovery times with sugammadex to recover times with neostigmine in the other two studies noting that the highest labeled dose (by weight) of neostigmine was administered in Study 302 at a time when spontaneous recovery from rocuronium had occurred, in essence, giving neostigmine a head start in the comparison to sugammadex given before spontaneous recovery had begun. Recognizing that caution is needed in making comparisons of data from different studies, this approach was taken to gain an appreciation of whether sugammadex would have been found to be superior to neostigmine had a neostigmine treatment arm been incorporated into Study 303. Table 8 compares the data for the three studies.

Table 8. Comparisons of the findings for Studies 301, 302 and 303 for reversal of rocuronium

| | Study 303 | Study 301 | Study 302 |
|---------------------------------|--|-------------------------|-------------------------|
| Treatment | Sugammadex (16 mg/kg) | Neostigmine (50 mcg/kg) | Neostigmine (70 mcg/kg) |
| N | 54 | 45 | 22 |
| Time of Administration | 3 minutes after administration of rocuronium | Reappearance of T2 | 1-2 PTCs |
| Time to $T_4/T_1 = 0.9$ [mm:ss] | | | |
| Mean (SD) | 5:23 (2:11) | 27:18 (25:12) | 60:57 (25:03) |
| Median | 4:50 | 18:31 | 57:04 |
| Range | 3:29-17:21 | 3:40 - 106:53 | 13:16 - 133:28 |

The data indicate that the 16 mg/kg dose of sugammadex can reverse the highest labeled dose of rocuronium, at the time of its peak effect, in a tenth of the time it took the highest dose of neostigmine to reverse a lesser level of rocuronium induced blockade. In fact, the longest time for a subject to achieve $T_4/T_1 = 0.9$ with the 16 mg/kg dose of sugammadex (17 minutes) was not much longer than the shortest time to reach

the same level of reversal with the high dose of neostigmine (13 minutes). In short, it appears that had a 70 mcg/kg neostigmine-treatment arm been included in Study 303, it is highly likely that sugammadex would have been found superior to an extent that it was determined to be in Studies 301 and 302.

6.1.6 Other Endpoints

Key endpoints that have been evaluated in studies reported in the current submission include:

- Residual paralysis in the PACU
- Grip strength in the PACU
- Pulmonary function test results in the PACU
- Time intervals measured from treatment with a reversal agent
- Airway management interventions

All of these endpoints were evaluated in Study P07981, which is described in Section 9.4.1 below.

6.1.7 Subpopulations

The data from pooled analyses across the different efficacy trials, included in the original NDA submission, indicated that the proposed dosing recommendations based on the dose-response trials for each time point of administration and both of the NMBAs were appropriate for all subpopulations evaluated. Special studies of dose requirements for patients with renal or hepatic impairment and patients with cardiac and pulmonary disease were also conducted. These indicated there was no need to adjust the dose in any of these populations. In the current submission, a report from an additional study of adults with renal impairment was included. The results from that study (P05769) indicated there was a different pharmacokinetic profile for sugammadex in patients with severe renal failure. For those subjects, exposure to sugammadex was prolonged and at least 8-fold higher compared to control patients. However, based on deviations that occurred during the bioanalysis of sugammadex, the Applicant concluded that the validity of the sugammadex concentration data from this study cannot be guaranteed, and therefore, the sugammadex pharmacokinetic results and conclusions from the study should be disregarded. At the time of this review, the Clinical Pharmacology team had not completed their review of this study and had not provided their input regarding the findings or the Applicant's recommendation to disregard them.

A limited number of elderly subjects were enrolled in the clinical trials. In all, there were 1,350 subjects who were ≥ 65 years of age; 850 of whom were treated with at least one dose of sugammadex. There were 321 subjects who were ≥ 75 years of age; all of whom received at least one dose of sugammadex. For these subjects there was no indication that the dose of sugammadex needed to be adjusted.

It should be noted that the safety and efficacy of sugammadex has not be fully evaluated in pediatric patients at this point in time.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the pivotal studies submitted in the original NDA, the Applicant provided sufficient evidence to support each of the three components of its dosing regimen for sugammadex. The additional efficacy studies that were completed since the original NDA submission and were included in the last and present resubmissions support the dosing recommendations and do not raise any concerns for the suitability of those recommendations in the general population or in any particular subpopulation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Based on the mechanism of action of sugammadex and its acute administration, there is no concern for its persistence of efficacy or tolerance of its effects.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues that were identified and no addition analyses performed.

7 Review of Safety

Safety Summary

On September 20, 2013, a Complete Response action was taken on the second submission of this NDA. The current submission contained the required study to address the deficiency and three additional clinical trials conducted for other purposes. To address the deficiency related to the risk of anaphylaxis with repeat exposures to sugammadex, the Applicant was required to take one of the following steps:

1. For Study P06042, identify all subjects with a major protocol violation, including those for whom treatment and adverse event evaluations could potentially be unblinded by the investigators and those whose data were potentially compromised because the site used an inadequate case report form that did not capture all adverse event data elements. Perform sensitivity analyses on the primary and key secondary endpoints with the data from the remaining subjects. Provide a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the findings, thereby allowing the study to address the deficiency cited above. Submit the source documents utilized to support the inclusion of the remaining subjects incorporated in the reanalyses.

OR

2. Repeat or conduct a trial similar to Study P06042 and submit the clinical study report to the Agency. If you choose to pursue this pathway, please discuss the trial protocol with the Agency prior to initiation.

The primary focus of this review was on the actions taken by the Applicant to address the deficiency and to determine whether the additional clinical trials raised new safety or efficacy concerns.

Since the original Not Approvable action was taken, the Applicant has completed 24 new clinical trials and in the process has nearly doubled the size of the safety database. In the original NDA submission, there were a total of 2,369 subject exposures to intravenous sugammadex in 2,054 unique subjects. The new clinical trials bring the totals to 6,050 subject exposures to sugammadex in 4,428 unique subjects. In addition, sugammadex was approved in the European Union on July 25, 2008, and is currently marketed in nations around the world. The Applicant reports the distribution of over (b) (4) vials for use in patients through June, 2012, and an additional (b) (4) vials were distributed through April, 2014, for a total of (b) (4) vials. Therefore, an additional secondary focus of this review was whether the new safety database or the postmarketing adverse event data present a risk profile that is similar to that characterized in the original NDA submission or whether any new safety signals exist.

Regarding the issues of hypersensitivity and anaphylaxis, both were observed in the original development program. A consultative review by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) concluded, at that time, that sugammadex is potentially allergenic and may cause anaphylaxis, with an estimated anaphylaxis frequency of 1.4% in a population of healthy subjects. When considering the entire database, the frequency of anaphylaxis was estimated to have been between 0.1% and 0.3%. DPARP was concerned that this frequency of anaphylaxis may be a significant underestimate of the true frequency, since the original clinical development program did not assess the safety of repeat exposures. Therefore, DPARP outlined that the Applicant should: 1) characterize the safety of sugammadex on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions, 2) define the frequency/time course of events related to sugammadex administration, and other characteristics of the adverse reactions, and 3) attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium.

As a part of the resubmission on December 20, 2012, the Applicant provided the results of a repeat-dose clinical study, P06042. P06042 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects, however due to concerns that investigators may have been unblinded to treatment assignment, the data was deemed to be of limited utility in defining the frequency of anaphylaxis associated with sugammadex administration, and a Complete Response letter was issued.

The focus of this review has been on the most recent submission, dated October 22, 2014. In this submission, the Applicant provided the results of a second dedicated hypersensitivity study, P101, a randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex in healthy subjects.

Using a predefined list of possible hypersensitivity signs and symptoms and a targeted hypersensitivity assessment, the Applicant identified 137 cases of suspected hypersensitivity in 94 subjects, and 1 case of anaphylaxis. DPARP agreed with the Applicant's single case identification of anaphylaxis. As Study P101 consisted of 299 unique healthy volunteer subjects who received sugammadex, the frequency of anaphylaxis was 0.33% (1/299). It was considered noteworthy that the case of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

Among the hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, pruritus, and urticaria. Several hypersensitivity symptoms, including erythema, eye disorders, nausea, sneezing, urticaria, and vomiting showed a dose-response, more frequently occurring in the high-

dose group when compared to the low-dose group and placebo. Hypersensitivity reactions were more frequently noted in the 16 mg/kg dose group, occurring \leq 35 minutes of dosing, and with the first dose of sugammadex.

Mechanistic data submitted did not elucidate a clear causal mechanism leading to anaphylaxis and hypersensitivity. While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available mechanistic and clinical data did not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.

DPARP concluded that sugammadex causes anaphylaxis and hypersensitivity events. This risk appears to increase with higher doses and does not appear to increase with repeated exposure. Whether this risk is greater than the risk for other drug products commonly used in the peri-operative setting is not possible to determine with currently available data. DPARP also noted that there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-benefit assessment for sugammadex depends primarily on the efficacy and safety data specific to sugammadex and its expected use in the clinical setting.

It should be noted that the clinical and central site inspections conducted by the Office of Scientific Investigations (OSI) revealed protocol deviations and data unblinding that raised concerns over the integrity of the data generated by Study P101. Based on discussions with the Applicant and with experts at the Agency, it was concluded that the specific findings would be unlikely to impact the results of the study. However, due to the importance of this study and the nature of the OSI findings, it was determined that the remaining clinical sites need to be inspected to further assure the integrity of the data and the findings from the study. Provided the inspections reveal no new reason to question the integrity of the study results, the deficiency identified in the Complete Response letter of September 20, 2013, will have been addressed. Based on the study findings, the cumulative safety data from the clinical development program, and the postmarketing adverse reactions reported to date, sugammadex produces hypersensitivity and anaphylactic reactions. These reactions generally occur within minutes of sugammadex administration and are often mild to moderate in severity. Repeat exposure does not appear to increase the risk of these reactions, and they tend to occur with the highest proposed dose of the product. Given these findings as well as the clinical setting in which these reactions occur, i.e., the operating room and PACU where routine monitoring and appropriately trained staff will minimize the risks from these reactions, an Approval action can be recommended provided the product labeling adequately captures the extent and nature of the risks of hypersensitivity and anaphylaxis as observed in both the clinical development program and the postmarketing experience to date.

In addition to issues of hypersensitivity and anaphylaxis, this safety review revisited the clinical trial safety database, which has more than doubled since the original NDA submission, and the postmarketing database, which has increased substantially since the previous submission, to determine whether any new safety signals exist.

Regarding the updated safety database from the clinical development program, the analyses of common adverse events demonstrated that sugammadex had a safety profile that, in general, posed only minimal additional risk compared to placebo and a level of risk that appeared to be no worse than that of neostigmine. The most common adverse events were nausea, vomiting, and pain. Only dysgeusia, nausea, nasopharyngitis, and possibly headache, appeared to be sugammadex-dose related. Similarly, the analysis of SAEs reported in the clinical trials indicated that, overall, the safety profile for sugammadex was not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm related adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it was only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appeared to differ substantially from placebo and neostigmine. Review of the postmarketing data produced similar findings; although, it was noted that many of the cardiovascular reactions occurred in the setting of hypersensitivity and anaphylactic reactions.

The review of the updated safety database indicated that there were no subpopulations at greater risk from sugammadex or for whom the dose of sugammadex needed to be adjusted.

Regarding the postmarketing adverse reaction database, the review of the data indicated that anaphylactic reactions were the most frequently reported adverse events followed by changes in heart rate and blood pressure. There was no indication of a new safety signal in the database.

In summary, the safety profile for sugammadex has been adequately characterized to perform a benefit-risk analysis, provided the OSI inspections for Study P101 raise no concerns over data integrity. The overall safety of sugammadex did not differ substantially from placebo in the clinical trials, and sugammadex appears to pose no greater risk than neostigmine, with the exception of hypersensitivity and anaphylactic reactions that have been generally mild to moderate in severity, readily diagnosed with standard patient monitoring, and successfully treated, when intervention was needed.

[N.B.: In the sections that follow, the tables, interpretations of the data, and comments contained therein are those of this reviewer unless they are specifically attributed to the Applicant or other entity.]

7.1 Methods

This resubmission contains the Applicant's responses to the issues raised in the second Complete Response letter as well as the final study reports and the associated data for the four additional clinical trials have been completed since the 2012 resubmission. The new trials include:

1. P101, which was conducted to characterized the frequency of hypersensitivity reactions after repeated administration of sugammadex.
2. P105, which was a pharmacokinetic study in subjects with moderate and severe renal impairment. It was conducted to address bioanalytical issues identified in a previous study of severe renal impairment (P05769).
3. P07981, which evaluated whether subjects who undergo reversal of neuromuscular blockade with sugammadex experience less residual blockade upon entry into the post-anesthesia care unit (PACU) than subjects treated with usual care, i.e., neostigmine.
4. P076, which evaluated the effects of the depth of neuromuscular blockade and insufflation pressure on laparoscopic surgical conditions.

The evaluation of safety for this submission consists of performing the safety analyses done in the first two submissions incorporating the new safety data from the four trials listed above. In addition, there is special focus on the hypersensitivity/anaphylaxis, cardiac, and bleeding adverse events in the current safety database, and an analysis of the post-marketing safety data that are currently available.

7.1.1 Studies and Clinical Trials Used to Evaluate Safety

Data from the studies listed in the table below formed the basis for the review of safety by the Applicant. For the purposes of this review, only the studies involving the intravenous administration of sugammadex were considered for the evaluation of safety. These trials are listed in Table 9 below.

Table 9. Clinical trials used for the evaluation of safety

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---------------------------------|--|---------------------------------|
| 19.4.101 | placebo | 29 | first in human study |
| 19.4.102 | placebo | 28 | Japanese vs. Caucasian PK study |
| 19.4.105 | placebo/moxifloxacin | 62 | QT study |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|-------------------------------------|--|------------------------------------|
| 19.4.106 | placebo | 19 | high-dose PK study |
| 19.4.107 | none | 6 | ADME study |
| 19.4.108 | none | 16 | Pre QT pilot study |
| 19.4.109 | placebo/moxifloxacin | 83 | QT study |
| 19.4.110 | histamine/histamine dihydrochloride | 23 | skin-prick testing |
| 19.4.112 | none | 24 | drug-drug interaction study |
| 19.4.113 | none | 22 | use of NMBA after sugammadex |
| 19.4.115 | placebo | 8 | assess effects on aPTT, PT and INR |
| 19.4.201 | placebo | 27 | dose-finding study |
| 19.4.202 | placebo | 98 | dose-finding study |
| 19.4.203 | none | 28 | dose-finding study |
| 19.4.204 | none | 36 | dose-finding study |
| 19.4.205 | placebo | 35 | dose-finding study |
| 19.4.206 | placebo | 171 | dose-finding study |
| 19.4.207 | placebo | 106 | dose-finding study |
| 19.4.208 | placebo | 191 | dose-finding study |
| 19.4.209 | none | 199 | dose-finding study |
| 19.4.210 | none | 42 | use with propofol vs. sevoflurane |
| 19.4.301 | neostigmine | 185 | pivotal efficacy study |
| 19.4.302 | neostigmine | 155 | pivotal efficacy study |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---|--|---|
| 19.4.303 | spontaneous recovery from succinylcholine | 108 | pivotal efficacy study |
| 19.4.304 | none | 30 | renal impairment study |
| 19.4.305 | none | 159 | elderly vs. adult patients (61 subjects: 65-75 yrs and 40 subjects: >75 yrs) |
| 19.4.306 | placebo | 90 | adult and pediatric patients (27 adults and 63 pediatric subjects 28 days - 17 yrs) |
| 19.4.308 | none | 77 | patients with pulmonary disease |
| 19.4.309 | placebo | 116 | patients with cardiac disease |
| 19.4.310 | Cis-atracurium reversed with neostigmine | 72 | Cis-atracurium study |
| 19.4.311 | none | 192 | open-label efficacy study |
| 19.4.312 | none | 51 | use with propofol vs. sevoflurane |
| 19.4.313 | none | 89 | manual detection of T ₄ vs. device detection |
| 19.4.316 | placebo | 136 | efficacy study |
| 19.4.318 | neostigmine | 132 | efficacy study |
| 19.4.319 | spontaneous recovery from succinylcholine | 132 | assess changes in K ⁺ levels |
| 19.4.328 | none | 67 | severe renal impairment study |
| 19.4.333 | none | 4 | dialysis study |
| 19.4.334 | neostigmine | 100 | residual blockade at time of extubation |
| P05768 | neostigmine | 291 | Chinese vs. Caucasian efficacy assessment |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---------------------------------|--|--|
| P05775 | none | 151 | Chinese vs. Caucasian efficacy assessment |
| P05997 | none | 12 | Chinese PK study |
| P06042 | placebo | 397 | assess anaphylaxis/hypersensitivity with repeat doses |
| P06101 | neostigmine | 120 | Korean vs. Caucasian efficacy assessment |
| P06315 | placebo | 132 | QT study in presence of propofol or sevoflurane |
| P07025 | placebo | 26 | assessment of sugammadex and aspirin on platelet aggregation and clotting |
| P07038 | placebo and neostigmine | 1137 | dedicated bleeding study |
| P07044 | placebo | 51 | effects of sugammadex and enoxaparin or unfractionated heparin on anticoagulation |
| P105* | none | 33 | effect of chronic renal impairment on sugammadex PK in subjects with severe or moderate renal impairment compared to |
| P076/ P07982* | none | 127 | Comparison of the use of deep or standard neuromuscular blockade in combination with low or standard insufflation pressures in patients having laparoscopic procedures |
| P101* | placebo | 375 | evaluate the incidence of hypersensitivity after repeated intravenous single dose administration of sugammadex |
| P07981* | neostigmine | 151 | assess whether there is less residual neuromuscular blockade with sugammadex than neostigmine in the PACU |

* These studies were included in the current resubmission.

In addition to the clinical studies, the Applicant searched their pharmacovigilance database for adverse events reported up to April 21, 2013. They have submitted all of these postmarketing reports and have analyzed those adverse events related to

anaphylaxis, hypersensitivity, cardiac arrhythmias, or post-operative bleeding events. For this review, the entire postmarketing database was analyzed for both safety concerns identified in the Complete Response letter and for safety signals not observed in the clinical studies.

7.1.2 Categorization of Adverse Events

The Applicant used MedDRA version 17.0 to code the adverse events (AEs) reported in the integrated safety database. They noted that some of the trials conducted early on in the development program used other versions of MedDRA, and some used the WHO-ART dictionary for coding the AEs; these events were recoded for the integrated database.

All of the AEs reported in the safety database were treatment emergent, defined as having an onset time after the start of study drug administration and within the 7 days following treatment with some exceptions for cross-over studies when the next treatment was administered on Day 7.

The system organ classification (SOC) used for individual AEs was variable among studies based on whether an event was considered possibly related to the surgical procedure or the anesthetic, e.g., reports of bradycardia occurring within minutes of sugammadex administration were sometimes coded as “injury, poisoning and procedural complications” and attributed to anesthetic agents used prior to the administration of sugammadex. In addition, some AEs were tabulated under the heading of “investigations” if they occurred in studies not involving surgical procedures, e.g., QTc prolongation occurring in one of the thorough QT studies. For the purposes of this review, AEs reported under these two SOCs were tabulated with those reported under the biological system involved, e.g., reports of bradycardia listed under “injury, poisoning and procedural complications” were counted with those listed under “cardiac disorders.”

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant analyzed safety data by pooling trials in multiple categories. These included the following:

- Pooled Phase 1 Trials: these included healthy subjects treated with sugammadex or placebo but were not administered a neuromuscular blocking agent (NMBA) or an anesthetic. This group consisted of 11 trials

- Pooled Phase 1-3 Trials: these included healthy volunteers and surgical patients who were administered an anesthetic and/or an NMBA, and who were treated with sugammadex, placebo, or an active comparator. This group consisted of 40 trials; it was further subdivided into two groups:
 - a. Pooled Placebo-Controlled Trials: 13 trials that compared sugammadex to placebo
 - b. Pooled Neostigmine-Controlled Trials: 7 trials that compared sugammadex to neostigmine

This approach to evaluating safety is useful for discerning AEs that may be related to the anesthetic or surgical procedure from those due to sugammadex and also allows an assessment as to whether the sugammadex-rocuronium or sugammadex-vecuronium complex has a different risk profile than sugammadex alone.

As the demographics of the subjects were similar in most of the clinical trials, the safety data were considered *en masse* for the purposes of this review in addition to being considered by the pooling methods used by the Applicant.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The table below summarizes the number of subjects and the number of intravenous study drug treatment exposures for the entire clinical development program.

Table 10. Subject counts and treatment exposures for the entire clinical development program

| Treatment (dose) | Number of Subjects | Number of Treatments |
|-------------------------|---------------------------|-----------------------------|
| Sugammadex (all doses) | 4,428 | 6,050 |
| Sugammadex (0.1 mg/kg) | 5 | 5 |
| Sugammadex (0.2 mg/kg) | 4 | 4 |
| Sugammadex (0.5 mg/kg) | 137 | 137 |
| Sugammadex (1 mg/kg) | 220 | 220 |
| Sugammadex (2 mg/kg) | 913 | 913 |
| Sugammadex (3 mg/kg) | 28 | 28 |
| Sugammadex (4 mg/kg) | 2505 | 3097 |
| Sugammadex (6 mg/kg) | 29 | 29 |
| Sugammadex (8 mg/kg) | 156 | 156 |
| Sugammadex (12 mg/kg) | 40 | 40 |
| Sugammadex (16 mg/kg) | 496 | 1067 |
| Sugammadex (20 mg/kg) | 6 | 6 |
| Sugammadex (32 mg/kg) | 165 | 324 |
| Sugammadex (64 mg/kg) | 12 | 12 |
| Sugammadex (96 mg/kg) | 12 | 12 |
| | | |
| Placebo | 1394 | 1980 |
| | | |
| Neostigmine (all doses) | 933 | 933 |
| Neostigmine (50 mcg/kg) | 875 | 875 |
| Neostigmine (70 mcg/kg) | 58 | 58 |

7.2.2 Explorations for Dose Response

During the development program, over 10 doses of sugammadex were evaluated in adult subjects. Table 11 below summarizes these exposures and indicates that they were adequate to allow meaningful assessments of whether adverse events were dose dependent, particularly, as they relate to the to-be-labeled doses of 2, 4, and 16 mg/kg of sugammadex. Although the majority of these exposures occurred in placebo-controlled trials, there were sufficient exposures in neostigmine- and succinylcholine-controlled trials to allow meaningful comparisons of safety for these agents as well.

Table 11. Numbers of subjects and exposures for all intravenous treatments

| Parameter | Placebo | Succinylcholine | Sugammadex Dose (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|-----------|---------|-----------------|-------------------------|-----|-----|----|------|----|-----|----|------|------|----------------------|----|
| | | | ≤0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | > 16 | 50 | 70 |
| N | 1394 | 134 | 140 | 220 | 913 | 28 | 2505 | 29 | 156 | 40 | 496 | 171 | 875 | 58 |
| Exposures | 1980 | 134 | 146 | 220 | 913 | 28 | 3097 | 29 | 156 | 40 | 1067 | 354 | 875 | 58 |

7.2.3 Special Animal and/or In Vitro Testing

The Applicant's preclinical information in the original NDA submission was evaluated by Drs. Zengjun Xu and Adam Wasserman of the Pharmacology-Toxicology review team. In their review of that data, they noted (in Dr. Wasserman's addendum dated July 7, 2008) that because "of the deposition of sugammadex into bone and the demonstration of an extended duration of retention with single administration (bone $t_{1/2(\beta)}$ mean of 172 days), an evaluation of the potential for bone carcinogenicity should be considered. This concern is especially relevant for the pediatric population due to the higher concentration of drug which is believed will be retained in this tissue, as well as the intrinsically high level of growth in this tissue prior to skeletal maturation and closure of the epiphyseal plates." In the Not Approvable letter, additional nonclinical studies were considered as necessary prior to any multiple-dose pediatric trials, approval of a pediatric indication, or inclusion of pediatric data in the label.

The Applicant adequately addressed those issues in the first resubmission, which was reviewed by Drs. Xu and Wasserman. Summaries of their reviews were included in Section 4.3 of the previous clinical review.

The Applicant also conducted *in-vitro* testing of the effects of sugammadex on coagulation parameters in the original NDA submission. Those studies indicated that sugammadex can prolong activated partial thromboplastin time (aPTT), prothrombin time (PT), and the international normalized ratio (INR). The findings of those studies were further described in the clinical safety review of that submission. Those findings, in part, led to the requirement in the Not Approvable letter for studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures, which was done and provided in the first resubmission. No additional nonclinical or *in-vitro* study information requiring clinical evaluation was included in the current NDA resubmission.

7.2.4 Routine Clinical Testing

The routine testing of subjects was adequate in terms of assessing biochemistry and hematologic laboratory parameters and for monitoring of vital signs and ECG. The lack of evaluations of coagulation parameters in any of the clinical trials in the original NDA submission was adequately addressed by the Applicant in the first resubmission in a clinical study comparing the effects of sugammadex versus neostigmine or spontaneous recovery on these parameters.

7.2.5 Metabolic, Clearance, and Interaction Workup

Sugammadex was found to have no metabolites in both nonclinical and clinical studies. Only renal excretion of unchanged product was observed as the means of elimination. In adults with normal renal function, the elimination half-life is 2 hours. More than 90% of the product is excreted within 24 hours. The Applicant has conducted studies that examined the safety and efficacy of sugammadex in surgical patients with moderate and severe renal impairment, including one study that was part of the current resubmission.

Sugammadex does not induce or inhibit drug metabolizing enzymes, and therefore, “classical” drug-drug interaction studies were not conducted. The Applicant conducted various pharmacokinetic simulations to assess the potential for other medications to displace rocuronium from sugammadex, and thereby increase the level of neuromuscular blockade, and the potential for the sugammadex-rocuronium complex to bind another medication. The displacement of rocuronium from sugammadex by flucloxacillin or diclofenac was evaluated in a clinical study. In addition, the effects of sugammadex on the anticoagulant activity of enoxaparin and unfractionated heparin and the anti-platelet-aggregation activity of aspirin were evaluated in clinical studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Sugammadex is unique in its mechanism of action as a reversal agent for neuromuscular blocking agents (NMBAs). Sugammadex directly binds to rocuronium and vecuronium removing them from the systemic circulation and the neuromuscular junction. The alternative reversal agents, neostigmine and edrophonium, are anticholinesterases and have risk profiles that reflect the physiological effects of excess acetylcholine. Eleven of the clinical studies compared sugammadex to neostigmine and provide for a comparison of the adverse events associated with use of each of these agents under similar clinical settings.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the clinical trials conducted and included in the current resubmission. Otherwise, in the overall sugammadex clinical development program, eight deaths have been reported, including three deaths reported in the original NDA submission. The Applicant notes that all of the deaths occurred after the trial was completed, and that none of them were considered drug-related according to the reporting investigators. In the safety review of the original NDA submission, this reviewer concurred that two of the deaths were unlikely to be drug related, but felt that sugammadex may have contributed, in part, to at least one of the deaths. All eight cases are described and discussed below. Four deaths followed sugammadex treatments (one subject for the 0.5 mg/kg dose and 2 mg/kg dose and four subjects for the 4 mg/kg dose); one death occurred following neostigmine treatment and three deaths occurred following placebo treatment.

Deaths following treatment with sugammadex

Subject 203104007 participated in trial 19.4.203 (sugammadex 0.5 mg/kg dose group) and was a 65 year old Caucasian female who died 42 days after surgery and the administration of sugammadex. She presented for an anterior resection of carcinoma of the large intestine. Her past medical history was significant only for hypertension, peptic ulcer and rheumatoid arthritis. From the data in her Case Report Form (CRF), it appears there were no surgical complications and the procedure lasted approximately 3 hours. At approximately 23 hours following the end of surgery, the patient experienced atrial fibrillation and respiratory failure. She was reported to have “recovered with sequelae” from these events. The list of concomitant medications administered following surgery included therapies for post-operative pain (including epidural infusions of fentanyl and levobupivacaine) and nausea, prophylaxis for deep vein thrombosis, and treatment of adrenal suppression (dexamethasone 5 mg IV administered 3 hours after the sugammadex); no medications for the treatment of either atrial fibrillation or respiratory failure were listed. Her death was attributed to a combination of factors, including myocardial infarction, cardiogenic shock, and pulmonary edema. According to the investigator, these post-trial SAEs were unlikely related to the trial medication. The Investigator and the Applicant judged the subject’s death as not related to the trial medication; however, this reviewer believes that sugammadex cannot be ruled out for having contributed to the subject’s demise. This belief is based on the lack of data between 3 and 23 hours postdose during which time the subject began to experience atrial fibrillation and respiratory failure. As she experienced sequelae from these events, to the extent that Sugammadex contributed to the occurrence of either adverse event, it was related to the outcome.

Subject 208107008, in trial 19.4.208B (sugammadex 2 mg/kg dose group), was a 61 year old male Caucasian who died 18 days after surgery and the administration of sugammadex due to a pulmonary embolus. The subject had no previous medical history except for his diagnosis of prostate cancer. He underwent a radical prostatectomy with radical iliacal lymphadenectomy that were complicated by an intraoperative 1-cm perforation of the colon. The perforation was surgically repaired and the patient was prophylactically treated with antibiotics. The patient was discharged 6 days following surgery with a surgical drain in situ. The drain was reported to have been removed a “few days” after surgery. The subject was reported to have “felt tired” 11 or 12 days post-operatively and was ultimately hospitalized on post-operative day 15, at which time he was diagnosed as having a pulmonary embolus. Due to his recent surgery, he was considered to have unacceptable risks for thrombolytic therapy and was, therefore, treated with low molecular weight heparin. The subject died two days later. According to the Investigator, thrombosis and embolus were complications of the subject’s surgical procedure, and pelvic thrombosis was a known complication of surgery of the lower abdomen. Given the nature of the surgery and the reported time sequence, the causal relationship for this SAE and death were assessed as “not related” by the Applicant. This reviewer concurs with the Applicant’s assessment.

Subject 333101006, in trial 19.4.333 (sugammadex 4 mg/kg dose group), was a 77 year-old male with a medical history that included cardiovascular disease, renal failure, diabetes, and coagulopathy. He underwent a thoracic artery endoprosthesis and esophageal stent placement due to “thoracic fissures” on [REDACTED] (b) (6). His condition deteriorated in the weeks following surgery with signs of sepsis, pneumonia and free air around the thoracic endoprosthesis reported. On [REDACTED] (b) (6), the endoprosthesis was replaced with a homograft during uneventful surgery. On [REDACTED] (b) (6), he underwent bronchoscopy following which he received 4 mg/kg of sugammadex. On [REDACTED] (b) (6) the subject experienced an acute pulmonary hemorrhage with blood entering the endotracheal tube. It was not possible to ventilate the subject, and he died about 1.5 hours later. The Investigator and the Applicant considered the hemorrhagic SAE and the subject’s subsequent death as unrelated to the use of sugammadex. This reviewer concurs with their assessment.

Subject 333101007, in trial 19.4.333 (sugammadex 4 mg/kg dose group), was a 63 year-old male with a history of cardiovascular disease, renal failure, cirrhosis, diabetes, and alcohol abuse. He underwent a mitral valvuloplasty, an aortic valve replacement, and a coronary artery bypass graft on [REDACTED] (b) (6), after which he was required inotropic support. On [REDACTED] (b) (6) he underwent transesophageal echocardiography to evaluate ongoing heart failure. After the procedure, he received 4 mg/kg of sugammadex. Over the next two days he experienced worsening hypotension, bowel ischemia, and liver insufficiency. The subject died on [REDACTED] (b) (6). The Investigator and the Applicant did not consider his SAEs of bowel ischemia, worsening heart failure and liver insufficiency or his death as related to the sugammadex. Of note, the outcome

for the SAEs "worsening of heart failure" and "liver insufficiency" were changed from "fatal" to "not recovered." Although hypotension has been observed within minutes following the administration of sugammadex, this subject's hypotension was first reported more than 12 hours following treatment. Given the severity of his underlying medical conditions, including cardiac disease, and the timing of onset of the events leading to his demise, this reviewer concurs with the Applicant's assessment that the subject's death was not related to sugammadex.

Deaths following treatment with placebo

Subject 309107003 (reported in the original NDA submission) in trial 19.4.309 (placebo group) was a 73-year-old male Caucasian who died 12 days after surgery and the administration of the trial medication. He had undergone a craniotomy for resection of a cerebral meningioma. His past medical history was significant for myocardial infarction, post-infarction angina pectoris, status post CABG, hypertension, meningioma with visual deficits, headache, and reduced cognitive functioning. On postoperative day 1, the patient was reported to have had a > 60 msec prolongation of QTc, which was not treated. CT scans performed at 2, 5, 9 and 10 days post-operatively showed edema, intraventricular and subarachnoidal blood, and midline shifts which worsened to the point of suspected subfalx and transtentorial herniation. He died on post-operative day 11; the cause of death was listed as cerebral edema and ventricular bleeding with hydrocephalus. Autopsy results showed a lesion in the left middle cerebral artery that had been caused by the surgery during removal of a meningioma. The Investigator and the Applicant judged the subject's death as not related to the trial medication. This reviewer concurs with the Applicant's assessment.

Subject P07038-96004, in trial P07038, was a 67 year old male with a history of cardiovascular disease, renal cell carcinoma, lung "neoplasm," and metastasis. He underwent knee surgery on (b) (6), with a combination of epidural and general anesthesia. He received a placebo treatment at the end of his surgery. He was discharged from the hospital 6 days after surgery and died on (b) (6), reportedly due to the metastatic renal cell carcinoma. His death was not considered to be due to the study drug; this reviewer concurs with that assessment.

Subject P07038-31832, in trial P07038, was a 65 year old male with a history of atrial fibrillation, bradycardia-tachycardia syndrome, hypertension and hyperuricemia. He underwent total hip arthroplasty on (b) (6), under general anesthesia. He received a placebo treatment at the end of his procedure. On (b) (6), he was found unconscious in asystole with pacemaker spikes. Cardiopulmonary resuscitation was begun but was not successful and discontinued after 24 minutes at which time the patient was pronounced dead. His death was not attributed to study drug treatment by the Investigator; this reviewer concurs with that assessment.

Deaths following treatment with neostigmine

Subject P07038-3021796, in trial P07038, was a 90 year old male with a history of cardiac disease and deep vein thrombosis who presented for internal fixation of a hip fracture. He had his surgery on [REDACTED] (b) (6) under general anesthesia. At the end of surgery he received treatment with neostigmine 0.05 mg/kg. He died in his sleep 43 days after surgery; the cause of death was listed as cardiac arrest. The Investigator considered the subject's death as unlikely related to the study drug; this reviewer concurs with that assessment.

In summary, the analysis of the deaths that occurred in the clinical development program does not indicate that sugammadex poses any greater risk than either placebo or neostigmine. There was a single death reported in the original NDA submission in which sugammadex may have played a role; however, with a near doubling of the safety database since that time, there is no additional evidence to suggest that sugammadex may increase patient mortality

7.3.2 Nonfatal Serious Adverse Events

There were a total of 479 serious adverse events (SAEs) in the safety database including all treatment groups. Table 12 includes all SAEs reported for intravenous injections or infusions of sugammadex grouped by SOC and compared to those of subjects treated with either placebo, neostigmine, or succinylcholine regardless of whether an anesthetic or an NMBA was administered. The data in the table indicate that, overall and for each individual SOC, there are no substantial differences between sugammadex and either placebo or neostigmine. The table also indicates that, overall and for each individual SOC, there is no dose-dependency for SAEs and sugammadex. Lastly, the rates of the SAEs are generally 2% or less. Single SAEs in the 3 mg/kg and 6 mg/kg groups, which had fewer than 30 subjects, were responsible for the 3% and 4% rates that were observed for sugammadex treatments.

Table 12. Serious adverse events alphabetically by system organ class, treatment, and dose

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | | Succinylcholine |
|---|-------------|--------------------|------------|------------|-----------|-------------|-----------|------------|------------|------------|------------|----------------------|------------|-----------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 32 | 50 | 70 | | |
| N | 1394 | 137 | 220 | 913 | 28 | 2505 | 29 | 156 | 496 | 165 | 875 | 58 | 134 | |
| System Organ Class | | | | | | | | | | | | | | |
| Blood and lymphatic system disorders | 1 (0%) | -- | -- | 1 (0%) | -- | 2 (0%) | -- | -- | -- | -- | -- | -- | -- | |
| Cardiac disorders | 4 (0%) | 3 (2%) | -- | 5 (1%) | -- | 7 (0%) | -- | -- | 1 (0%) | -- | 3 (0%) | -- | -- | |
| Cardiovascular disorders, general | -- | -- | -- | -- | 1 (4%) | -- | -- | -- | -- | -- | -- | -- | -- | |
| Ear and labyrinth disorders | -- | -- | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | |
| Eye disorders | 1 (0%) | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | |
| Gastrointestinal disorders | 4 (0%) | 3 (2%) | 3 (1%) | 12 (1%) | -- | 14 (1%) | -- | -- | -- | -- | 14 (2%) | 4 (7%) | 1 (1%) | |
| Gastrointestinal disorders; Infections and infestations | -- | -- | -- | -- | -- | 2 (0%) | -- | -- | -- | -- | -- | -- | -- | |
| General disorders and administration site conditions | 3 (0%) | -- | -- | 3 (0%) | -- | 8 (0%) | -- | -- | -- | 3 (2%) | 8 (1%) | -- | -- | |
| Hepatobiliary disorders | -- | -- | -- | -- | -- | 2 (0%) | -- | -- | -- | -- | -- | -- | -- | |
| Immune system disorders | 1 (0%) | -- | -- | -- | -- | 0 (0%) | -- | -- | 1 (0%) | -- | -- | -- | -- | |
| Infections and infestations | 5 (0%) | 1 (1%) | 1 (0%) | 6 (1%) | -- | 21 (1%) | -- | 1 (1%) | -- | -- | 10 (1%) | -- | -- | |
| Injury, poisoning and procedural complications | 24 (2%) | 2 (1%) | -- | 21 (2%) | -- | 46 (2%) | -- | 3 (2%) | 4 (1%) | -- | 18 (2%) | 3 (5%) | -- | |
| Investigations | 2 (0%) | -- | -- | 16 (2%) | -- | 9 (0%) | -- | 1 (1%) | 8 (2%) | -- | -- | -- | 2 (1%) | |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | Neostigmine (mcg/kg) | | Succinylcholine |
|---|-------------|--------------------|------------|------------|-----------|-------------|-----------|------------|------------|------------|----------------------|-----------|-----------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 32 | 50 | 70 | |
| N | 1394 | 137 | 220 | 913 | 28 | 2505 | 29 | 156 | 496 | 165 | 875 | 58 | 134 |
| System Organ Class | | | | | | | | | | | | | |
| Metabolism and nutrition disorders | 1 (0%) | -- | -- | 2 (0%) | -- | 0 (0%) | -- | | | -- | 1 (0%) | -- | -- |
| Musculoskeletal and connective tissue disorders | 3 (0%) | -- | 2 (1%) | | -- | 11 (0%) | -- | | | -- | 4 (0%) | -- | -- |
| Neoplasms benign, malignant and unspecified | 2 (0%) | -- | -- | 1 (0%) | -- | 2 (0%) | -- | -- | -- | -- | 3 (0%) | -- | -- |
| Nervous system disorders | 9 (1%) | -- | -- | 5 (1%) | -- | 4 (0%) | 1 (3%) | -- | -- | 2 (1%) | 1 (0%) | -- | -- |
| Psychiatric disorders | -- | -- | -- | | -- | 8 (0%) | -- | -- | -- | -- | -- | -- | -- |
| Renal and urinary disorders | 1 (0%) | 4 (3%) | -- | 1 (0%) | -- | 6 (0%) | -- | -- | -- | -- | 4 (0%) | -- | -- |
| Reproductive system and breast disorders | -- | -- | -- | | -- | -- | -- | -- | -- | -- | | -- | 1 (1%) |
| Respiratory, thoracic and mediastinal disorders | 2 (0%) | 2 (1%) | -- | 10 (1%) | -- | 11 (0%) | 1 (3%) | -- | -- | -- | 5 (1%) | -- | -- |
| Skin and subcutaneous tissue disorders | -- | -- | -- | | -- | 1 (0%) | -- | -- | 1 (0%) | -- | | -- | -- |
| Surgical and medical procedures | -- | -- | -- | 2 (0%) | -- | 1 (0%) | -- | -- | -- | -- | 4 (0%) | -- | -- |
| Vascular disorders | 4 (0%) | 1 (1%) | -- | 3 (0%) | -- | 12 (0%) | -- | -- | 2 (0%) | -- | 4 (0%) | -- | -- |
| Vascular disorders; Respiratory, thoracic and mediastinal disorders | -- | -- | -- | | -- | 3 (0%) | -- | -- | -- | -- | -- | -- | -- |

7.3.3 Dropouts and/or Discontinuations

For most of the clinical development program, sugammadex was administered as an intravenous bolus, the way it would be used in clinical practice. Therefore, discontinuations of administration were possible only in the trials where the study drug was infused or in crossover trials where a subject did not proceed to a subsequent period. Trials 19.4.108 and 19.4.109 involved infusions of study drugs over 4-minute periods; trial 19.4.109 was also a crossover study. The Applicant reported that the infusion of sugammadex was not discontinued in any subject in these two trials. Therefore, there were only subject withdrawals from the trials due to an adverse event (AE) rather than discontinuations of treatment per se.

Nearly all subjects in the sugammadex-treatment groups completed the trials. A total of 53 subjects were withdrawn from the trials and 3 subjects had their dose reduced due to an adverse event. Overall, there were 75 different adverse reactions that led to discontinuations. Of the discontinued subjects, 50 were treated with IV sugammadex, 2 were treated with skin testing of sugammadex, 23 were treated with placebo, and 1 was treated with neostigmine. There was no dose-dependent adverse event that accounted for sugammadex-treatment discontinuations. The most noteworthy adverse events associated with the sugammadex treatments included: a single discontinuation for anaphylactic shock (16 mg/kg); 2 discontinuations due to hypersensitivity reactions (4 mg/kg and 32 mg/kg); and a single discontinuation for tachycardia (8 mg/kg).

7.3.4 Significant Adverse Events

Of the 25,151 treatment-emergent adverse events that occurred with all of the study drug treatments, 852 were rated as “severe” by the Investigators and occurred with intravenous study drug administration. Table 13 compares the incidence of severe adverse events across the three treatment groups, placebo, sugammadex, and neostigmine, with the sugammadex and neostigmine groups further subdivided by dose. The table indicates that there is no dose dependency for these events with sugammadex treatment and that there is no substantial difference between the incidence rates for sugammadex, neostigmine and succinylcholine; although all of the active treatments have higher rates than treatment with placebo.

Table 13. Distribution of severe adverse events across treatment arms

| Treatment | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | | Succinylcholine |
|------------|---------|--------------------|-----|-----|----|------|----|-----|-----|----|-----|----------------------|----|-----------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 20 | 32 | 50 | 70 | |
| N | 1394 | 137 | 220 | 913 | 28 | 2505 | 29 | 156 | 496 | 6 | 165 | 875 | 58 | 134 |
| Severe AEs | 86 | 29 | 33 | 187 | 5 | 276 | 6 | 13 | 19 | 1 | 2 | 157 | 14 | 24 |
| % of N | 6 | 21 | 15 | 20 | 18 | 11 | 21 | 8 | 4 | 17 | 1 | 18 | 24 | 18 |

Table 14. Distribution of adverse events and serious adverse events across treatments and doses

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | | | | | Neostigmine (mcg/kg) | |
|--------------|---------|--------------------|-----|-----|-----|------|-----|------|----|-----|-----|------|-----|-----|-----|----------------------|-----|
| | | 0.1 | 0.2 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 64 | 96 | 50 | 70 |
| Dose | N/A | | | | | | | | | | | | | | | | |
| N | 1394 | 5 | 4 | 137 | 220 | 913 | 28 | 2505 | 29 | 156 | 40 | 496 | 165 | 12 | 12 | 875 | 58 |
| Exposures. | 1980 | 5 | 4 | 137 | 220 | 913 | 28 | 3097 | 29 | 156 | 40 | 1067 | 324 | 12 | 12 | 875 | 58 |
| AEs | 3892 | 6 | 5 | 531 | 754 | 3250 | 76 | 9234 | 58 | 415 | 94 | 1716 | 491 | 19 | 22 | 3457 | 236 |
| % Exposures. | 197 | 120 | 125 | 388 | 343 | 356 | 271 | 298 | 2 | 266 | 235 | 161 | 152 | 158 | 183 | 395 | 407 |
| SAEs | 67 | 0 | 0 | 16 | 7 | 91 | 1 | 171 | 2 | 5 | 6 | 17 | 5 | 0 | 0 | 79 | 7 |
| % Exposures. | 3 | 0 | 0 | 12 | 3 | 10 | 4 | 6 | 7 | 3 | 15 | 2 | 2 | 0 | 0 | 9 | 12 |

Of the 479 SAEs in the database, 203 (42%) were classified as severe. The percentages of severe SAEs were different across treatments groups: 48%, 40%, and 46% for placebo, sugammadex, and neostigmine, respectively, with none of the treatments substantially different from one another. For sugammadex, there is no apparent dose dependency for the occurrence of severe adverse events based on the two types of adverse events (AE and SAE) and the total number of severe adverse events per dose group as seen in Table 14 above.

For each SOC, there was no apparent difference between sugammadex and the neostigmine and placebo treatments, and no indication that severe adverse events were sugammadex-dose dependent for any of the SOCs.

In summary, the analysis of the severe adverse events occurring for the four treatment groups and various dose groups of sugammadex did not indicate that sugammadex was associated with greater risk for such events compared to placebo, neostigmine or succinylcholine or that the risk for such events was greater with increased doses of sugammadex. These findings were consistent across SOCs and preferred terms for the most frequently occurring events.

7.3.5 Submission Specific Primary Safety Concerns

The review of safety conducted at the time of the original NDA submission resulted in the identification of three issues for which the risks associated with sugammadex had not been adequately evaluated to allow the benefit-risk analysis to be completed, and therefore, resulted in the Division taking a Not Approvable action. These issues included the following two deficiencies:

- Anaphylaxis/hypersensitivity reactions
- Insufficient information on the effects of sugammadex on coagulation pathways and perioperative bleeding

In addition to the above, it was also recommended that:

A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

After further discussions with the Applicant regarding data already available about QTc prolongation and arrhythmias, and upon consultation with the Division of Cardiovascular and Renal Products, the Division of Anesthesia, Analgesia, and Addiction Products

concluded with the Applicant that sugammadex is not likely to pose an increased risk for QTc prolongation or arrhythmias in the surgical setting, and therefore, it was not necessary to conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation as previously requested. It was noted that if sugammadex were to be approved, the cardiac adverse events observed in the clinical trials would be included in the label and monitoring for these events in the postmarketing period would need to be continued.

In the last submission, i.e., the 2012 submission, the Applicant addressed both of the deficiencies identified in the Not Approvable letter issued in 2008. At the end of that review cycle, it was determined that the Applicant had adequately resolved the issues surrounding the effects of sugammadex on the coagulation profile and the risk of postoperative bleeding. However, the study conducted to address the concerns about anaphylaxis occurring on repeat exposures to sugammadex (P06042), while appropriately designed to address the issue, was executed in a manner that unblinded investigators to the treatment administered and may have introduced bias in the safety data collected. Because of this data integrity issue, the Applicant was required to either repeat the study or to identify those subjects from the original trial whose data were potentially compromised and perform a sensitivity analyses on the primary and key secondary endpoints with the data from the remaining subjects providing a rationale for why the reduction in the study's power and the selective elimination of subjects from the analyses would not adversely affect the findings, thereby allowing the study to address the deficiency cited above. The Applicant opted to repeat the study and included the result from this new study (P101) in the current submission. Due to the number and severity of the protocol deviations that occurred during the execution of P101, but which have been determined to not have likely to have affected data integrity, it was decided that all of the investigative sites needed to be inspected to provide reasonable assurance that data integrity has not been compromised by any protocol violation that, heretofore, has not been identified. If the data integrity from P101 is reasonably assured, the results will have adequately addressed the safety concern, and there would be no impediment to recommending an approvable action. However, the necessary inspections cannot be completed during this review cycle, and therefore, a Complete Response action has been recommended. In the subsection below, the issues related to anaphylaxis and hypersensitivity and how they have been adequately addressed, if the concerns for data integrity can be resolved, are described and discussed. For completeness, the issues concerning the deficiency regarding the effects of sugammadex on coagulation and bleeding, resolved during the second review cycle, are described as are the issues concerning cardiac arrhythmias, which were resolved during the first review cycle. Postmarketing safety data available to data related to each of these three issues are considered in Section 8 below.

7.3.5.1 Anaphylaxis and Hypersensitivity

Preliminary Note

On July 12, 2013, the Office of Scientific Investigations notified the Division that they had uncovered a problem with the conduct of Trial P06042 during their inspection of Site #2 located in the United Kingdom. The inspection revealed there was potential unblinding of 53 out of 95 randomized subjects. Specifically, sugammadex is different in color from the normal saline placebo. To maintain the study blinding, the syringes were to have been masked, and the investigator giving the product was not to have been involved with adverse event evaluation. That did not occur at this site. The investigator both administered the study drugs and performed adverse event evaluations. The investigator was reported to have noticed that the viscosity of the product changed as the dosing increased. This situation persisted for 6-8 weeks of the study before the Applicant was made aware of the problem and took steps to address it. Although a note to file was made, which was discovered by the FDA inspector, the Applicant failed to notify the Agency of the problem and made no mention of it in the clinical study report. There were only 4 centers involved with Trial P06042; the only site in the United States had been closed due to bankruptcy proceedings and the source documents were unavailable for inspection. The two remaining sites were located in Germany and the Netherlands.

The unblinding of the subjects' treatments in this study raised concerns for the validity of the findings from that site as the assessment of hypersensitivity and anaphylaxis symptoms is subjective. The failure to report the protocol violation in the clinical study report and to notify the Division when the issue became known to the Applicant raised additional concerns over the validity of the study as a whole. The inability to examine source documents at the U.S. site only worsened the situation.

Due to these findings, the Advisory Committee meeting scheduled for July 18, 2013, was cancelled. At the time the original primary clinical review was completed, the issue had not been resolved and, it was unclear whether the Applicant will be able to salvage this study, which was pivotal to the product being approved in that cycle. Therefore, a recommendation for a Complete Response action was made by this reviewer and ultimately taken by the Division. To address the deficiency, the Applicant was required to provide the following information:

Characterization of the safety of sugammadex sodium on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. Exposure of subjects to repeat doses of sugammadex sodium should occur at time intervals sufficient to permit formation of drug-specific IgE, such as at least a minimum of 5 to 6 weeks. Define the frequency, time course of events related to sugammadex sodium administration, and other characteristics of the adverse reactions. Attempt to define the immunological basis or other pathophysiology of

these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium. The clinical program will inform the safety risk of sugammadex sodium on repeat exposure. Development of a predictive test will be useful in predicting risk and potentially in avoiding exposures to patients at risk for an anaphylactic reaction.

A Post-Action meeting was held with the Applicant on December 1, 2008. The following were the key discussion points related to sugammadex-related anaphylaxis:

1. The Applicant reported that all antibody testing for Trial 19.4.110 had been negative and concluded that the underlying mechanism for the sugammadex-related hypersensitivity reactions were not immunoglobulin-mediated. DPAP did not agree with this assessment as the negative predictive value of these assays is limited. While positive antibody results would be consistent with the skin testing results and provide insight into the pathophysiology, a negative result does not exclude the possibility of an immunoglobulin-mediated reaction. In addition, whether results of IgE/IgG testing were positive or negative, the risk of repeated exposures still needed to be assessed in a clinical setting given the anticipated widespread use of the drug. Delineating the underlying mechanism might be helpful in developing ways to minimize risk but would not replace the need for a formal safety assessment of repeated exposures.
2. The Applicant was encouraged to explore both IgE/IgG-mediated and non-IgE/IgG mediated mechanisms; however, they were reminded that a negative ELISA test result would not be sufficient to eliminate the possibility of antibody-based hypersensitivity reactions.
3. The strength of animal data to support repeat exposure in man was limited given the lack of a good animal model for anaphylaxis. Controlled data in humans was required. The original clinical program did not formally assess the safety of repeat exposure at time intervals sufficient to permit formation of drug-specific IgE in an adequate number of patients.
4. The Agency would review any protocols to address these issues and provide feedback to assure the trials were adequately designed.

Study P101 was conducted by the Applicant to address the deficiency. The protocol is described and the findings are summarized in Section 9.4 of this review. They are considered in greater detail by the clinical reviewers from the Division of Pulmonary, Allergy and Rheumatology Products, whose review and recommendations were not finalized at the time this review was completed. If the integrity of the data from the trial is deemed to be reasonably unaffected by the protocol violations, the conclusions drawn would be upheld and the deficiency would likely be adequately addressed.

Anaphylaxis and Hypersensitivity Findings in the Current Safety Database

Potential events of hypersensitivity and anaphylaxis were investigated by the Applicant based on exposure to sugammadex from all clinical trials conducted in the clinical development program. For the analysis, three methods were used:

1. Automated searches
2. Searches of AEs related to hypersensitivity/anaphylaxis as diagnosed by the investigator and considered to be drug-related in the opinion of the investigator
3. Retrospective adjudication of events suggestive of hypersensitivity

These approaches were reported to be similar to those used in the first resubmission.

The Standardized MedDRA Query (SMQ) for 'Hypersensitivity' was used to identify subjects in the Clinical Trial database who may have experienced an allergic/hypersensitivity reaction. The SMQ analysis consisted of data from subjects who received sugammadex or placebo and also received a NMBA and/or anesthesia (Pooled Phase 1-3 trials) as well as data from subjects who did not receive a NMBA or anesthesia (Pooled Phase 1 trials). Not analyzed were subjects who participated in trials with neostigmine-control arms.

The results of the Applicant's SMQ analysis for "anaphylactic reaction" and "hypersensitivity" in the Pooled Phase 1-3 trials by placebo, dose group of sugammadex, and total sugammadex are presented in Table 15. They reported that there was no evidence suggesting a dose response across sugammadex doses for any of the searches. For the "anaphylactic reaction" narrow-term search, circulatory collapse was the event identified at similar incidences for total sugammadex and placebo (0.1% total sugammadex, and 0.4% placebo) in the Pooled Phase 1-3 dataset. Specifically, 2 (0.4%) events of circulatory collapse were identified for exposure to placebo and 3 (0.2%) events were observed for exposure to 4 mg/kg sugammadex. No events were identified in the 16 mg/kg group for this narrow category. The algorithmic search showed that incidences for total sugammadex (0.8%) and placebo (0.6%) were similar. For the broad-term search, the incidences for total sugammadex (11.0%) and placebo (8.6%) were also similar. For the "hypersensitivity" narrow-term search, the incidences for total sugammadex and placebo were reported to be similar (3.1% for sugammadex; 2.6% for placebo) in the Pooled Phase 1-3 dataset. For the broad-term search, the incidences for total sugammadex (6.8%) and placebo (6.1%) were also reported to be similar.

Table 15. Applicant findings of anaphylaxis and hypersensitivity in the Pooled Phase 1-3 trials (based on Table 46, p. 146 of the ISS)

| | | 0 mg/kg (Placebo) | Sugammadex | | | Total Sugammadex ^A |
|-----------------------|-------------|----------------------|------------|------------|-----------|----------------------------------|
| | | | 2 mg/kg | 4 mg/kg | 16 mg/kg | |
| | | N=544 | N=895 | N=1921 | N=98 | N=3601 |
| SMQ | SMQ search | n (%) | n (%) | n (%) | n (%) | n (%) |
| Anaphylactic reaction | Narrow | 2 (0.4) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.1) |
| | Algorithmic | 3 (0.6) | 5 (0.6) | 20 (1.0) | 0 (0.0) | 30 (0.8) |
| | Broad | 47 (8.6) | 90 (10.1) | 214 (11.1) | 16 (16.3) | 395 (11.0) |
| Hypersensitivity | Narrow | 14 (2.6) | 28 (3.1) | 66 (3.4) | 4 (4.1) | 113 (3.1) |
| | Broad | 33 (6.1) | 62 (6.9) | 147 (7.7) | 5 (5.1) | 245 (6.8) |

N = total number of exposures per treatment; n= number of subject exposures per dose.

SMQ = Standardized MedDRA query.

^A Total column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg)

The results of the SMQ analysis for anaphylactic reaction and hypersensitivity in the Pooled Placebo-controlled trials by sugammadex and placebo are shown in Table 16 below. The Applicant reported that the incidences for both reactions were comparable between treatment groups for all searches, i.e., the confidence intervals included zero for the weighted and non-weighted differences. For the anaphylactic reaction narrow search, the overall incidences were 0.1% for sugammadex and 0.4% for placebo. For the algorithmic search, the overall incidences were 0.9% for sugammadex and 0.6% for placebo. For the broad search, the incidences were 10.8% for sugammadex and 8.6% for placebo. For the hypersensitivity narrow search, the overall incidences were 2.8% for sugammadex and 2.6% for placebo. For the broad search, the incidences were 4.4% for sugammadex and 6.1% for placebo.

Table 16. Applicant findings of anaphylaxis and hypersensitivity in the Placebo-Controlled trials (based on Table 47, p. 147 of the ISS)

| | | Total Sugammadex ^A | Placebo | | |
|-----------------------|-------------|-------------------------------|----------|---|---|
| | | N=1078 | N=544 | | |
| SMQ | SMQ search | n (%) | n (%) | Difference (95% CI) non-weighted ^B | Difference (95% CI) study-weighted ^B |
| Anaphylactic reaction | Narrow | 1 (0.1) | 2 (0.4) | -0.3 (-1.2, 0.2) | -0.2 (-1.2, 0.5) |
| | Algorithmic | 10 (0.9) | 3 (0.6) | 0.4 (-0.7, 1.2) | 0.4 (-0.8, 1.4) |
| | Broad | 116 (10.8) | 47 (8.6) | 2.1 (-1.0, 5.0) | 0.4 (-2.8, 3.5) |
| Hypersensitivity | Narrow | 30 (2.8) | 14 (2.6) | 0.2 (-1.7, 1.8) | 0.7 (-1.3, 2.6) |
| | Broad | 47 (4.4) | 33 (6.1) | -1.7 (-4.3, 0.5) | -1.5 (-4.2, 0.9) |

N = number of subject exposures; SMQ = Standardized MedDRA query.

^A Total column includes subjects exposed to all doses of intravenous sugammadex (<2 to 32 mg/kg)

^B 95% confidence interval according to Miettinen and Nurminen method

Postmarketing Findings

An updated review of the postmarketing reports of adverse events related hypersensitivity and anaphylaxis is provided in Section 8 below.

Summary and Conclusions

Due to the OSI investigation findings for Trial P06042, it is not possible, at this time, to draw definitive conclusions regarding the potential for increased risk of anaphylaxis with repeat exposures to sugammadex. Based on the findings from Trial P06042, the data in the original NDA submission, and the postmarketing data available to date, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) has concluded that sugammadex causes anaphylaxis and hypersensitivity reactions. The risk for these reactions appears to increase with higher doses. They have also indicated that whether the risk related to sugammadex is greater than the risk for other drug products commonly used in the perioperative setting is difficult to determine; furthermore, they have stated that there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the benefit-risk analysis will have to be used to make that determination.

7.3.5.2 Coagulation and Perioperative Bleeding

Background

In the original NDA submission, the Applicant did not assess coagulation parameters as part of the clinical laboratory investigations. Instead, they conducted two *in-vitro* studies mixing whole blood with sugammadex. These studies indicated that sugammadex causes statistically significant increases in the mean measured values of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the international normalized ratio for PT (INR); although, the mean values were reported to have been within normal limits of the laboratory performing the analyses. The Applicant indicated that the values were increased for concentrations of sugammadex comparable to peak plasma concentrations associated with a 16 mg/kg dose; however, changes for comparable concentrations of the other proposed doses were not evaluated.

In an effort to determine whether there was a clinical impact from these changes, the Applicant conducted a post hoc analysis in which aggregated data from the Phase 2 and 3 trials were evaluated for adverse events related to hemorrhage. Overall, there were such events reported in 6% of sugammadex-treated subjects but only in 3% of placebo-treated subjects. By repeating the analysis and limiting the preferred terms and expanding the sugammadex-treatment group to the Total Sugammadex group, i.e., adding subjects from studies not involving surgical procedures, the difference between treatment groups dropped to 0.5%.

It was noted that the Applicant, in discussing the potential mechanism of sugammadex interference with the coagulation parameters, stated that the mechanism is unknown and that “it is unknown what the clinical relevance of this is.”

Due to the safety concerns related to postoperative bleeding and the need for some patients to be anticoagulated perioperatively and for other patients to be anticoagulated during certain surgical procedures and then have the anticoagulation reversed at the end of the procedure, e.g., coronary artery bypass grafting using a cardiopulmonary bypass machine, it was considered imperative that the mechanism by which sugammadex affects coagulation and the extent to which it affects bleeding in patients be elucidated prior to the product being approved for marketing. An understanding of any drug-drug interaction that might occur between sugammadex and commonly used anticoagulants was also considered critical for the safe use of the product in the surgical population.

Initial Regulatory Action and Follow Up

In the Complete Response letter of July 31, 2008, the following deficiency, which precluded approval of the product, was noted:

The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program. The *in vitro* assessment

indicated that sugammadex increased activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and the International Normalized Ratio (INR). In a comparison of hemorrhagic adverse events between placebo- and sugammadex- treated subjects, which were not included in protocol-specified safety assessments, fewer events were observed in the placebo- treated groups. A difference in these events persisted when the comparison was further refined. The mechanism and the clinical significance of the effects of sugammadex on coagulation are not known.

To address the deficiency, the Applicant was required to provide the following information:

Studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting.

During the Post-Action meeting that was held on December 1, 2008, the following issues were discussed:

1. The Applicant stated that they had conducted a study (Trial 19.4.115) to assess coagulation parameters and observed mild transient increases for aPTT/PT. The PK-PD analysis revealed no statistically significant relationship between sugammadex plasma concentrations and aPTT. A statistically significant relationship was found for PT (INR). At the mean maximum sugammadex plasma concentration after a 4 mg/kg or 16 mg/kg sugammadex dose, the predicted PT(INR) increase was 6% and 22%, respectively.
2. The Applicant stated that sugammadex was interacting with Factor 10a, but not in a clinically relevant manner that would translate into a bleeding risk.
3. The Applicant reported that they observed additive effects with Vitamin K.
4. The Division stated that to have its concerns fully addressed, data regarding the mechanism of action, the dose response, the pharmacodynamic effect and possible interactions between sugammadex and other drugs affecting coagulation (e.g., heparin, warfarin, aspirin, and clopidogrel bisulfate) would need to be submitted.
5. The Division indicated that mechanistic data from vitro studies, studies in appropriate nonclinical models of bleeding, and data on coagulation parameters in a healthy volunteer trial may provide a substantial understanding of the effects of sugammadex on coagulation and may help limit the data needed from a clinical study to complete the benefit:risk analysis. However, the effects of sugammadex when it binds with non-NMBA moieties and the impact that has on postadministration bleeding would not likely be addressed by these studies. There was a concern that the effects of sugammadex on coagulation may present differently when used as intended in the clinical setting compared to

carefully controlled studies that do not expose subjects to all the medications typically used in the perioperative period. Therefore, clinical trials assessing bleeding were needed.

6. The Agency would review any protocols to address these issues and provide feedback to assure the trials were adequately designed.

2012 NDA Resubmission

The Applicant conducted two drug-drug interaction studies, one that evaluated a potential interaction between sugammadex and aspirin (Trial P07025) and one that evaluated a potential interaction between sugammadex and enoxaparin or unfractionated heparin (Trial P07044). These trials were designed with input from the Division of Hematology Products (DHP).

Trial P07025 was a Phase 1, randomized, double-blind, placebo-controlled, 4- period cross-over, drug-drug interaction study that evaluated the effect of sugammadex and aspirin on platelet aggregation and coagulation parameters in healthy male volunteers. The primary objective of the trial was to investigate the potential for an interaction between sugammadex (4 mg/kg) and aspirin on platelet aggregation (PA) using collagen-induced whole blood aggregometry following multiple daily doses of 75 mg of aspirin. The Applicant concluded from the study that:

1. There was no clinically significant interaction between sugammadex and aspirin on platelet aggregation.
2. There was no clinically significant interaction between sugammadex and aspirin on aPTT and PT.
3. There was no clinically significant interaction between sugammadex and aspirin on the cutaneous bleeding time.

DHP had the following comments and conclusions regarding this study:

1. There was no evidence of a clinically meaningful additive antiaggregant effect of sugammadex when administered with aspirin.
2. There was no evidence of an additive effect of sugammadex with aspirin compared to aspirin alone on the prolongation of aPTT and PT.

Study P07044 was a Phase 1, randomized, double-blind, placebo-controlled, 4 period, two-part cross-over study to that evaluated the potential interaction between 4 mg/kg and 16 mg/kg dose of sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity in healthy volunteers. The primary objective of the trial was to investigate the potential effect of 4 mg/kg and 16 mg/kg sugammadex on the anti-Xa activity of enoxaparin and on the aPTT activity of unfractionated heparin (UFH).

Pharmacokinetic data indicated there was no effect of either enoxaparin or UFH on the C_{max} or AUC_{0-6 hr} of sugammadex. The PK/PD data showed that there was a sugammadex dose-related increase in both the aPTT and the PT whether sugammadex

was given with placebo, enoxaparin or UFH. The Applicant concluded that there was no clinically significant effect of sugammadex on the anti-Xa activity induced by enoxaparin, or on the prolongation of the aPTT induced by UFH.

DHP reviewed the study report and had the following comments and conclusions:

1. The metrics used by the Applicant were those most commonly used to measure the anticoagulant adequacy of enoxaparin and UFH.
2. There was no clinically relevant effect of 4 mg/kg and 16 mg/kg doses of sugammadex on the anti-Xa activity of enoxaparin.
3. The administration of sugammadex induced a dose-dependent prolongation of both the PT and the aPTT as had been previously noted. All prolongations reverted to baseline within 1 hour.

Based on the data from these two studies, DHP concluded that there was a noticeable, but small, dose-related, short term effect of sugammadex on the anticoagulant activity of both enoxaparin and UFH. Based on the data from the sponsor's companion clinical study (P07038, discussed below), these changes induced by sugammadex were not clinically significant because they did not lead to an increase in the frequency of bleeding in patients who had undergone major orthopedic surgery of the lower extremity. Additionally, there was probably no clinically meaningful drug-drug interaction on platelet aggregation, the aPTT or the PT when sugammadex is given together with aspirin as compared to the effects of aspirin alone on these parameters.

To evaluate the frequency of bleeding in patients undergoing surgery with the use of rocuronium or vecuronium that was reversed with sugammadex, the Applicant conducted Trial P07038, which was a randomized, controlled, parallel-group, double-blind trial comparing sugammadex to "usual care" (i.e., neostigmine or placebo/spontaneous recovery) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin. The protocol for this study was reviewed by DHP and, after revisions, was determined to be appropriately designed to address the issue. Its key features included the following:

1. The study would enroll subjects who were to have major orthopedic surgery on the hip or knee, thereby providing a reasonably homogeneous population whose frequency of bleeding was quite well known and that was enriched for possible hemorrhagic events because of the use of drugs given for thromboprophylaxis.
2. Subjects must have received anticoagulant/antiplatelet therapy prior to surgery to better capture of any drug-drug interactions that increase bleeding. The short-lived effects of sugammadex on aPTT and PT might not be evaluable if thromboprophylaxis were administered after surgery.
3. Enrollees would receive thromboprophylaxis using one of several approved regimens because of the high frequency (40-60%) of venous thromboembolic events that occurs without the use of anticoagulants.

4. Enrollment of this population would include many elderly subjects with mild to moderate renal dysfunction (Creatinine clearance ≥ 30 ml/min and ≤ 60 ml/min). Since previous studies had shown that this degree of renal dysfunction was not associated with an increase in peak concentrations of sugammadex (but only a somewhat longer half-life) and that the effect of sugammadex on the increase in aPTT and PT was dissipated over approximately 30 minutes, it would be important to assess bleeding in such patients. The protocol was designed to assess the frequency of bleeding over the 24 hour period following administration of sugammadex so that any effects of renal dysfunction on bleeding after sugammadex use could be determined.
5. The primary endpoint was the incidence of adjudicated bleeding events within 24 hours of the administration of study drug.

The major findings from the study included the following, for which the Applicant and DHP were in agreement:

1. The adjudicated incidence of bleeding was 2.9% of subjects randomized to the sugammadex arm versus 4.1% in the usual care arm. These events included both major bleeding (2.0% vs 3.4% in the sugammadex and usual care arms, respectively) as defined in the protocol and unexpected non-major bleeding (0.9% versus 0.7% in the sugammadex and usual care arms, respectively) as determined by the Adjudication Committee. For the majority of events, the relationship between the trial drug and bleeding was determined to be "possible".
2. The frequency of the bleeding endpoint in this trial was lower than anticipated based on a review of the experience in patients undergoing orthopedic surgery of the lower extremity (5%), particularly for subjects assigned to the sugammadex arm. This led to an extension of the study with an increase in the number of subjects enrolled, i.e., from the planned 800 subjects to when either the number of adjudicated, suspected unanticipated adverse events of bleeding reached 33 or a total of 1200 subjects had been enrolled. These findings suggested that although sugammadex is associated with a brief period of elevation in the aPTT and PT, these laboratory findings do not predict an increase in the frequency of bleeding.
3. Despite the use of drugs designed to impair the coagulation response (particularly heparin or one of its congeners) in all of these patients, there did not appear to be a synergistic effect on post-operative bleeding.
4. A secondary endpoint for the trial extended the time of observation for the bleeding from the first 24 hours after surgery to 14 days after surgery. There was some increase in major and unexpected non-major bleeding during the extension, but most of those events were considered to be unlikely related to trial drug administration.
5. Patients with a reduced creatinine clearance appeared to have a greater frequency of bleeding than those with a normal creatinine clearance, but there was no difference in the relative risk of bleeding whether patients were treated with sugammadex or placebo in each subgroup.

6. At 10 minutes after trial drug administration, there was a small, but statistically significant, increase in the aPTT in subjects in the sugammadex arm compared to baseline [4.7% (CI, 3.4%, 5.9%)] and in subjects in the sugammadex arm compared to the usual care arm [5.5% (CI, 3.7%, 7.3%)]. Similar comparative increases were noted in the PT measurements [4.5% (CI, 3.3%, 5.8%) and 3.0% (CI, 1.3%, 4.7%)], respectively. At 60 minutes after trial drug administration, the laboratory findings had dissipated.
7. All bleeding endpoints occurred at a lesser frequency in the sugammadex treated subjects than in the usual care subjects, but these differences were not statistically significant.
8. There were no significant differences between sugammadex and usual care treatments for incidence of postoperative anemia or venous thromboembolic events.
9. There was a small, but noticeable, increase in aPTT at 3 minutes after trial drug administration in subjects who received sugammadex but not in those in the usual care arm. Most of the increase had dissipated by 30 minutes and was completely ablated at 60 minutes.

DHP did not find issues with any of the results presented for this study or disagree with any of the conclusions reached by the Applicant. They concurred that there is no evidence that the administration of sugammadex to patients undergoing major orthopedic surgery of the lower limb and receiving thromboprophylaxis with heparin have a greater frequency of hemorrhage than patients receiving usual care (with neostigmine or placebo), even though patients treated with sugammadex have some prolongation of the aPTT and the PT that lasts for less than 60 minutes after administration. From the perspective of DHP, the trial was performed in accord with the agreed upon protocol.

Postmarketing Findings

Hemorrhage events that were reported to the Applicant from the initial approval of sugammadex in July 2008 through June 15, 2012, totaled five. All of the events were serious adverse events including two deaths. These events were also reviewed by DHP.

Four of the cases reported an actual bleeding event

1. Two cases of bleeding at the operative site:
 - a. One report for bleeding of the parotid gland, which required additional surgery at 8 hours after administration of sugammadex. The reporter attributed the cause of the bleed to “sutural insufficiency” and not to sugammadex.
 - b. One report of bleeding of the tonsil, which occurred several hours after the administration of sugammadex, required additional surgery, but was not attributed to the product as the bleeding “occurred in the surgical field.”

2. One case involved a patient who developed disseminated intravascular coagulation after the onset of anaphylaxis. He was found to have bleeding at multiple surgical sites following total gastrectomy. This patient died 3 days after his initial surgery from a combination of multiorgan failure and cardiac arrest.
3. One case involved a patient who experienced bradycardia leading to cardiac arrest within a minute of receiving sugammadex. The patient was treated with an intra-aortic balloon pump and went on to have an intra- abdominal hemorrhage due to laceration of the aorta. The patient died 19 days following her surgery.
4. One case had little detailed information but described a patient who underwent an orthopedic surgery involving the femur and late that day was reported to have hypotension, bradycardia, increased vascular permeability, and hemorrhagic shock.

DHP concurred with the Applicant that these reports do not suggest a bleeding problem that is related to the use of sugammadex. From an anesthesia perspective, these reports did not suggest that sugammadex causes bleeding; they were consistent with events that might be expected to occur in a small number of patients following surgery. While the risk of bleeding from sugammadex appears to be small, the cardiovascular changes following sugammadex administration that ultimately to the patients' bleeding events are noteworthy, particularly as they appear to be related to possible anaphylactic reactions.

Summary and Conclusions

DHP indicated that on the basis of the data generated in Study P07038, there is no evidence that there is an increase in bleeding after the administration of sugammadex compared to neostigmine/placebo to patients who have undergone major orthopedic surgery of the lower limb and have received thromboprophylaxis with heparin or low molecular weight heparin. Furthermore, while sugammadex may transiently increase aPTT and PT (INR), the effect does not impact the risk for bleeding. The use of sugammadex in conjunction with aspirin has no effect on platelet aggregation, aPTT and PT, and cutaneous bleeding time. There is no clinically relevant effect of 4 mg/kg and 16 mg/kg doses of sugammadex on the anti-Xa activity of enoxaparin.

From an anesthesia perspective, the studies conducted have demonstrated that sugammadex has a transient effect on aPTT, PT and INR that may need to be taken into account for laboratory assessments made within an hour of sugammadex administration, but that does not affect postoperative bleeding or the risk of thromboembolic events. Sugammadex was shown to not have a clinically meaningful effect on the anticoagulant properties of aspirin, enoxaparin, heparin and low molecular weight heparin. The risk of postoperative bleeding following administration of sugammadex is no greater than that following neostigmine or spontaneous recovery from either rocuronium or vecuronium. These studies have addressed the deficiency listed in the Complete Response letter.

7.3.5.3 Cardiac Arrhythmias

Background

In the original NDA submission, the Applicant included the clinical study reports for two thorough QT studies: Trial 19.4.109 and Trial 19.4.105.

Trial 19.4.109 was a single-center, randomized, double-blind, placebo-controlled, 6-period crossover trial that evaluated the occurrence of QTc prolongation in healthy volunteers for:

- Single intravenous doses, 4 mg/kg or 32 mg/kg, of sugammadex alone
- A combination of a 32 mg/kg intravenous dose of sugammadex with rocuronium (1.2 mg/kg) or vecuronium (0.1 mg/kg) administered simultaneously with the sugammadex, but via separate catheter lumens, over 4 minutes
- An intravenous dose of 400 mg moxifloxacin administered over 60 minutes was used to establish assay sensitivity.

The Applicant reported that for all treatment groups (sugammadex alone and sugammadex in combination with rocuronium or vecuronium), the largest upper limit of the 95% confidence interval (CI) for the time-matched change from baseline in the individually corrected QT intervals (QT_{CI}) compared to placebo for all time points, at both sugammadex doses, was less than 10 milliseconds, the margin of regulatory concern. For moxifloxacin, the positive control, the estimate of the maximum time-matched change from baseline in QT_{CI} compared to placebo was 20.8 milliseconds (90% CI: 18.5 to 23.1 milliseconds, which supported assay sensitivity for the trial. They concluded that this thorough QT/QTc trial with 4 mg/kg and 32 mg/kg doses of sugammadex alone and 32 mg/kg sugammadex in combination with rocuronium or vecuronium was negative according to the criteria of ICH-E14 and that sugammadex alone or in combination with rocuronium or vecuronium was not associated with QTc prolongation of clinical concern.

Trial 19.4.105 was a single-center, placebo-controlled, 5-period crossover trial designed to determine the effect of single intravenous (IV) doses of 4 and 32 mg/kg sugammadex on QTc interval prolongation in healthy volunteers. An intravenous dose of 400 mg moxifloxacin was used to demonstrate assay sensitivity. The trial was open-label for moxifloxacin and double-blind for sugammadex and placebo. The primary parameter was the QT_{CI}.

The Applicant reported that the time-matched mean QT_{CI} difference between the sugammadex and the placebo groups was close to zero for each time point. In addition, the upper limits of the one-sided 95% CIs for the largest time-matched mean QT_{CI} differences from placebo were below the 10-millisecond margin of regulatory concern. They noted that the maximum mean QT_{CI} difference from placebo was 1.8 milliseconds (upper limit 95% CI: 4.3 milliseconds) and 2.8 milliseconds (upper limit 95% CI: 5.3 milliseconds) after 4 mg/kg and 32 mg/kg sugammadex, respectively. For moxifloxacin,

the estimate for the maximum time-matched mean QT_{Cl} difference to placebo was 18.6 milliseconds (90% CI: 15.4 to 21.8 milliseconds) thereby establishing assay sensitivity. They concluded that, according to the criteria of the ICH E14 guidance, 4 mg/kg and 32 mg/kg doses of sugammadex are not associated with QTc prolongation of clinical concern.

The two studies were reviewed by the Agency's Interdisciplinary Review Team for QT Studies. They concluded that the Study 19.4.109 was conducted in a satisfactory manner, and although there was a concentration-dependent increase in the QT_{Cl}, the increase for the supratherapeutic dose (32 mg/kg) did not result in a clinically significant increase. The results for Study 19.4.105 were comparable, and the Interdisciplinary Review Team opted to not repeat their analysis, since the Applicant assessed the same doses as in the other study.

The Applicant also analyzed the morphological features of ECGs collected across studies. They reported that no differences from placebo were noted for heart rate, the PR interval, as well as the QRS complex, T wave, and U wave morphologies.

In the review of the original NDA submission, a tabulation of the adverse event database for cardiac arrhythmias resulted in the findings shown in Table 17. The data indicated that bradycardia, QTc interval prolongation, and tachycardia were reported more frequently than the other arrhythmias and that these adverse events occurred in more sugammadex dose groups than did the others. The data in the table indicate that, for bradycardia and tachycardia, the frequencies are similar to those of neostigmine and not sugammadex-dose dependent. For QTc prolongation, the findings appear to be similar; although the 8% occurrence with the less-than-maximum labeled sugammadex dose of 12 mg/kg raised the concern that there may be a safety signal here despite the findings from the two thorough QT studies. It should be noted that none of the prolonged QTc intervals was associated with an incidence of Torsade de Pointes.

Table 17. Summary of cardiac arrhythmia adverse events from the original NDA safety database occurring within 72 hours of study drug administration [2007 safety database (original submission)]

| Adverse Event | Placebo | Sugammadex (mg/kg) | | | | | | | Neostig. (mcg/kg) | | Spont. Recov. From Sux. | Moxi. 400 mg |
|---------------------------------------|------------|--------------------|------------|------------|------------|-----------|-----------|-----------|-------------------|-----------|-------------------------|--------------|
| | | < 2 | 2 | 4 | 8 | 12 | 16 | > 16 | 50 | 70 | | |
| N | 174 | 321 | 616 | 611 | 126 | 39 | 97 | 38 | 168 | 41 | 54 | 94 |
| Number of Exposures | 174 | 321 | 616 | 611 | 126 | 39 | 97 | 38 | 168 | 41 | 54 | 94 |
| QTc interval prolonged | 2 (1%) | 2 (1%) | 12 (2%) | 7 (1%) | 2 (2%) | 3 (8%) | 4 (4%) | -- | -- | -- | -- | 1 (1%) |
| Atrial fibrillation | 2 (1%) | 1 (0%) | 8 (1%) | -- | -- | -- | -- | -- | -- | 1 (2%) | -- | -- |
| Sinus tachycardia | -- | 1 (0%) | 1 (0%) | 4 (1%) | 1 (1%) | -- | 1 (1%) | 1 (3%) | 1 (1%) | -- | -- | -- |
| Sinus bradycardia | 1 (1%) | -- | 4 (1%) | 1 (0%) | -- | 1 (3%) | -- | -- | -- | -- | -- | -- |
| Ventricular tachycardia | -- | -- | 2 (0%) | 0 (0%) | -- | -- | -- | 1 (3%) | -- | -- | -- | -- |
| Extrasystoles | 3 (2%) | -- | 1 (0%) | 1 (0%) | -- | -- | 1 (1%) | 1 (3%) | 2 (1%) | -- | 1 (2%) | -- |
| Electrocardiogram T wave abnormal | 2 (1%) | -- | 1 (0%) | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- |
| Atrioventricular block | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- |
| Electrocardiogram ST segment abnormal | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Electromechanical dissociation | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- |

A similar analysis was conducted with only the serious adverse events (SAEs). As indicated in Table 18, QTc prolongation was the only SAE to occur in multiple sugammadex dose groups and at a frequency that suggests a possible safety signal when compared to the neostigmine and placebo treatments.

Table 18. Summary of cardiac arrhythmia and acute myocardial infarction SAE data from the original NDA safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | Neostigmine (mcg/kg) | |
|-----------------------------|------------|--------------------|-----------|----------|----------|----------|----------|----------------------|----|
| | | 0.5 | 2 | 4 | 8 | 12 | 16 | 50 | 70 |
| N | 336 | 124 | 613 | 729 | 154 | 39 | 127 | 135 | 74 |
| Adverse Event | | | | | | | | | |
| Acute myocardial infarction | 1 | | | | | | | | |
| Atrial fibrillation | | 1 | 3 | | | | | | |
| QTc interval prolonged | 2 | | 13 | 4 | 1 | 3 | 4 | | |
| % of N | 1 | | 2 | 1 | 1 | 8 | 3 | | |
| Ventricular tachycardia | | | 1 | | | | | | |
| Total | 3 | 1 | 17 | 4 | 1 | 3 | 4 | | |
| % of N | 1 | 1 | 3 | 1 | 1 | 8 | 3 | | |

These data were presented to the Anesthetic and Life Support Drugs Advisory Committee in 2008. Although some of the committee members expressed concern over the serious nature of some of the arrhythmias, the concern was assuaged by the following:

1. The arrhythmias generally occurred within minutes of the administration of sugammadex at a time while patients are intensively monitored for cardiac problems and treatments are readily available if needed.
2. Most of the events resolved either spontaneously or with minimal intervention.
3. The numbers of adverse events were in the same range of those for neostigmine, and the data for neostigmine may have been affected by the coadministration of glycopyrrolate.
4. While the effect size for sugammadex was almost double that of the placebo group, it might have been possible that the confidence intervals overlapped.

Ultimately, the committee recommended that sugammadex be approved; however, they considered postmarketing surveillance for cardiovascular events to be an important aspect of the product's approval.

Initial Regulatory Action and Follow-Up

Based on the safety analyses conducted during the review of the NDA, there was no clear evidence that sugammadex, on its own, caused the cardiac arrhythmias observed in the clinical studies. Whether the product in some way contributed to the risk for these events was uncertain. Although the thorough QTc studies appeared to exonerate sugammadex from the QTc prolongation, those studies did not assess the risk in the presence of an anesthetic or at the end of a surgical procedure. Whether sugammadex, in combination with the stress, blood loss, and hemodynamic changes associated with surgical procedures or with the numerous anesthetic agents used during the procedure, may increase the risk for arrhythmias was not known.

In addition to the issues above, sugammadex was a new molecular entity and little was known about the arrhythmogenic potential of cyclodextrins when used in the perioperative setting. Based on these considerations, it was recommended in the complete response letter that the Applicant conduct:

A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

Due to the size of the safety database in the original NDA submission, the benign outcomes for most of the arrhythmias, and the ability of clinicians to detect and treat the arrhythmias should they occur in the clinical setting for which sugammadex is intended, it was determined that the risk for these adverse events had been sufficiently evaluated such that the study described above was not essential for the product's approval. Rather, the study would help determine whether sugammadex poses a risk for arrhythmias, and if so, it would better define that risk.

Following the issuance of the Complete Response letter, the Applicant submitted the results of a meta-analysis of the QTcF data from the placebo-controlled studies that included ECG assessments. In that analysis, a total of 374 patients treated with sugammadex and 77 patients treated with placebo were evaluated. ECG data were available for these subjects at 2 and 30 minutes following the administration of study drug. The results, as reported by the Applicant, revealed that both at 2 and 30 minutes after treatment there was no relevant average QTcF prolongation comparing sugammadex to placebo (-1.1 and -0.9 ms respectively). Furthermore, they noted that when investigating QTcF outliers using criteria as suggested by ICH E14, observed data provided no indication that patients treated with sugammadex had a significantly increased frequency of prolonged QTcF values as compared to placebo treated patients; when summarizing patients with a value satisfying any outlier criterion (i.e., a

QTcF value > 450 ms and/or a change from baseline > 30 ms), the frequency of patients was 41% for sugammadex versus 38% on placebo.

Based on all the information available to that point and internal discussions with the Division of Cardiovascular and Renal Products, the Division of Anesthesia, Analgesia, and Addiction Products concurred with the Applicant that sugammadex is not likely to pose an increased risk for QT prolongation or arrhythmias in the surgical setting, and therefore, it was not necessary to conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation as previously requested. It was noted that if sugammadex were to be approved, the cardiac adverse events observed in the clinical trials would be included in the label and monitoring for these events in the postmarketing period would need to be continued.

Despite the Division's position regarding the need for another cardiac study, the Applicant conducted Trial P06315 to evaluate the effect of a therapeutic dose, 4.0 mg/kg, of sugammadex in combination with maintenance anesthesia using propofol or sevoflurane, on QTc prolongation. The trial was a double-blind, randomized, multi-site, placebo-controlled, parallel-group, 2-factorial study with factors for single-blind anesthetic maintenance (propofol versus sevoflurane) and double-blind reversal agent (sugammadex versus placebo), in healthy subjects. Study drug was administered after anesthesia had been maintained for 20 minutes. An additional arm of subjects treated with neostigmine (50 mcg/kg) and glycopyrrolate (10 mcg/kg) was also evaluated using a single-center, open-label design.

The Applicant reported that sugammadex 4 mg/kg was not associated with relevant QT/QTc prolongation as compared to placebo when combined with maintenance anesthesia with propofol or sevoflurane. For all prespecified timepoints, up to 30 minutes after study drug administration, the estimated differences between sugammadex and placebo in change of QTcF from baseline and corresponding upper one-sided 95% confidence limits were below the margin of 10 msec for each type of maintenance anesthetic separately as well as combined over both anesthetic arms. In addition, the Applicant noted that mean QTcF increases exceeding the level of regulatory relevance were observed during maintenance anesthesia, i.e., prior to study drug administration, with both propofol and sevoflurane. The mean QTcF prolongations compared to pre-anesthesia baseline were most pronounced for sevoflurane (mean QTcF prolongations exceeding 30 msec), while during maintenance anesthesia with propofol, mean QTcF prolongations exceeding 10 msec were observed. Furthermore, during maintenance anesthesia with propofol, incidental QTcF values between 450 and 480 ms were reported, but no QTcF values exceeding 480 msec. During maintenance anesthesia with sevoflurane, the incidence of QTcF values between 450 and 480 msec was higher than during maintenance with propofol, and QTcF values between 480-500 msec or exceeding 500 msec were observed.

The Interdisciplinary Review Team for QT Studies reviewed the study findings and concurred that no significant QTc prolongation effect of sugammadex was detected, and the largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/sugammadex were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

The First (2012) NDA Resubmission

Since the time of the initial regulatory action, sugammadex has been approved and marketed in a number of countries. Its use in the intended clinical setting has resulted in a number of cardiac arrhythmias being reported as adverse events to the IND. In addition, the Applicant has conducted another 20 clinical trials during the same time period, and in the process, has doubled the safety database. As part of the resubmission of the NDA, the Applicant was instructed to analyze both the clinical trial data and the postmarketing data evaluating the occurrence of all arrhythmias. Each analysis will be considered below.

Clinical Trial Safety Database

To compare the incidence of arrhythmias across treatment groups, the Applicant performed Broad and Narrow Standardized MedDRA Query (SMQ) analyses for “Cardiac Arrhythmias” in both the pooled placebo-controlled trials and the pooled neostigmine-controlled trials. The analyses were performed only for adverse events captured during the “treatment period,” defined as starting with the administration of the study drug and ending 7 days later. The findings from the two analyses are combined in Table 19. For both sets of pooled data, the Applicant calculated the 95% confidence intervals according to the method of Miettinen and Numinen. They reported no significant differences between sugammadex and its comparators for any of the SMQs in either the broad or narrow searches.

Table 19. Number (%) of subject exposures with AEs within Cardiac Arrhythmias related SMQs during the treatment period (combined data from Tables 69 and 70 on pp. 197-198 and 200-201 in Section 5.3.5.3 of the 2012 resubmission)

| Standardized MedDRA Query | SMQ search | Pooled Placebo-Controlled Trials | | Pooled Neostigmine-Controlled Trials | |
|---|------------|----------------------------------|---------------|--------------------------------------|-------------------|
| | | Sugammadex N=1078 | Placebo N=544 | Sugammadex N=797 | Neostigmine N=804 |
| Cardiac arrhythmias | Narrow | 2 (1.1) | 9 (1.7) | 4 (0.5) | 7 (0.9) |
| | Broad | 39 (3.6) | 21 (3.9) | 26 (3.3) | 39 (4.9) |
| Cardiac arrhythmia terms (includes bradyarrhythmias and tachyarrhythmias) | Narrow | 12 (1.1) | 9 (1.7) | 4 (0.5) | 7 (0.9) |
| | Broad | 13 (1.2) | 10 (1.8) | 6 (0.8) | 7 (0.9) |
| Bradyarrhythmias (includes conduction defects and disorders of sinus node function) | Narrow | 10 (0.9) | 4 (0.7) | 0 (0.0) | 0 (0.0) |
| Conduction defects | Narrow | 10 (0.9) | 4 (0.7) | 0 (0.0) | 0 (0.0) |
| Disorders of sinus node function | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Bradyarrhythmia terms, nonspecific | Narrow | 0 (0.0) | 1 (0.2) | 1 (0.1) | 0 (0.0) |
| Cardiac arrhythmia terms, nonspecific | Narrow | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| Tachyarrhythmias (both supraventricular and ventricular tachyarrhythmias) | Narrow | 2 (0.2) | 6 (1.1) | 4 (0.5) | 7 (0.9) |
| | Broad | 3 (0.3) | 7 (1.3) | 6 (0.8) | 7 (0.9) |
| Supraventricular tachyarrhythmias | Narrow | 1 (0.1) | 2 (0.4) | 4 (0.5) | 6 (0.7) |
| | Broad | 1 (0.1) | 3 (0.6) | 6 (0.8) | 6 (0.7) |

| Standardized MedDRA Query | SMQ search | Pooled Placebo-Controlled Trials | | Pooled Neostigmine-Controlled Trials | |
|---|------------|----------------------------------|------------------|--------------------------------------|----------------------|
| | | Sugammadex N=1078 | Placebo N=544 | Sugammadex N=797 | Neostigmine N=804 |
| Ventricular tachyarrhythmias | Narrow | 1 (0.1) | 4 (0.7) | 0 (0.0) | 2 (0.2) |
| | Broad | 2 (0.2) | 4 (0.7) | 0 (0.0) | 2 (0.2) |
| Tachyarrhythmia terms, nonspecific | Narrow | 2 (0.2) | 0 (0.0) | 2 (0.3) | 0 (0.0) |
| Arrhythmia related investigations, signs and symptoms | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Broad | 27 (2.5) | 11 (2.0) | 21 (2.6) | 35 (4.4) |
| Congenital and neonatal arrhythmias | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Broad | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Shock-associated circulatory or cardiac conditions (excluding torsade de pointes) | Narrow | 2 (0.2) | 3 (0.6) | 2 (0.3) | 3 (0.4) |
| | Broad | 4 (0.4) | 4 (0.7) | 3 (0.4) | 5 (0.6) |
| Torsade de pointes, shock-associated conditions | Narrow | 16 (1.5) | 6 (1.1) | 2 (0.3) | 2 (0.2) |
| | Broad | 18 (1.7) | 7 (1.3) | 3 (0.4) | 4 (0.5) |

The next step taken by the Applicant was an evaluation of the individual components of the broad SMQ for arrhythmia. The results are shown in Table 20. The Applicant noted that a similar rate of “bradycardia” following sugammadex treatment (0.5%) compared to placebo treatment (0.6%) and that the incidences of bradycardia in the neostigmine-controlled trials was 1.6% in the neostigmine group and 0.1% in the sugammadex group.

They also noted a higher rate of “tachycardia” was observed for sugammadex than placebo (0.9% and 0.6%, respectively) but stated that the “remaining AEs of the “arrhythmia related investigations” collection term (i.e. syncope, palpitations, loss of consciousness, electrocardiogram abnormal) occurred at rates expected in the adult surgical population.” A source to support this statement was not provided.

Table 20. Arrhythmia-related Investigations (signs and symptoms) (Broad SMQ) in pooled Phase 1-3 placebo-controlled studies (Table 67 on p. 193 of Section 5.3.5.3 of the 2012 resubmission)

| Standardized MedDRA Query Search Preferred Term | Placebo | | Sugammadex | |
|---|------------|------------|-------------|------------|
| | N | % | N | % |
| Number of Treated Subjects | 544 | 100 | 3407 | 100 |
| Total | 11 | 2.0 | 78 | 2.3 |
| Bradycardia | 3 | 0.6 | 16 | 0.5 |
| Cardiac arrest | 0 | 0.0 | 1 | 0.0 |
| Electrocardiogram abnormal | 0 | 0.0 | 2 | 0.1 |
| Heart rate decreased | 1 | 0.2 | 3 | 0.1 |
| Heart rate increased | 0 | 0.0 | 4 | 0.1 |
| Loss of consciousness | 0 | 0.0 | 1 | 0.0 |
| Palpitations | 1 | 0.2 | 8 | 0.2 |
| Syncope | 3 | 0.6 | 13 | 0.4 |
| Tachycardia | 3 | 0.6 | 32 | 0.9 |

The Applicant did not conduct a similar analysis for the pooled Phase 1-3 neostigmine-controlled trials.

Bradycardia and Tachycardia

The Applicant performed additional analyses looking at bradycardia and tachycardia, the two most common cardiac adverse events reported in the clinical studies. To this end, the Applicant evaluated the pooled Phase 1-3 trials for the percentage of exposures in subjects with treatment-emergent markedly abnormal pulse rate values, i.e., a heart rate outside the range of 50-120 bpm that was also a change from baseline ≥ 15 bpm. Their findings are summarized in Table 22; they reported the number of

incidents as small and the incidences of markedly abnormal values were similar for sugammadex subjects and placebo subjects.

Table 21. Markedly Abnormal pulse rates at any In-Treatment post-baseline timepoint in pooled Phase 1-3 placebo-controlled studies (Table 113 on p. 300 of Section 5.3.5.3 of the 2012 NDA resubmission)

| Parameter | Total ^A Sugammadex (N=1078) | Placebo (N=544) |
|---|--|-----------------|
| Pulse Rate markedly decreased (n [%] of subjects) | 17 (2) | 6 (1) |
| Minimum Pulse Rate value at any timepoint | 37.0 bpm | 35.0 bpm |
| Pulse Rate markedly increased (n [%] of subjects) | 12 (1) | 7 (1) |
| Maximum Pulse Rate value at any timepoint | 134.0 bpm | 136.0 bpm |

The Applicant also reported that no time point trends were observed for the percent of exposures in subjects with markedly abnormal values. However, a dose trend for markedly decreased pulse rate was present as was a dose trend for the bradycardia AEs exhibited in Table 22.

Table 22. Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 112 on p. 299 of Section 5.3.5.3 in the 2012 NDA resubmission)

| MedDRA Preferred Term | Placebo (N=544) | Sugammadex | | | |
|-----------------------|--------------------|--------------------|---------------------|--------------------|--------------------------------|
| | | 2 mg/kg (n=838) | 4 mg/kg (n=1798) | 16 mg/kg (n=98) | Total ^A (N=3407) |
| At least one AE | 8 (1.5) | 12 (1.4) | 29 (1.6) | 6 (6.1) | 58 (1.7) |
| Tachycardia | 3 (0.6) | 9 (1.1) | 18 (1.0) | 3 (3.1) | 32 (0.9) |
| Bradycardia | 4 (0.7) | 2 (0.2) | 7 (0.4) | 2 (2.0) | 17 (0.5) |
| Heart rate increased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 1 (1.0) | 4 (0.1) |
| Heart rate decreased | 1 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Heart rate irregular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |

In the pooled placebo-controlled trials, the Applicant states that the overall percentage of subjects with treatment-emergent markedly abnormal pulse rate values was small,

and the AEs related to pulse rate abnormalities were similar in incidence between the sugammadex group and the placebo group, as indicated in Table 23.

Table 23. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled placebo-controlled trials in order of decreasing incidence in the total sugammadex group (Table 114 on p. 300 in Section 5.3.5.3 of the 2012 NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex | Placebo |
|-----------------------|-------------------------------|---------|
| | (N=1078) | (N=544) |
| At least one AE | 22 (2.0) | 8 (1.5) |
| Bradycardia | 12 (1.1) | 4 (0.7) |
| Tachycardia | 5 (0.5) | 3 (0.6) |
| Heart rate decreased | 2 (0.2) | 1 (0.2) |
| Heart rate increased | 2 (0.2) | 0 (0.0) |
| Heart rate irregular | 1 (0.1) | 0 (0.0) |

^A Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

In a shift analyses of heart rate changes, from vital sign data, the Applicant looked at the proportion of patients in all pooled Phase 1-3 studies who were not bradycardic (>50 beats/minute) at baseline but became bradycardic (<50 beats/minute) after study drug administration. For all doses of sugammadex, there were a greater proportion of patients who experienced a decrease in heart rate below 50 beats/minutes compared with those in the placebo group as seen in Table 24.

In a similar fashion, the Applicant determined the proportion of patients in each group in the pooled Phase 1-3 trials database who were not bradycardic at baseline (heart rate >50 bpm) but had a marked reduction (>20 bpm) after study drug administration. They considered the proportion of patients with a marked reduction to be very small in all groups and not different between groups at 2 minutes, though there was a slight increase in the sugammadex group when instances were pooled across all timepoints. The results are summarized in Table 25.

Lastly, the Applicant looked to see if there was a difference in the occurrence of clinically significant bradycardia, as indicated by the administration of atropine within an hour of study drug administration, based on NMBA, i.e., rocuronium or vecuronium. The findings are summarized in Table 26. Rocuronium had the greater incidence of atropine treatment. There did not appear to be any dose dependence for the use of atropine with either NMBA.

Table 24. Number (%) of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline for exposures in pooled Phase 1-3 studies by time point (Table 77 on p. 208 of Section 5.3.5.3 of the 20121 resubmission)

| Time after study drug administration | Placebo | | | Sugammadex | | | | | | | | | | | |
|--------------------------------------|---------|----|-----|------------|----|-----|----------|-----|-----|----------|----|------|------------------|-----|-----|
| | | | | 2 mg/kg | | | 4 mg/kg | | | 16 mg/kg | | | Total sugammadex | | |
| | (N=544) | | | (N=838) | | | (N=1798) | | | (N=98) | | | (N=3407) | | |
| N | n | % | N | n | % | N | n | % | N | n | % | N | n | % | |
| 2 min | 464 | 5 | 1.1 | 811 | 30 | 3.7 | 1680 | 68 | 4.0 | 89 | 5 | 5.6 | 3042 | 122 | 4.0 |
| 5 min | 422 | 7 | 1.7 | 699 | 34 | 4.9 | 1592 | 60 | 3.8 | 56 | 4 | 7.1 | 2768 | 108 | 3.9 |
| 10 min | 476 | 8 | 1.7 | 806 | 30 | 3.7 | 1662 | 51 | 3.1 | 93 | 6 | 6.5 | 3202 | 107 | 3.3 |
| Any timepoint | 467 | 15 | 3.2 | 818 | 52 | 6.4 | 1696 | 112 | 6.6 | 94 | 10 | 10.6 | 3249 | 202 | 6.2 |

N=Number of subject exposures in treatment group or with heart rate measure

n=number of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline.

Table 25. Number (%) of subject exposures for subjects with a decrease ≥ 20 bpm resulting in a heart rate ≤ 50 bpm for exposures pooled Phase 1-3 trials by time point (Table 78 on p. 210 of Section 5.3.5.3 of the 2012 resubmission)

| Time after study drug administration | Placebo | | | Sugammadex | | | | | | | | | | | |
|--------------------------------------|---------|---|-----|------------|---|-----|----------|---|-----|----------|---|-----|------------------|----|-----|
| | | | | 2 mg/kg | | | 4 mg/kg | | | 16 mg/kg | | | Total sugammadex | | |
| | (N=544) | | | (N=838) | | | (N=1798) | | | (N=98) | | | (N=3407) | | |
| N | n | % | N | n | % | N | n | % | N | n | % | N | n | % | |
| 2 min | 464 | 1 | 0.2 | 811 | 1 | 0.1 | 1680 | 3 | 0.2 | 89 | 1 | 1.1 | 3042 | 6 | 0.2 |
| 5 min | 422 | 0 | 0.0 | 699 | 2 | 0.3 | 1595 | 5 | 0.3 | 56 | 1 | 1.8 | 2768 | 8 | 0.3 |
| 10 min | 466 | 0 | 0.0 | 806 | 5 | 0.6 | 1662 | 4 | 0.2 | 93 | 1 | 1.1 | 3202 | 10 | 0.3 |
| Any timepoint | 467 | 1 | 0.2 | 818 | 7 | 0.9 | 1696 | 8 | 0.5 | 94 | 3 | 3.2 | 3249 | 19 | 0.6 |

N=Number of subject exposures in treatment group or with heart rate measure

n=number of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline.

Table 26. Number of exposures for adult subjects who received NMBA and placebo or sugammadex in pooled Phase 2-3 studies who were administered atropine within one hour after study drug, by NMBA (Table 79 on p. 212 of Section 5.3.5.3 of the 2012 resubmission)

| NMBA | Placebo | | | Sugammadex | | | | | | | | | | | |
|------------|---------|---|-----|------------|---|-----|----------|---|-----|----------|-----|-----|------------------|----|-----|
| | | | | 2 mg/kg | | | 4 mg/kg | | | 16 mg/kg | | | Total sugammadex | | |
| | (N=467) | | | (N=812) | | | (N=1709) | | | (N=93) | | | (N=3108) | | |
| | N | n | % | N | n | % | N | n | % | N | n | % | N | n | % |
| Rocuronium | 321 | 3 | 0.9 | 713 | 9 | 1.3 | 1269 | 8 | 0.6 | 93 | 1 | 1.1 | 2437 | 19 | 0.8 |
| Vecuronium | 146 | 0 | 0.0 | 96 | 0 | 0.0 | 436 | 1 | 0.2 | --- | --- | --- | 652 | 1 | 0.2 |

N=Number of subject exposures per treatment group
 n=number of subject exposures administered atropine

Using the pooled neostigmine-controlled trials, the Applicant conducted similar analyses and reported that the overall percentage of subjects with treatment- emergent markedly abnormal pulse rate values was small regardless of timepoint Table 28. They also noted that the incidence of markedly abnormal pulse rate increases was low and similar between the two treatment groups; however, there were more incidences of markedly decreased pulse rate present in the neostigmine group, 7% versus 1% for the total sugammadex group

Table 28. Markedly abnormal values at any in-treatment timepoint and minimum and maximum pulse rate values in pooled Phase 3 neostigmine-controlled studies (Table 115 on p. 301 of Section 5.3.5.3 of the 2012 resubmission)

| Parameter | Total ^A Sugammadex (N=797) | Neostigmine (N=804) |
|---|---|------------------------|
| Pulse Rate markedly decreased (n [%] of subjects) | 9 (1) | 55 (7) |
| Minimum Pulse Rate value at any timepoint | 38.0 bpm | 32.0 bpm |
| Pulse Rate markedly increased (n [%] of subjects) | 7 (1) | 14 (2) |
| Maximum Pulse Rate value at any timepoint | 135.0 bpm | 140.0 bpm |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

In the pooled neostigmine-controlled trials, heart-rate adverse events occurred with greater frequency following treatment with neostigmine than with sugammadex as indicated in Table 29.

Table 29. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled neostigmine-controlled trials in order of decreasing incidence in the total sugammadex group (Table 116 on p. 302 in Section 5.3.5.3 in the 2012 resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex | Neostigmine |
|-----------------------|----------------------------------|-------------|
| | (N=797) | (N=804) |
| At least one AE | 16 (2.0) | 32 (4.0) |
| Tachycardia | 13 (1.6) | 15 (1.9) |
| Bradycardia | 2 (0.3) | 13 (1.6) |
| Heart rate irregular | 1 (0.1) | 0 (0.0) |
| Heart rate increased | 0 (0.0) | 4 (0.5) |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

The Applicant did not perform shift analyses using the vital signs data for the pooled-neostigmine trials as they had for the pooled Phase 1-3 trials.

In summary, the Applicant concluded the following based on their analyses of the clinical trial data available at the time of the NDA resubmission:

1. Sugammadex is not associated with QT/QTc prolongation beyond the level of regulatory concern when dosed alone, in combination with the NMBA's rocuronium or vecuronium, or in combination with the anesthetics sevoflurane or propofol, based on the results of dedicated ECG studies.
2. Sugammadex does not demonstrate any clinically relevant QT/QTc prolongation, or an increase in the incidence of categorical or change-from-baseline outliers when compared to placebo in a meta-analysis of QTc data across the clinical development program.
3. Sugammadex is not associated with an increase in the incidence of AEs of QTc prolongation compared to placebo, when the QT interval is appropriately corrected for HR using the Fridericia formula, in an analysis of reported AEs of the integrated clinical development database.
4. 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.
5. For bradycardia in particular, there appears to be a small mean overall effect on heart rate when sugammadex is administered for the reversal of some NMBA's. This effect seems to be dependent on the choice of background NMBA and more consistently observable with rocuronium than in the setting of vecuronium. Furthermore, this effect seems to translate in rare bradycardic events that are easily detected. The clinical trial database did not suggest a risk for clinically important bradycardia.

For the purposes of this review, the same approach that was used for analyzing the cardiac arrhythmias in the original NDA submission was repeated here.

The safety database that was analyzed for this portion of the review consisted of all subjects who received treatment in the clinical studies in which sugammadex, placebo, or neostigmine were administered intravenously. The serious adverse events from this database that were related to cardiac arrhythmias or acute myocardial infarction are summarized in Table 27. Since the original NDA submission, 12 new SAEs have been added to this list bringing the total to 42 with an overall frequency for SAEs of 1%. The only SAE that occurred with a frequency greater than 1% in any sugammadex dose group was QTc prolongation. With a doubling of the size of the safety database compared to the original NDA submission, only three additional incidents of QT prolongation have been reported as SAEs: two more in the 4 mg/kg dose group and one more in the 16 mg/kg dose group. (See Table 19 for the summary of SAEs from the original NDA submission.) Overall, this represents a decrease in frequency from 1.4% to 0.7% for SAEs of QTc prolongation with sugammadex treatment, which is not

substantially different than that observed with placebo treatment, i.e., 0.2%. It should be noted that there were no reports of Torsades de Pointes associated with any of the QTc prolongations or in the entire safety database.

Atrial fibrillation was the only other arrhythmia to occur more than once in any dose group and more than twice with sugammadex treatment. Two new incidents were reported with the resubmission, but the overall incidence remains less than 0.2%.

Also of note is that there were no SAEs of bradycardia; two SAEs for tachycardia; and a single incident of cardiac arrest, all of which occurred since the original NDA submission.

Table 27. Summary of serious adverse events related to cardiac arrhythmia and acute myocardial infarction in the 2012 resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | Neostigmine |
|--------------------------------|---------|--------------------|-----|------|-----|----|-----|-------|-------------|
| | | 0.5 | 2 | 4 | 8 | 12 | 16 | Total | 50 mcg/kg |
| N | 1318 | 137 | 856 | 2198 | 156 | 39 | 348 | 3734 | 814 |
| Preferred Term | | | | | | | | | |
| Acute myocardial infarction | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 |
| Atrial fibrillation | 0 | 1 | 4 | 1 | 0 | 0 | 0 | 6 | 0 |
| Bradycardia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| QTc interval prolonged | 2 | 0 | 13 | 6 | 1 | 3 | 5 | 28 | 0 |
| % | 0 | 0 | 2 | 0 | 1 | 8 | 1 | 1 | 0 |
| Electromechanical dissociation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Tachycardia | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 0 |
| Ventricular fibrillation | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular tachycardia | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 6 | 2 | 18 | 11 | 1 | 3 | 6 | 42 | 1 |
| % | 0 | 1 | 2 | 1 | 1 | 8 | 2 | 1 | 0 |

All adverse events related to cardiac arrhythmias and acute myocardial infarction are summarized for the 2012 NDA resubmission in Table 28. Compared to the events reported in the original NDA submission (see Table 17), 68 new AEs have been reported resulting in an overall decline in the incidence from 6% to 5%.

The AE table indicates that the more commonly occurring adverse events are, as it was with the original NDA submission, bradycardia, QTc prolongation, and tachycardia.

With the resubmission, there were 29 new AEs of bradycardia; a single new AE of QTc prolongation and 28 new AEs for tachycardia. The overall incidence of each of these AEs has decreased since the original NDA submission such that they do not differ substantially from neostigmine or placebo treatments. For each of these AEs, there is no indication of dose dependence with sugammadex treatment.

The other AE of note in the table is atrial fibrillation. There are 5 new AEs for this arrhythmia for a total of 13 events. The overall frequency has decreased from 0.4% to 0.3%, which is between the frequencies observed for placebo (0.2%) and neostigmine (0.5%). As with the other AEs, there is no indication that the occurrence of atrial fibrillation is dose dependent with sugammadex treatment.

Table 28. Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the 2012 resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|--|-----------|--------------------|----------|-----------|-----------|----------|-----------|-----------|-----------|----------|------------|----------------------|-----------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | Total | 50 | 70 |
| N | 1318 | 137 | 220 | 856 | 2198 | 29 | 156 | 39 | 348 | 164 | 4147 | 814 | 42 |
| Adverse Event | | | | | | | | | | | | | |
| Acute myocardial infarction | 2 | | | | 1 | | | | | | 1 | 2 | |
| Atrial fibrillation | 2 | 1 | | 7 | 5 | | | | | | 13 | 4 | |
| Atrial flutter | | | | | 2 | | | | | | 2 | | |
| Atrioventricular block (1°) | 1 | | | | | | | | | | 0 | | |
| Atrioventricular block (2°) | 1 | | | | | | | | | 1 | 1 | | |
| Bradycardia | 9 | 1 | 1 | 14 | 30 | 1 | 6 | 1 | 8 | | 62 | 65 | |
| % | 1 | 1 | 0 | 2 | 1 | 3 | 4 | 3 | 2 | 0 | 1 | 8 | 0 |
| Cardiac arrest | | | | | | | | | | | 0 | 1 | |
| T wave abnormality | 1 | | | | | | | | | | 0 | 1 | |
| PR interval prolonged | | | | | | | | | | | 0 | | |
| QTc interval prolonged | 3 | | 1 | 13 | 6 | | 2 | 3 | 4 | | 29 | | 2 |
| % | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 8 | 1 | 0 | 1 | 0 | 5 |
| Supraventricular and Ventricular extrasystoles | 1 | | | 1 | 2 | | | | | 1 | 3 | 4 | |
| Tachycardia | 7 | | 5 | 26 | 47 | 1 | 2 | | 11 | 1 | 93 | 21 | 2 |
| % | 1 | 0 | 2 | 3 | 2 | 3 | 1 | 0 | 3 | 1 | 2 | 3 | 5 |
| Ventricular fibrillation | 1 | | | | | | | | | | | | |
| Ventricular tachycardia | | | | 1 | | | | | | 1 | | 1 | |
| WPW | | | | 1 | | | | | | | | | |
| Total | 28 | 2 | 7 | 63 | 93 | 2 | 10 | 4 | 23 | 4 | 208 | 99 | 4 |
| % of N | 2 | 1 | 3 | 7 | 4 | 7 | 6 | 10 | 7 | 2 | 5 | 12 | 10 |

The cardiac arrhythmia adverse event data for the current (2014) submission are summarized in Table 29 below. It should be noted that in this table, compared to Table 17 and Table 28, the timeframe of the adverse events was limited to 24 hours following study drug administration, which would capture only those events occurring within a 3 half-life time period for the study drugs (with the exception of the severely renally impaired subjects). The data in the table indicate that there is more tachycardia and bradycardia with sugammadex than with placebo treatments; however, sugammadex appears to pose no greater risk for these adverse events than neostigmine or succinylcholine. The only difference between sugammadex and the other treatments remains QT prolongation, which does not appear to be dose dependent.

An additional analysis was performed to assess whether changes in heart rate, and therefore the potential for bradycardia or tachycardia, were time dependent following treatment with sugammadex versus placebo or neostigmine. The Applicant was asked to provide the heart rate data collected as part of vital signs assessments for both the pooled placebo-controlled and pooled neostigmine- controlled trials. Those data that were collected within half an hour of study drug administration were then analyzed and used to populate Table 30 and Table 31 below. The data in neither of the tables suggests a time dependent change in heart rate associated with sugammadex or neostigmine. However, there appeared to be a steady increase in heart rate for the 30 minutes following placebo treatment. Given clinical setting during which the study drugs were administered, i.e., the end of surgery with the effects of the anesthetic agents wearing off while the patient is still intubated, it would be generally expected for the patients to experience increases in their heart rates barring some pharmacological intervention. The responses to placebo, therefore, are not unexpected. Similar responses were observed with neostigmine despite its cholinergic effect, which may have been counterbalanced with the co-administration of an anticholinergic agent such as atropine. The mixed responses observed with sugammadex are, therefore, somewhat perplexing. While the mean values of the heart rate changes are not clinically significant, the possibility that some patients may experience clinically relevant increases in heart rate while others experience clinically relevant decreases for a particular dose would explain the occurrence of AEs for both bradycardia and tachycardia reported within individual sugammadex dose groups.

Table 29. Cardiac AEs occurring within 24 hours of study drug administration [2014 safety database (current submission)]

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | Neostigmine (mcg/kg) | | Spont. Recov. From Sux. | Moxi 400 mg |
|------------------------------------|-------------|--------------------|------------|------------|-------------|-----------|------------|------------|-------------|------------|----------------------|-----------|-------------------------|-------------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 | | |
| N | 1394 | 137 | 220 | 913 | 2505 | 29 | 156 | 40 | 496 | 165 | 875 | 58 | 134 | 139 |
| Exposures | 1980 | 137 | 220 | 913 | 3097 | 29 | 156 | 40 | 1067 | 324 | 875 | 58 | 134 | 139 |
| Adverse Event | | | | | | | | | | | | | | |
| Tachycardia | 6 (0%) | -- | 3 (1%) | 18 (2%) | 46 (2%) | 1 (3%) | 2 (1%) | -- | 12 (2%) | 4 (2%) | 26 (3%) | 4 (7%) | 3 (2%) | -- |
| Bradycardia | 9 (1%) | 1 (1%) | 1 (0%) | 12 (1%) | 25 (1%) | 1 (3%) | 5 (3%) | 1 (3%) | 6 (1%) | -- | 49 (6%) | 3 (5%) | 7 (5%) | -- |
| Electrocardiogram QT prolonged | 4 (0%) | -- | 1 (0%) | 14 (2%) | 7 (0%) | -- | 2 (1%) | 6 (15%) | 7 (1%) | -- | -- | -- | -- | 1 (1%) |
| Extrasystoles | -- | -- | -- | 1 (0%) | 4 (0%) | -- | -- | -- | -- | 1 (1%) | 4 (1%) | -- | 1 (1%) | -- |
| Ventricular tachycardia | -- | -- | -- | 1 (0%) | 1 (0%) | -- | -- | -- | -- | 1 (1%) | 1 (0%) | -- | -- | -- |
| Atrial flutter | -- | -- | -- | -- | 2 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Atrioventricular block: 1st or 2nd | 2 (0%) | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | 1 (1%) | -- | -- | -- | 2 (1%) |
| Bundle branch block right | -- | -- | -- | 1 (0%) | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Electrocardiogram PR prolongation | -- | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Pulseless electrical activity | -- | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| Supraventricular tachycardia | -- | -- | -- | -- | -- | -- | -- | -- | -- | 1 (1%) | 1 (0%) | -- | -- | -- |
| Ventricular arrhythmia | -- | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | 1 (0%) | -- | -- | -- |
| Wolff-Parkinson-White syndrome | -- | -- | -- | 1 (0%) | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |

Table 30. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Placebo (N=544) | Sugammadex | | | |
|--|-----------------|-----------------|-----------------|-----------------|----------------|
| | | 2 mg/kg (N=156) | 4 mg/kg (N=592) | 16 mg/kg (N=38) | Total (N=1078) |
| 2 | 2.2% (1.1) | 0.0% (-0.5) | -0.1% (-0.3) | -1.0% (-1.9) | 0.4% (-0.1) |
| 5 | 4.9% (2.7) | -3.8% (-2.8) | 5.1% (2.8) | * | 3.3% (1.6) |
| 10 | 9.7% (5.4) | -1.1% (-1.3) | 10.4% (5.8) | -1.1% (-1.7) | 5.7% (2.9) |
| 30 | 11.7% (6.5) | 4.2% (2.1) | 16.4% (9.4) | -2.1% (-2.4) | 10.4% (5.6) |

* No measurements were made at this time point for the 16 mg/kg dose.

Table 31. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Neostigmine (N=804) | Sugammadex | | |
|--|---------------------|-----------------|-----------------|---------------|
| | | 2 mg/kg (N=305) | 4 mg/kg (N=491) | Total (N=797) |
| 2 | 5.0% (5.0) | -0.6% (-0.7) | 1.6% (1.6) | 0.3% (0.2) |
| 5 | 7.2% (7.0) | 0.8% (0.7) | 7.1% (6.7) | 4.7% (4.4) |
| 10 | 2.7% (2.3) | 4.8% (4.7) | 4.8% (4.8) | 4.8% (4.7) |
| 30 | 16.7% (16.6) | 12.0% (12.0) | 20.4% (19.8) | 17.2% (16.8) |

Comments and Conclusions

Based on the additional QT study conducted by the Applicant and the analyses of the safety database from the clinical trials, which has doubled in size since the original NDA submission, the following conclusions were made:

1. sugammadex, at doses intended for clinical use, does not prolong the QTc interval when administered:
 - a. Alone, i.e., not in the presence of anesthetic agents or neuromuscular blocking agents (NMBAs) In combination with rocuronium or vecuronium but not in the presence of anesthetic agents
 - b. In the presence of anesthetic agents but not in combination with an NMBA

2. The risk of QTc prolongation with sugammadex does not exceed the risk with placebo or neostigmine to a clinically relevant extent.
3. QTc prolongation that was observed in the clinical trials was not associated with any episodes of Torsades de Pointes.
4. The risk of cardiac arrhythmias and acute myocardial infarction were not increased to a clinically significant degree by treatment with sugammadex compared to treatment with placebo or neostigmine.
5. Episodes of tachycardia and bradycardia that qualified as adverse events occurred following administration of sugammadex but not at frequencies that substantially differed from neostigmine or that exceeded that from placebo by a clinically relevant amount.

Based on the information provided in the NDA submission, the Applicant had sufficiently characterized the risk of cardiac arrhythmias and QTc prolongation to allow an informed benefit:risk assessment and appropriate labeling of the product without the need for further clinical studies.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant reported a total of 25,151 treatment-emergent adverse events (AEs) categorized under 1,189 preferred terms for their entire clinical development program. To identify common AEs for the purposes of evaluating the safety of sugammadex for its intended use and product labeling, the following steps were taken to refine the AE database:

1. Those AEs that were not associated with the intravenous administration of study drug were removed. This included AEs from intradermal and skin prick testing conducted as part of studies to assess immunogenicity.
2. AEs associated with moxifloxacin and succinylcholine were removed because these products were not relevant as comparators for the intended clinical use of sugammadex.

The adverse events for the three treatment groups are summarized by system organ class (SOC) in Table 32 below. In Table 33, the adverse events are summarized by preferred term for the three treatment groups for those adverse events that occurred in greater than 1% of the sugammadex. It should be noted that some of the preferred terms have been split. For example, anemia and anemia postoperative both occurred following administration of study drug, which was administered at the end of surgery shortly before discharge from the operating room; therefore, all of these cases are “postoperative” in time of occurrence. Additional examples include hypertension and procedural hypertension, and tachycardia and increased heart rate. While the data provide sufficient information to make the assessment of safety, the adverse events that are similar in nature should be lumped together when reported in the labeling to provide clinicians with a better sense which risks will most likely occur and will most need to be taken into consideration for individual patients.

The differences between treatment groups for the rates of the various adverse events is marked with sugammadex having substantially higher rates than both placebo and neostigmine, which had similar rates for all of the SOCs and preferred terms. Although the more common adverse events, e.g., postoperative pain, nausea, vomiting, and pyrexia, tend to be commonly associated with the postoperative period, their occurrence with sugammadex treatment is substantially more frequent than with either placebo or neostigmine. There is no clear reason, based on mechanism of action, why the incidence should be so skewed.

Table 32. Summary of adverse events by system organ class in descending rates for sugammadex treatments

| System Organ Class | Treatment | | | |
|--|----------------|--------------|---------------|----------------|
| | Sugammadex | Placebo | Neostigmine | All Subjects |
| Injury, poisoning and procedural complications | 2007 (37%) | 322 (6%) | 552 (10%) | 2881 (52%) |
| Gastrointestinal disorders | 1339 (24%) | 243 (4%) | 396 (7%) | 1970 (36%) |
| General disorders and administration site conditions | 748 (14%) | 159 (3%) | 219 (4%) | 1117 (20%) |
| Nervous system disorders | 681 (12%) | 172 (3%) | 145 (3%) | 964 (18%) |
| Vascular disorders | 458 (8%) | 116 (2%) | 148 (3%) | 721 (13%) |
| Respiratory, thoracic and mediastinal disorders | 410 (7%) | 83 (2%) | 105 (2%) | 595 (11%) |
| Musculoskeletal and connective tissue disorders | 408 (7%) | 123 (2%) | 91 (2%) | 619 (11%) |
| Psychiatric disorders | 405 (7%) | 105 (2%) | 154 (3%) | 664 (12%) |
| Investigations | 353 (6%) | 48 (1%) | 70 (1%) | 471 (9%) |
| Skin and subcutaneous tissue disorders | 270 (5%) | 50 (1%) | 95 (2%) | 414 (8%) |
| Infections and infestations | 250 (5%) | 99 (2%) | 59 (1%) | 404 (7%) |
| Renal and urinary disorders | 209 (4%) | 42 (1%) | 44 (1%) | 294 (5%) |
| Metabolism and nutrition disorders | 207 (4%) | 48 (1%) | 60 (1%) | 315 (6%) |
| Cardiac disorders | 196 (4%) | 65 (1%) | 55 (1%) | 316 (6%) |
| Blood and lymphatic system disorders | 180 (3%) | 57 (1%) | 50 (1%) | 287 (5%) |
| Ear and labyrinth disorders | 56 (1%) | 15 (0%) | 21 (0%) | 92 (2%) |
| Reproductive system and breast disorders | 55 (1%) | 12 (0%) | 18 (0%) | 83 (2%) |
| Eye disorders | 48 (1%) | 16 (0%) | 15 (0%) | 79 (1%) |
| Body as a whole - general disorders | 39 (1%) | 4 (0%) | 0 (0%) | 42 (1%) |
| Respiratory system disorders | 30 (1%) | 5 (0%) | 0 (0%) | 32 (1%) |
| Urinary system disorders | 22 (0%) | 6 (0%) | 0 (0%) | 25 (0%) |
| Surgical and medical procedures | 20 (0%) | 2 (0%) | 11 (0%) | 33 (1%) |
| Cardiovascular disorders, general | 17 (0%) | 3 (0%) | 0 (0%) | 20 (0%) |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| System Organ Class | Treatment | | | |
|--|----------------|----------------|---------------|-----------------|
| | Sugammadex | Placebo | Neostigmine | All Subjects |
| Immune system disorders | 16 (0%) | 4 (0%) | 2 (0%) | 22 (0%) |
| Gastrointestinal system disorders | 15 (0%) | 2 (0%) | 0 (0%) | 16 (0%) |
| Hepatobiliary disorders | 11 (0%) | 1 (0%) | 2 (0%) | 14 (0%) |
| Centr & periph nervous system disorders | 10 (0%) | 8 (0%) | 0 (0%) | 17 (0%) |
| Heart rate and rhythm disorders | 10 (0%) | 1 (0%) | 0 (0%) | 11 (0%) |
| Metabolic and nutritional disorders | 8 (0%) | 0 (0%) | 0 (0%) | 8 (0%) |
| Secondary terms | 6 (0%) | 1 (0%) | 0 (0%) | 7 (0%) |
| Platelet, bleeding & clotting disorders | 6 (0%) | 1 (0%) | 0 (0%) | 7 (0%) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 5 (0%) | 3 (0%) | 4 (0%) | 12 (0%) |
| Special senses other, disorders | 3 (0%) | 0 (0%) | 0 (0%) | 3 (0%) |
| Social circumstances | 2 (0%) | 0 (0%) | 0 (0%) | 2 (0%) |
| Skin and appendages disorders | 1 (0%) | 2 (0%) | 0 (0%) | 3 (0%) |
| Hearing and vestibular disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| Liver and biliary system disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| Red blood cell disorders | 1 (0%) | 1 (0%) | 0 (0%) | 2 (0%) |
| Musculoskeletal system disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| Endocrine disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| Vision disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| White cell and res disorders | 1 (0%) | 0 (0%) | 0 (0%) | 1 (0%) |
| Congenital, familial and genetic disorders | 0 (0%) | 0 (0%) | 1 (0%) | 1 (0%) |
| Total Subjects | 3903 (71%) | 1318 (24%) | 856 (16%) | 5489 (100%) |

Table 33. Summary of adverse events by system organ class in descending rates for sugammadex treatments

| Preferred Term | Treatment | | | |
|-------------------------|----------------|--------------|--------------|----------------|
| | Sugammadex | Placebo | Neostigmine | All Subjects |
| Procedural pain | 1288 (23%) | 185 (3%) | 372 (7%) | 1845 (34%) |
| Nausea | 779 (14%) | 106 (2%) | 213 (4%) | 1097 (20%) |
| Procedural hypotension | 656 (12%) | 104 (2%) | 114 (2%) | 874 (16%) |
| Vomiting | 377 (7%) | 54 (1%) | 103 (2%) | 534 (10%) |
| Hypotension | 293 (5%) | 70 (1%) | 111 (2%) | 474 (9%) |
| Headache | 289 (5%) | 116 (2%) | 59 (1%) | 449 (8%) |
| Constipation | 277 (5%) | 76 (1%) | 120 (2%) | 473 (9%) |
| Pyrexia | 209 (4%) | 18 (0%) | 46 (1%) | 273 (5%) |
| Pain | 187 (3%) | 18 (0%) | 109 (2%) | 314 (6%) |
| Dizziness | 162 (3%) | 26 (0%) | 60 (1%) | 247 (4%) |
| Insomnia | 159 (3%) | 29 (1%) | 63 (1%) | 251 (5%) |
| Anemia | 151 (3%) | 54 (1%) | 42 (1%) | 247 (4%) |
| Procedural hypertension | 149 (3%) | 28 (1%) | 33 (1%) | 210 (4%) |
| Dysgeusia | 142 (3%) | 7 (0%) | 4 (0%) | 150 (3%) |
| Sleep disorder | 122 (2%) | 62 (1%) | 49 (1%) | 233 (4%) |
| Back pain | 120 (2%) | 30 (1%) | 18 (0%) | 167 (3%) |
| Procedural complication | 119 (2%) | 8 (0%) | 35 (1%) | 162 (3%) |
| Incision site pain | 115 (2%) | 6 (0%) | 60 (1%) | 181 (3%) |
| Pharyngolaryngeal pain | 113 (2%) | 11 (0%) | 20 (0%) | 144 (3%) |
| Anemia postoperative | 112 (2%) | 70 (1%) | 21 (0%) | 203 (4%) |
| Hypertension | 98 (2%) | 21 (0%) | 16 (0%) | 135 (2%) |
| Bradycardia | 98 (2%) | 35 (1%) | 27 (0%) | 160 (3%) |
| Diarrhea | 97 (2%) | 32 (1%) | 23 (0%) | 151 (3%) |

| Preferred Term | Treatment | | | |
|------------------|-------------|-------------|-------------|--------------|
| | Sugammadex | Placebo | Neostigmine | All Subjects |
| Edema peripheral | 91 (2%) | 23 (0%) | 31 (1%) | 145 (3%) |
| Chills | 89 (2%) | 14 (0%) | 12 (0%) | 115 (2%) |
| Hypokalemia | 88 (2%) | 31 (1%) | 34 (1%) | 153 (3%) |
| Abdominal pain | 88 (2%) | 15 (0%) | 23 (0%) | 125 (2%) |
| Pruritus | 85 (2%) | 11 (0%) | 24 (0%) | 120 (2%) |
| Arthralgia | 83 (2%) | 46 (1%) | 8 (0%) | 136 (2%) |

Analysis of the adverse events for the individual doses of sugammadex revealed no dose dependency for any of the events.

7.4.2 Laboratory Findings

The Applicant summarized the hematology and biochemistry data using the following time points and values of interest:

- Baseline (i.e., last measurement before administration of the trial medication)
- Post-baseline (20 min, 60 min, +4-6 hr, 8 hr, and 24 hr)
- Minimum and maximum values
- Endpoint values
- Post-anesthetic visit for surgical subjects (from 7 to 48 hours after IMP administration); the post-anesthetic visit is not an accurate term within Pooled Phase 1 Trials, however, to be consistent with the Pooled Phase 1-3 Trials the same label is attached to the time interval.
- Follow-up – on or after Day 4.

For urinalysis data, the Applicant used a similar approach, which was identical to the hematology and biochemistry data with the exception of post-baseline summaries that begin at 4 hours for urinalysis data but at 20 minutes for the other laboratory investigations. The time points and values of interest for the urinalysis data were the following:

- Baseline (i.e., last measurement before administration of the trial medication)
- Post-baseline (+4-6 hr, 8 hr and 24 hr)
- Minimum and maximum values

- Endpoint values
- Final visit (i.e., post-anesthetic visit for surgical subjects)

The Applicant used descriptive statistics, shift analyses and markedly abnormal laboratory values to compare the laboratory assessments data for sugammadex-, placebo-, and neostigmine-treated subjects. Their approach for each of these analyses is summarized below.

Descriptive Statistics

Descriptive statistics used by the Applicant included mean, median, minimum, and maximum observed values, and absolute and percent mean, median, minimum, and maximum changes from baseline.

Shift Analysis

Based on predefined normal ranges and safety ranges, the results of the clinical laboratory tests were classified into one of the following categories:

- Category A: value \leq lower safety range
- Category B: value $>$ lower safety range and value \leq lower normal range
- Category C: value $>$ lower normal range and value $<$ upper normal range
- Category D: value \geq upper normal range and value $<$ upper safety range
- Category E: value \geq upper safety range

Shift tables were constructed to determine the categorical shifts from baseline to post-baseline. Each shift was designated by a code. For example, code "AD" denoted a shift of a value from Category A (below or equal to the lower safety range) at baseline to Category D (above or equal to the upper normal range but below the upper safety range) at post-baseline assessment. The percentage of subjects with categorical shifts was presented by treatment group. Shifts of particular interest were called notable shifts. Notable shifts in downward direction defined as those downward shifts resulting in a value belonging to Category A or B (i.e., EA, DA, CA, BA, EB, DB, or CB). Notable shifts in upward direction were defined as those upward shifts resulting in a value belonging to Category D or E (i.e., AD, BD, CD, AE, BE, CE, or DE). The notable shift categories are illustrated in Table 34 below.

Table 34. Notable shift categories (Table 84 on p. 251 in Section 5.3.5.3 of the NDA resubmission)

| Baseline Category | Post-baseline Category | | | | |
|-------------------|------------------------|----------|----|--------|--------|
| | A | B | C | D | E |
| A | -- | -- | -- | Upward | Upward |
| B | Downward | -- | -- | Upward | Upward |
| C | Downward | Downward | -- | Upward | Upward |
| D | Downward | Downward | -- | -- | Upward |
| E | Downward | Downward | -- | -- | -- |

Markedly Abnormal Values

The number and percent of exposures for subjects with markedly abnormal post-baseline values, identified as having values outside of the safety ranges, were summarized by treatment group.

In addition to the above, those laboratory values that were out-of-range and considered by the Investigator to be clinically significant were to be recorded as AEs.

Each analysis was conducted on the Pooled Phase 1-3 trials, the Placebo-Controlled trials, and the Neostigmine-Controlled trials.

Biochemistry and Urinalysis Results

Descriptive Statistics

The Applicant reported that, for the Pooled Phase 1-3 trials, baseline values for all biochemistry analytes were similar across the dose groups, and there were no dose trends or clinically significant differences in mean and median changes from baseline. They reported the same findings for the Pooled Placebo- and Pooled Neostigmine-Controlled trials.

A review of the data confirmed the Applicant’s findings.

Shift Analysis

The Applicant reported that for the Pooled Phase 103 trials, no apparent dose trends were detected in the shift analysis. Overall, there were more notable downward than upward shifts for albumin, alkaline phosphatase, bilirubin, calcium, fasting triglycerides, total cholesterol, haptoglobin, haptoglobin type 2-1, lactate dehydrogenase,

magnesium, potassium, total protein, sodium, and urea nitrogen. There were also more notable upward than downward shifts for alanine aminotransferase, aspartate aminotransferase, chloride, creatine phosphokinase, fasting glucose, triglycerides, and creatinine. These shifts were not considered clinically relevant as the percentages of exposures of subjects with shifts in a particular category and overall shifts between sugammadex and placebo were generally similar. The exception was the percentage of subject exposures with notable overall upward shifts for chloride was higher for placebo (19%) than sugammadex (9%).

Shift analysis for biochemistry in sugammadex versus placebo was reported by the Applicant to be similar to the biochemistry by dose shift analyses. These shifts were not considered clinically relevant as percentages of exposures of subjects with shifts in a particular category and overall shifts between sugammadex and placebo were generally similar. The Applicant noted that the percentage of subject exposures with notable downward shifts for decreased albumin was higher for placebo (22%) than sugammadex (12%).

For the Pooled Neostigmine-Controlled trials, the Applicant reported that shift analysis results in the sugammadex versus neostigmine pooling group were similar to the biochemistry by dose shift analyses except for bilirubin which had a more notable upward shifts in this pooling group than in the Pooled Phase 1-3 or Placebo-controlled groups. These shifts were not considered clinically relevant by the Applicant because the percentages of exposures of subjects with shifts in a particular category and overall shifts between sugammadex and neostigmine were generally similar.

A review of the data confirmed the Applicant's findings.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, the Applicant reported that there were no apparent dose trends for the percentage of exposures of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria. The percentage of exposures of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was similar between the sugammadex-dose groups and the placebo-treatment group except for fasting glucose (increased) which was 11% in the sugammadex group and 0% for placebo. Of note in both treatment groups (27% for sugammadex and 26% for placebo) were high incidences of markedly low biochemistry values for haptoglobin. Most AEs related to abnormalities of biochemistry clinical laboratory tests occurred in 1% or less of exposures in the total sugammadex group, and no dose trends were observed. One biochemistry-related AE that occurred in more than 1.0% of exposures in the total sugammadex group was hypokalemia (1.9%), but this occurred in the placebo group (5.0%) as well.

In the Pooled Placebo-Controlled trials, the percentage of subject exposures with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was generally similar between the two treatment groups; of note both treatment groups (32% for sugammadex and 28% for placebo) had similarly high incidences of markedly low values for haptoglobin. The incidence of AEs related to abnormalities of biochemistry clinical laboratory tests was low overall (<1%), and the differences in incidence between the sugammadex group and the placebo group were not considered clinically relevant by the Applicant.

In the Pooled Neostigmine-Controlled trials, the percentage of subject exposures with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was generally similar between the two treatment groups. As observed with the Pooled Placebo-Controlled trials, there was a high percentage of subject exposures with markedly low values for haptoglobin; percentages were the same for sugammadex and neostigmine. The incidence of AEs related to abnormalities of biochemistry clinical laboratory tests was low overall and there were no clinically significant treatment group differences

A review of the data confirmed the Applicant's findings.

Urinalysis Results

Descriptive Statistics

The Applicant reported that the Pooled Phase 1-3 dose groups were similar for mean and median baseline values and no dose trends or trends by time point were observed for mean or median changes from baseline. The sugammadex dose group descriptive statistics were similar to the Pooled Placebo-Controlled and the Pooled Neostigmine-Controlled group descriptive statistics

A review of the data confirmed the Applicant's reported findings.

Shift Analysis

In the Pooled Phase 1-3 group there were more notable downward than upward shifts in erythrocyte count, leukocyte count, and N-acetylglucosaminidase and more notable upward than downward shifts in beta-2-microglobulin and microalbumin (creatinine-dependent). Differences between the amount of notable upward and downward shifts were small and no dose trends were detected in the shift analysis. Shift analyses in the Pooled Placebo-Controlled group were similar to the urinalysis by dose shift analyses except that creatinine and N-acetylglucosaminidase had a similar amount of shifts. In the Pooled Neostigmine-Controlled groups there were small, if any, differences between notable upward and downward shifts. The Applicant noted that the notable shifts that occurred in general were in, at most, 8 exposures per treatment group.

A review of the data confirmed the Applicant's reported findings.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, the Applicant reported that there were no dose trends for the percentage of exposures in subjects with markedly abnormal post-baseline urinalysis values that met the pre-specified criteria. In the sugammadex group, there were markedly abnormal increased post-baseline values for beta-2-microglobulin, microalbumin (creatinine-dependent), microalbumin (non-creatinine-dependent) and N-acetylglucosaminidase. In addition, there were markedly abnormal decreased post-baseline values for urine creatinine. However, the percentages of exposures with these markedly abnormal increases and decreases were generally similar between sugammadex and placebo.

For the Pooled Placebo-Controlled trials, the incidences of markedly high urine values for beta-2-microglobulin were higher in the sugammadex-treatment group, while for microalbumin and NAG, the incidences were higher in the placebo-treatment groups; however these differences were considered by the Applicant as not likely to be clinically relevant.

In the Pooled Neostigmine-Controlled trials, the percent of subjects with markedly abnormal post-baseline values at the final visit that met the prespecified was generally similar between the two treatment.

The Applicant concluded that most of the AEs related to abnormalities of the urinalysis occurred in 2.0% or less of subject exposures in the total sugammadex group, no apparent dose trends were observed, and the incidences were similar between sugammadex, neostigmine and placebo treatment groups.

A review of the data confirmed the Applicant's reported findings.

Hematology Results

Descriptive Analysis

The Applicant reported that in the pooled Phase 1-3 trials, baseline values for all hematology analytes were similar across the dose groups, and there were no dose trends for mean and median changes from baseline. For specific analytes related to coagulation, i.e., activated partial thromboplastin time, prothrombin time, and INR, absolute change from baseline was similar between the time, and INR, absolute change from baseline was similar between the sugammadex dose groups and placebo. Overall, total white blood cell and absolute neutrophil count increased slightly, while absolute eosinophils, hemoglobin, and lymphocyte count decreased slightly. The analytes had similar changes from baseline between the sugammadex dose groups and placebo. For the timepoints 20 minutes, 60 minutes, and 3 hours the neutrophil count

increase was greater in the sugammadex treatment groups than placebo treatment groups.

The Applicant also noted that the results for the pooled Phase 1-3 neostigmine-controlled trials and the pooled placebo-controlled trials did not differ from those of the overall pooled Phase 1-3 trial statistics.

A review of the data confirmed the Applicant's reported findings.

Shift Analysis

The Applicant reported that no dose trends were detected in their shift analysis for the Pooled Phase 1-3 trials. Overall, there were more notable downward shifts than notable upward shifts in hemoglobin, hematocrit, lymphocyte, and red blood cell count. There were more notable upward shifts in aPTT, total white blood cell count, absolute neutrophil count, and prothrombin time.

The Applicant reported that the largest treatment group differences were observed for the following:

- Activated partial thromboplastin time (aPTT) overall upward shifts: 22% sugammadex and 11% placebo
- Prothrombin time overall upward shifts: 28% sugammadex and 17% placebo. They noted that these two findings are likely not to be clinically relevant as the majority of the shifts occurred from categories C to D and in addition, there was only one adverse event (mild intensity) of prolonged prothrombin time in the total sugammadex group and one in the placebo group (mild intensity).
- Total white blood cell count notable upward shifts C to D: 24% sugammadex, 12% placebo; overall upward shifts: 36% sugammadex and 14% placebo. They noted that these two findings are likely not to be clinically relevant as the majority of the shifts occurred from categories C to D and in addition, the adverse event incidence of white blood cell count increased in the total sugammadex group and in the placebo group was similar and of low incidence (0.3% and 0.4%, respectively).
- Absolute neutrophil count notable upward shifts from C to E: 39% sugammadex, 14% placebo; overall upward shifts: 40% sugammadex and 14% placebo. They noted that the incidence of adverse events of infections was low and comparable between treatment groups (3% for placebo and 2% for sugammadex). In addition, the incidence of markedly abnormal increases in absolute neutrophil count was comparable between treatments for the post-anesthetic and follow up periods, therefore the shifts are likely not clinically relevant.

For the Pooled Placebo-Controlled trials, the Applicant reported that, overall, there were more notable downward shifts than notable upward shifts in, hemoglobin, hematocrit, lymphocyte, and red blood cell count. There were more notable upward shifts in aPTT,

total white blood cell count, monocytes, absolute neutrophil count, and prothrombin time; however, there were no meaningful differences between treatment groups in percentages of exposures with shifts in a particular category.

The largest treatment group differences were observed for the following:

- Activated partial thromboplastin time (APTT) overall upward shifted: 21% sugammadex and 11% placebo. This result was similar to that for Pooled Phase 1-3.
- Prothrombin time overall upward shifted: 28% sugammadex and 17% placebo. This result was identical to that for Pooled Phase 1-3 trials.
- Neutrophil % overall shifted upward: 29% with sugammadex treatment and 18% with placebo treatments. The Applicant noted that the majority of the shifts were from Category C to Category D and there was only one adverse event of neutrophil count increased in the placebo treatment group. Therefore, they thought these shifts were not likely to be clinically relevant.

The Applicant reported that, for the Pooled Neostigmine-Controlled Trials, there were no meaningful differences between treatment groups in percentages of subject exposures with shifts in a particular category or overall shifts.

In summary, the shift analysis results for the Pooled Placebo- and the Pooled Neostigmine-Controlled trials were similar to the Pooled Phase 1-3 trials shift analysis by dose.

A review of the data confirmed the Applicant's report of the findings. The shifts in aPTT and PT are discussed in further detail in section 7.3.5.2 above.

Treatment Emergent Markedly Abnormal Values

The Applicant reported that in the Pooled Phase 1-3 trials, there were no dose trends and the percent of number of exposures of subjects with markedly abnormal post-baseline hematology values was similar between sugammadex and placebo dose groups. The only hematology-related AEs that occurred in more than 1.0% of the total sugammadex group were anemia (3.6%) and anemia postoperative (2.1%). No distinction was provided for these two preferred terms; because the AEs occurred after administration of study drug, which was after the surgical procedure was completed, they would both qualify as "postoperative." There was no dose trend and the values for these two AEs were higher in the placebo group than the values for the total sugammadex group.

The results reported by the Applicant for both the Pooled Placebo- and the Pooled Neostigmine-controlled trials were similar. The percentage of subject exposures with markedly abnormal post-baseline hematology values that met the pre-specified criteria was similar between the two treatment groups. The incidence of AEs related to

abnormalities of hematology clinical laboratory tests was low overall and the incidences of AEs were similar between the treatment groups

A review of the data confirmed the Applicant's findings.

7.4.3 Vital Signs

The Applicant used descriptive statistics, including the mean, standard deviation (SD), median, minimum, and maximum observed values, and absolute and percent mean, median, minimum, and maximum changes from baseline to characterize the effects on vital signs that were observed with the various treatment groups. The number and percent of subjects with markedly abnormal values, according to the pre-defined safety ranges, were also summarized by treatment group. The subjects with markedly abnormal values were identified as were adverse events (AEs) that were considered related to vital signs abnormalities.

In all trials, blood pressure and pulse rate were to be measured in the supine position after a 5-minute rest. In addition, out-of-range vital signs values that were considered by the Investigator to be clinically significant were to be recorded as AEs.

Pooled Phase 1-3 trials

In the Phase 1-3 trials where a neuromuscular blocking agent (NMBA) was administered, vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and central body temperature. Blood pressure and pulse rate data were summarized by the Applicant according to the following time intervals:

- Baseline (i.e., last measurement before the administration of study drug)
- Post-baseline (2, 5, 10, 30, 60, and 120 min and 3 hours)
- Minimum and maximum values (from start of study drug to 6 hours later)
- Final visit (last measurement after study drug till 6 hours later).
- Post-anesthetic visit (from 6 hours after study drug until 48 hours after study drug, or Day 2)
- Follow-up visit (from Day 4 onwards)

In the pooled Phase 1-3 trials, the Applicant summarized respiratory rate data only at baseline (i.e., screening) and the final visit. Central body temperature (CBT) was measured continuously throughout the anesthetic period; "yes" or "no" responses to the question "Was the CBT maintained at $\geq 35^{\circ}$ C during the entire NMT monitoring?" were summarized.

Phase 1 trials

In the pooled Phase 1 dataset of non-anesthetized healthy volunteers who did not receive an NMBA, vital signs included blood pressure, pulse rate, respiratory rate, temperature, and body weight. Blood pressure and pulse rate data were summarized according to the following time intervals:

- Baseline (i.e., before the administration of the trial medication)
- At 2 min, 10 min, 15 min, 30 min, 35 min, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-baseline

Body temperature, body weight, and respiratory rate data were summarized for the pooled Phase 1 population only at baseline and follow-up. Similarly, body weight, height, and body temperature data were summarized for screening and follow-up.

The Applicant excluded data from Trial 19.4.105 in the pooled Phase 1 dataset for the analysis of blood pressure and pulse rate. In this trial, the protocol did not require any post-baseline vital signs measurements were required by protocol, and follow-up vital signs were taken at least 7 days after dosing.

Vital sign data from trial 19.4.107 were also excluded from the pooled analysis by the Applicant because SBP, DBP, and pulse rate data were collected only for the following time intervals:

- Screening, baseline (i.e., prior to drug administration),
- At 2 min, 35 min, and 60 min post-baseline, and
- At follow-up.

The Applicant used the values in Table 35 for determining changes in blood pressure and heart rate that were classified as “markedly abnormal.” To qualify, a parameter had to meet both conditions, i.e., it had to be outside the safety range and be a change from baseline that met or exceeded the “criteria value.”

Table 35. Absolute value cutoffs and changes for blood pressure and heart rate that were used to determine “markedly abnormal values” (from Table 138 on p. 4317 in Appendix A of Section 5.3.5.3 in the NDA resubmission)

| Parameter | Safety Range | | Criteria Value | |
|---------------------------------|--------------|------|----------------|----------|
| | Low | High | Decrease | Increase |
| Systolic blood pressure (mmHg) | 90 | 160 | 20 | 20 |
| Diastolic blood pressure (mmHg) | 45 | 95 | 15 | 15 |
| Heart rate (bpm) | 50 | 120 | 15 | 15 |

The Applicant reported the vital signs findings in a similar manner as used for the clinical laboratory parameters: by descriptive statistics and markedly abnormal values for the Pooled Phase 1-3 trials, the Pooled Placebo-Controlled trials, and the Pooled Neostigmine-Controlled trials.

Systolic Blood Pressure (SBP)

Descriptive Statistics

In the Pooled Phase 1-3 trials, the total sugammadex group, mean baseline SBP was 108.0 mmHg, and median baseline SBP was 106.0 mmHg. Mean and median baseline values across the dose groups were similar, ranging from 92.7 mmHg to 124.0 mmHg (mean) and from 91.5 mmHg to 130.5 mmHg (median). No apparent dose response trend was observed for change from baseline across all the dose groups. The mean percent (mean absolute) changes from baseline at each time point in the 2, 4 and 16 mg/kg dose groups were small and the total sugammadex group was similar to placebo group.

The Applicant reported that, for the Placebo-Controlled trials and the Neostigmine-Controlled trials, the descriptive statistics for SBP in the sugammadex treatment group were similar to the placebo treatment group.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, there were more markedly abnormal decreases in SBP that met the pre-specified criteria than markedly abnormal increases, and a dose-related trend for decreased SBP was observed. However, no meaningful differences between total sugammadex and placebo were observed.

An apparent dose trend for “procedural hypotension,” an AE related to abnormalities of BP, was found in the sugammadex treatment groups. In the total sugammadex group the most frequent AEs (incidence of at least 1% of subject exposures) included procedural hypotension (3.1%), procedural hypertension (2.7%), hypertension (2.2%), and hypotension (1.7%). Incidences in the 16 mg/kg group were generally somewhat higher as compared to the other dose groups.

For the Placebo-Controlled trials, the percentage of subject exposures associated with markedly abnormal post-baseline SBP values that met the pre-specified criteria was small and the percentages in the sugammadex-treatment groups were similar to the percentages in placebo-treatment groups. The lowest post-baseline SBP value observed in any sugammadex subject exposures in Pooled Placebo-controlled trials was 50 mmHg, and the highest post-baseline SBP value was 240 mmHg.

The Applicant reported the incidence of AEs related to abnormalities of blood pressure was low overall, in the Placebo-Controlled trials, and the differences in incidence between the sugammadex group and the placebo group were not clinically relevant. There was only one adverse event of systolic hypertension in the sugammadex treatment group (0.1%).

In the Pooled Neostigmine-Controlled trials, the percentage of subject exposures with markedly abnormal post-baseline SBP values that met the pre-specified criteria was reported by the Applicant to be small and comparable between the sugammadex and neostigmine groups. The lowest post-baseline SBP value observed in any sugammadex subject in Pooled Neostigmine-controlled Trials was 65 mmHg, and the highest post-baseline SBP value was 237 mmHg with comparable ranges in both treatment groups. The incidence of AEs related to abnormalities of blood pressure was low overall, and the differences in incidence between the sugammadex group and the neostigmine group were not considered clinically relevant. There was only one adverse event of “systolic blood pressure increased” each in the sugammadex treatment group (0.1%) and the placebo group (0.1%).

A review of the data confirmed the Applicant’s findings.

Diastolic Blood Pressure (DBP)

Descriptive Statistics

In the total sugammadex group in the Pooled Phase 1-3 trials, mean baseline DBP was 61.5 mmHg, and median baseline DBP was 60.0 mmHg. Mean and median baseline values across the dose groups were similar, ranging from 54.0 mmHg to 68.8 mmHg (mean) and from 51.5 mmHg to 69.0 mmHg (median). The mean percent (absolute) changes from baseline at each time point in the 2, 4 and 16 mg/kg dose groups were small.

Descriptive statistics for DBP in the sugammadex treatment group of the Pooled Placebo-Controlled trials were generally similar to the placebo treatment group. Similarly, for the Pooled Neostigmine-Controlled trials, the descriptive statistics for DBP in the sugammadex treatment group were similar to the neostigmine treatment group

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, there were more markedly abnormal decreases in DBP that met the pre-specified criteria than markedly abnormal increases; however, there were no apparent differences between placebo and total sugammadex. No time point trends were observed. The percent of subject exposures associated with markedly abnormal decreased post-baseline DBP values that met the pre-specified criteria was similar in sugammadex (5%) and placebo (3%). AEs specific to DBP included blood

pressure diastolic increased and occurred in 0.1% (2 subject exposures) of the total sugammadex group and 0% in the placebo group.

In the Pooled Placebo-controlled trials, the overall percentage of subjects with treatment-emergent markedly abnormal DBP values that met the pre-specified criteria was small and similar between the two treatment groups regardless of time point. There were no specific AEs related to abnormalities of DBP.

In the Pooled Neostigmine-controlled trials, the overall percentage of subjects with treatment-emergent markedly abnormal DBP values that met the pre-specified criteria was small and similar between the two treatment groups regardless of time point. AEs specific to DBP included blood pressure diastolic increased and occurred in 0.1% (1 subject exposure) of the total sugammadex group and 0% in the neostigmine group.

A review of the data confirmed the Applicant's findings.

Pulse Rate

Descriptive Statistics

In the Pooled Phase 1-3 trials in the total sugammadex group, mean baseline pulse rate was 65.8 bpm, and median baseline pulse rate was 64.0 bpm. Mean and median baseline values across the dose groups ranged from 55.2 bpm to 73.7 bpm (mean) and from 52.0 bpm to 73.5 bpm (median). No apparent dose trend was observed for change from baseline across all the dose groups. The mean percent (mean absolute) changes from baseline at each time point in the 2, 4 and 16 mg/kg dose groups were small and the observed changes in the total sugammadex group was similar to placebo group.

In the Placebo-controlled trials, descriptive statistics for pulse rate in the sugammadex-treatment group were similar to those in the placebo-treatment group. The same was reported by the Applicant to be the case for the Pooled Neostigmine-Controlled trials.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials the percentage of exposures in subjects with treatment-emergent markedly abnormal pulse rate values that met the pre-specified criteria was small. No time point trends were observed for the percent of exposures in subjects with markedly abnormal values. Adverse events related to abnormalities of pulse rate occurred in 2.6% of the total sugammadex group and 1.7% in the placebo group. The majority of events in this category occurred for the event of tachycardia at >1% across the 2, 4, and 16 mg/kg sugammadex dose groups. There was a slight increase in pulse

rate abnormalities for exposures in the 16 mg/kg sugammadex dose group (8.2%). No particular dose trends were found for each individual adverse event.

In the Placebo-controlled trials, the overall percentage of subjects with treatment-emergent markedly abnormal pulse rate values that met the pre-specified criteria was small, and the incidences of markedly abnormal values were similar for sugammadex subjects and placebo subjects. No time point trends were observed for the percent of exposures in subjects with markedly abnormal values in pulse rate. The AEs related to pulse rate abnormalities were low and similar in incidence between the sugammadex group and the placebo group.

In the Pooled Neostigmine-controlled trials, the overall percentage of subjects with treatment-emergent markedly abnormal pulse rate values that met the pre-specified criteria was small regardless of time point. The incidence of markedly abnormal pulse rate increases was low overall, and there was a slightly higher incidence of markedly decreased pulse rate present in the neostigmine group (7%) compared to the sugammadex group (1%). For adverse events of bradycardia and heart rate increased, the incidences in the sugammadex group (0.3% and 0.0%, respectively) were similar to the neostigmine group (1.6% and 0.5%, respectively). For other AEs related to pulse rate, AE incidences were similar for exposures to sugammadex and neostigmine.

A review of the data confirmed the Applicant's findings.

Respiratory Rate

Descriptive Statistics

For the Pooled Phase 1-3 trials, The Applicant reported that, in the total sugammadex group, mean baseline respiratory rate was 13.9 breaths /minute, and median baseline respiratory rate was 14.0 breaths/minute. Mean and median baseline values across the dose groups ranged from 13.2 breaths /minute to 17.6 breaths/ minute (mean) and from 12.0 breaths/min to 18.0 breaths/ minute (median). Mean and median changes from baseline to the final visit were small, and no dose trend was apparent for change from baseline.

For the Pooled Placebo-Controlled trials, the descriptive statistics for respiratory rate were similar between sugammadex and placebo treatment groups.

The descriptive statistics for respiratory rate were similar between sugammadex and neostigmine treatment groups in the Pooled Neostigmine-Controlled trials.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, no dose trends were apparent for the AEs related to abnormalities of respiratory rate, which each occurred at 0.5% in the total sugammadex group. AEs related to respiratory rate did not occur in the placebo group. None of these AEs were serious. None of the subjects who were treated with sugammadex and who experienced an AE related to respiratory rate discontinued the trial due to this type of AE.

In the Pooled Placebo-controlled trials, AEs related to respiratory rate did not occur in the placebo group. With respect to the sugammadex group incidences were low (<0.4%) for each individual. None of these AEs were serious. None of the subjects who were treated with sugammadex and who experienced an AE related to respiratory rate discontinued the trial due to this type of AE.

In the Pooled Neostigmine-controlled trials, incidences of AEs related to respiratory rate abnormalities were very low, occurring at 0.1% in the total sugammadex group and 0.3% in the total neostigmine group. None of these AEs were serious. None of the subjects who were treated with sugammadex and who experienced an AE related to respiratory rate discontinued the trial due to this type of AE.

A review of the data confirmed the Applicant's findings.

Central Body Temperature (CBT)

Descriptive Statistics

CBT was reported by the Applicant to have been maintained, by the "vast majority" of subjects, at $\geq 35^{\circ}\text{C}$ during the entire process of neuromuscular transmission monitoring.

Treatment Emergent Markedly Abnormal Values/Adverse Events

In the Pooled Phase 1-3 trials, the Applicant reported that no dose trends were apparent for the AEs related to abnormalities of CBT as displayed. Overall the total number of exposures associated with AEs related to CBT was similar between treatment groups (10.3% sugammadex, 8.3% placebo). Incidences of pyrexia were slightly higher in the sugammadex exposures (6.3%) than in placebo exposures (3.1%). The other AE related to CBT was chills, but was slightly higher in placebo subject exposures (5.0%) than sugammadex subject exposures (3.2%).

In the Pooled Placebo-Controlled trials, the incidences of AEs were similar between the placebo treated group (8.3%) and the total sugammadex treated group (9.0%). Pyrexia was seen at comparable rates between sugammadex and placebo (4.1% sugammadex vs 3.1% placebo) but again, the placebo group had a slightly higher percentage of

exposures for chills compared to sugammadex (5.0% vs 3.8%, respectively) which was similar to the finding from the Pooled Phase 1-3 trials.

In the Pooled Neostigmine-Controlled trials, the incidences of AEs were similar between the neostigmine treated group (7.8%) and the total sugammadex treated group (9.4%). There was a slightly higher incidence of pyrexia in the sugammadex treated group (7.2%) versus the neostigmine group (5.8%) but the incidence of chills was similar between treatment groups (2.0% sugammadex, 1.7% neostigmine).

A review of the data confirmed the Applicant's findings.

Overall Summary and Conclusions

Despite a near doubling of the safety database, the updated vital signs data analyses do not indicate any substantial changes in the overall safety of sugammadex compared to that observed with the data contained in the original NDA submission. The various analyses of the vital signs data related to blood pressure, respiratory rate and core body temperature do not indicate that sugammadex, at the doses proposed for clinical use, poses a clinically relevant risk that would affect any of these parameters.

7.4.4 Electrocardiograms (ECGs)

All issues related to ECG data are addressed in Section 7.3.5.3 above.

7.4.5 Special Safety Studies/Clinical Trials

The special safety studies conducted to address the deficiencies noted in the Complete Response letter are reviewed in Section 7.3.5 above.

7.4.6 Immunogenicity

Although sugammadex is not a therapeutic protein, the occurrence of anaphylactic reactions in several of the clinical trials led to the product being investigated for potential immunogenic properties. The findings of those investigations are summarized in Section 7.3.5.1 of this review. The input provided by the Division of Pulmonary, Allergy, and Rheumatology Products regarding this issue, which was not finalized at the time this review was completed, should also be consulted.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency is described in greater detail in the adverse events and serious adverse events sections above. Dysgeusia and possibly anaphylaxis are sugammadex-dose dependent.

7.5.2 Time Dependency for Adverse Events

Most adverse events occurred within 12 hours of sugammadex administration in the pooled placebo-controlled studies with 42% of AEs occurring between 1 and 12 hours following administration of sugammadex, which was similar to the 48% for placebo treatment reported in the same timeframe. After 24 hours, the incidence of AEs was 37% with sugammadex but 52% for placebo treatments. The findings were similar in the pooled neostigmine-controlled studies.

7.5.3 Drug-Demographic Interactions

The Applicant performed an evaluation of AE incidence rates for sugammadex and its comparators by the sub-populations of age, race, gender, and ethnicity for the pooled datasets by treatment group. The intrinsic factor groups were defined as:

- Age (< 65 year vs. ≥ 65 year)
- Gender (male vs. female)
- Race (Caucasian vs. non-Caucasian)
- Ethnicity (Hispanic or Latino vs. non-Hispanic or Latino)

The Applicant's findings are reported below.

Age

The majority of reported AE incidences were not clinically significantly different between the sugammadex and placebo groups or between the age groups. There is an increase in incidence of most AEs with increasing age. This difference occurred in both the sugammadex and the placebo treatment groups. For example, procedural pain was the most frequently reported AE, and it was reported more frequently for subject exposures ≥ 65 years of age in the sugammadex group (45%) and the placebo group (38%) than

for subject exposures < 65 years of age at 30% and 26% in the sugammadex and placebo groups, respectively.

Gender

More incidences of AEs occurred in females than males, however they were evenly distributed between the sugammadex and placebo treatment groups. Overall there were no clinically relevant differences in AEs reported between genders.

Race

There were too few subject exposures in the non-Caucasian placebo group (n=31) to make meaningful comparisons with this group. No clinically meaningful differences between sugammadex and placebo were observed with respect to Caucasian exposures. Compared to neostigmine, for most AEs, incidences were higher for Caucasian subjects than for non-Caucasian subjects, but these were reported evenly between treatment groups.

Ethnicity

Only comparisons of non-Hispanic ethnicity between treatment groups could be made due to the small sample sizes in the Hispanic/Latino groups. Between the sugammadex and placebo treatment groups, there were similar incidences of AEs for the non-Hispanic/Latino exposures.

A review of the data tables used by the Applicant to generate the findings above determined them to be accurate. In summary, older, Caucasian, and female demographics were associated with higher incidence rates for adverse events compared to their counterparts; however, within any demographic subgroup there was no substantial difference in the incidence rates of AEs by treatment.

7.5.4 Drug-Disease Interactions

The effects of sugammadex were studied on individuals with renal impairment (mild to severe), hepatic impairment, cardiac conditions and pulmonary conditions. None of the studies indicated an exacerbation or worsening of the subject's underlying condition, and there was no indication from the data that a dose adjustment of sugammadex was necessary for patients with any of these conditions.

7.5.5 Drug-Drug Interactions

Drug-drug interactions relate to its pharmacodynamics: the complex formation with other molecules. Therefore, there are three types of drug-drug interactions that can occur, alone or in combination:

1. Uptake by sugammadex of a co-administered non-NMBA drug resulting in reduced free concentration of this co-administered drug
2. Preferential binding of sugammadex to a non-NMBA molecule resulting in diminished sugammadex-NMBA complex formation and a reduced NMB reversal effect of sugammadex
3. Displacement of bio-inactivated NMBA from the sugammadex-NMBA complex by another molecule, leading to potential recurrence of NMBA activity and risk of recurrent NMB

The Applicant has conducted four drug-drug interaction trials since the original submission to investigate these possible interactions. The findings are summarized below:

1. Toremifene has a relatively high binding affinity for sugammadex; it may also have a relatively high plasma concentration such that some displacement of vecuronium or rocuronium from sugammadex might occur.
2. The interaction between 4 mg/kg of sugammadex and a progestogen was predicted to lead to a decrease in progestogen exposure (34% of AUC) similar to the decrease seen when a daily dose of an oral contraceptive is taken 12 hours too late, which might lead to a reduction in effectiveness, i.e., the equivalent to one missed daily dose of oral contraceptives containing a progestogen. Non-oral contraceptives are also affected, and the Applicant recommends use of a non-hormonal contraceptive for 7 days following sugammadex administration.
3. There was no clinically relevant displacement of NMBA observed after administration of high doses of flucloxacillin (not approved in the U.S.).

In addition to the above, no clinically relevant interactions were reported during the clinical trials.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not required of this product due to the acute indication and the relatively short half-life. Although sugammadex is absorbed by bone, the amount absorbed in adults is small, and the duration of its presence in bone is short enough that preclinical and clinical assessments of carcinogenicity were not indicated.

7.6.2 Human Reproduction and Pregnancy Data

There is no human reproduction or pregnancy data available for sugammadex.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of the effects of sugammadex on growth were made as a pediatric indication is not sought at present.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose of sugammadex would be considered a dose greater than that required to reverse the level of neuromuscular blockade present at the time of administration. Alternatively, a dose greater than the to-be-labeled maximum dose (16 mg/kg) could be considered as an overdose. In a human tolerance trial, sugammadex was reported to be well tolerated at doses up to 96 mg/kg. The only adverse events that appeared to be dose related were dysgeusia and possibly anaphylaxis. Overall, the risk from overdose is small, and the most serious reaction, anaphylaxis, is one for which the patient can be monitored and readily treated, if necessary.

Sugammadex is administered in a controlled setting by medical professions to patients who are unconscious. In addition, sugammadex does not readily cross the blood-brain barrier, is not structurally similar to known drugs of abuse, and undergoes relatively rapid systemic clearance. In the clinical trials, there was no evidence of behavioral changes or alterations in mood or mentation. All of these factors would indicate that it has low abuse potential.

7.7 Additional Submissions and Safety Issues

There were multiple requests for information that were issued to the Applicant during this review cycle. The information provided in response was incorporated into this review in the appropriate sections. There was no safety update provided at the 120-day point of this review cycle.

8 Postmarket Experience

Sugammadex was first authorized for use on July 25, 2008, in the European Union. Since that time, it has received authorization in 48 countries including Japan, Australia, New Zealand, and nations in Central and South America, Asia, the Middle East, and Africa. During the first four years of marketing (from July 25, 2008, through June 15, 2012), the Applicant estimated that there were (b) (4) vials of sugammadex distributed. From that time through the data lock point of the current submission (June 16, 2012, to April 21, 2014), they estimated that an additional (b) (4) vials were distributed for a total of (b) (4) vials. The increase in distribution over the last two years suggests a substantial increase in exposure to the product.

The Applicant has used their pharmacovigilance database (Merck Adverse Reaction and Review System [MARRS]) to search for postmarketing adverse experience reports received from healthcare providers, consumers, and “non-interventional studies” to analyze safety from market introduction through the data lock point date in 2014. They identified 886 case reports involving 1,798 adverse events (AEs) in their database. These adverse events were the basis for evaluating the postmarketing safety of sugammadex both by the Applicant and for the purposes of this review. The adverse reactions from the database are tabulated by system organ class in Table 36 below.

Table 36. Postmarketing adverse event counts in decreasing order by System Organ Class

| System Organ Class | Count |
|--|--------------|
| Skin and subcutaneous tissue disorders | 273 |
| Immune system disorders | 226 |
| Respiratory, thoracic and mediastinal disorders | 213 |
| Investigations | 208 |
| General disorders and administration site conditions | 193 |
| Injury, poisoning and procedural complications | 140 |
| Cardiac disorders | 121 |
| Gastrointestinal disorders | 89 |
| Surgical and medical procedures | 72 |
| Vascular disorders | 64 |
| Nervous system disorders | 54 |
| Musculoskeletal and connective tissue disorders | 38 |
| Eye disorders | 26 |
| Psychiatric disorders | 26 |
| Metabolism and nutrition disorders | 16 |
| Blood and lymphatic system disorders | 12 |
| Hepatobiliary disorders | 11 |

| System Organ Class | Count |
|---|--------------|
| Renal and urinary disorders | 7 |
| Infections and infestations | 6 |
| Ear and labyrinth disorders | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 1 |
| Reproductive system and breast disorders | 1 |
| Total | 1798 |

The majority of the reports (486) came from Australia with the second most reports coming from Spain (76). As reported by the Applicant on page 321 of the ISS in the 2014 submission, the most frequently reported events in each of the most commonly affected SOCs were, by decreasing frequency:

1. Skin and subcutaneous tissue disorders:
 - a. urticaria (81 events)
 - b. events related to erythema (79 events which includes generalized erythema)
 - c. rash (64 events which include rash erythematous, rash generalized, rash maculopapular, rash papular and rash pruritic)
2. Immune system disorders:
 - a. events associated with hypersensitivity reactions which included anaphylactic shock (82 events)
 - b. anaphylactic reaction (77 events)
 - c. anaphylactoid reaction (33 events)
 - d. hypersensitivity (28 events which include drug hypersensitivity and Type 1 hypersensitivity)
3. Respiratory, thoracic and mediastinal disorders:
 - a. bronchospasm (36 events)
 - b. dyspnea (25 events)
 - c. laryngospasm (18 events)
 - d. wheezing (17 events)
 - e. pulmonary edema (14 events)
 - f. respiratory arrest (13 events)
4. Investigations:
 - a. blood pressure decreased (84 events)
 - b. oxygen saturation decreased (24 events)
 - c. hemoglobin decreased (15 events)
 - d. heart rate increased (13 events)
 - e. blood albumin decreased (8 events);
5. General disorders and administration site conditions:
 - a. events related to drug ineffective (59 events including drug ineffective for unapproved indication and therapeutic product ineffective)
 - b. no adverse event (36 events)
 - c. chills (14 events)

- d. pyrexia (10 events)
- 6. Injury, poisoning and procedural complications:
 - a. recurrence of neuromuscular blockade (43 events)
 - b. exposure during pregnancy (14 events)
 - c. post procedural haemorrhage (8 events);
- 7. Cardiac disorders:
 - a. bradycardia (38 events including bradyarrhythmia and sinus bradycardia)
 - b. tachycardia (27 events including sinus tachycardia supraventricular tachycardia and ventricular tachycardia)
 - c. cardiac arrest (27 events including cardio-respiratory arrest and pulseless electrical activity)

The Applicant focused their analyses of the postmarketing data on the safety topics that were raised in the previous NDA reviews and at the Advisory Committee meeting held on March 11, 2008. Specifically, they analyzed the data related to hypersensitivity/anaphylaxis, coagulation/bleeding, cardiovascular reactions, and respiratory reactions. Each of these topics are considered below followed by an assessment of the remaining reactions as to whether they raise any new safety concerns for the intended use of sugammadex.

In an effort to estimate the frequency of the postmarketing AEs, the Applicant did the following:

1. To estimate the rate of occurrence of the AEs, the assumption was made that only 10% of cases were reported.
2. The number of exposures to sugammadex was estimated as 90% of the vials sold. Since the exact number of used vials out of those sold is not known, the estimate of 90% of vials sold was considered appropriate for a drug with a number of returned doses that was less than 5% in most countries and lower than 1% for many countries. Thus for the (b) (4) vials of sugammadex distributed over the timeframe of this safety review, the Applicant estimated (b) (4) doses of the product were administered.

Hypersensitivity and Anaphylaxis

The Applicant took the following approach to identify cases of serious hypersensitivity and anaphylaxis reported in postmarketing use of sugammadex:

1. Anaphylaxis reports were identified by querying the narrow "Anaphylactic reaction" SMQ, along with narrow terms from the "Anaphylactic/anaphylactoid shock" sub-SMQ in the Shock SMQ.
2. Serious hypersensitivity reports were identified by querying broad terms in the "Anaphylactic reaction" SMQ (excluding narrow terms) and narrow and broad terms in the "Hypersensitivity" SMQ for cases with serious events for these preferred terms.

They identified a total of 318 cases, of which 201 represented reports of anaphylaxis and 117 represented reports of serious hypersensitivity. All 318 identified reports were adjudicated by an independent external adjudication committee (AC) that reviewed each report for signs and symptoms of anaphylaxis and hypersensitivity, using the criteria of Sampson, et al. as the basis for adjudication. Cases were adjudicated as anaphylaxis, hypersensitivity, neither, or as containing insufficient information for adjudication. The adjudication results showed that of the 318 cases, 133 were determined to be anaphylaxis and 47 were determined to be hypersensitivity.

The most commonly described clinical feature of the reports of anaphylaxis was signs or symptoms of hypotension, which were noted in 80% (106/133) of the cases. For the serious hypersensitivity reactions, skin reactions such as erythema, rash and urticaria constituted the most common feature occurring in 89% (42/47) of the patients. The 5 remaining cases of serious hypersensitivity reported reactions that included laryngospasm, bronchospasm with musculoskeletal stiffness and respiratory arrest, hypotension, and angioedema. In the reports where outcome was provided, all describe the patient as recovered. All the patients were reported to have responded to standard treatments for anaphylaxis and hypersensitivity reactions such as epinephrine, antihistamines, bronchodilators, steroids, vasopressors and enhanced ventilatory support.

Based on their assumptions about reporting and exposure described above, the incidences of post-marketing reports per 100,000 operations were calculated by the Applicant as follows:

- Nonadjudicated hypersensitivity and anaphylaxis combined = 17.9 [95% CI: 16.9; 18.8]
- Nonadjudicated anaphylaxis alone = 11.3 [95% CI: 10.5; 12.1]
- Adjudicated hypersensitivity and anaphylaxis combined = 10.1 [95% CI: 9.4; 10.8]
- adjudicated anaphylaxis alone = 7.5 [95% CI: 6.8; 8.1]

Their review of the postmarketing data and the reports in the literature for the use of sugammadex in adult and pediatric patients led the Applicant to conclude:

1. The majority of the postmarketing adverse events and serious events were symptoms of hypersensitivity, including anaphylaxis and anaphylactic shock, and did not reveal any new safety concerns. These data were consistent with the observations in clinical trials and support that the product labeling adequately characterizes the safety profile of the product.
2. Examination of the cumulative postmarketing data and ongoing analysis of the postmarketing safety experience of sugammadex confirms the positive benefit/risk profile of sugammadex and the appropriateness of the reference safety information in communicating these benefits and risks.
3. The comprehensive review of the literature published between August 1, 2012, and August 15, 2014, for use of sugammadex in adults and pediatric patients

identified 75 citations and abstracts for use of sugammadex in adults and 16 abstracts for exposure in pediatric patients. In these, they found there were no new or unexpected safety or efficacy concerns. Therefore, they concluded that the literature supports the finding that sugammadex is generally well-tolerated and efficacious for the reversal of neuromuscular blockade from rocuronium or vecuronium.

4. To the extent that anaphylaxis associated with sugammadex does occur, it presents in a setting where all the tools needed to treat the condition rapidly and effectively are already in place, including a highly trained medical staff that can respond to the situation without delay.
5. 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.

Reviewer's Comments

The Applicant's approach to analyzing the hypersensitivity and anaphylaxis cases was a reasonable one. Their method for estimating the rate of anaphylaxis provided incidences that were 2 orders of magnitude less than those seen in the clinical studies. Based on the clinical trials, the rates of anaphylaxis were estimated to be between 0.3% and 1.4%, which are substantially greater than the postmarketing rates estimated to be 0.01% (nonadjudicated) and 0.008% (adjudicated). Their descriptions of the timing and treatment of these events (where reported) is accurate. Perhaps the key finding from the postmarketing database is that, unlike in the clinical trials, when anaphylaxis occurred, it was often associated with life-threatening cardiovascular changes that required aggressive intervention. These data do not warrant further investigation of anaphylaxis induced by sugammadex nor impede an approval action for the NDA. However, they do indicate the need to properly label the product and educate physicians that not all the reactions that occur will be mild to moderate in nature and resolve with minimal, if any, intervention; rather, they need to be made aware that the reactions may be life-threatening and require vigilance and vigorous intervention to assure patient survival.

Cardiac Arrhythmias

The Applicant's review of the cardiac postmarketing events was summarized as follows. In the total of 105 cases reviewed, bradyarrhythmias (44 cases), were the most commonly reported of the arrhythmias, followed by tachyarrhythmias (39 cases) and cardiac arrest. A total of 23 reports of cardiac arrest were received. Most cases of cardiac arrest were reported in patients with serious comorbidities and/or surgical complications and without a pattern or common element that suggested a sugammadex-related safety concern. Cumulatively through 21Apr2014, no

postmarketing reports of QT/QTc prolongation or Torsade de pointes have been received.

The Applicant noted that the 44 postmarketing cases of bradyarrhythmia reports have been identified as potentially representing a distinct clinical pattern with onset of bradycardia during the emergence phase of anesthesia in otherwise stable patients shortly after administration of sugammadex. These cases occurred in a highly monitored environment, were readily detectable, and typically responded well to standard administration of anticholinergic agents. In their dedicated post hoc analysis of changes after sugammadex in the pooled Phase 1-3 database showed a transient, clinically insignificant reduction in mean HR (-1.5, 95% CI -2.4, -0.6) for the sugammadex group relative to placebo at 2 minutes only after treatment in the Pooled Phase 1-3 group; no differences were not observed at either 5 or 10 minutes after treatment. In a shift analysis to identify potential outliers, sugammadex only showed a modestly greater proportion of patients who experienced a decrease in HR below 50 bpm (4-7%) compared with those in the placebo group (1-3%). Appreciating the clinical standard of close routine monitoring of heart rate in the operative and peri-operative setting, the available data provides evidence that when bradycardia does occur, it is readily manageable and responsive to usual interventions.

The Applicant stated that the other cardiac arrhythmias in the postmarketing database did not appear to be associated with sugammadex. The current proposed product label reflects the features presented in the postmarketing reports of cardiac arrhythmia received through 21Apr2014. Arrhythmias are typically described in patients with underlying cardiac risk factors, are often confounded by other medications given in an operating room setting, and occur in complicated post-operative settings. These patients, being in an operating room setting, are uniquely placed to receive timely and appropriate treatment from trained personnel.

The Applicant has drawn the following conclusions regarding the cardiovascular safety data:

- 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.
- The overall number of reports of cardiac arrhythmias is low based on postmarketing data.
- No reports of Torsade de pointes have been reported in the cumulative clinical trial database nor were there spontaneous postmarketing reports received after > (b) (4) sugammadex vials sold (status as of April 21, 2014).
- In postmarketing data, very rare cases of marked bradycardia and 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 readily manageable and responsive to usual interventions.

- The overall number of reports of cardiac arrest is low, the overall number of fatalities is lower yet, and do not suggest an increase in risk relative to the expected perioperative risk profile in the general clinical setting. Several of the events reported as cardiac arrest appear more likely to have actually been prolonged pauses associated with bradycardia that would be expected to respond to usual treatment. While information from post-marketing reports is limited and typically incomplete, among the other events described as cardiac arrest, including the fatal cases, most appear to have occurred in patients with serious underlying illness or conditions including coronary artery disease or pulmonary edema, as well as acute processes that in themselves would put the patient at significant risk including post-operative complications such as massive hemorrhage and multi-organ failure. Examination of these cases reveals no apparent pattern or common element to suggest that these events were associated with sugammadex administration.

Reviewer's Comments

In the table below, the cardiac postmarketing reports related to rhythm are summarized.

Table 37. Postmarketing cardiac rhythm-related adverse events by decreasing frequency

| Preferred Term | Counts | | |
|--------------------------------|------------|------|-------------------|
| | All Events | SAEs | Fatalities |
| Bradycardia | 38 | 19 | 1 ¹ |
| Cardiac arrest | 26 | 22 | 3 ^{1, 2} |
| Tachycardia | 22 | 17 | |
| Ventricular fibrillation | 5 | 5 | |
| Supraventricular tachycardia | 3 | 2 | |
| Atrioventricular block | 3 | 3 | |
| Ventricular tachycardia | 2 | 0 | |
| Supraventricular extrasystoles | 2 | 1 | |
| Arrhythmia | 2 | 0 | |
| Pulseless electrical activity | 1 | 1 | |
| Atrial fibrillation | 1 | 0 | |
| Ventricular arrhythmia | 1 | 1 | |
| Extrasystoles | 1 | 0 | |

¹ One case of bradycardia and one case of cardiac arrest were thought to be related to sugammadex by the reporter.

² One case was not reported as related or unrelated to sugammadex.

For one patient (2011SP018197), the episode of bradycardia was reported to have a fatal outcome. This patient was a 56-year-old female who presented with ovarian cancer but was otherwise healthy. She underwent total abdominal hysterectomy, salpingo-oophorectomy, lymph node excision, excision of para-aortic nodes and omentectomy. She was administered 200 mg of sugammadex at the end of surgery, and about one minute later, her blood pressure fell to unreadable levels; she experienced bradycardia and then cardiac arrest. Anaphylactic shock was diagnosed. She was treated with epinephrine, atropine and cardiac massage. A spontaneous pulse returned. Later, an intra-aortic balloon pump was inserted to support her circulation. The following day, she experienced an intra-abdominal hemorrhagic shock due to bleeding at the site of one of the aortic lymph node dissections. She was successfully treated for the hemorrhage; however, she later went into renal failure, developed disseminated intravascular coagulation, and cerebral edema. She died 19 days after sugammadex administration of an unknown cause.

Cardiac Reactions Associated with Hypersensitivity and Anaphylaxis

There were 30 patients who had a hypersensitivity/anaphylactic reaction who also had cardiac adverse reactions. These reactions are summarized in Table 38 below; it should be noted that some patients had more than one cardiac reaction.

Table 38. Cardiac reactions occurring in patients who had an anaphylactic or hypersensitivity reaction

| Adverse Event | Number of Patients | Number That were SAEs |
|--------------------------|---------------------------|------------------------------|
| Tachycardia | 19 | 16 |
| Cardiac arrest | 8 | 8 |
| Bradycardia | 4 | 4 |
| Ventricular fibrillation | 2 | 2 |
| Arrhythmia | 1 | 0 |

The serious cardiac adverse events are described briefly below using the text from the CIOMS reports.

1. 1207JPN001482 – A 78 year old male undergoing thoracic aneurism repair. Two minutes after sugammadex sodium administration, the electrocardiogram revealed sudden asystole and no pressure waveform was displayed on the artery pressure monitor. Chest compressions were started. Atropine 0.5 mg and epinephrine 0.5 mg were administered via central line. Redness and wheals were noted on the chest and periorbitally 4 minutes after sugammadex administration. The patient responded to the chest compressions and an infusion of epinephrine was started and hydrocortisone was administered. Three hours later, the skin symptoms disappeared and the circulatory dynamics stabilized. Dopamine hydrochloride and epinephrine were reduced and propofol

was stopped. Two to three hours after the onset of cardiac arrest, the patient was extubated and transferred to the ICU.

2. 1209FRA009340 – A 65 year old female undergoing colectomy. She experienced an anaphylactic reaction to rocuronium. Sugammadex was administered and the patient experienced tachycardia 10 minutes later.
3. 1211JPN012816 – A 68 year old male undergoing laminectomy. Ten minutes following sugammadex administration, the patient's face became pale, and the electrocardiogram waveform indicated ventricular tachycardia that changed to ventricular fibrillation. Cardiopulmonary resuscitation was initiated. The patient was defibrillated 4 times without improvement. He was given epinephrine and lidocaine. He responded to “percutaneous cardio-pulmonary support” and was given methylprednisolone out of concern he had an anaphylactic reaction. He recovered without sequelae.

These and the other reactions, as the Applicant indicated, mostly occurred within minutes of sugammadex administration and were readily detected and treated. However, the Applicant appears to have downplayed the need for intervention as some of the cases required more than just medical intervention. As noted in the cases above, cardiopulmonary resuscitation, defibrillation, and other aggressive actions had to be instituted. Based on the clinical trial experience, the postmarketing reactions were more severe in terms of the types of interventions required. The reasons for this are not clear; it may be due, in part, to the larger numbers of patients exposed, possible differences in trial populations compared to the populations presenting in clinical practice, and to differences in the manner patients are cared for during a clinical trial compared to clinical practice. Despite the differences, the postmarketing experience does not provide evidence that would alter the approvability of sugammadex, but it does require that clinicians be made aware of the nature and severity of the cardiac reactions that may occur and that they be vigilant in their monitoring and be fully prepared to treat these reactions.

Other Reactions

Most of the other reactions that were reported in the postmarketing period include:

- reactions that are not uncommon following surgery under general anesthesia, e.g., nausea (35 reactions), vomiting (26 reactions), and chills (14 reactions)
- reactions indicating that sugammadex was not fully efficacious, e.g., drug ineffective (44 reactions), recurrence of neuromuscular blockade (43 reactions), and drug effect decreased, delayed, or incomplete (6 reactions)
- reactions related to hypersensitivity and anaphylactic reactions, e.g., urticaria (81 reactions), erythema (79 reactions), and rashes (56 reactions)

- reactions related to the airways that could be exacerbations of underlying pulmonary disease, associated with hypersensitivity or anaphylaxis, or due to manipulation of the airways, e.g., bronchospasm (36 reactions), dyspnea (25 reactions), oxygen desaturation (25 reactions), laryngospasm (18 reactions), wheezing (17 reactions)

While some of these reactions were severe, they were all easily detected and treatable. Many were more severe than those observed in the clinical trials, and therefore, clinicians need to be made aware of the possibility of these reactions and the need to be prepared to treat the reactions as well as their underlying causes.

There were generally fewer than 10 each of the remaining reactions; most could be attributed to causes listed above, were readily identifiable with routine monitoring of patients in the operating room and PACU settings, and were treatable. Importantly, there were no reactions that raised the concern of a new safety signal or the need for additional safety investigations.

9 Appendices

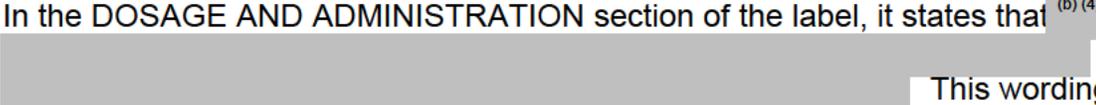
9.1 Literature Review/References

PubMed was utilized to determine whether there were any additional clinical studies using sugammadex that substantially impacted the findings reported by the Applicant to date. There were 539 publications that were found by the search using only the term sugammadex; 82 of these were published in 2014, and 14 were published in 2015.

There were a number of case reports of adverse reactions, which appear to have been captured by the Applicant in their postmarketing database. There were reports of the trials conducted by or on behalf of the Applicant. And there were several other small trials reported that provided little or no new information that would impact the approvability or the labeling of the product.

9.2 Labeling Recommendations

Listed below are broad recommendations regarding the Applicant's proposed labeling that was submitted in the current review cycle. Internal discussions with other Divisions, and ultimately, negotiations with the Applicant will determine the final wording. The recommendations are listed below in the order they are encountered in the label.

1. INDICATIONS AND USAGE. The Applicant includes the words moderate and deep to describe the level of neuromuscular blockade. These are relative terms that are not in common usage in the anesthesia community. As the Applicant has clearly identified the level of blockade, using peripheral nerve stimulation, at which points the proposed doses of sugammadex should be administered, these descriptors should be used as the Applicant has done in the DOSAGE AND ADMINISTRATION section.
2. In the DOSAGE AND ADMINISTRATION section of the label, it states that ^{(b) (4)}
 This wording eliminates the previous concerns that the product may be marketed for use with high-dose rocuronium as a substitute for succinylcholine during rapid sequence inductions. It also eliminates concerns regarding the use of the words "immediate reversal." However, the wording raises two new issues:
 - a. There is no definition as to what constitutes an "urgent or emergent" need for reversal.



9.3 Advisory Committee Meeting

An Advisory Committee meeting was scheduled for this review cycle. However, due to concerns related to the conduct of Study P101 that were evaluated during the OSI inspection, it was determined that all of the clinical sites needed to be inspected before a decision could be made as to whether the integrity of the data was retained despite missteps made. These inspections could not be made in time to determine the status of the study's data integrity prior to the Advisory Committee meeting date; therefore, the meeting was cancelled. It will be rescheduled when the inspections are completed, provided no issues related to data integrity are discovered.

9.4 Review of Clinical Studies Conducted Since the Last NDA Submission

9.4.1 Study P07981

Title: Effect of sugammadex compared with usual care for reversal of neuromuscular blockade induced by rocuronium on incidence of residual blockade at PACU entry

Study Dates: December 12, 2011 through November 5, 2012

Objectives:

Primary Objective:

- To assess whether patients who undergo reversal of neuromuscular blockade with sugammadex experienced less residual blockade (as defined by train-of-four (TOF) ratio <0.9) upon entry into the post-anesthesia care unit (PACU) than patients treated with usual care, i.e., neostigmine/glycopyrrolate.

Secondary Objective:

- To assess whether the time from start of study medication administration to operating room (OR) discharge ready was shorter for patients who were administered sugammadex compared to patients treated with usual care. i.e., neostigmine/glycopyrrolate).

Other Objectives:

- Other trial objectives were to assess information related to the assessment of the effect of sugammadex on overall surgical efficiency. Clinical exploratory endpoints and time intervals, and surgical case parameters were assessed and collected. These included:
 - time from start of study medication administration to extubation
 - time from start of study medication administration to PACU discharge ready
 - time from PACU entry to PACU discharge ready
 - time from PACU entry to hospital discharge
 - grip strength
 - pulmonary function tests, including:
 - forced inspiratory volume in 1 second
 - maximal expiratory flow and maximal inspiratory flow at 50%

Study Design:

This trial was a randomized, parallel-group, single-site trial comparing sugammadex to “usual care,” i.e., neostigmine/glycopyrrolate, in subjects undergoing elective abdominal surgery under general anesthesia with rocuronium-induced neuromuscular blockade.

Efficacy Endpoints:

Primary Endpoint

- the TOF ratio achieved upon entry into the PACU

Secondary Endpoints

- the time from start of study medication administration to OR discharge ready
- Time from start of study medication (reversal) administration to extubation
- Time from start of study medication (reversal) administration to PACU discharge ready
- Time from PACU entry to PACU discharge ready
- Time from PACU entry to hospital discharge
- Grip strength (to measure return of neuromuscular function) – assessed pre-operatively when Richmond Agitation-Sedation Scale (RASS) score is zero (+/- 1), when patient was able to answer basic demographic questions after entering the PACU, and at the first time a RASS score of zero (+/- 1) was achieved upon PACU entry. If the patient did not return to baseline value, the patient was to undergo follow-up assessments (each preceded by confirmed RASS score of 0 [+/-1]) at 30 minute intervals thereafter until their return to baseline or PACU discharge.
- Ambulatory Pulmonary Function Tests – assessed pre-operatively when RASS score was zero (+/-1), when patient was able to answer basic demographic questions after entering the PACU, and at the first time a RASS score of zero (+/- 1) was achieved upon PACU entry. If the patient did not return to baseline value, the patient was to undergo follow-up assessments (each preceded by confirmed RASS score of 0 [+/-1]) at 30 minute intervals thereafter until their return to baseline or PACU discharge.
- Forced Inspiratory Volume in 1 second (FIV₁)
- Maximal Expiratory Flow and Maximal Inspiratory Flow at 50% (MEF₅₀/MIF₅₀)

Population

Adult patients scheduled to undergo an abdominal surgical procedure under general anesthesia requiring neuromuscular relaxation for endotracheal intubation and maintenance of neuromuscular blockade and planned to recover in the PACU were recruited for this trial.

Inclusion Criteria: (verbatim from pp 51-52 of final study report)

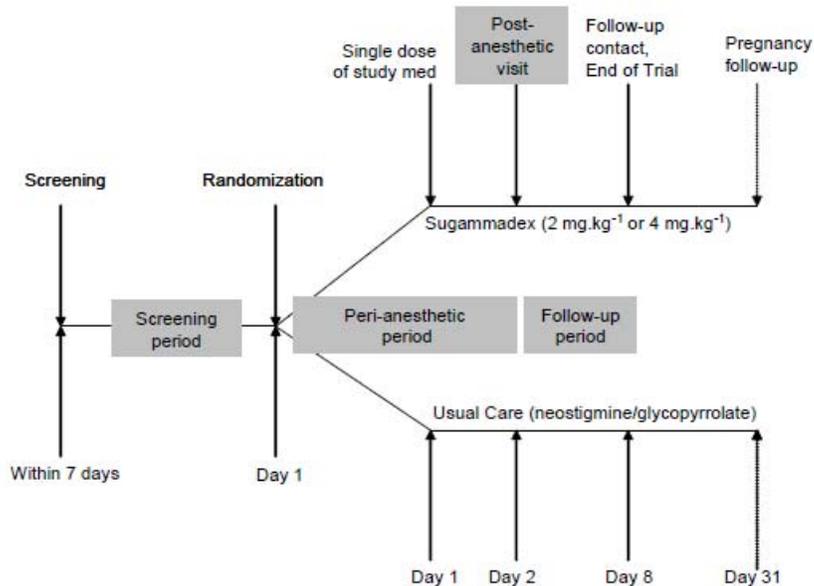
1. Each subject must be willing and able to provide written informed consent for the trial.
2. Each subject must be ≥ 18 years of age.
3. Each subject must be American Society of Anesthesiologists (ASA) Class 1 or 2 or 3.
4. Each subject is scheduled to undergo an elective abdominal surgical procedure under general anesthesia; and
 - expected to undergo neuromuscular relaxation with rocuronium for endotracheal intubation; and
 - expected to require at least one maintenance dose of rocuronium; and
 - expected to require active reversal of neuromuscular blockade; and
 - expected to require clinical or subjective neuromuscular monitoring only (ie, no objective neuromuscular transmission monitoring with TOF-Watch® SX device during surgery); and
 - expected to recover in the PACU.
5. Each subject is expected to have an arm accessible for measuring the TOF ratio in the PACU.
6. Each subject must be able to adhere to dose and visit schedules.
7. Each sexually active female patient of child-bearing potential must agree to use a medically accepted method of contraception through seven days after receiving protocol-specified medication. Medically accepted methods of contraception include condoms (male or female) with a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed intrauterine device (IUD), inert or copper-containing IUD, surgical sterilization (eg, hysterectomy or tubal ligation). Further, for patients using hormonal contraceptives, if study medication is administered on the same day an oral contraceptive is taken, the patient must follow the missed dose advice in the package leaflet of the oral contraceptive. In the case of non-oral hormonal contraceptives, the patient must use an additional non hormonal contraceptive method and refer to the advice in the package leaflet of the product. Postmenopausal women are not required to use contraception. Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period

Exclusion Criteria: (verbatim from pp. 52-53 of final study report)

1. The subject has anatomical malformations that may lead to difficult intubation.
2. The subject has neuromuscular disorder(s) that may affect neuromuscular blockade and/or trial assessments.
3. The subject is dialysis-dependent or has or is suspected of having severe renal insufficiency (defined as estimated creatinine clearance of < 30 mL/min).
4. The subject has or is suspected of having significant hepatic dysfunction that would prevent participation in the trial as determined by the investigator.

5. The subject has or is suspected of having a (family) history of malignant hyperthermia.
6. The subject has a condition requiring the use of a cardiac pacemaker.
7. The subject has or is suspected of having an allergy to study treatments or its/their excipients, to opioids / opiates, sugammadex, muscle relaxants or their excipients, or other medication(s) used during general anesthesia.
8. The subject has received or is planned to receive toremifene within 24 hours before or within 24 hours after IMP administration.
9. The subject has any condition that would contraindicate the administration of rocuronium, sugammadex or neostigmine/glycopyrrolate.
10. The subject is scheduled for an overnight stay (or >12 hours) in PACU.
11. The subject is expected to be transferred to an Intensive Care Unit after surgery.
12. The subject is a premenopausal female of childbearing potential who is pregnant or intends to become pregnant between randomization and the Day 30 pregnancy follow-up visit.
13. The subject is a female who is breast-feeding.
14. The subject has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
15. The subject has used any investigational drugs within 30 days of randomization.
16. The subject has participated in any other clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial.
17. The subject or a family member is among the personnel of the investigational or Sponsor staff directly involved with this trial.

Schematic:
(Figure 9-1 on p. 45 of the final study report)



Summary of Methodology:

After a screening period of up to 7 days, subjects were have been randomized on the day of surgery (Day 1), to one of two treatment groups (sugammadex or usual care, i.e., neostigmine) in a 1:1 ratio. Study drug doses were to have been one of the following:

1. 2 or 4 mg/kg sugammadex IV per usual practice and per the product label or
2. Neostigmine/glycopyrrolate IV per usual practice and per the product label

After wound closure and when the surgical team determined that it was imminently acceptable for the subject to begin to move spontaneously, trial medication was to be administered within 10 seconds by means of a fast running infusion. After surgery, subjects were to be monitored according to routine anesthetic procedures at the trial site's PACU during which time measurements of the efficacy endpoints were made. A post-anesthetic visit was to occur between 10 and 48 hours after trial medication administration, and a follow-up visit was to occur 7 days after trial medication administration. A pregnancy follow-up was scheduled for > 30 days after administration of trial medication.

A more detailed listing of the procedures and their timing is provided in the Schedule below.

Amendments:

The protocol was amended three times as described below:

1. This amendment was made on August 29, 2011, and replaced the visual analog scale with a Surgeon Assessment of Adequacy of Muscle Relaxation scale. Due to this change, additional text was added to the Statistical Methods for Surgical Efficiency Analyses section. Additionally, all relevant text related to pharmacogenomics sampling was deleted from the protocol.
2. This amendment was made on October 21, 2011, and updated and/or delete some wording in the Inclusion, Exclusion and Discontinuation sections. Some terms and abbreviations were also updated. Details were added regarding when local labs may be drawn and Appendix 2 “Laboratory Assessments” was added to the protocol. Text was added to clarify that a total of three measurements should be taken for each grip strength assessment. An addition to the analyses was that subjects with clinical evidence of recurrence of neuromuscular blockade or residual neuromuscular blockade would be listed by treatment group.
3. This amendment was made on March 28, 2012, and added text to the Chronological Flow Chart, Study Flow Chart by Assessment and Trial Procedures sections regarding clarification on measuring grip strength, ambulatory pulmonary function tests and RASS. Modified text was added to the secondary and exploratory endpoints sections in order to make these sections more concise. Specific text regarding adjudication of hypersensitivity and bleeding was clarified

The following changes to planned statistical analyses were implemented in Amendments 1, 2, and 3 of the protocol:

- The Surgeon Assessment of Adequacy of Muscle Relaxation scale added in Amendment 1 was analyzed using descriptive statistics by treatment group for each of the three questions as well as for the average of the three questions for each procedure. The average was not computed if any answer was missing.
- The statistical analyses were updated in Amendment 2 by adding that grip strength (the maximum value of three measurements) and pulmonary function tests would be presented descriptively by treatment group and assessment.
- An additional update from Amendment 2 included subjects with clinical evidence of recurrence of neuromuscular blockade or residual neuromuscular blockade (ie, significant change in the respiratory rate and/or significant decrease in SpO2 level) were to be listed by treatment group.
- The grip strength and ambulatory pulmonary function tests endpoint bullets were updated in Amendment 3 to clarify that the first of these measurements in the PACU should be taken when a patient was able to answer basic demographic questions.

- No subgroup analysis on the primary endpoint by dose of sugammadex (2 mg/kg or 4 mg/kg) was performed, because no subject received a dose of 2 mg/kg.
- Subgroup analysis by renal status was restricted to summary statistics on the primary endpoint by renal status (renal impairment or not) but no Mantel-Haenszel statistics were created by that subgroup, due to the low number of subjects with renal impairment.
- Additional summary statistics were created on procedural time intervals, grip strength and pulmonary function tests split into subjects with and without residual NMB (within the usual care group).
- No scatter plots were created for illustration of correlations.

[Reviewer Comment: These amendments would not be expected to significantly impact the findings of the study, in particular, the efficacy endpoints.]

Schedule: (based on Table 9-2 on pp. 47-48 of the final study report)

| Event / Assessment Scheduled Day / Window | Screening Period From ≤ 7 Days Prior To Study Medication Administration Until Randomization | Peri-Anesthetic Period From Randomization Until The Post-Anesthetic Visit (Day 1) | Post-Anesthetic Visit At Least 10 Hours After Study Medication Or On The Post-Operative Day (Day 2) | Follow-Up Period From Post-Anesthetic Visit Until Follow-Up Visit (Day 8) | Pregnancy Follow-Up 30 Days After Study Medication (Day 31) |
|---|---|---|---|---|---|
| Explain Study And Obtain Informed Consent(s) | X | | | | |
| Patient Identification Card | X | | | | |
| Medical History Incl. Comorbidity Index | X | | | | |
| Demographic Information | X | | | | |
| Physical Examination | X | | X | | |
| Vital Signs (Heart Rate, Respiratory Rate, And Blood Pressure) ^B | X | X | X | | |
| Pregnancy Test, If Applicable ^C | <24 H Before Surgery | | | | |
| Inclusion / Exclusion Criteria | X | | | | |
| Subject Randomization ^D | | X | | | |
| Administration Of Rocuronium (NMBA) | | X | | | |
| Administration Of Reversal Agent | | Sugammadex or Neostigmine + Glycopyrrolate | | | |
| Clinical Interaction ^E And Recovery Data | | X | | | |
| • TOF Ratio At Pacu Entry ^F (TOF Operator Blinded) | | X ^G | X ^G | | |
| • Clinical Evidence Of Residual Neuromuscular Blockade ^H | | X | X | | |
| • O ₂ Flow Rate /Method Of | | X | X | | |

| Event / Assessment Scheduled Day / Window | Screening Period From ≤ 7 Days Prior To Study Medication Administration Until Randomization | Peri-Anesthetic Period From Randomization Until The Post-Anesthetic Visit (Day 1) | Post-Anesthetic Visit At Least 10 Hours After Study Medication Or On The Post-Operative Day (Day 2) | Follow-Up Period From Post-Anesthetic Visit Until Follow-Up Visit (Day 8) | Pregnancy Follow-Up 30 Days After Study Medication (Day 31) |
|---|---|---|---|---|---|
| Delivery | | | | | |
| • RASS ^I | | X | X | | |
| • Grip Strength ^J | | X | X | | |
| • Ambulatory PFTs ^J | | X | X | | |
| Time And Motion Parameters (Or/PACU/Hospital) | | X | X | | |
| Surgical Case Parameters | | X | X | | |
| Concomitant Medications | X | X | X | X | |
| Safety Assessments ^K | AEs AND SAEs | AEs, SAEs, MDRs | AEs, SAEs | AEs, SAEs | |
| Safety Assessor Blinding | | X | X | X | |
| End Of Trial | | | | X | |
| Pregnancy Follow-Up ^L | | | | | X |

LOS = length of stay MDR = medical device reporting reportable event, NMBA = neuromuscular blocking agent, PACU = post anesthesia care unit, PFT = pulmonary function test, (S)AE = (serious) adverse event., RASS= Richmond Agitation-Sedation Scale

^A Cannot occur prior to 7 days post-treatment.

^B Heart rate and blood pressure will be assessed at the following time points: pre-rocuronium, pre-IMP, at 2, 5, 10 and 30 minutes (if applicable) post-IMP. Respiratory rate, heart rate, and blood pressure will be assessed at screening, PACU arrival, 5 mins after arrival and then at 15, 30, 45, 60 minutes after arrival or every 15 minutes until patient is discharged from the PACU.

^C A medically acceptable test (such as a urine hCG or serum hCG test).

^D Randomization is the time point when the treatment code is appointed to a subject.

^E Clinical interactions should be assessed up to end of trial date.

^F The assessment of TOF data in the PACU, PACU endpoints, safety endpoints, and evaluation of PACU discharge-readiness will be assessed by a qualified blinded assessor.

^G TOF assessment at PACU entry may occur between peri-anesthetic and post-anesthetic visit.

^H Any clinical evidence of residual neuromuscular blockade or re-occurrence of neuromuscular blockade (e.g., significant change in the respiratory rate, significant decrease in SpO2 level) from administration of IMP until 60 minutes after recovery of T4/T1 ratio to 0.9 or up to PACU discharge, whichever comes first, will be recorded.

^I RASS is to be assessed and confirmed to be a score of 0 (+/-1) prior to each evaluation of Grip strength and ambulatory PFTs, including the pre-operative baseline assessments. RASS is also to be assessed at entry to PACU and then at subsequent 10 minutes intervals until the patient recovers to a score of zero (+/- 1) at which time the first post-operative evaluations of Grip strength and PFTs are to be assessed. RASS should then be assessed and confirmed to be a score of 0 (+/-1) prior to any subsequent evaluation of Grip strength and ambulatory PFTs (for those patients requiring subsequent Grip strength and PFTs).

^J *After PACU entry, grip strength and ambulatory PFTs are assessed as soon as the patient is able to answer basic demographic questions. If the patient cannot provide the requested answers, the questions will be repeated at 10 minute intervals thereafter until they are able to. In addition, grip strength and PFTs are assessed (see instruction sheets) in subjects with a RASS score of zero (+/- 1) pre-operatively (baseline) and at the first time a RASS score of zero (+/- 1) is achieved after PACU entry. If a patient does not have a pre-operative RASS score of zero (+/- 1) so that baseline Grip strength and PFTs may be assessed, do not collect additional post-operative RASS, Grip strength or ambulatory PFT data. If the patient's Grip strength or PFT parameters do not return to baseline value at the first post-operative assessment, conduct follow-up assessments (each preceded by confirmed RASS score of 0 [+/-1]) at 30 minute intervals thereafter until their return to baseline or PACU discharge.*

^K Blinded Safety Assessor will evaluate the IMP causality assessment of all AEs collected in the trial.

^L Applies to female patients of child-bearing potential.

Subject Disposition:

A total of 183 subjects were screened; 154 subjects were randomized; 151 subjects were treated with study medication. Two subjects treated with neostigmine were lost to follow-up. The sugammadex treatment group consisted of 74 subjects (27 females and 47 males), and the usual care group, i.e., neostigmine/glycopyrrolate treatment, consisted of 77 subjects (34 females and 43 males).

Reported Efficacy Findings:

The Applicant summarized the findings for the two assessments of the primary endpoint as indicated in Table 39 below. There was a significant difference between the treatment groups on admission to the PACU, with no instances of $T_4/T_1 < 0.9$ for sugammadex-treated subjects.

Table 39. Results for primary endpoint measurements (based on Table 11-3, p. 89 of the final study report)

| Endpoint | Treatment Group | | p-value |
|--|--|---|----------|
| | Sugammadex (N=74) ¹ n (%) | Neostigmine (N=77) ² n (%) | |
| Incidence of residual neuromuscular blockade at PACU entry | 0 (0.0) | 33 (43.4) | < 0.0001 |

¹ Fourteen subjects received a dose of sugammadex that deviated more than 10% (approximately 3mg/kg) from the dose prescribed in the protocol. The increased dose was attributed primarily to the patients' obesity

² Two subjects received a dose of neostigmine above the maximum total dose of 5 mg: Subject 055 (6 mg) and Subject 152 (7 mg).

The Applicant also summarized the T_4/T_1 ratio distribution for the neostigmine-treated subjects as described in Table 40 below. The findings indicate that more than 10%, i.e., 8 of these subjects, had T_4/T_1 ratios less than 0.7, the minimum value generally cited in the literature as an acceptable level of reversal to support maintenance of a patent airway and adequate ventilation. Despite these findings, there were only two subjects in this treatment group who had adverse events suggesting recurrence of neuromuscular blockade:

1. Subject 020 (T_4/T_1 ratio 0.53 at PACU entry) treated with 50 mcg/kg of neostigmine was reported to have "partial paralysis" (verbatim term) for 16 minutes.
2. Subject 023 (T_4/T_1 ratio 0.74 at PACU entry) treated with 70 mcg/kg of neostigmine was reported to have "inadequate reversal of neuromuscular blocking agent" (verbatim term) for 11 minutes.

Neither of these adverse events was classified as serious. In the sugammadex group, there were no such adverse events reported.

Table 40. Distribution of T_4/T_1 ratios for the neostigmine-treated subjects (based on Table 11-2, p. 87 of the final study report)

| T_4/T_1 ratio at PACU entry | Treatment Group | |
|--------------------------------|-------------------------------|--------------------------------|
| | Sugammadex (N=74) n (%) | Neostigmine (N=77) n (%) |
| T_4/T_1 ratio < 0.6 | 0 | 5 (6.6) |
| $0.6 \leq T_4/T_1$ ratio < 0.7 | 0 | 3 (3.9) |
| $0.7 \leq T_4/T_1$ ratio < 0.8 | 0 | 9 (11.8) |
| $0.8 \leq T_4/T_1$ ratio < 0.9 | 0 | 16 (21.1) |
| T_4/T_1 ratio \geq 0.9 | 74 (100) | 43 (56.6) |

The results for the various time-intervals measured as secondary endpoints are summarized in Table 41 below. With the exception of the 4-minute differences observed for both the time from study drug administration to extubation and the time from study drug administration to discharge from the OR, there were no other significant differences between the treatment groups.

Table 41. Results for secondary time-interval measurements (based on Table 11-4, p. 91 of the final study report)

| Time Interval Parameter | Geometric Means by Treatment Group | | p-value |
|---|------------------------------------|-----------------------|---------|
| | Sugammadex (N=74) | Neostigmine (N=77) | |
| Time from study drug administration to tracheal extubation (min:sec) | 11:01 | 15:10 | p=0.01 |
| Time from study drug administration to actual OR discharge (min:sec) | 19:51 | 24:05 | p=0.02 |
| Time from study drug administration to PACU discharge ready (hrs:min) | 2:42 | 2:42 | p=0.9 |
| Time from study drug administration to actual PACU discharge (hrs:min) | 3:56 | 4:28 | p=0.2 |
| Time from PACU entry to PACU discharge ready (hrs:min) | 2:15 | 2:12 | p=0.6 |
| Time from PACU entry to actual PACU discharge (hrs:min) | 3:29 | 3:55 | p=0.2 |
| Time from PACU entry to hospital discharge (hrs:min) | 50:00 | 55:02 | p=0.8 |

Perhaps more important than the various time intervals measured above are the assessments of the recovery of strength and pulmonary function that were made by the Applicant both on initial admission to the PACU and later when the subject was more fully awake as indicated by a Richmond Agitation Sedation Scale (RASS) of -1 to 1. The results of these analyses for grip strength and pulmonary function assessments are shown in Table 42 and Table 42, respectively, below.

There were no significant differences between the treatment groups in grip strength in either the dominant or non-dominant hand or on entry to the PACU or when the RASS score was between -1 and 1. The findings were the same for the pulmonary function assessments on admission to the PACU and when the subjects were more fully awake.

Table 42. Results of grip strength testing (based on Table 11-6, p. 95 of final study report)

| Hand Assessed | Measurement | Grip strength (kg) Mean (SD) | | p value |
|---|----------------------|---------------------------------|-----------------------|---------|
| | | Sugammadex (N=73) | Neostigmine (N=72) | |
| First measurement in the PACU | | | | |
| Dominant hand | actual | 7.56 (9.66) | 7.88 (10.31) | p=0.6 |
| | change from baseline | -9.45 (6.86) | -8.85 (7.54) | |
| Non-dominant hand | actual | 6.38 (8.93) | 6.47 (9.26) | P=0.6 |
| | change from baseline | -8.39 (7.07) | -7.82 (7.54) | |
| First value after return of RASS to 0 (±1) | | | | |
| Dominant hand | actual | 7.85 (9.83) | 8.37 (10.69) | p=0.6 |
| | change from baseline | -9.16 (6.86) | -8.62 (7.58) | |
| Non-dominant hand | actual | 6.63 (9.01) | 6.85 (9.54) | p=0.5 |
| | change from baseline | -8.14 (7.02) | -7.58 (7.52) | |

Table 43. Results of pulmonary function testing (based on Tables 11-7 and 11-8, pp. 96-97 of the final study report)

| Pulmonary Function Assessed | Measurement | PFT Value Mean (SD) | | p-value |
|--|----------------------|---------------------|--------------------|---------|
| | | Sugammadex (N=73) | Neostigmine (N=72) | |
| First measurement in the PACU | | | | |
| Forced Inspiratory Volume in 1 second (FIV ₁) (L) | actual | 1.30 (0.68) | 1.25 (0.62) | p = 0.6 |
| | change from baseline | -1.32 (0.70) | -1.16 (0.75) | |
| Forced Expiratory Volume in 1 second (FEV ₁) (L) | actual | 1.36 (0.58) | 1.34 (0.73) | p = 0.9 |
| | change from baseline | -1.27 (0.78) | -1.24 (0.87) | |
| Forced Vital Capacity (FVC) (L) | actual | 1.75 (0.79) | 1.71 (0.90) | p = 0.6 |
| | change from baseline | -1.33 (0.97) | -1.38 (1.03) | |
| Max. Expiratory Flow/ Max. Inspiratory Flow at 50% (MEF ₅₀ /MIF ₅₀) | actual | 1.16 (0.97) | 1.11 (0.88) | p = 0.6 |
| | change from baseline | 0.29 (0.98) | 0.31 (0.88) | |
| First value after return of RASS to 0 (±1) | | | | |
| Forced Inspiratory Volume in 1 second (FIV ₁) (L) | actual | 1.38 (0.69) | 1.30 (0.62) | p = 0.8 |
| | change from baseline | -1.24 (0.70) | -1.20 (0.75) | |
| Forced Expiratory Volume in 1 second (FEV ₁) (L) | actual | 1.44 (0.66) | 1.35 (0.73) | p = 0.5 |
| | change from baseline | -1.20 (0.80) | -1.28 (0.88) | |
| Forced Vital Capacity (FVC) (L) | actual | 1.83 (0.84) | 1.72 (0.91) | p = 0.4 |
| | change from baseline | -1.25 (0.98) | -1.41 (1.06) | |
| Max. Expiratory Flow/ Max. Inspiratory Flow at 50% (MEF ₅₀ /MIF ₅₀) | actual | 1.08 (0.72) | 1.12 (1.04) | p = 0.8 |
| | change from baseline | 0.21 (0.74) | 0.31 (1.04) | |

Summary of Reported Safety Findings:

The Applicant indicated that sugammadex was generally well tolerated in subjects undergoing abdominal surgery, with the incidences of treatment emergent AEs and SAEs being similar in the two treatment groups. Although they noted that treatment with sugammadex showed a lower incidence of treatment-related adverse events (5% with sugammadex and 13% with neostigmine), there were no significant differences in events of clinical interest based on adjudication or reporting, and no clinically significant changes in vital sign data. Adverse events of hypertension, which occurred at a higher rate in the sugammadex group [14% with sugammadex vs. 3% with neostigmine], were transient in duration, in most cases of mild intensity. No SAEs suggestive of hypersensitivity or suspected events of anaphylaxis were reported. Overall, the

Applicant considered there to be no clinically significant safety findings of concern were observed with the use of sugammadex or neostigmine.

Discussion:

The Applicant concluded that treatment with sugammadex was associated with a significantly lower risk of residual neuromuscular blockade compared with neostigmine reversal as part of usual care and that treatment with sugammadex may shorten the time from administration of the reversal agent to OR discharge ready and to extubation, as compared with neostigmine. Given the substantial differences in the extent of residual neuromuscular blockade, it was somewhat surprising that there was no significant difference observed between the treatment groups in regards to pulmonary function tests (especially, FIV1, MEF₅₀/MIF₅₀), grip strength, time from PACU entry to PACU discharge ready or hospital discharge, and time from study medication administration to PACU discharge ready.

Conclusions:

This trial demonstrated that sugammadex reversal of rocuronium is associated with less residual paralysis in the PACU compared to neostigmine reversal, and that sugammadex was also associated with a shorter time to extubation and discharge of the patient from the operating room. However, the differences in residual paralysis between the two treatment groups was not associated with any difference in grip strength, pulmonary function tests, or discharge from either the PACU or hospital, which suggests there is no clinical benefit to the use of sugammadex over the standard of care with the exception of a 4 minute difference in time to extubation and discharge from the operating room. The relevance of these 4-minute differences has not been associated with any clinically meaningful outcome.

Given the clinical implications for residual paralysis post-operatively, and the recent level of discussion in the anesthesia literature about concerns for patient safety due to residual paralysis, it is important that the labeling for sugammadex clearly state that despite the differences in the levels of neuromuscular blockade that persisted into the PACU for subjects treated with neostigmine compared to those treated with sugammadex, there was no evidence of significantly diminished strength, pulmonary function, or ability to maintain a patent airway to adequately ventilate in subjects treated with neostigmine compared to those treated with sugammadex.

9.4.2 Study P07982

Title: Randomized, Controlled, Parallel-Group, Double-Blind Trial to Compare the Use of Deep or Standard Neuromuscular Blockade in Combination With Low or Standard Insufflation Pressures Using a 2x2 Factorial Design in Patients Undergoing Laparoscopic Cholecystectomy

Study Dates: January 30, 2013 to April 29, 2014

Objectives

Primary Objective:

- To assess the benefit of deep neuromuscular blockade in surgical conditions when compared to standard neuromuscular blockade

Secondary Objective:

- To assess whether the use of low insufflation pressure improves the overall patient's pain score within 24 hours (average of all pain assessments at 1, 2, 4 and 24 h) as compared to standard insufflation pressure, based on a standard pain scale following a laparoscopic cholecystectomy

Efficacy Endpoints

Primary Endpoint:

- Surgeon's overall satisfaction with the surgical conditions rated at the end of the surgery using a numerical scale with scores from 0 (=poor, needed intervention) to 10 (=excellent)

Secondary Endpoint:

- Patient's overall reported pain as measured by a numerical scale with scores from 0 (no pain) to 10 (severe) within 24 hours (average of all pain assessments at 1, 2, 4 and 24 hours) after administration of sugammadex
- Surgeon's satisfaction with the visibility of the surgical field rated at the end of the surgery using a numerical scale with scores from 0 (unacceptable visibility) to 10 (excellent)
- Surgeon's overall rating of the adequacy of muscle relaxation and insufflation pressure during surgery using a numerical scale with scores from 0 (=unacceptable muscle relaxation, required intervention) to 10 (=excellent)
- Number of patient's movements that interfered with the surgical conditions during laparoscopy (includes abdominal muscle contractions, diaphragm movement, breathing/coughing against the ventilator, hiccups, patient movements)

- Surgeon's assessment on the effect that these variables had on the overall surgical procedure (using numerical scale with scores of 0-10)
- Number of rescue actions performed during surgery in order to improve insufficient surgical conditions
- Daily assessments of patient reported overall pain and shoulder pain at rest and provoked (i.e. in connection with the transition from lying to sitting position) using a numerical scale with scores (0 to 10) starting on Day 2 up to and including the Follow-Up Visit (Day 8)
- Post-operative consumption of analgesic medications

Inclusion Criteria (verbatim from p. 9 of the final study report)

1. Each subject must be willing and able to provide written informed consent for the trial.
2. Male or Female, ≥ 18 years of age,
3. Categorized as American Society of Anesthesiologists (ASA) Class 1, 2, or 3.
4. Scheduled to undergo an elective in-patient laparoscopic cholecystectomy (standard 4-hole) procedure under general anesthesia with total intravenous anesthesia (TIVA) using propofol and remifentanyl and is eligible to undergo rocuronium-induced NMB for endotracheal intubation and maintenance of NMB. Subjects are expected to recover in the PACU and remain in the hospital for at least 48 hours (unless local practice does not allow for 48 hours, then a minimum of 24 hours is required as the period of observation) following the surgical procedure.
5. Body mass index (BMI) < 35
6. An arm accessible during surgery for monitoring the NMB using the TOF Watch SX® which will be used for objective NM transmission monitoring.
7. Willing and able to adhere to visit schedules including all required study assessments on Day 3 through 8 (daily pain and medication diary entry).
8. Able to use a medically accepted method of contraception through 7 days after receiving protocol-specified medication [for sexually active female subjects of child-bearing potential]. For subjects using hormonal contraceptives, if study medication is administered on the same day an oral contraceptive is taken, the subject must follow the missed-dose advice in the package leaflet of the oral contraceptive. In the case of non-oral hormonal contraceptives, the subject must use an additional non-hormonal contraceptive method and refer to the advice in the package leaflet of the product. Postmenopausal women are not required to use contraception. Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period.
9. Subjects must be willing to give written informed consent for pharmacogenetic testing, and able to adhere to dose and visit schedules.
Note: Subjects who are unwilling to sign the informed consent for pharmacogenetic testing may be included into the trial, however, pharmacogenetic samples must not be obtained.

Exclusion Criteria (verbatim from p. 10 of the final study report)

1. Anatomical malformations that may lead to difficult intubation.
2. Neuromuscular disorders that may affect NMB and/or trial assessments.
3. A lifetime history of previous abdominal surgery, including laparotomies, Cesarean section, laparoscopic procedures or diagnostic laparoscopies.
4. A subject must not currently (within the past 6 months) meet the DSM -IV-TR™ criteria for substance abuse or dependence (excluding nicotine).
5. A history of a chronic pain condition (requiring continuous/daily pain medication prior to surgery).
6. Female subjects with a lifetime history of a Cesarean section, or who have given birth to one or more children within the last year, or are currently pregnant or have the intention to become pregnant between randomization and the ≥ Day 30 pregnancy follow-up contact.
7. Evidence of acute cholecystitis.
8. Dialysis-dependency or suspected of having severe renal insufficiency (defined as estimated creatinine clearance of < 30 mL/min).
9. Significant hepatic dysfunction that would prevent participation in the trial as determined by the investigator.
10. A history of or family history of malignant hyperthermia.
11. An allergy to trial treatments (rocuronium or sugammadex) or their excipients, to opioids/opiates, or other medication used during general anesthesia.
12. Received or is planned to receive toremifene or fusidic acid within 24 hours before or after IMP administration.
13. An expected transfer to an Intensive Care Unit after surgery.
14. Any clinically significant condition or situation, other than the reason for the cholecystectomy that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
15. Used any investigational drugs within 30 days of randomization.
16. Participated in any other clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial.
17. Been a study subject or involved a family member who is among the personnel of the investigational or Sponsor staff directly involved with this trial.

Summary of Methodology

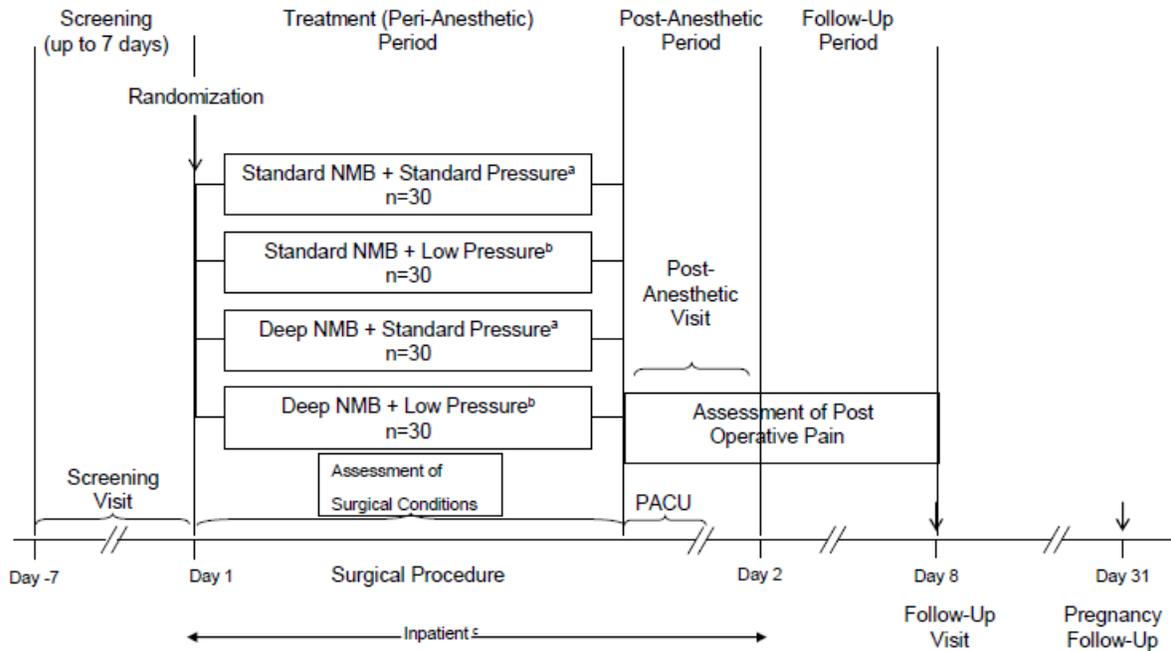
This was a randomized, controlled, parallel group, blinded (subjects, surgeons, and safety-assessors blinded to treatment), multi-site pilot trial to compare the use of deep or standard neuromuscular blockade (NMB) in combination with low (starting at 8 mm Hg) or standard (starting at 12 mm Hg) insufflation pressure using a 2x2 factorial design in subjects of both sexes undergoing laparoscopic cholecystectomy. The timing of events are described in the Schematic and Schedule provided below.

Amendments

Three protocol amendments were implemented during the course of the study.

1. The first amendment was dated July 19, 2012, and included the following major changes:
 - The definition of standard neuromuscular blockade was changed to a targeted TOF ratio of 10% (range TOF count 2-3 TOF ratio 20%).
 - For neuromuscular blockade a bolus dose of 0.45 mg/kg rocuronium was to be used for intubation and to induce NMB in all patients. Neuromuscular blockade was to be maintained as needed using rocuronium bolus dose or infusion according to the randomly assigned treatment condition by the unblinded anesthetist.
 - Scoring instructions on the surgical conditions questionnaire were updated to include the following wording, "The surgeon will rate the surgical conditions according to his opinion but if a rescue maneuver has been applied, an analysis will be performed in which that individual patient will be counted with a score of zero".
2. The second amendment was dated May 14, 2013, and included the major change of allowing discontinued patients to be replaced:
 - A subject that prematurely discontinued from the trial and had missing outcome for the primary/key secondary endpoint(s) was to be replaced, i.e., a discontinued subject was replaced by a subject assigned to the same surgeon with the same treatment assignment as the discontinued subject.
3. The third amendment was dated July 8, 2013, and allowed major edits to be made to two exclusion criteria and the corresponding analyses. Specifically, the edits included the following:
 - They updated the exclusion criteria to include:
 - "A lifetime history of previous abdominal surgery, including laparotomies, Cesarean section, laparoscopic procedures or diagnostic laparoscopies."
 - "Female subjects with a lifetime history of a Cesarean section, or who have given birth to one or more children within the last year, or are currently pregnant or have the intention to become pregnant between randomization and the \geq Day 30 pregnancy follow-up contact."

Schematic



^a Standard insufflation pressure: starting at 12 mmHg

^b Low insufflation pressure: starting at 8 mmHg

^c Patients may be discharged from the hospital 48 hour (Day 2) following the surgical procedure
 NMB = neuromuscular blockade; PACU = Post-Anesthesia Care Unit

Figure 4. Trial design schematic (Figure 2.1, p. 5 of protocol in Appendix 16.1.1 of the final study report)

Schedule

Table 44. (based on Table, pp. 9-10 of protocol in Appendix 16.1.1 of the final study report)

| Visit Title | Timing of Evaluation and Procedures | | | | |
|---|-------------------------------------|--|--|-----------|--|
| | Screening | Treatment (Peri-anesthetic Period) | Post-Anesthetic Period ^a | Follow-Up | Pregnancy Follow- Up ≥ 30 Days After Study Medication |
| | Scheduled Day Day -7 to Day -1 | Day 1b | Day 1 to Day 3 | Day 8 | \geq Day 30 |
| Explain Study and Obtain Informed Consent ^c | X | | | | |
| Subject Identification Card | X | | | | |
| Medical History | X | | | | |
| Prior Medication Review | X | | | | |
| Physical Exam | X | | | | |
| Vital Signs ^d | X | X | X | | |
| Pregnancy Teste | X | | | | |
| Inclusion/Exclusion Criteria | X | X | | | |
| Pharmacogenetic sample ^c | X | | | | |
| Randomization | | X | | | |
| Administration of NMBA (rocuronium) | | X | | | |
| Neuromuscular Assessments ^f | | X | | | |
| Assessment of Neuromuscular Blockade | | X | | | |
| Assessment of Insufflation Pressure | | X | | | |
| Physical Assessments of Abdominal Wall Relaxation | | X | | | |
| Administration of Reversal Agent (sugammadex) ^g | | X | | | |
| Surgeon Satisfaction with the overall Surgical Conditions ^h | | X | | | |
| Surgeon assessments of surgical | | X | | | |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

| Visit Title | Timing of Evaluation and Procedures | | | | |
|--|-------------------------------------|------------------------------------|-------------------------------------|-----------|--|
| | Screening | Treatment (Peri-anesthetic Period) | Post-Anesthetic Period ^a | Follow-Up | Pregnancy Follow- Up ≥ 30 Days After Study Medication |
| | Scheduled Day -7 to Day -1 | Day 1b | Day 1 to Day 3 | Day 8 | \geq Day 30 |
| conditions (overall, visual field, muscle relaxation, pt movements) ^h | | | | | |
| Assessment of Post-Operative Pain prior to hospital discharge ⁱ | | | | | |
| Overall pain (at rest and provoked) | | X ⁱ | X ⁱ | X | |
| Post-operative shoulder pain (at rest and provoked) | | X ⁱ | X | X | |
| Daily Assessment of Pain After Discharge up to Day 8k | | | | | |
| Overall pain (at rest and provoked) | | | | X | |
| Shoulder pain (at rest and provoked) | | | | X | |
| Concomitant Medications (includes analgesics and anti-emetic medications) | X | X | X | X | |
| Safety assessments (AE, SAE, MDR) | X | X | X | X | |
| Pregnancy Follow-Up (females only) | | | | | X |
| End of Trial | | | | X | |

E=adverse event; hCG=human chorionic gonadotropin; MDR=medical device reportable event; PACU=post-anesthesia care unit; PTC=post-tetanic count; SAE=serious adverse event;

(S)AE=serious or non-serious adverse event

^a The Post-Anesthetic Period begins when the subject is discharged from the operating room to the PACU and extends up to and including the Post-Anesthesia Visit. Patients may be discharged from the hospital after discharge from the PACU and a Post-Anesthetic Visit (24 hrs post surgery)

^b Day 1 is the day of surgery (Peri-anesthetic period) and includes administration of sugammadex.

- ^c Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized patients only, or at a later date as soon as the informed consent is obtained.
- ^d At screening, prior to administration of rocuronium, prior to administration of sugammadex, at 2, 5, 10, and 30 minutes after administration of sugammadex, and at the Post-Anesthetic Visit in the supine position.
- ^e Urine or serum hCG test, within 24 hours prior to surgery.
- ^f Recording of the depth of neuromuscular blockade.
- ^g According to the approved sugammadex label.
- ^h These assessments should be completed by the surgeon prior to leaving the operating room suite.
- ⁱ These assessments should occur at 1, 2, 4 and 24 hours after administration of sugammadex, and daily (morning) from Day 3 to Day 8. Day 3 assessment to occur prior to discharge from the hospital. Patients will assess their level of post-operative pain using a score of 0 to 10 using an ePRO device. Pain assessment questionnaire may be administered by study staff while the subject is in the hospital.
- ^j After discharge, subjects will continue to record pain assessments on a daily basis from Day 3 to Day 8 until the Follow-Up Visit. *Subjects will receive a phone call from the study staff on Day 5 as a reminder to complete the required assessments.* During the Screening Period: trial procedure related events and (S)AEs. During the Peri-Anesthetic Period: trial procedure related events, MDR reportable events, and (S)AEs. During the Post-Anesthetic Period: trial procedure related events and (S)AEs. During the Follow-Up Period: trial procedure related events and (S)AEs until 7 days after administration of sugammadex.

Subject Disposition

The Applicant summarized the subject disposition in the table copied below.

Table 45. Subject disposition (based on Table on p. 5 of final study report)

| | Standard NMB + Standard Pressure n (%) | Standard NMB + Low Pressure n (%) | Deep NMB + Standard Pressure n (%) | Deep NMB + Low Pressure n (%) | Total n (%) |
|---|---|---|---|-------------------------------------|----------------|
| Not Randomized | | | | | 10 |
| Subjects in population | 36 | 30 | 31 | 30 | 127 |
| Trial Disposition | | | | | |
| Completed | 28 (77.8) | 30 (100.0) | 30 (96.8) | 29 (96.7) | 117 (92.1) |
| Discontinued | 8 (22.2) | 0 (0.0) | 1 (3.2) | 1 (3.3) | 10 (7.9) |
| Adverse Event | 1 (2.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.8) |
| Other | 1 (2.8) | 0 (0.0) | 0 (0.0) | 1 (3.3) | 2 (1.6) |
| Physician Decision | 4 (11.1) | 0 (0.0) | 1 (3.2) | 0 (0.0) | 5 (3.9) |
| Screen Failure | 1 (2.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.8) |
| Withdrawal By Subject | 1 (2.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.8) |
| Subject Study Medication Disposition | | | | | |
| Discontinued | 1 (2.8) | 0 (0.0) | 0 (0.0) | 1 (3.3) | 2 (1.6) |
| Other | 1 (2.8) | 0 (0.0) | 0 (0.0) | 1 (3.3) | 2 (1.6) |
| Unknown | 35 (97.2) | 30 (100.0) | 31 (100.0) | 29 (96.7) | 125 (98.4) |

Reported Efficacy Findings

For the primary endpoint of surgeon's assessment score of overall satisfaction with surgical conditions during surgery, the estimated difference in LS Means between Deep vs. Standard NMB was 1.09 (95% CI [0.13, 2.04]; p-value = 0.026), indicating a statistically significant difference between Deep vs. Standard NMB favoring Deep NMB.

For the key secondary endpoint of overall average pain score within 24 hours post-surgery (average of all pain assessments at 1, 2, 4 and 24 h), the estimated difference in LS means between Low vs. Standard Pressure was -0.17 (95% CI [-0.67, 0.33]; p-value = 0.494), indicating no statistically significant difference in overall patient's pain score within 24 hours between Low vs. Standard pressure.

Summary of Reported Safety Findings

The Applicant stated that the AE incidence rates between the four treatment groups were similar. There were no discontinuations due to "drug related" adverse events. There were no deaths.

Discussion

With this pilot study, the Applicant appeared to be attempting to identify a surgical procedure for which sugammadex would be ideally suited, compared to the currently available neostigmine. If they were able to demonstrate that maintaining a deep level of neuromuscular blockade throughout a procedure that required minimal time for closure of the incision(s) at its termination, the differences in recovery times for the two reversal agents would be substantial, and the difference could be clinically meaningful in terms of reduced anesthetic exposure if sugammadex is used. This study did not assess recovery time from NMB and looked at surgeons' overall satisfaction with surgical conditions, rather than a surgical outcome, as the primary endpoint. The findings suggest that there is a need for standard insufflation pressure and deeper levels of NMB to enhance the visual field and operating conditions for the surgeon. As the closure of the incisions follow laparoscopy take only a few minutes following the procedure, maintenance of a deep level of NMB to the end of the procedure clearly favors the use of sugammadex over neostigmine to reduce the recovery time from NMB and potentially reduce overall exposure to anesthetic agents, time to extubation, and time to discharge from the operating room.

The Applicant made the following conclusions regarding this trial in patients undergoing laparoscopic cholecystectomy:

1. The use of sustained deep NMB improves the surgeon's overall satisfaction with surgical conditions as compared to standard NMB.
2. Insufflation pressure was not demonstrated to have an effect on pain as measured by the average pain score within 24 hours post-surgery.
3. It appears that the use of standard insufflation pressure improves the surgeon's overall satisfaction with surgical conditions and creates a more prominent role in affecting the assessment score of surgical conditions, as compared to low insufflation pressure.
4. The use of sustained deep NMB improves the surgeon's visual field as compared to standard NMB.
5. The most frequently recorded AEs were in the category of pain. The majority of AEs were associated with the surgical procedures. Overall, the AE incidence rates between the four treatment conditions are similar.
6. Sugammadex is generally well tolerated in subjects undergoing laparoscopic cholecystectomy surgery. Overall, no clinically significant safety findings of concern were observed in this trial.

Conclusions

This study indicated that laparoscopic cholecystectomy performed under standard insufflation pressures and deeper levels of NMB enhance the surgeon's visual field and overall satisfaction with the surgical conditions compared to lower insufflation pressures and less NMB. Because of the limited time required for incision closure at the end of the procedure, maintenance of a deep level of NMB may significantly impact recovery

time to adequate motor function to permit extubation of the trachea and discharge of the patient from the operating room. Sugammadex may be better suited for use in this clinical setting than neostigmine based on previous clinical trials. However, this study did not evaluate recovery time from NMB and did not include neostigmine as an alternative reversal agent. It will be up to the Applicant to determine whether a follow-up study will be appropriate. If they opt to further evaluate this clinical use of sugammadex, it will be important for them to include the two reversal agents and evaluate clinical outcomes that may support a claim of enhanced safety or efficacy with sugammadex treatment.

9.4.3 Study P105

Title: An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics of MK-8616 in Subjects With Moderate and Severe Renal Insufficiency

Study Dates: December 20, 2013 to June 6, 2014

Objectives

Primary Objective:

To evaluate the plasma pharmacokinetics of a single 4 mg/kg dose of MK-8616 administered to subjects with moderate and severe renal insufficiency compared to subjects with normal renal function

Secondary Objectives:

To evaluate the safety and tolerability of MK-8616 in subjects with moderate and severe renal insufficiency

Efficacy Endpoints

No efficacy endpoints were evaluated in this trial.

Pharmacokinetic assessments

Blood samples for MK-8616 concentration in plasma were collected as follows in subjects with severe and moderate renal insufficiency and in healthy control subjects following a single 4 mg/kg dose of MK-8616 administered as an IV bolus in Parts 1 and 2:

- Part 1:
 - Severe renal insufficiency (Panel A): Predose through Day 35
 - Moderate renal insufficiency (Panel B): Predose through Day 28
 - Healthy control subjects (Panel C): Predose through 48 hours postdose.
- Part 2:
 - Severe renal insufficiency (Panel D): Predose through Day 10 (216 hours) postdose. Flexibility was included to extend pharmacokinetic assessment as needed up to 3 additional samples (Days 14 ± 1, 18 ± 1, and Day 21) based on the presence of measurable MK-8616 on Day 7 and/or Day 10. Sampling was extended to Day 14 (312 hours postdose) for a single subject.
 - Moderate renal insufficiency (Panel E): Predose through Day 10 (216 hours postdose).
 - Healthy control subjects (Panel F): Predose through 48 hours postdose.

Safety assessments

For each part, the safety and tolerability of MK-8616 was evaluated by clinical assessment of adverse events and other safety measurements. Safety and tolerability was assessed by clinical evaluation of adverse experiences and other safety measurements including vital signs, medical history, physical examination, 12-lead ECGs, and standard laboratory safety tests (hematology, chemistry, and urinalysis) that were obtained at pre-specified time points throughout the study.

Inclusion Criteria (verbatim from pp. 49-51 of the final study report)

All Subjects

1. Healthy adult male or female, at least 18 years of age.
2. Body mass index (BMI) ≥ 18 to ≤ 40.0 kg/m².
3. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using 1 of the following acceptable birth control methods:
 - a. intrauterine device in place for at least 3 months prior to dosing with a barrier method (condom or diaphragm) and spermicide throughout the study;
 - b. double barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study; or,
 - c. surgical sterilization of the partner (vasectomy for 6 months minimum) with a barrier method (e.g., condom or diaphragm) and spermicide throughout the study;

Female subjects who claim to be sexually inactive, but become sexually active during the course of the study must agree to use a double barrier method (e.g., condom and diaphragm) with spermicide from the time of the start of sexual activity through completion of the study.

In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 14 days following study medication administration.

4. Females of non-childbearing potential must have undergone 1 of the following sterilization procedures at least 6 months prior to dosing:
 - hysteroscopic sterilization and be using a barrier method (e.g., condom or diaphragm) and spermicide throughout the study;
 - bilateral tubal ligation or bilateral salpingectomy and be using a barrier method (e.g., condom or diaphragm) and spermicide throughout the study;
 - hysterectomy;
 - bilateral oophorectomy;

- or be postmenopausal with amenorrhea for at least 1 year prior to dosing and have follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status.
5. Male subjects must agree not to donate sperm from dosing until 90 days after dosing.
 6. Able to comply with the dietary and fluid restrictions/requirements for the study.
 7. Willing to answer inclusion and exclusion criteria questionnaire at check-in.
 8. Understands the study procedures in the ICF. In Part 1 only, the subject may also provide consent/assent for FBR. However, the subject may participate in the main trial without participating in FBR.
 9. Be willing and able to comply with the protocol and the assessments therein.

Subjects With Moderate and Severe Renal Impairment:

In addition, subjects with moderate and severe renal impairment must fulfill all of the following inclusion criteria to be eligible for participation in the study.

10. Baseline health is judged to be stable based on medical history, laboratory profiles, vital signs, or ECGs at screening, as deemed by the Investigator.
11. Part 1: Subject has a clinical diagnosis of impaired stable renal function, and creatinine clearance (Cr_{CL}) based on Cockcroft-Gault equation, as described below. Baseline Cr_{CL} will be obtained twice (at screening and check-in), the 2 Cr_{CL} values taken at least 72 hours apart have ≤ 30% difference (stable renal function), and the mean of the 2 values will be used for group assignment:

| Panel | Stage | N – Part 1 | CrCL (mL/min) [†] |
|-------|----------|------------|----------------------------|
| A | Severe | 8 | < 30, not on dialysis |
| B | Moderate | 8 | 30 - < 50 |

[†] Cr_{CL} based on Cockcroft-Gault equation
 The Cockcroft-Gault equation is (for females multiply result by 0.85):

$$\text{Cr}_{\text{CL}} = \frac{(140 - \text{age}[\text{yr}])(\text{body wt}[\text{kg}])}{(72)(S_{\text{cr, std}}[\text{mg/dL}])}$$

Scr, std: serum creatinine (mg/dL) measured with a standardized assay

Note: For the severe renal impairment group, reasonable efforts will be made to enroll an adequate number of subjects (~ 3 subjects) with CrCL < 20 mL/min.

Data Source: [16.1.1]

Part 2: Subject has a clinical diagnosis of impaired stable renal function, and a Cr_{CL} based on Cockcroft-Gault equation, as described below. Baseline Cr_{CL} will be obtained twice (once at screening and check-in), the 2 Cr_{CL} values taken at least 72 hours apart, the check-in Cr_{CL} will have ≤ 30% difference from screening (stable renal function) [calculated as (check-in – screening)/screening multiplied by 100]], and the mean of the 2 values will be used for group assignment.

Allowance can be made for differences greater than 30% in subjects with a Cr_{CL} less than or equal to 24 mL/min, following discussion with the Sponsor.

| Panel | Stage | N – Part 1 | CrCL (mL/min) [†] |
|-------|----------|------------|----------------------------|
| D | Severe | 6 | < 30, not on dialysis |
| BE | Moderate | 6 | 30 - < 50 |

† Cr_{CL} based on Cockcroft-Gault equation
 The Cockcroft-Gault equation is (for females multiply result by 0.85):

$$\text{Cr}_{\text{CL}} = \frac{(140 - \text{age}[\text{yr}])(\text{body wt}[\text{kg}])}{(72)(S_{\text{cr, std}}[\text{mg/dL}])}$$

Scr, std: serum creatinine (mg/dL) measured with a standardized assay

Note: For the severe renal impairment group, reasonable efforts will be made to enroll an adequate number of subjects (~ 2 subjects) with Cr_{CL} < 20 mL/min.
 Data Source: [16.1.1]

12. Subject has had no clinically significant change in renal status at least 1 month prior to study medication administration, and is not currently or has not previously been on hemodialysis.

Healthy Control Subjects

In addition, healthy control subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study.

13. The age of the individual healthy subjects is aimed to be within the range of the mean age ± ~15 years of all subjects with renal impairment combined. No matching is necessary for gender and weight (weight is already corrected for by dosing mg/kg).
14. Subject is medically healthy with no clinically significant laboratory profiles, vital signs, or ECGs at screening, as deemed by the Investigator.
15. Subject's Cr_{CL} based on the Cockcroft-Gault equation at screening is ≥ 80 mL/min. Baseline Cr_{CL} will be obtained twice (at screening and check-in), and the mean of the 2 values will be used for group assignment. In order that inclusion criteria be consistent with the previous sugammadex study, a Cr_{CL} ≥ 80 was selected instead of a Cr_{CL} ≥ 90 as proposed in the Draft Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling – Mar-2010 [16.1.12.4].

Exclusion Criteria (verbatim from pp. 51-53 of the final study report)

1. Mentally or legally incapacitated, has significant emotional problems at the time of screening visit or expected during the conduct of the study or has a history of a

clinically significant psychiatric disorder over the last 5 years. Subjects who have had situational depression may be enrolled in the study at the discretion of the Investigator.

2. History or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, or neurological disease whose current condition is considered unstable in the opinion of the Investigator. Subjects with a history of uncomplicated kidney stones, uncomplicated appendectomy, or childhood asthma may be enrolled in the study at the discretion of the Investigator.
3. History of any illness that, in the opinion of the Investigator, might confound the results of the study or poses an additional risk to the subject by their participation in the study.
4. History or presence of alcoholism and drug abuse within the past 6 months.
5. History or presence of hypersensitivity or idiosyncratic reaction to the study medication(s) or related compounds.
6. Female subjects who are pregnant or lactating.
7. Positive results for the urine or saliva drug screen, or for the urine or breath alcohol screen at screening or check-in unless the positive drug screen is due to prescription drug use and is approved by the Investigator and Sponsor.
8. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).
9. Heart rate is lower than 40 bpm or higher than 99 bpm at screening.
10. Subject is a regular user of any medication (including over the counter) that would significantly alter glomerular filtration rate (GFR), which, by the determination of the Investigator might interfere with the study, e.g., cimetidine.
11. Have been on a diet incompatible with the on-study diet within the 28 days prior to study medication administration, and throughout the study.
12. Donation of blood or significant blood loss within 56 days prior to dosing.
13. Plasma donation within 7 days prior to dosing.
14. Participation in another clinical trial within 28 days prior to dosing. The 4-week window will be derived from the date of the last dose of investigational drug in the previous study to Day 1 of Period 1 of the current study.
15. No subject may enroll in the protocol more than once within Part 1. Subjects from Part 1 may be enrolled in Part 2, but subjects within Part 2 are not to be enrolled more than once in Part 2.

Healthy Control Subjects

In addition, healthy control subjects must not be enrolled in the study if they meet any of the following criteria:

16. Semi-recumbent blood pressure is less than 90/40 mmHg or greater than 150/90 mmHg at Screening.
17. Subject has had a renal transplant or has had nephrectomy.

Summary of Methodology

The Applicant described this trial as a 2-center, 2-part, open-label, single-dose study to evaluate the plasma pharmacokinetics of a single 4 mg/kg dose of sugammadex (MK-8616) in subjects with moderate and severe renal insufficiency compared with healthy control subjects.

Part 1:

Eight (8) subjects with severe renal insufficiency (Panel A) and 8 subjects with moderate renal insufficiency (Panel B) were enrolled. Eight (8) healthy control subjects (Panel C) matched to the mean age of subjects in Panels A and B with renal insufficiency were enrolled in parallel. On Day 1, each subject received a single 4 mg/kg dose of MK-8616 administered as an intravenous (IV) bolus (within 10 seconds) through a straight needle directly into a peripheral vein.

The protocol was amended to add a second part (Part 2) to the study as a preliminary review of the concentration data from the original study (now Part 1) indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue based on substantial delays in T_{max} and an apparent absorption phase.

Part 2:

Six (6) subjects with severe renal insufficiency (Panel D) and 6 subjects with moderate renal insufficiency (Panel E) were enrolled. Six (6) healthy control subjects (Panel F) matched to the mean age of subjects in Panels D and E were enrolled in parallel. On Day 1, each subject received a single 4 mg/kg dose of MK-8616 administered as an IV bolus (within 10 seconds) through an IV catheter into which free-flowing access to a peripheral vein was confirmed immediately prior to dose administration, followed by saline flush.

More details regarding the assessments made during the trial can be found in the Schedule below.

Amendments

The Applicant noted that a preliminary review of the MK-8616 concentration data from Part 1 of the study combined with dosing issues reported from the clinical research units, indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue, based on substantial delays in T_{max} and an apparent absorption phase. In Part 1 of the study, each subject received a single 4 mg/kg dose administered as an IV bolus through a straight needle into a peripheral vein. As a result of these dosing issues, the protocol was amended to add a second part (Part 2) to the study.

Amendment 1 outlined the change in the method of administration in Part 2 of the study whereby the IV bolus administration was through an IV catheter into which free-flowing access to the vein was confirmed immediately prior to dose administration, followed by saline flush. In Part 2, 3 cohorts of 6 subjects each (subjects with severe renal insufficiency [Panel D], moderate renal insufficiency [Panel E], and healthy control subjects [Panel F]), received a single IV bolus dose of 4 mg/kg MK-8616. Subjects who participated in Part 1 of the study were considered eligible to participate in Part 2 of the study.

Amendment 1 also described the period of pharmacokinetic assessment for moderate and severe renally impaired subjects which was shortened to 10 days in Part 2 of the study. In subjects with severe renal impairment, flexibility was included to extend pharmacokinetic collection based on the presence of measurable concentrations on Day 7 and/or Day 10 for up to 3 additional samples (Day 14 ± 1, 18 ± 1, and Day 21).

Exclusion Criteria #16, was also modified in Amendment 1 to indicate that blood pressure was to be taken with subjects in a semi-recumbent position and not seated.

The protocol was amended a second time to include a third clinical site and Investigator to the study. In addition, a change to MK-8616 administration was made, whereby approximately 250 mL saline in total and not 100 mL saline in total as specified in the protocol would be used pre and post flow for all subjects.

Clinical Review

Arthur Simone, MD, PhD

NDA 022225 (2nd Complete Response)

Bridion (sugammadex sodium)

- h. To be performed at the end of the study or prior to early termination of the study.
- i. To be performed within 24 hours prior to dosing.
- j. Samples for serum chemistry will be obtained following a fast of approximately 8 hours; however, in case of dropout or rechecks, subjects may not have fasted for 8 hours before serum chemistry sample is taken.
- k. For female subjects only.
- l. For postmenopausal female subjects only.
- m. Pharmacokinetic samples to be drawn from the arm opposite to the injection (dosing) arm.
- n. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose on Day 1 (or with the next scheduled blood draw), on treated subjects only, as the last sample drawn, or at a later date as soon as the informed consent is obtained.
- o. Subjects may remain longer in the clinical facility and be discharged on a later day, if needed, based on clinical judgment of the Investigator.

Abbreviations: AE = Adverse events; BP = Blood pressure; Chem = Serum chemistry; C-I = Check-in; ConMeds = Concomitant medication; DNA = Deoxyribonucleic acid; ECG = Electrocardiogram; FBR = Future biomedical research; FSH = Follicle stimulating hormone; FU = Follow-Up; Hem = Hematology; Hep = Hepatitis; HIV = Human immunodeficiency virus; HR = Heart rate; Phys Exam = Physical examination; PK = Pharmacokinetic; RR = Respiration rate; Screen = Screening; T = Temperature; UA = Urinalysis.

Subject Disposition

All subjects enrolled completed the trial, in both Part 1 and Part 2.

Reported Pharmacokinetic Findings

The Applicant summarized the pharmacokinetic properties of sugammadex (MK-8616) in Part 2 of the trial in the three subsets of patients in tabular format (see Table 47 below).

Table 47. Summary of pharmacokinetic findings for Part 2 (Table 11-1, p. 85 of the final study report

| Pharmacokinetic Parameter | Severe Renal Insufficiency Subjects | | | Moderate Renal Insufficiency Subjects | | | Healthy Control Subjects | | |
|---|--|--------------|--|---------------------------------------|-------|----------------|--------------------------|-------|----------------|
| | N | GM | 95% CI | N | GM | 95% CI | N | GM | 95% CI |
| AUC _{0-∞} ‡ (ug•hr/mL) | 6 | 339 | (268, 428) | 6 | 151 | (120, 191) | 6 | 62.5 | (49.5, 79.0) |
| AUC _{0-last} ‡ (ug•hr/mL) | 6 | 335 | (265, 424) | 6 | 148 | (117, 187) | 6 | 61.1 | (48.3, 77.3) |
| C _{max} ‡ (ug/mL) | 6 | 62.2 | (50.2, 77.1) | 6 | 60.6 | (49.0, 75.1) | 6 | 66.1 | (53.3, 81.8) |
| AUC _{%extrap} § (%) | 6 | 0.850 | 43.5 | 6 | 2.14 | 29.2 | 6 | 2.10 | 45.3 |
| CL § (L/hr) | 6 | 0.961 | 26.8 | 6 | 2.27 | 39.6 | 6 | 5.70 | 16.0 |
| V _z § (L) | 6 | 18.3 | 24.8 | 6 | 18.8 | 24.2 | 6 | 20.4 | 25.7 |
| MRT § (hr) | 6 | 15.7 | 26.2 | 6 | 7.02 | 30.8 | 6 | 2.48 | 13.4 |
| V _{ss} § (L) | 6 | 15.1 | 19.7 | 6 | 15.9 | 21.9 | 6 | 14.1 | 20.4 |
| T _{max} (hr) | 6 | 72.00 | (0.03, 0.08) | 6 | 0.03 | (0.02, 0.08) | 6 | 0.03 | (0.03, 0.08) |
| T _{last} (hr) | 6 | 72.00 | (71.99, 143.99) | 6 | 24.00 | (23.99, 47.99) | 6 | 12.00 | (11.99, 12.00) |
| Apparent terminal t _½ § (hr) | 6 | 13.24 | 35.50 | 6 | 5.73 | 29.79 | 6 | 2.47 | 13.49 |
| t _{½eff} § (hr) | 6 | 10.89 | 26.15 | 6 | 4.87 | 30.84 | 6 | 1.72 | 13.36 |
| λ _z § (1/hr) | 6 | 0.0524 | 35.5 | 6 | 0.121 | 29.8 | 6 | 0.280 | 13.5 |
| Pharmacokinetic Parameter | Severe Renal Insufficiency/Healthy Control | | Moderate Renal Insufficiency/Healthy Control | | rMSE† | | | | |
| | GMR | 90% CI | GMR | 90% CI | | | | | |
| AUC _{0-∞} ‡ (ug•hr/mL) | 5.42 | (4.12, 7.11) | 2.42 | (1.84, 3.17) | 0.269 | | | | |
| AUC _{0-last} ‡ (ug•hr/mL) | 5.49 | (4.18, 7.22) | 2.42 | (1.84, 3.18) | 0.270 | | | | |
| C _{max} ‡ (ug/mL) | 0.94 | (0.73, 1.21) | 0.92 | (0.72, 1.18) | 0.246 | | | | |

A single IV dose of 4 mg/kg MK-8616 administered on Day 1.

† rMSE: Square root of conditional mean squared error (residual error) from the ANOVA model.

rMSE×100% approximates the %CV on the normal scale.

‡ Back-transformed least-squares mean and confidence interval from the ANOVA linear fixed-effect model performed on natural log-transformed values.

§ Geometric mean and geometric coefficient of variation reported for AUC_{%extrap}, CL, V_z, MRT, V_{ss}, apparent terminal t_½, t_{½eff}, and λ_z.

|| Median and (Minimum, Maximum) reported for T_{max} and T_{last} .
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.

Summary of Reported Safety Findings

The Applicant indicated that the safety analyses for Parts 1 and 2 were performed separately so that the Part 2 analysis was not confounded by the re-enrollment of 9 subjects from Part 1. The findings for each part are listed below.

Part 1

Administration of a single 4 mg/kg IV dose of MK-8616 was generally well tolerated in the male and female subjects with moderate to severe renal insufficiency and matched healthy control subjects. Seven (29%) subjects reported a total of 9 adverse events, 5 of which were considered drug-related by the Investigator (4 in severe renal insufficiency subjects and 1 in control subjects). Prior to MK-8616 dosing there was 1 serious nonfatal adverse experience reported in this part of the study; 1 subject with severe renal insufficiency, experienced severe urinary retention which required hospitalization during the screening period. Following resolution of this serious adverse experience, the subject was approved for dosing and completed the study as per protocol. No subject discontinued from the study due to an adverse event, and no events of clinical interest (ECIs), or deaths were reported. Drug-related adverse events reported in this part of the study included dizziness, headache, injection site reaction, pain in extremity, and oral paresthesia, which were each reported by 1 (4%) subject. Other adverse events reported in the study included contusion, hypoesthesia, injection site extravasion, and tooth infection. No adverse events of hypersensitivity were reported in this part of the study. No clinically meaningful relationships were observed for differences between clinical laboratory values, vital signs, or ECG safety parameters as a function of treatment.

Part 2

Administration of a single 4 mg/kg IV dose of MK-8616 was generally well tolerated in the male and female subjects with moderate to severe renal insufficiency and matched healthy control subjects. Three (17%) subjects reported a total of 3 adverse events, none of which were considered drug-related by the Investigator. There were no serious adverse events, discontinuations due to adverse events, laboratory adverse events, ECIs, or deaths reported in this part of the study. The most frequently reported adverse event was headache which was reported by 2 (11%) subjects. The only other adverse experience reported was muscular weakness which was reported by 1 (6%) subject. No adverse events of hypersensitivity were reported in this part of the study. No clinically meaningful relationships were observed for differences between clinical laboratory values, vital signs, or ECG safety parameters as a function of treatment. Repeat dosing in the 9 subjects who were enrolled in both parts of the study was well

tolerated; 2 of these 9 subjects reported a total of 2 adverse experiences of headache following repeat dosing, both of which were considered unrelated to study drug.

Discussion

The Applicant appears to have taken the correct step in instituting Part 2 of the trial, given the findings in Part 1. The Applicant drew the following conclusions from this trial:

1. Exposure ($AUC_{0-\infty}$) to MK-8616 increased approximately 5.42 times and 2.42 times in subjects with severe and moderate renal insufficiency, respectively, relative to healthy control subjects.
2. Clearance progressively decreased and apparent terminal $t_{1/2}$, $t_{1/2\text{eff}}$, MRT, and T_{last} were progressively prolonged with increased levels of renal dysfunction. Although measurable plasma concentrations were detected for a longer duration after dosing in subjects with severe renal insufficiency compared to subjects with moderate renal insufficiency and healthy controls, plasma concentrations were not measurable ($< \text{LLOQ}$) in the majority of subjects 5 days postdose and in any subject with severe renal insufficiency beyond 7 days postdose.
3. C_{max} , T_{max} , V_z , and V_{ss} values in subjects with severe and moderate renal insufficiency were comparable to those in the healthy control subjects.
4. Administration of a single 4 mg/kg IV dose of MK-8616 was generally well tolerated in male and female subjects with moderate to severe renal insufficiency and matched healthy control subjects.

In discussion with Dr. Nallani from the Clinical Pharmacology review team, the findings from the analyses of the Part 2 data are consistent with those from previous trials.

Conclusions

Exposure to sugammadex is increased approximately 2.4 to 5.4 times in patients with moderate and severe renal impairment, respectively, compared to individuals with normal renal function. This finding is consistent with the decreased renal clearance in the impaired patients. Although exposure is prolonged with renal impairment, the C_{max} and T_{max} , are not affected, as would be expected for an intravenously administered drug product.

The adverse events that occurred in the renally impaired subjects were similar to those in healthy individuals. The trial raised no special safety concerns for the use of sugammadex in renally impaired patients; however, the number of subjects exposed was too small for this finding to be considered definitive.

9.4.4 Study P101

Title: A randomized, double-blind, placebo-controlled, parallel group study to evaluate the incidence of hypersensitivity after repeated single dose administration of sugammadex (MK- 8616) in healthy subjects

Study Dates: January 7, 2014 through July 1, 2014

Objectives

Primary Objectives:

- To determine the number and percentage of subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo.

Secondary Objectives:

- To determine the number and percentage of subjects with adjudicated anaphylaxis according to the definition of Sampson (Criterion 1) for each dose group of sugammadex and placebo.
- To investigate the change over time in frequency and severity of adjudicated HS symptoms for each dose group of sugammadex and placebo.
- To evaluate the safety and tolerability of administration of repeated single doses of sugammadex in healthy subjects.

Exploratory Objectives:

- To measure levels of anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of hypersensitivity and in a subset of subjects without adjudicated symptoms of hypersensitivity.
- To measure mast cell tryptase levels in subjects referred for adjudication of Potential Hypersensitivity.
- To collect samples for potential hypersensitivity research.

Efficacy Endpoints

There were no efficacy endpoints for this study.

Safety Endpoints

Primary Endpoint:

- Number and percentage of subjects with adjudicated symptoms of hypersensitivity for each sugammadex dose group and placebo

Secondary Endpoints:

- Number and percentage of subjects with adjudicated anaphylaxis according to the definition of Sampson (Criterion 1)
- Change over time in frequency and severity of adjudicated hypersensitivity symptoms for sugammadex and placebo

Exploratory Endpoints:

- Levels of anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of hypersensitivity and in a subset of control subjects
- Tryptase levels in subjects with potential hypersensitivity

Inclusion Criteria (verbatim from pp. 51-52 of the final study report)

1. understand the study procedures and agree to participate in the study by giving written informed consent, including consent for Future Biomedical Research.
2. be male, or non-pregnant and non-breast feeding female 18 to 55 years of age at the pre-trial (screening) visit; further:
 - a. if female with reproductive potential: subject must demonstrate a serum β -human chorionic gonadotropin (β -hCG) level consistent with the nonpregnant state at the pretrial (screening) visit and agree to use (and/or have their partner use) two (2) acceptable methods of birth control beginning at the pretrial (screening) visit, throughout the trial (including washout intervals between treatment periods/panels) and until after the post-study follow-up visit. Acceptable methods of birth control are defined in Protocol Section 5.7.2.5.
 - b. if postmenopausal female: subject is without menses for at least 1 year and have an FSH value in the postmenopausal range upon pretrial (screening) evaluation.
 - c. if surgically sterile female: subject is status post hysterectomy, oophorectomy or tubal ligation.
NOTE: Information regarding the procedure may be based on the subject's recall of her medical history, and details of the recall must be captured appropriately within the site's source documents.
1. have a Body Mass Index (BMI) ≥ 19 and ≤ 32 kg/m². BMI = weight (kg)/height (m)²
2. be judged to be in good health based on medical history, physical examination, vital sign measurements, ECG, and capillary refill time measurement of < 3 seconds prior to randomization
3. be judged to be in good health based on laboratory safety tests (Protocol Section 7.1.3) obtained at the screening or prior to administration of the initial dose of trial drug. Protocol Section 12.7 provides an algorithm for the assessment of out-of-range laboratory values
4. be a non-smoker or smoke ≤ 10 cigarettes/ day or equivalent (2 pipes/day, 1 cigar/day) and agree not to smoke while confined at the Clinical Research Unit

5. be willing to comply with the trial restrictions (see Protocol Section 5.7 for a complete summary of trial restrictions)
6. must have systolic blood pressure \geq 110 mm Hg and diastolic blood pressure \geq 60 mmHg at screening.

Exclusion Criteria (verbatim from PP. 52-53 of the final study report)

1. is under the age of legal consent
2. is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.
3. has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory (including current asthmatic disease), genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator.
4. has a history of cancer (malignancy)
5. has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction (as defined by Sampson [16.1.12.1] or significant intolerance to prescription or non-prescription drugs or food
6. is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV
7. had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit
8. has participated in another investigational trial within 4 weeks prior to the pretrial (screening) visit. The 4 week window will be derived from the date of the last trial procedure (i.e., poststudy, AE follow-up, etc.) in a previous trial and/or AE related to trial drug to the pretrial/screening visit of the current trial
9. has QTcF interval \geq 470 msec (for males) or \geq 480 msec (for females)
10. is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the posttrial visit. There may be certain medications that are permitted, see Protocol Section 5.5.
11. has received subcutaneous or sublingual immunotherapy within the past 1 year
12. consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Subjects that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator

13. consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day
14. is currently a regular user (including “recreational use”) of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 12 months
15. is any concern by the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial
16. has a recollection of previously receiving sugammadex, Bridion™, SCH 900616, ORG 25969, or MK-8616
17. has a history of chronic urticaria or angioedema
18. is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

Discontinuation is “permanent”. Once a subject is discontinued, he/she shall not be allowed to enroll again.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.
- The subject has a confirmed positive serum pregnancy test.
- Subjects with signs and symptoms suggestive of HS that are classified as ‘serious’ or severe in intensity will be discontinued from the treatment at any time. To ensure subject safety, full resuscitative equipment and rescue treatment, including EpiPen® (epinephrine) 0.3 mg, will be available at each participating study center during the trial. Subjects who have mild to moderate signs and symptoms of HS may continue in the study as described by the algorithm.

Summary of Methodology

Subjects were to have been screened approximately 4 weeks prior to randomization. On Day -1, baseline assessments were to have been performed to confirm eligibility. Randomization was to have been performed prior to dosing in Period 1 in randomized

blocks of 5 subjects. Eligible subjects were to have been randomized to receive one of three treatments:

1. Treatment Arm A: Sugammadex 4 mg/kg single intravenous bolus injection in each of 3 periods
2. Treatment Arm B: Sugammadex 16 mg/kg single intravenous bolus injection in each of 3 periods
3. Treatment Arm C: Placebo single intravenous bolus injection in each of 3 periods

Subjects were to have been admitted to the study center the day before each scheduled dose and were to have been discharged from the unit the morning of the day after each dose.

After each dose, subjects were to have been assessed with the Targeted Hypersensitivity Assessment (THA) for the presence of the predefined signs and symptoms of hypersensitivity. The THA was designed to elicit the defined signs and symptoms of hypersensitivity arising within the first 24 hours after administration of study drug. Any subject with a sign or symptom identified in any THA was considered a case of potential hypersensitivity and referred to the blinded external CAC for evaluation. It was noted that two of the signs and symptoms of hypersensitivity required the presence of multiple components:

1. The first multicomponent sign was diagnosis of uncompensated shock, which required the presence of at least three out of the four following signs: tachycardia (pulse ≥ 100), capillary refill time >3 sec, reduced central pulse volume, decreased, or loss of, consciousness.
2. The second multicomponent sign was respiratory distress, which required the presence of two or more of the following: tachypnea (>30 /minute), recession, cyanosis, increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.), grunting, decrease of oxygen saturation by pulse oximetry (SpO₂) on room air $\geq 5\%$ (absolute) from baseline, or PEF $< 70\%$ of baseline.

The finding of a single subcomponent of these two multicomponent signs of hypersensitivity, such as isolated tachycardia, was not considered a sign or symptom of hypersensitivity and did not result in referral to the CAC. The PI provided a narrative for each positive THA and recorded associated adverse events (AEs) in the AE log. A clinical adjudication package was prepared for each potential case of hypersensitivity associated with a particular dosing period for a particular subject and was provided for evaluation to the blinded CAC. The CAC was composed of 4 experts in allergy and/or anesthesia who were blinded to study treatment and as to which dosing occasion for a given subject was being referred. Each event was evaluated independently of any other dosing occasion for a given subject. In general, each referred case was evaluated by two members of the CAC and a third member evaluation was required if there was any disagreement in the assessments.

The CAC made the following determinations:

1. Was the referred case a case of hypersensitivity
2. If yes, whether the case was related or not related to study drug and how the CAC rated the severity of hypersensitivity independent of the Investigator assessment of individual AE intensity
3. Whether the case was a case of anaphylaxis according to the criteria of Sampson.

Disposition for subjects with potential hypersensitivity was pre-specified as follows. Subjects with potential hypersensitivity remained confined to the study center until the Investigator considered it safe for the subject to leave the study center. An algorithm was employed for subjects referred to the CAC for potential hypersensitivity prior to proceeding to the next dosing period in the following sequential manner, as described below

1. If the subject experienced an AE of hypotension, the subject should be discontinued from the study.
2. The signs and symptoms of hypersensitivity must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment.
3. A blinded independent external expert with clinical expertise in the treatment of allergy will make a recommendation as to whether it would be safe for the subject to proceed to the next dosing period based on a review of the signs and symptoms of hypersensitivity for this dosing period, as well as any previous dosing period. This expert may also be a member of the CAC.

Thus, all subjects who received treatment for AEs of potential hypersensitivity were discontinued from the study regardless of the investigator rated severity of the AEs.

In order for a subject referred to the CAC with potential hypersensitivity to continue in the study to the next dosing period, the following sequential algorithm was employed, with each step affirmed:

1. The subject must not experience an AE of hypotension
2. The signs and symptoms of hypersensitivity must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment
3. An independent external expert with clinical expertise in the treatment of allergy would make a recommendation as to whether it would be safe for the subject to proceed to the next dosing period based on a blinded review of the signs and symptoms of hypersensitivity for this dosing period, as well as any previous dosing period.

Each participating investigator was trained in recognizing hypersensitivity symptoms and was instructed on how to act in the event of severe hypersensitivity symptoms. To ensure subject safety, resuscitative equipment and rescue treatment, including EpiPen™ (epinephrine) 0.3 mg, were available at each participating study center during the trial. Physicians trained in establishing an airway in acute emergencies were to be

present in the unit or accessible for support per standard emergency timelines for at least 2 hours after each dose administration.

In addition, there was to have been regular monitoring throughout the study of recorded AE's by the Applicant using the current version of the MedDRA SMQ's for hypersensitivity and anaphylactic reaction that led to additional referrals to the CAC.

Amendments

Three protocol clarifications were during the course of the study:

1. On December 23, 2013, the Applicant issued a letter regarding who can perform the Targeted HS assessments and the leeway provided for performing those assessments at specific time points. It stated:

The protocol Section 7.1.2.10 (Targeted HS assessment) contains the following sentence: "AE assessment and the Targeted HS assessment are to be performed by a physician who does NOT administer study drug or prepare medication." This sentence is also present in Section 2. 1 (Trial Design), Section 5.2.3 (Trial Blinding/Masking) and Section 6 (Flowchart). The expectation is that an investigator who is a qualified physician will evaluate the Targeted HS Assessment and will provide the narrative on this assessment if needed as well as make the determination of the outcome of this assessment: either (i) No signs or symptoms [of hypersensitivity] present or (ii) Presence of at least one sign or symptom in the HS Signs and Symptoms (protocol Section 12.6). When available, a qualified physician should conduct the Targeted HS Assessment. In cases where a qualified physician is unavailable, the initial conduct of the Targeted HS Assessment may be performed by a designee of the investigator, such as a nurse practitioner, a physician assistant, or paramedic. The individual initially conducting the Targeted HS Assessment, as well as the investigator evaluating the results of the initial Targeted HS Assessment conduct must not administer study drug or prepare medication. Furthermore, the individual who administers study drug is to be blinded to treatment and should not be involved in the conduct of the study (assessment of AEs and performance of other study procedures such as vital sign measurements).

Footnote "J" of the study flow chart indicates that the Targeted HS Assessment is to be "performed at 0.5, 4 and 24 hrs post dose. Scheduled assessment may occur +/-5 min for the 0.5 hour time point or +/- 15 min for the 4 hr and 24 hr time points respectively." This protocol clarification is written to allow for the 0.5 hr Targeted HS Assessment to be performed within +/- 10 min of the scheduled

timepoint, the 4 hr Targeted HS Assessment to be performed within +/-20 min of the scheduled timepoint, and the 24 hr Targeted HS Assessment to be performed within +/- 1 hr of the scheduled timepoint.

2. On January 29, 2014, the Applicant issued a letter regarding the Informed Consent. It stated:

The protocol Section 6, Trial Flow Chart, indicates that study specific Informed Consent and Informed Consent for Future Biomedical Research are to be completed at the Screening visit (Day -28 to Day -2).

If a site uses a generic Screening Informed Consent, subjects may instead complete the study specific Informed Consent and Informed Consent for Future Biomedical Research upon admission to the clinical research unit on Day -1 of Period 1. In that case, the consents are to be signed upon admission in the unit, prior to the other trial related procedures planned on Day -1.
3. On January 31, 2014, the Applicant issued a letter regarding the timing of treatment randomization. It stated:

The protocol Section 6, Trial Flow Chart, indicates that randomization is to take place on Day 1 of Period 1.

A clinical site may randomize subjects on Day -1 of Period 1 instead of Day 1 if all Day -1 procedures are complete, including receipt of the Day -1 laboratory safety test results prior to the randomization. A subject is considered to be randomized once the weight based treatment preparation is started for that subject based on the allocation schedule.

Schematic

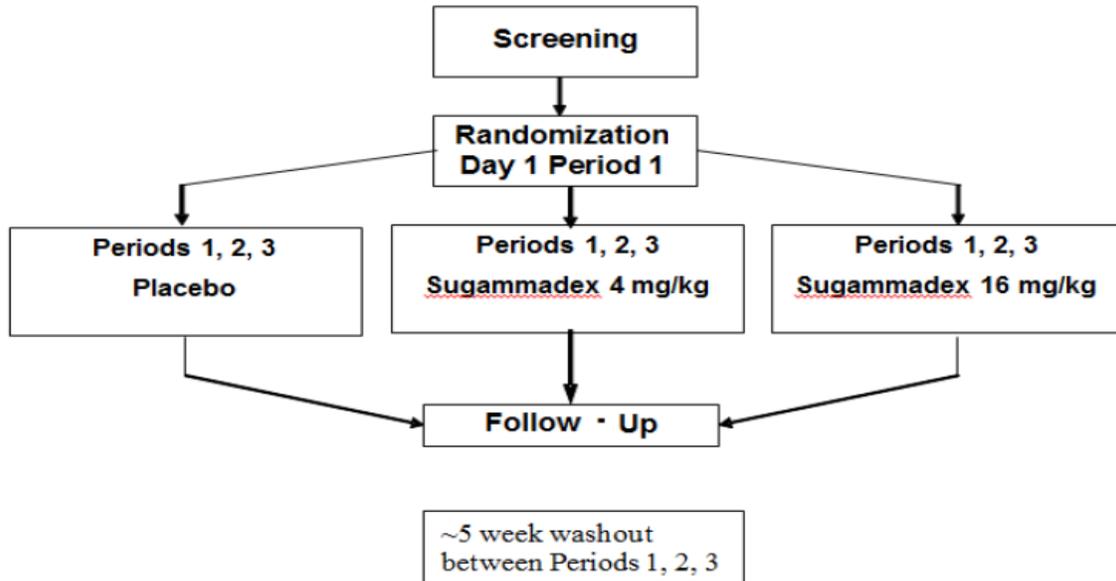


Figure 5. Schematic of the protocol for study P101 (Figure 9-1, p. 44 of the final study report)

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (2nd Complete Response)
 Bridion (sugammadex sodium)

Schedule

Table 48. Schedule for Study P101 (Table 9-1, pp.48-50)

| Visit | Screening Visit 1 | Visit 2 ^{c, s} | | | Visit 3 ^{c, s} | | | Visit 4 ^{c, s} | | | Visit 5 (F/U) ^b |
|--|----------------------|-------------------------|----------------|----------------|-------------------------|----------------|----------------|-------------------------|----------------|----------------|-------------------------------|
| Period | | Period 1c | | | Period 2c | | | Period 3c | | | |
| Period Day | Day -28 to -2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | 2 | |
| Administrative Procedures | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | |
| Informed Consent for Future Biomedical Research | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | X | X ^d | | X | X ^d | | X | X ^d | | |
| Subject Identification Card | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Record AEs ^k and Prior/ ConMeds | X-----X | | | | | | | | | | |
| Screening Number Assignment | X | | | | | | | | | | |
| Randomization | | | X | | | | | | | | |
| Clinic Procedures/Assessments | | | | | | | | | | | |
| Physical Exam | X | X ^a | | | X ^a | | | X ^a | | | X |
| Body Weight (kg) | X | X ⁺ | | | X ^e | | | X ^e | | | |
| Body Height and Body Mass Index (BMI) | X | | | | | | | | | | |
| Administration of trial medication ^f | | | X | | | X | | | X | | |
| ECG (12-Lead) | X | X | | | | | | | | | X |
| Peak Expiratory Flow (PEF) ^f | X | | X | X | | X | X | | X | X | |
| Vital Signs (BP, Pulse Rate, RR, Body Temperature ^g) | X | X | X ^h | X ^h | X | X ^h | X ^h | X | X ^h | X ^h | X |
| SPO ₂ | | | X ⁱ | X | | X ⁱ | X | | X ⁱ | X | |
| Targeted HS Assessment ^{l, k} | | | X | X | | X | X | | X | X | |
| Confinement | | X | X | X ^l | X | X | X ^l | X | X | X ^l | |
| Ambulant visit | X | | | | | | | | | | X |
| Laboratory Procedures | | | | | | | | | | | |
| Clinical Laboratory Tests ^p | X | X | | | X | | | X | | | X |

| Visit | Screening Visit 1 | Visit 2 ^{c, s} | | | Visit 3 ^{c, s} | | | Visit 4 ^{c, s} | | | Visit 5 (F/U) ^b |
|---|-------------------|-------------------------|----------------|---|-------------------------|----------------|---|-------------------------|----------------|---|----------------------------|
| Period | | Period 1c | | | Period 2c | | | Period 3c | | | |
| Period Day | Day -28 to -2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | 2 | |
| Administrative Procedures | | | | | | | | | | | |
| IgG, IgE blood sampling | | | X ^m | | | X ^m | | | X ^m | | X ^m |
| Tryptase blood sampling | | | X ⁿ | | | X ⁿ | | | X ⁿ | | |
| Blood sample for hypersensitivity research | | | X ⁿ | | | X ⁿ | | | X ⁿ | | |
| Blood for Future Biomedical Research ^q | | | X | | | | | | | | |
| HIV/HbsAg/HCV | X | | | | | | | | | | |
| Drug/Alcohol Screen | X | X | | | X | | | X | | | |
| FSH (post-menopausal females only) | X | | | | | | | | | | |
| Pregnancy Test (females of childbearing potential) ^o | X | X | | | X | | | X | | | X |

^a Limited to a review of the skin, respiratory and cardiovascular systems for AE.

^b All subjects will return to the study center for a follow-up visit approximately 28 days after final dosing for IgG/IgE blood sampling and follow-up visit procedures.

^c An approximately 5 week washout will occur between Periods 1, 2 and 3.

^d Prior to dosing

^e Body weight (kg) will be used to calculate the treatment dose.

^f PEF to be assessed at screening, predose (baseline), 5 min, 30 min, 4 hrs and 24 hrs post-dose for each period.

^g Body temperature only to be taken at screening and Day -1 in each period.

^h Predose vital signs will be obtained in triplicate (baseline will be the median of the three values), with each assessment being made at least 2 minutes apart. Single vital sign assessments will then be obtained at 2, 10, and 30 minutes, and at 1, 4, 8 and 24 hours following drug administration. Additional vital sign measurements may be obtained as required, and will be recorded in the eCRF (unscheduled) in case of suspect HS signs/symptoms. Vital sign measurements are to be taken after the subject has been resting in a semi-recumbent position for 10 minutes.

ⁱ For all subjects; from prior to dosing up until 4 hours post-dose, with single values recorded at predose (baseline, taken approximately 30 mins. predose), 0.5 and 4 hours post dose. SPO2 monitoring is to resume approximately 23 hrs post dose with a value recorded at 24 hrs post dose.

^j Performed at 0.5, 4 and 24 hrs post dose. Scheduled assessment may occur +/-5 min for the 0.5 hour time point or +/- 15 min for the 4 hr and 24 hr time points respectively. The first time point may be triggered earlier by presence of any AE in Signs/Symptoms

of HS (Section 12.6) prior to the 0.5 hr time point and the “unscheduled” time point documented instead of the 0.5 hr time point. Refer to “Targeted HS Assessment” in Section 7 for more information.

^k AE assessment and the Targeted HS assessment are to be performed by a physician who does NOT administer study drug or prepare medication.

^l Subjects are to remain confined to the study center until the completion of 24 hr post-dose procedures. In cases of potential HS symptoms, subjects will remain confined to the study center at least until these symptoms have regressed, and the investigator considers it safe for the subject to leave the study center.

^m IgG/IgE blood samples will be taken pre-dose in Periods 1, 2 and 3, as well as at the follow-up visit (~Day 28 after the final dose).

ⁿ Tryptase and hypersensitivity research blood samples will be taken pre-dose and 3 hrs post-dose in Periods 1, 2 and 3. Any leftover samples will be stored for future biomedical research.

^o Refer to Section 5.7.2.5.

^p Complete Blood Count (CBC) and differential, chemistry panel, and urinalysis.

^q Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained.

^r Treatment is to be administered over approximately 10 seconds to match clinical practice.

^s Subjects are to remain in a semi-recumbent from the time of clinical procedures predose until 4 hours post-dose except as required for study related procedures and events.

Protocol Deviations

The Applicant reported the following protocol deviations for the protocol:

Deviations regarding amount of dose administered

In the monitoring plan for the study, deviations greater than 15% from the intended dose (either below or above) were defined as major protocol deviations.

1. There were 2 subjects (AN 1001, AN 1004) at Site 001 that received less than 85% of the intended dose in Period 1, due to incomplete depression of the plunger in the masked syringe, as the masking prevented direct assessment of the volume remaining in the syringe by the dosing staff member. The dosing staff member was retrained to ensure that the plunger was fully depressed for future dose administrations to ensure that the intended dose was administered. AN 1001 received 10.3 mg/kg instead of the intended 16 mg/kg of sugammadex, and AN 1004 received 3 mg/kg instead of the intended 4 mg/kg of sugammadex. Though the dose received in Period 1 for these 2 subjects was less than intended, there was no reassignment of treatment group.
2. There was one subject (AN 3031) that received less than 85% of the intended dose due to the use of an incorrect subject weight by the pharmacist during study drug preparation in Period 1. This error only occurred for the 1st dose for this subject. As a result, the dose in Period 1 was 2.7 mg/kg instead of the intended 4 mg/kg of sugammadex.
3. There was one subject (AN 3033) that received more than 115% of the intended dose due to use of an incorrect subject weight by the pharmacist during study drug preparation in Period 1. This error only occurred for the 1st dose for this subject. As a result, the dose in Period 1 was 27 mg/kg instead of the intended 16 mg/kg of sugammadex.

Deviations regarding the duration of the IV bolus administration

In the monitoring plan for the study, the duration of the IV bolus was to be approximately 10 seconds, and duration of dose outside of 7 to 15 seconds was to be considered major protocol deviation. There were no administrations of study medication of less than 7 seconds in duration. In the following three instances, the dose duration was > 15 seconds.

1. AN 1018's Period 1 dose was administered over 18 seconds due to the need for a recheck of the catheter placement.
2. AN 6042's Period 1 dose was administered over 18 seconds due to infiltration.
3. AN 6049's Period 2 dose was administered over 16 seconds due to administrator error in timing.

Deviation in treatment assignment

1. Subject AN 1007 was randomized to treatment on 03-Feb-2014 (Period 1, Day - 1), but was discontinued prior to dosing on 04-Feb-2014 due to elevated blood pressure. Another subject was subsequently randomized as AN 1011 on 04-Feb-2014. Treatment was prepared according to subject AN 1011's Day-1 weight;

however, due to pharmacy error, the treatment prepared and administered to the subject was that assigned to AN 1007, not AN 1011. With the exception of the designated unblinded pharmacist/designee, all study site personnel remained blinded to the subject's treatment.

2. At Site 002, subject AN 2070 (Screening Number 106) verbally consented to participate in the study on 27-Jan-2014 and had screening procedures performed, but due to staff error, signed consent of this subject was not obtained. The subject was scheduled to sign the consent prior to Period 1 Day-1 assessments; however, the consent was signed in error by a different subject on this day. Subject AN 2070 provided signed consent on 26-Mar-2014, after she had already received study drug in Period 1 on 24-Feb-2014.

Deviations in which staff member who assessed Adverse Events also administered study drug

1. Section 2.1 of the protocol indicated that, "*AE assessments and the Targeted Hypersensitivity (HS) assessment (Section 12.5) are to be performed by a physician who does NOT administer study drug or prepare medication.*" At Site 003, subjects were enrolled and scheduled for dosing in groups. The staff member who dosed Group 2 for Period 1 (AN 3001 to AN 3010) also participated in the assessment of AEs for some subjects for the Period 1 dose in Group 4, specifically ANs 3016, 3017 and 3020. Also at Site 003, the staff member who dosed Group 4 for Period 1 (AN 3011 to AN 3020) participated in the assessment of AEs for some subjects for the Period 1 dose in Group 6, specifically in ANs 3021, 3024 and 3030. While this was a procedural deviation from the protocol, there was no potential for unblinding in the assessment of AEs for these subjects. In no case did the staff member who assessed a subject also administer study drug to the same subject. In order to prevent future deviations at Site 003, these 2 staff members at Site 3 who dosed the subjects in Groups 4 and 6 did not participate in study conduct subsequent to the first dosing period of Groups 4 and 6. For the remainder of the study conduct at Site 003, dose administration was performed by blinded individuals that had no other roles in the study.

Deviation involving assignment of a second randomization number

1. As stated in Section 7.1.1.7 of the protocol, "A single subject cannot be assigned more than 1 randomization number." At Site 005, Subject AN 5021 was randomized on 28-Jan-2014 but did not receive study medication during that visit and returned for his initial (Period 1) dose of study drug on 06-Feb-2014. Due to a miscommunication between the clinic and pharmacy staff, the subject was re-randomized as AN 5049. Study drug, prepared according to the treatment assigned by this second allocation number (AN 5049), was administered to the subject on 06-Feb-2014. Not until after the dosing event had occurred was the error realized and the Sponsor informed. As agreed upon by the Sponsor study team (including the departments of Early Stage Development and Biostatistics),

since the protocol design calls for a subject to receive the same dose of study medication in all three periods, the subject continued in the study as AN 5049 and randomization number 5021 was not used for the study.

Subjects Whose Treatment Was Prematurely Unblinded

1. One subject (AN 3033) was prematurely unblinded by the Site when informing the Sponsor of the overdose. The subject experienced SAEs of dysgeusia, feeling hot, and headache associated with an overdose (26.9 mg/kg sugammadex, and was referred to the CAC in Period 1. Due to the overdose, the CAC was informed that the subject received active drug, but they remained blinded to the subject's assigned treatment. The CAC's assessment that the case was not hypersensitivity did not change following notification of the overdose.
2. During routine analysis and reporting (A&R) activities, staff from the Sponsor's Department of Biostatistics and Research Decision Sciences (BARDS) with access to study clinical trial data sets in the statistical Computing Platform (CPI) had the potential to view an unblinded exposure domain variable in both the test and production area of the CPI between 11-Mar-2014 and 02-Apr-2014. The variable in question is the "Calculated Dose Prepared" study medication. This variable was not blinded in the Clinical Data Repository (CDR) data extracted into CPI by BARDS between 11-Mar to 13-Mar-2014. In the A&R process, these extracted datasets are converted to enriched, analyses datasets. The potential unblinding issue was discovered on 02-Apr-2014 and corrective actions were taken immediately. The variable was blinded within the CDR as of 04-Apr-2014 and all unblinded datasets were deleted from the CPI system on or before 07-Apr-2014. BARDS confirmed that no person who had the access to CPI and the file that contained potential unblinding information (variable EXIVDOSE in dataset EX) before 08-Apr-2014 was actually unblinded to the treatment assignment for any subject.

Subject Disposition

A total of 375 subjects were randomized and received at least one dose of the assigned study treatment and were in the All-Subjects-as-Treated (ASaT) analysis population (148 subjects in the 16 mg/kg sugammadex treatment group, 151 subjects in the 4 mg/kg sugammadex treatment group, and 76 subjects in the placebo treatment group). The disposition of these subjects is summarized in Table 49 below.

Table 49. Disposition of subjects in P101 (based on Table 2, p. 5 of the final study report)

| | Placebo n (%) | Sugammadex 4 mg/kg n (%) | Sugammadex 16 mg/kg n (%) | Total n (%) |
|--------------------------|------------------|--------------------------------|---------------------------------|----------------|
| Subjects in population | 76 | 151 | 148 | 375 |
| Trial Disposition | | | | |
| Completed | 64 (84.2) | 136 (90.1) | 134 (90.5) | 334 (89.1) |
| Discontinued | 12 (15.8) | 15 (9.9) | 14 (9.5) | 41 (10.9) |
| Adverse Event | 3 (3.9) | 3 (2.0) | 5 (3.4) | 11 (2.9) |
| Lost To Follow-Up | 2 (2.6) | 4 (2.6) | 6 (4.1) | 12 (3.2) |
| Physician Decision | 1 (1.3) | 0 (0.0) | 0 (0.0) | 1 (0.3) |
| Protocol Violation | 1 (1.3) | 4 (2.6) | 0 (0.0) | 5 (1.3) |
| Withdrawal By Subject | 5 (6.6) | 4 (2.6) | 3 (2.0) | 12 (3.2) |

Reported Efficacy Findings

Not applicable.

Summary of Reported Safety Findings

Hypersensitivity and Anaphylaxis

Of the 375 subjects in the ASaT population, there were a total 94 subjects with AEs potentially consistent with hypersensitivity that were referred to the CAC for evaluation based on the pre-defined list of Signs and Symptoms of Hypersensitivity or based on the Applicant's review. These included 45 and 35 subjects treated with sugammadex 16 mg/kg and 4 mg/kg, respectively, and 14 subjects in the placebo treatment group. The CAC identified 25 subjects with hypersensitivity after receiving at least one dose of study medication, as shown in Table 50 below. Fourteen of the 25 subjects were in the 16 mg/kg sugammadex treatment group, 10 were in the 4 mg/kg sugammadex treatment group, and 1 was in the placebo treatment group.

Table 50. Applicant-reported findings for hypersensitivity and anaphylaxis (based on Table 4, p. 7 of the final study report)

| Parameter | Treatment | | |
|---|-----------------------------|---|--|
| | Placebo | Sugammadex | |
| | | 4 mg/kg | 16 mg/kg |
| Subjects in population | 76 | 151 | 148 |
| Adjudicated Hypersensitivity | | | |
| n(%) [95% CI] † Estimated Difference vs. Placebo [95% CI] ‡ | 1 (1.3) [0.0, 7.1] NA | 10 (6.6) [3.2, 11.8] 5.3 [-0.9, 10.7] | 14 (9.5) [5.3, 15.4] 8.1 [1.7, 14.2] |
| Anaphylaxis According to Sampson (Criterion 1) | | | |
| n(%) [95% CI] † Estimated Difference vs. Placebo [95% CI] ‡ | 0 (0.0) [0.0, 4.7] NA | 0 (0.0) [0.0, 2.4] 0.0 [-4.8, 2.5] | 1 (0.7) [0.0, 3.7] 0.7 [-4.2, 3.7] |

† Based on exact binomial method by Clopper & Pearson.

‡ Based on Miettinen & Nurminen method.

CI = Confidence interval; NA = Not applicable.

For 13 of the subjects with adjudicated hypersensitivity, the onset of the first symptom of hypersensitivity occurred within 10 minutes after dose administration; the remaining subjects, except one, had symptoms that began within 1 hour of dose administration with resolution of the symptoms within 24 hours after dose administration. There was one delayed “mild” hypersensitivity event in a subject who had onset of urticaria 22 hours after dosing and spontaneous resolution of symptoms 4 days later.

Of the 25 subjects with adjudicated hypersensitivity, only 3 received treatment for their symptoms; these 3 subjects were in the 16 mg/kg sugammadex treatment group and were treated for symptoms developing within 5 minutes after receiving the first dose of sugammadex. All were discontinued from the study per protocol. One (AN 5020) was a case of adjudicated anaphylaxis described below. The remaining two subjects received treatment with intravenous antihistamine for adjudicated hypersensitivity, and both improved shortly after treatment, with complete resolution of symptoms in less than 24 hours.

The Applicant reported that a single subject (AN 5020), experienced adjudicated anaphylaxis according to Sampson Criterion 1 after receiving the first dose of sugammadex 16 mg/kg. This subject had onset of the initial symptoms immediately after dose administration; these included sneezing, nasal congestion and conjunctival

edema, and urticaria and swelling of the uvula. There was no hypotension and no evidence of lower airway involvement reported. The symptoms were treated with intravenous antihistamine and corticosteroid and resolved within 3 hours of receiving sugammadex, except for the conjunctival edema that did not resolve until 9 hours after the sugammadex administration.

There were no subjects with adjudicated anaphylaxis in the 4 mg/kg sugammadex or placebo treatment groups.

With respect to the potential for increasing incidence of adjudicated hypersensitivity with repeated exposures, the frequency of adjudicated hypersensitivity was similar for each exposure for each treatment group, except for the placebo group that had a single event that occurred with the third dose.

With respect to the potential for increasing severity of adjudicated hypersensitivity with repeated exposures, there was no clear worsening of hypersensitivity with repeated administration of sugammadex, and no subject who received sugammadex in a subsequent exposure after having adjudicated hypersensitivity went on to have adjudicated anaphylaxis. As noted above, the only case of adjudicated anaphylaxis occurred with the first exposure of subject AN 5020 to 16 mg/kg sugammadex.

The severity of the adjudicated hypersensitivity events in the 25 subjects is summarized in Table 51 below. The severity spanned a range from mild to severe, with the majority rated by the CAC as mild. All four adjudicated hypersensitivity events that were rated by the CAC as moderate or severe occurred in the 16 mg/kg sugammadex treatment group. One event of adjudicated hypersensitivity (in subject AN 5020) which was rated as severe by the CAC, occurred with the first dose of 16 mg/kg sugammadex. Another subject (AN 1032) in the 16 mg/kg sugammadex treatment group had a mild event on the first exposure and two moderate events on the second and third exposures. There was one additional subject (AN 2032) in the 16 mg/kg treatment group with adjudicated hypersensitivity rated as moderate in intensity on the second exposure but did not have adjudicated hypersensitivity on the first and third exposures.

Table 51. Severity of hypersensitivity reactions in P101 (based on Table 5, p. 10 of the final study report)

| | Placebo n (%) | 4 mg/kg Sugammadex n (%) | 16 mg/kg Sugammadex n (%) | Total n (%) |
|------------------------|------------------|--------------------------------|---------------------------------|----------------|
| First Dose | | | | |
| Subjects in population | 76 | 151 | 148 | 375 |
| Mild | 0 (0.0) | 6 (4.0) | 7 (4.7) | 13 (3.5) |
| Moderate | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Severe | 0 (0.0) | 0 (0.0) | 1 (0.7) | 1 (0.3) |

| | Placebo n (%) | 4 mg/kg Sugammadex n (%) | 16 mg/kg Sugammadex n (%) | Total n (%) |
|------------------------|------------------|--------------------------------|---------------------------------|----------------|
| Second Dose | | | | |
| Subjects in population | 69 | 140 | 138 | 347 |
| Mild | 0 (0.0) | 7 (5.0) | 6 (4.3) | 13 (3.7) |
| Moderate | 0 (0.0) | 0 (0.0) | 2 (1.4) | 2 (0.6) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Third Dose | | | | |
| Subjects in population | 64 | 136 | 134 | 334 |
| Mild | 1 (1.6) | 4 (2.9) | 8 (6.0) | 13 (3.9) |
| Moderate | 0 (0.0) | 0 (0.0) | 1 (0.7) | 1 (0.3) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Anti-sugammadex IgG and IgE Antibodies

Of the 25 subjects with adjudicated hypersensitivity, two subjects were positive for IgG specific for sugammadex. No subjects had IgE specific for sugammadex. The first subject positive for anti-sugammadex IgG received 16 mg/kg sugammadex in the 3 treatment periods and had adjudicated hypersensitivity on each dosing occasion. This subject had positive IgG in Period 1, prior to receiving sugammadex. The Confirmatory assay in Periods 2 and 3 and the follow-up visit were negative indicating that there was no longer any immunoglobulin specific for sugammadex. The second subject positive for anti-sugammadex IgG received 4 mg/kg sugammadex in the 3 treatment periods and had an event of adjudicated hypersensitivity in Period 2 only. The Screening and Confirmatory assays were positive at predose for Periods 1, 2 and 3 as well as the follow up visit. Testing for IgG was negative at baseline (predose for Period 1), but positive for Periods 2, 3 and the follow up visit.

Of the 69 subjects who were referred to the CAC but whose events were not confirmed as hypersensitivity reactions, no subjects had IgG or IgE specific for sugammadex at baseline (Period 1) or Periods 2, 3 and the follow up visit.

Of the 91 control subjects, none had IgG or IgE specific for sugammadex at baseline (Period 1) or Periods 2, 3 and the follow up visit.

Overall there was no evidence for the generation of anti-sugammadex IgE antibodies from repeated exposure to sugammadex. There was no consistent evidence that repeated exposure to sugammadex may result in the generation of antisugammadex IgG antibodies.

Tryptase Levels

The mean tryptase level predose and post-dose for all treatment groups in subjects with adjudicated hypersensitivity was in the normal range (2-10 ng/mL), and less than a 1 ng/mL change from the predose value in the post dose mean tryptase values measured for these subjects.

There were no subjects with adjudicated hypersensitivity that met the predetermined criteria of tryptase levels > 11 ng/mL at either predose or post-dose. Overall there was no biochemical evidence of mast cell degranulation in subjects with adjudicated hypersensitivity based on the measurements of serum tryptase.

Other Safety Findings

There was an increase in the proportion of subjects receiving sugammadex with one or more AEs, and an apparent dose-response increase in drug-related AEs. The incidence of dysgeusia, and to a lesser extent, nausea exhibited a dose-response relationship. For the 16 mg/kg and the 4 mg/kg sugammadex treatment groups, the proportions of subjects with AEs were approximately 20% and 15%, respectively, higher as compared to the placebo treatment group. For the 16 mg/kg and the 4 mg/kg sugammadex treatment groups, the proportions of subjects with drug-related AEs were approximately 35% and 10%, respectively, higher as compared to the placebo treatment group. The sugammadex groups were similar to placebo with respect to the proportions of subjects with SAEs as well as subjects who discontinued due to an AE.

Serious adverse events (SAEs) were reported for 5 subjects in the study. For one subject in the 16 mg/kg sugammadex group, mild drug-related AEs were reported as SAEs due to their association with an overdose that occurred for the subject in the first exposure. Drug-related SAEs were reported for 4 subjects: 2 in the 4 mg/kg sugammadex group and 2 in the placebo group.

No subjects died in the study. Eleven (11) subjects were discontinued due to AEs. Ten of these subjects were discontinued due to a treatment-emergent AE and 1 subject was discontinued due to a non-treatment emergent AE. Three subjects were discontinued per protocol after receiving concomitant medications for the treatment of drug-related non-serious adverse events (NSAEs) associated with adjudicated hypersensitivity. One subject was discontinued per protocol after receiving treatment for drug-related moderate intermittent nausea that was not confirmed as hypersensitivity by the CAC. Four subjects were discontinued due to non-drug related NSAEs not considered in the protocol as signs or symptoms of hypersensitivity. One subject was discontinued due to a non-drug related NSAE that started prior to subject's receipt of study drug but was not known by the investigator until after the subject's first dosing occasion. Two of the 11 subjects discontinued due to AE were discontinued due to an SAE. These subjects in the placebo treatment group were discontinued due to non-drug related SAEs of brain contusion and appendicitis. No subject was discontinued due to a drug related SAE.

All AEs in the study were of mild to moderate intensity with the exception of 2 severe non-drug related AEs of alcohol poisoning and appendicitis in the placebo group. No clinically relevant changes were observed in any of the vital signs, peak expiratory flows, oxygen saturations by pulse oximetry, laboratory assessments, ECGs, or other routine safety parameters in the 16 mg/kg sugammadex or 4 mg/kg sugammadex groups compared to the placebo group.

Discussion

This study marked the second attempt by the Applicant to assess the immunogenic potential for sugammadex and the risk for an anaphylactic reaction on repeat exposure. The findings from this study are not very dissimilar to those of the previous study in that the risk of anaphylaxis related to sugammadex exposure is on the order of 1%, the risk does not increase with multiple exposures, and hypersensitivity and anaphylactic reactions do not appear to be mediated through sugammadex-specific IgG or IgE stimulation of mast cells.

However, the extent to which these findings can be relied upon has not yet been adequately determined. During their inspection of the central and clinical sites involved in the study, the Office of Scientific Investigations' (OSI) investigators were concerned about the impact of the data unblinding that occurred with the statisticians during the conduct of the study and the protocol violation that occurred at one clinical site where investigators were administering the study drug and making the hypersensitivity assessments, albeit (reportedly) not on the same subjects. Based on discussions with the Applicant and internal discussions that included statisticians with industry experience, it was considered unlikely that the protocol deviations identified to date, including the unblinding of the statisticians, adversely affected the integrity of the data or the validity of the study findings. Given the importance of these study results to the characterization of the safety profile for sugammadex, and in light of the data integrity issues that occurred with the first protocol to address this deficiency, it was considered imperative that all of the clinical sites be investigated to assure, to the extent possible, the integrity of the data generated by this study and the validity of the study findings. As the necessary investigations cannot be completed during this review cycle, these issues are the basis for making a recommendation for a Complete Response action at the conclusion of this cycle.

Conclusions

Whether this study adequately addresses the deficiency in last Complete Response letter requires the completion of the inspection of the remaining clinical sites and the recommendations from the Office of Scientific Investigations (OSI) regarding the validity of the data. If OSI determines that there is no new reason to question the integrity of the study results and the Division of Pulmonary, Allergy, and Rheumatology Products concurs with the study findings, the deficiency will have been addressed and an

Clinical Review
Arthur Simone, MD, PhD
NDA 022225 (2nd Complete Response)
Bridion (sugammadex sodium)

Approval action can be recommended provided the product labeling adequately captures the extent and nature of the risks of hypersensitivity and anaphylaxis as observed in both the clinical development program and the postmarketing experience to date.

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/s/

ARTHUR F SIMONE
04/03/2015

RIGOBERTO A ROCA
04/03/2015

Summary Basis for Regulatory Action

| | |
|---|--|
| Date | September 20, 2013 |
| From | Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II |
| Subject | Summary Review |
| NDA/BLA # Supp # | 22-225 |
| Applicant | Merck/Organon USA |
| Proprietary / Established (USAN) Names | (b) (4) Sugammadex Sodium |
| Dosage Forms / Strength | Sterile solution, injectable 100 mg/mL |
| Proposed Indication(s) | 1. Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium 2. Immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Action: | <i>Complete Response</i> |

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding sugammadex, and I refer the reader to the reviews in the action package for a more detailed discussion. This is a review of the Complete Response (CR) to the Not Approvable action that was taken on July 31, 2008, during the first review cycle.

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex was designed so that the negatively charged sugar groups within its center would attract the positively charged ammonium groups of rocuronium bromide (RCB) and vecuronium bromide (VCB) and hold these neuromuscular blocking agents within its core by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of RCB and VCB within sugammadex renders them inactive and thereby reverses paralysis due to their activity at the neuromuscular junction.

The Applicant proposes the following indications and doses of the product:

- For "routine reversal" of RCB or VCB, a dose of 4 mg/kg should be administered if recovery has reached 1 to 2 post tetanic counts (PTC) ("profound blockade") and 2 mg/kg if recovery has reached the reappearance of T2 ("shallow blockade").
- For "immediate reversal," if there is a clinical need, at three minutes following administration of 1.2 mg/kg of RCB, a dose of 16 mg/kg should be administered.

This application was not approved on the first cycle due to safety concerns observed during clinical development related to hypersensitivity/anaphylaxis reactions and the effects of the product on coagulation and bleeding. During the first cycle review, this application was

granted a priority review, and the application was presented at a meeting of the Anesthesia and Life Support Drugs Advisory Committee (ALSDAC) on March 11, 2008. The ALSDAC has since been renamed the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). The anaphylaxis concern was noted late in the review, just before the advisory committee (AC) meeting, and did not benefit from a full analysis prior to the AC meeting. Therefore, committee members (mainly anesthesiologists or pain experts) had minimal information regarding the anaphylactic potential of sugammadex to use in safety considerations when advising about marketability. While the Committee voted for approval, I determined that they did not have access to all the relevant safety information upon which to draw conclusions and make recommendations of marketability. Also, the coagulation and bleeding concerns were not presented at the meeting, as they had not yet been discovered by the clinical review team. Another issue of concern noted in the Not Approvable action was the possibility of cardiac arrhythmias. I ultimately recommended a Not Approvable action because the safety concerns had not been adequately explored to inform an approval action.

During the previous review cycle, the Applicant had demonstrated adequate evidence of clinical efficacy that would support an indication of routine reversal of neuromuscular blockade caused by RCB and VCB. The 'immediate reversal' indication for a 'Cannot Intubate/Cannot Ventilate' scenario sought by the Applicant was not evaluated in a clinically meaningful fashion (b) (4). Please refer to my original review for a discussion of efficacy.

This CR included several new studies and trials to address the three issues noted above, the most relevant for the hypersensitivity/anaphylaxis issues is Trial P06042. This trial was a repeat administration of the mid (4 mg/kg) and high dose (16 mg/kg) of sugammadex. This trial was designed to be conducted in a blinded fashion to obtain further information on anaphylaxis with sugammadex use regarding the incidence, time course and risks associated with re-exposure.

Noted in this cycle also was Trial P05774, which evaluated the extent of reversal at the time of extubation for patients treated with sugammadex compared to those treated with neostigmine. (b) (4)

Please refer to Drs. Breder's and Simone's reviews and conclusions of this trial, with which I agree, (b) (4)

With this CR response, the Applicant seems to have successfully addressed the issues of sugammadex-induced coagulation abnormalities and cardiac arrhythmias. Regarding the anaphylaxis issue however, the Office of Scientific Investigation (OSI) investigators found during the course of inspection of site #2 for Trial P06042 (hypersensitivity/anaphylaxis trial) that there had been unblinding, calling into question the integrity of the data. A site sub-investigator that performed the dosing had become unblinded and had also evaluated for adverse events in violation of the protocol, potentially affecting approximately 53 of the 95 randomized subjects. This sub-investigator had noted a viscosity difference when administering sugammadex compared to placebo and the higher concentration of sugammadex

compared to the lower one. Therefore, he knew when sugammadex was administered and apparently the dose (despite the syringes being covered). This was communicated to the Applicant back in 2009, but not to the Agency. This has caused a need to investigate all sites associated with this trial (4 in total). However, one of the sites was owned by contract research organization (CRO) (b) (4) which went out of business and for which the records were unobtainable until just prior to the action date for this application. Also, despite earlier assurances of site integrity, the Applicant has recently notified us that there may be protocol violations at the remaining 3 sites where study staff administered the study medication and also performed the safety evaluations. This will call into question whether these evaluations were truly performed in a blinded fashion. In any regard, these events led us to cancel the AC meeting and schedule further site investigations.

2. Conclusions and Recommendations

As noted above, there were two deficiencies that were cited for the Not Approvable action in the first review cycle; a third concern, cardiac dysthymias, did not rise to the level of a deficiency, but the Applicant was encouraged to better quantify the risk with additional studies. Two of these issues, coagulation abnormalities and cardiac arrhythmias, have been resolved. The remaining issue, anaphylaxis, at first appeared to be adequately explored by the Applicant, and we were preparing to present all three issues at an AC meeting. However, when only days before the AC meeting, the findings from the OSI inspections called the data integrity from Trial P06042 into question, it became necessary to cancel the AC meeting and require the Applicant to provide evidence that the protocol deviations did not adversely impact the results of trial P06042. The remediation of this issue may range from accepting that P06042 was unblinded, but the results remain valid when viewed in conjunction with substantial foreign marketing to designing and conducting a new trial.

As the deficiency related to sugammadex-induced anaphylaxis and hypersensitivity remains unresolved, I recommend a Complete Response action.

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/s/

CURTIS J ROSEBRAUGH
09/20/2013



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

| | |
|---|---|
| Date | September 10, 2013 |
| From | Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products |
| Subject | Division Director Summary Review |
| NDA # | 22225 |
| Applicant Name | Merck/Organon USA |
| Date of Submission | December 12, 2012 |
| PDUFA Goal Date | September 20, 2013 (with 3-month clock extension) |
| Proprietary Name / Established (USAN) Name | (b) (4) Sugammadex sodium for intravenous injection |
| Dosage Forms / Strength | 100 mg/mL |
| Proposed Indication | 1. Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium 2. Immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Recommended Action: | Complete Response |

| Material Reviewed/Consulted | |
|------------------------------------|---|
| OND Action Package, including: | |
| CDTL | Christopher D. Breder, M.D., Ph.D. |
| Clinical Review | Arthur Simone, M.D., Ph.D. |
| Biostatistics Review | Yan Zhou, Ph.D.; Janice Derr, Ph.D. |
| Pharmacology Toxicology Review | Zengjun Xu, Ph.D.; Adam M. Wasserman, Ph.D. |
| ONDQA-CMC/Quality Review | Yong Hu, Ph.D.; Prasad Peri, Ph.D. |
| OPS/NDMS-Microbiology Review | Steven P. Donald, M.S.; Stephen Langille, Ph.D. |
| Clinical Pharmacology Review | Srikanth C. Nallani, Ph.D.; Atul V. Bhattaram, Ph.D.; Yun Xu, Ph.D. |
| OSI-DGCPC | Cynthia F. Kleppinger, M.D.; Janice Pohlman, M.D., M.P.H.; Susan D. Thompson, M.D. |
| Project Management | Diana Walker, Ph.D.; Parinda Jani |
| OSE/DMEPA | Vicky Borders-Hemphill, Pharm.D.; Jamie Wilkins Parker, Pharm.D.; Carol Holquist, R.Ph. |
| DPARP | Erika Torjusen, M.D. M.H.S.; Banu Karimi-Shah, M.D.; Lydia Gilbert-McClain, M.D. |
| DHP | George G. Shashaty, M.D.; Kathy Robie Suh, M.D., Ph.D.; Ann Farrell, M.D. |
| IRT-QTSC | Janice B. Brodsky, Ph.D.; Qianyu Dang, Ph.D.; Jeffry Florian, Ph.D.; Kevin M. Krudys, Ph.D.; Norman L. Stockbridge, M.D., Ph.D. |
| DBRUP | Gemma Kuijpers, Ph.D. |

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error and Prevention Analysis
 OSI=Office of Scientific Investigations
 CDTL=Cross Discipline Team Leader
 ONDQA=Office of New Drug Quality Assessment
 OPS/NDMS=Office of Pharmaceutical Sciences/New Drug Microbiology Staff
 DPARP=Division of Pulmonary, Allergy and Rheumatology Products
 DHP=Division of Hematology Products
 DGCPC=Division of Good Clinical Practice Compliance
 IRT-QTSC=Interdisciplinary Review Team for QT Study Consultation
 DBRUP=Division of Bone, Reproductive and Urologic Products

1. Introduction

This response to the Not-Approvable Letter (NAL) issued on July 31, 2008, for NDA 22225, was received on December 12, 2012. Due to data quality concerns on the part of the clinical and statistical review teams which could not be resolved on the initial 6-month PDUFA timeline, a 3-month clock extension was incorporated into the time line so that the current PDUFA action date is September 20, 2013. The product, sugammadex sodium, has a currently approved brand name of (b) (4). However, as the product has had a number of

NDA 22225

(b) (4)

2

Division Director's Review and Recommendation for Complete Response Action
 September 10, 2013

brand names approved since the original NDA submission, and as the application is not likely to be approved based on this current submission, I will refer to it as sugammadex throughout my review.

Sugammadex is a new molecular entity and belongs to the γ -cyclodextrin class of pharmaceuticals. The Applicant's proposed indications are for the reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium, and for the immediate reversal of NMB at 3 minutes after the administration of rocuronium.

2. Background

The original NDA was submitted by Organon USA on October 31, 2007. My review of that submission is appended to this document and in this current review I will only address the applicant's response to the NAL letter, and any new data or information submitted with this supplement. In 2007, Organon USA was acquired by Schering-Plough. Schering-Plough merged with Merck in 2009.

The specific concerns that were raised during the first review cycle prior to the advisory committee meeting were related to possible adverse events of hypersensitivity and anaphylaxis, and events related to possible cardiac toxicity, including QT prolongation. In particular, anaphylaxis and/or cardiac arrhythmias that might occur after a patient was discharged or moved to a ward, and events that might occur upon re-exposure, were of most concern. The Division concurred with the Applicant's assessment that sugammadex was effective for reversing NMB from rocuronium or vecuronium using the Applicant's proposed dosing regimen. However, it is important to note that an indication or claim for "immediate reversal" from the "Cannot Intubate/Cannot Ventilate" scenario has not been adequately supported by data demonstrating efficacy or safety in that setting.

The NDA was presented to a meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) late in the first review cycle. (The ALSDAC has since been renamed the Anesthetic and Analgesic Drug Products Advisory Committee, or AADPAC.) Due to the timing of that meeting, only preliminary data regarding the safety findings were presented to the committee. Upon further review between the time of that meeting and the action date, additional concerns about the adverse events, and new concerns regarding possible events related to effects on coagulation, were noted by the clinical review team. Therefore, although the ALSDAC members voted for approval of the application, the Division and the signatory authority for the application, Dr. Curtis Rosebraugh, Director of the Office of New Drugs II, determined that additional data and analyses would be required in order to assure an acceptable risk-benefit balance for the product, and a NAL was issued.

While the Applicant's response to the NAL appeared to provide sufficient data and analyses to demonstrate a favorable risk-benefit balance for sugammadex based on our review of this submission, concerns regarding the integrity of the data were raised late in

NDA 22225

(b) (4)

3

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

this review cycle. As such, a planned presentation to the AADPAC was canceled, and additional inspections of clinical sites and the Applicant's Trial Master File will be undertaken, especially focusing on all data transfer and storage from the previous sponsor, as well as all deviations regarding unblinding. While some of the inspections have been completed, the limited time remaining in the review cycle, in addition to a problem with the Applicant providing access to one critical data set, has resulted in completion of these efforts by the PDUFA action date not being possible. Therefore, we are unable to recommend approval at this time as the integrity of the data supporting the safety of the product remains unclear.

3. CMC

There were no outstanding CMC concerns that would have precluded approval of the application based on the initial review cycle. The following summary of the CMC information included in this submission has been reproduced from pages 9 through 11 of Dr. Breder's review:

During the review of this Complete Response the following issues were addressed:

- General product quality considerations
 1. The applicant has fulfilled the following agreements with respect to specifications in this resubmission:
 - An agreement to tighten the impurity specifications for the drug substance once the applicant has manufactured drug substance at full scale using at least 10 different production lots of the (b) (4)
 - An agreement to tighten the specifications for degradants in the drug product following additional experience with the commercial manufacturing process.

It should be noted that both CMC and Pharmacology/Toxicology accepted the impurities acceptance criteria in the original NDA during the last review cycle. In the resubmission, the applicant tightened the acceptance criteria for the impurities.

2. In this resubmission, the long term stability data was updated to support 36 months shelf life at room temperature.
 3. A comparability protocol was submitted in this resubmission but retracted after the review team identified several deficiencies related to sterility assurance 1. The 12/19/2012 submission also included a comparability protocol for an alternate manufacturing location. After review of the comparability protocol and subsequent teleconference on 4/24/2013 between members of the FDA review team (CMC team, New Drug Microbiology Staff, and the Office of Compliance) and the Applicant, the applicant submitted a formal request dated 5/8/2013 to the NDA to withdraw the comparability protocol.
- Facilities review/inspection

¹ Primary CMC Review of Yong Hu, pp. 73 of 78

NDA 22225

(b) (4)

4

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

The manufacturing facility is Organon (Ireland) Limited in Swords, Ireland. The recommendation from the Office of Compliance for this establishment is "Acceptable" with a recommendation date of 8/21/2013.

The Office of Compliance's overall recommendation, made on August 27, 2013 in EES, is "Acceptable" for this NDA.

- Other notable issues (resolved or outstanding)
 1. During the labeling review for NDA 22-225, the CMC team identified the following issues that need to be addressed to label the product consistent with current Agency policies.
 - The current USP policy is to name and designate the strength of drug products according to the neutral, active moiety unless the salt ion contributes substantively to the desired ADME profile. In those cases where the salt form contributes to the desired ADME profile, the salt form may be used in the name provided the strength designation matches the salt form. The labels currently use the non-proprietary established name "sugammadex sodium".
 - The labeled strength (100 mg/mL) of the drug product is based on the combined concentration of the free acids of Org 25969 (sugammadex sodium) and Org 48302 (sodium salt). Since the assay accounts for both Org 25969 and Org 48302, the non-proprietary name should reflect the inclusion of Org 48302.
 - The USAN entry currently lists "sugammadex sodium", which aside from listing the salt, does not include the (b) (4) Org 48302 (the related (b) (4)).
 - The code names need to be updated or revised to reflect the correct status of the molecule (neutral species or sodium salt and designate strength accordingly) and current ownership of the application (e.g., Org 25969 to Mrk 25969).

A teleconference was conducted between members of the Review team and the Applicant on August 27, 2013 and an email summarizing the issues was sent later that day.

2. This NDA is recommended by Drs. Hu and Peri for Approval pending satisfactory labeling revision by the applicant.
3. There were no Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

I concur with the review team that there are no outstanding concerns related to the CMC data submitted in this response to the NAL that would preclude approval of the application.

4. Nonclinical Pharmacology/Toxicology

At the time of the first action, there were no outstanding nonclinical pharmacology or toxicology concerns that would have precluded approval of the application. Additional preclinical studies would be required, however, to further assess the potential for bone toxicity in juvenile animals prior to approval for use in the pediatric patient population.

NDA 22225

(b) (4)

5

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

The following summary of the toxicology data included in this submission has been reproduced from pages 11 through 16 of Dr. Breder's review:

- General Considerations

Further nonclinical studies were also not required to initiate single-dose clinical trials in pediatric patients. However, several nonclinical evaluations were deemed necessary prior to any multiple-dose pediatric trials, approval of a pediatric indication, or inclusion of pediatric data in the label. The following five comments were communicated in the Not Approvable letter:

1. *Provide an evaluation of sugammadex in a nonclinical model of bone fracture to examine potential effects of the drug on bone healing. You are encouraged to submit protocols of such studies to the Agency for comment prior to their conduct.*
- A. Applicant Response - The effect of Org 25969 on bone repair was evaluated in adult animals (Study number: 090319). The results of the data did not show evidence of adverse change on bone healing in animals with pre-fracture treatment in any Org 25969 dosing group as compared to control as assessed by pQCT scan, μ CT scan, bone strength test, and histopathology examination. With post-fracture treatment, statistically significant changes in some of the bone healing indices were observed at 500 mg/kg groups as compared to the concurrent control. Specifically, histopathology examination revealed an increase in callus formation, a decrease in bone formation, and decrease in the extent of bridging at the fracture site by new bone at 500 mg/kg.
 - B. Nonclinical Assessment - These data suggest a slight delay in bone healing process. The NOAEL in post-fracture treated animals is identified to be 120 mg/kg, while in pre-fracture treated animals the NOAEL is 500 mg/kg. The post fracture findings are not considered to be clinically concerning because
 - The dose level and dosing regimen are well above the anticipated use, and
 - Other parameters of bone strength and density were not changed.
 The safety margins (**Table 4**) are calculated based on the AUC and bone concentration comparison between animals in this bone repair study and human.

Table 1 Safety margin for multiple-dose administration at 4 mg/kg in adult and pediatric patients with bone fracture

| | | Rat | Human | Safety margin |
|--------------------|------------------|-----------|-------------------|---------------|
| Young adult rat | Dose | 120 NOAEL | 4 | |
| (Fx healing study) | AUC (ug*h/mL) | 230 | 40 | 5.8x |
| | Bone conc (ug/g) | 235 | 9 (adult) | 26x |
| | | | 18 (child 10 yrs) | 13x |
| | | | 24 (child 4 yrs) | 10x |
| | Dose | 500 NOAEL | 4 | |
| | AUC (ug*h/mL) | 1101 | 40 | 28x |
| | Bone conc (ug/g) | 480 | 9 (adult) | 53x |
| | | | 18 (child 10 yrs) | 27x |
| | | | 24 (child 4 yrs) | 20x |

NDA 22225

(b) (4)

Source: Table from Dr. Xu's review, p. 10 of 60

The Study was considered supportive of dosing 4 and 16 mg/kg in (b) (4) adults (b) (4) patients, since the bone growth process is continuous in rats during adulthood.

2. *Provide data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study.*
- A. Applicant Response / Division assessment – This is addressed in Non-Approvable Letter Issue #3 below.
3. *Provide a repeat-dose study of sugammadex in the juvenile rat with an extended period of recovery, such that bone length, material properties, and integrity at full skeletal maturity may be evaluated in order to clarify the observation of slight but lasting decreased bone length and body weight observed in the 28-day juvenile toxicity study. Within this study, micro-computed tomography (μ CT), bone turnover markers, and bone strength assessment should be obtained and evaluated. Also, the study should incorporate positive control arms to verify assay sensitivity. Lastly, though not required, the inclusion of vertebral evaluation would be helpful to interpret bone effects since vertebrae have a more homogenous trabecular structure than long bones such as femur. You are encouraged to consider an alternative, intermittent dosing paradigm in order to minimize effects of sugammadex on body weight while allowing for significant drug accumulation in the skeleton.*

In the previously submitted 28-day juvenile rat toxicity study in the original NDA (Study 063592), minor decrease in ulna length ($\leq 5\%$), femur length ($\leq 3.5\%$) and weight ($\leq 6.5\%$) were observed at 120 and 500 mg/kg Org 25969 after 28-day daily dosing. The Applicant indicated that the minor change was due to smaller size of the animals in Org 25969 treated groups likely due to decreased food consumption, and thus did not represent bone effect of Org 25969. The Division did not agree with this conclusion because the bone length decrease was not coincident with the body weight decrease and thus requested more information to clarify this finding.

Further the NOAEL was identified to be 30 mg/kg which corresponds to approximately 22 $\mu\text{g}\cdot\text{hr}/\text{ml}$ in plasma AUC and 150 $\mu\text{g}/\text{g}$ bone Org 25969. By plasma AUC comparison, exposure at NOAEL in juvenile rats, the NOAEL (22 $\mu\text{g}\cdot\text{hr}/\text{ml}$) did not cover human exposure at 4 mg/kg (40 $\mu\text{g}\cdot\text{hr}/\text{ml}$). Although estimated bone concentration provided sufficient coverage, it is uncertain whether AUC level or local bone concentration level shall be used for safety margin calculation since the bone effect in juvenile rats has not been well characterized from the nonclinical data in the original NDA submission.

- A. Applicant Response – The Applicant responded by providing a reanalysis of the previous 28-week study to evaluate the contribution of body weight to the observed effects and by conducting an 8-week intermittent dosing toxicity in juvenile rats (Study 080229).

Data for femur length from the 4-week juvenile rat study were re-analyzed using ANCOVA analysis with body weight as the covariate. The results showed that the minor bone length decrease was still statistically significant, further suggesting that the decreased bone length following Org 25969 administration in juvenile rats might not be associated with body weight change.

In the new 8-week study, juvenile rats were dosed weekly from postnatal day (PND) 7 for 8 doses at 0, 7.5, 30, and 120 mg/kg Org 25969, and the animals were sacrificed the second day after last dosing and at the end of 8-week recovery. Bone effects of Org 25969 were evaluated by in vivo ulna length measurement, blood concentration analysis of bone turnover markers including

NDA 22225

(b) (4)

7

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

osteocalcin and C-telopeptide crosslinks (CTx), histopathology examination of the bone, postmortem measurement of femur and terminal ulna length, μ CT evaluation, and bone strength tests. The results of the study did not show significant changes in the parameters tested except a statistically significant decrease (15%) of osteocalcin at the end of 8-week recovery period but not at the end of dosing.

- B. Nonclinical Assessment – The significance of this finding was unclear since there were no effects on bone density or strength.

In order to determine the sufficiency of the 8-week weekly dosing juvenile rat study to support the safety of future clinical trial in pediatrics, safety margins (**Table 5**) were calculated based on AUC and estimated bone concentration comparison between animals and human

Table 2 Safety Margin for sugammadex multiple-dose treatment at 4 mg/kg in pediatric subjects

| | | Rat | Human | Safety Margin |
|--------------|------------------|-----------|-------------------|---------------|
| Juvenile rat | Dose | 120 NOAEL | 4 | |
| | AUC (ug x h/mL) | 254 | 40 | 6.4x |
| | Bone conc (ug/g) | 400 | 18 (child 10 yrs) | 22x |
| | | | 24 (child 4 yrs) | 16.5x |

Source: Table from Dr. Xu’s review, pp. 7-8 of 60

As shown above, the 8-week intermittent bone study in juvenile provide 6.4-fold and ≥ 16.5 -fold safety margin for pediatric use at 4 mg/kg with weekly administration up to the same duration (8 weekly dosing) based on AUC and bone concentration comparison. Assuming a linear increase of plasma exposure (AUC) and bone concentration, which is the worst scenario for bone concentration estimation because bone deposition of Org 25969 was found to be less than dose proportional, the 8-week toxicity study in juvenile provides sufficient margin for 8-week weekly dosing clinical study in pediatric patients based on plasma AUC ($6.4/4 = 1.6$ -fold) and bone concentration ($\geq 16.5/4 = 4$ -fold).

This juvenile rat study successfully fulfills the nonclinical request 3 list in the Non-Approvable letter. In addition, this study also fulfills the request 2 because growth plate morphology was included in this study.

4. *Provide definitive information on the binding site of sugammadex in bone as well as a reevaluation of bone localization of sugammadex as presentation of the data on bone localization was not clear and errors in descriptions were noted in the submitted materials.*
- A. Applicant Response – An in vitro [14C]-Org 25969 binding study (Study number 090085) and a microautoradiography study in rats were included in this submission (Study 090071). While initially radiolabel was present in the metaphysis directly adjacent to the growth plate and only at trabecular and cortical bone surfaces, label was located more distally in the diaphysis and more centrally inside the cortical and trabecular bone compartments at the later 3- and 12-week observation times.
- B. Nonclinical Assessment - The data showed that Org 25969 did not bind in growth plate in the bone. The redistribution or movement of the compound to hydroxyapatite sites elsewhere in the bone does not represent a safety concern. These studies fulfill the nonclinical request 4 listed in the Non-Approvable letter.
5. *Provide data, which may be derived from published literature, in vitro studies, and/or in vivo studies, along with a persuasive, well-supported rationale, to show that the risk of administration*

NDA 22225

(b) (4)

8

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

and long-term retention of sugammadex in the bones of pediatric patients will not confer a risk for bone tumor development in this population. Otherwise, an evaluation of the carcinogenic potential of sugammadex may be required. Although plasma levels of sugammadex rapidly decline with acute administration, the long retention of sugammadex in skeletal bone may be considered to be chronic exposure (i.e., greater than six months) and raises concern regarding the potential for development of tumors of this tissue, especially in the pediatric population, which is known to develop primary bone tumors at rates that exceed those in the adult population.

In a meeting with the Applicant on December 1st, 2008, the Agency indicated demonstration of binding to hydroxyapatite as well as submission of bone metabolism and histopathology data from the requested juvenile rat study with extended duration of follow-up would address the carcinogenicity concern.

- A. Applicant Response – In this submission, the Applicant submitted an in vitro study clearly demonstrating that Org 25969 binds with hydroxyapatite, a component of bone extracellular matrix, at the same site for bisphosphonate binding. In addition, a microautoradiography study indicated that Org 25969 does not deposit in the growth plate of long bones, the area responsible for bone growth and elongation. In addition, histopathology examination did not show signs of carcinogenicity such as hyperplasia or hypertrophy of bone cells after 16-week Org 25969 exposure in the bone. Furthermore, bisphosphonate which binds the same site at hydroxyapatite does not cause bone-related cancer after long-term exposure (Whitaker et al., 2012).
- B. Nonclinical Assessment – The Applicant’s response suggests that Org 25969 may not be associated with significant risk for bone tumor development. Therefore, the request 5 in the Non-Approvable letter is considered to be sufficiently fulfilled.

- Overall Assessment

- 1. The Nonclinical group (Dr. Xu and Wasserman) recommend that from the nonclinical standpoint, the application for use of sugammadex in the adult population may be approved.
- 2. [REDACTED] (b) (4)
- 3. Outstanding issues
 - a. The label will be finalized in a subsequent cycle due to deficiencies identified by other disciplines and so specific labeling language will not be described until that time. The following issues identified in this review cycle will need to be addressed.
 - i. It will be necessary to define the Established Pharmacologic Class for the label: the proposed [REDACTED] (b) (4) is not considered acceptable to the Division. Others, such as [REDACTED] (b) (4) [REDACTED] are being considered and will be finalized for the next cycle.
 - ii. The revision of the proposed label in order to be in conformance with the Pregnancy and Lactation Labeling Rule will be negotiated with members of the Pediatric and Maternal Health Staff as well.
 - iii. The extent to which nonclinical data will be described in the Animal Toxicology section remains to be decided.

I concur with the review team that there are no outstanding nonclinical pharmacology or toxicology concerns that would preclude approval of this application.

NDA 22225

[REDACTED] (b) (4)

9

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

5. Clinical Pharmacology/Biopharmaceutics

While there were no outstanding concerns specific to clinical pharmacology or biopharmaceutics at the time of the last action that would have precluded approval, several studies were recommended by the review team and the Applicant has provided some additional studies as well. The following summary of the clinical pharmacology and biopharmaceutics data that were included in this submission has been reproduced from pages 16 through 22 of Dr. Breder's review:

Clinical Pharmacology was reviewed by Dr. Lei Zhang in the first review cycle. From a Clinical Pharmacology point of view, the application was considered acceptable, providing agreement was reached on the labeling. No Clinical Pharmacology studies were required in the Not Approvable Letter of July 31, 2008. However, as part of the Applicant's response to the deficiency in the Not Approvable Letter related to coagulation (see **Section C. Division's Final Review of the Original 2007 NDA Submission**), the following studies were conducted:

1. Clinical Study (P07044) in healthy subjects to assess sugammadex-anticoagulant (enoxaparin or heparin) interaction.
 - a. Results – There was no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin.
2. Clinical Study (P07025) in healthy subjects to assess sugammadex-aspirin interaction.
 - a. Result – There was no effect of 4 mg/kg of platelet aggregation effects of aspirin.

Several studies were recommended in the Not Approvable letter:

3. A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

As part of the response to this request, Study 19.4.116 (or P06315), a TQT study, was conducted to evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers.

- a. Result – No significant QTc prolongation effect of sugammadex was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/ sugammadex were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The overall summary of findings is presented in the table below:

NDA 22225

(b) (4)

10

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

| Treatment | Time (min) | $\Delta\Delta QTcF$ (ms) | 90% CI (ms) |
|------------------------|------------|--------------------------|-------------|
| Propofol/Sugammadex | 120 | 2.7 | (-3.1, 8.5) |
| Sevoflurane/Sugammadex | 30 | 2.0 | (-1.6, 5.7) |

Source: Table from Dr. Nallani's review, p. 7 of 59

There was no significant concentration-QT relationship observed for the studied sugammadex dose of 4 mg/kg. In addition, there was no suprathreshold dose evaluated in this study, and the evaluated dose is not sufficient to address the high exposure scenario (e.g., elderly subject with moderate renal impairment treated with 16 mg/kg for immediate reversal), which would result in an 8.8-fold increase in AUC compared to sugammadex 4 mg/kg. However, Study 19.4.109 from the previous submission, evaluated a suprathreshold dose of sugammadex 32 mg/kg, and the mean QT prolongation was less than 10 ms. The combination of the previous study results where an appropriate suprathreshold dose was evaluated and the current study results, which demonstrate no significant concentration-QT relationship support that substantial QT prolongation under the high exposure scenario is unlikely with the proposed maintenance regimens.

4. A study to assess clearance of sugammadex-rocuronium complexes in patients with renal failure who undergo hemodialysis using high flux filtration.

Related to this comment, the following studies were conducted:

- Clinical study to evaluate the dialyzability of the sugammadex-rocuronium complex in vivo in subjects with renal impairment (Study 19.4.333 or P05773).
 - a. Result – In Study 19.4.333 (or P05773), over an average six hours of dialysis episode a mean reduction in plasma sugammadex and rocuronium concentration was about 70% and 75% during the first episode and about 50% during the sequential episodes.
- Clinical study evaluating effectiveness of sugammadex in subjects with normal or severely impaired renal function (Study 19.4.328 or P05769).
 - b. Results – In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment), the median reduction in sugammadex plasma concentrations after a 3 to 4 hours of dialysis for the high-flux filter (n=5) was 70.2% and for the low-flux filter (n=5) the reduction was only 29.8%.
- Clinical study evaluating effectiveness, PK, and safety of sugammadex after rocuronium in subjects with normal or impaired renal function (updated Study 19.4.304 or P05948, previously reviewed by Dr. Zhang in 2008).
 - c. Results – In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment. Using high-flux dialysis filter, compared to low- flux filter, results in a more efficient clearance of sugammadex (and sugammadex+ rocuronium) from plasma.

The PK of sugammadex was not been evaluated in patients with renal impairment whose NMB are induced by vecuronium. Because vecuronium or rocuronium show little effect on sugammadex PK, the studies conducted with rocuronium-induced NMB was felt by the reviewer² to be extrapolated to vecuronium-induced NMB.

² Dr. Zhang's 2008 review, pp. 5-6

NDA 22225

(b) (4)

11

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

5. Studies to assess safety, efficacy, and dosing requirements for sugammadex when used in patients with hepatic impairment. The studies should characterize the pharmacokinetics and pharmacodynamics of rocuronium and vecuronium in these patients following the administration of sugammadex.
 - a. Result – The applicant does not plan to propose specific recovery times of T4/T1 ratio to 0.9 in the label in patients with hepatic impairment. Therefore, a dedicated PK-PD trial in subjects with hepatic impairment has not been conducted. The Applicant states that hepatic impairment is unlikely to affect PK of sugammadex, as it is predominantly, if not exclusively, eliminated via renal excretion of the unchanged product. The Applicant also states that it cannot be entirely excluded that in some individuals with severe hepatic impairment (especially in cases of ascites or general edema in severe hepatic impairment with significantly impaired protein synthesis function) the time of distribution of sugammadex and/or rocuronium/vecuronium may be altered, potentially resulting in some delay in the recovery time from NMBA effects. Therefore, the Applicant proposes a general statement in the label stating that sugammadex should be used with caution in subjects with severe hepatic impairment with coagulopathy or severe edema.

This was deemed as an acceptable approach by the Clinical Pharmacology reviewer. This is acceptable from my perspective as well, pending a review of the proposed labeling.

6. Studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. Such studies should not be started until the safety issues for the adult population have been fully vetted by the Agency.
 - a. Results – This is discussed in **Section 11**.

Several other Clinical Pharmacology studies were included in this resubmission

7. Clinical study to assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by IV diclofenac or IV flucloxacillin 5 minutes after reversal of NMB by sugammadex (Study 19.4.112 or P05861).
 - a. Results – Diclofenac or flucloxacillin did not alter pharmacokinetic disposition of rocuronium or vecuronium in plasma. No reoccurrence of neuromuscular block was observed after the administration of the administration of IV diclofenac or IV flucloxacillin based on TOF Watch SX monitoring during anesthesia. At this time, IV formulations of diclofenac or flucloxacillin are not available in the United States and hence this study has not impact on labeling.
8. Clinical study to evaluate re-use of rocuronium and vecuronium after NMB with Sugammadex (Study 19.4.113 or P05861). This was an open-label study to assess the safety and evaluate the onset of neuromuscular blockade at variable times of re-use of 1.2 mg/kg rocuronium (Part 1) and 0.1 mg/kg vecuronium (Part 2) after reversal of neuromuscular blockade by 4 mg/kg sugammadex in anesthetized healthy volunteers. The concern leading to this study was that use of sugammadex would preclude use of certain aminosteroid NMBs immediately thereafter.
 - a. Results – Subjects were given rocuronium in Part 1 in decreasing intervals from the time of sugammadex administration (see Table 6). For the 6 subjects with rocuronium re-use at 5 min, NMB onset time ranged from 1.92 to 4.72 min (arithmetic mean: 3.06). For longer re-use time points (30 min onwards) NMB onset

NDA 22225

(b) (4)

12

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

times decreased, ranging between 1.23 and 1.43 min. Clinical duration of the NMB among the 6 subjects with rocuronium re-use time-point at 5 minutes, ranged from 17.8- 41.0 min (arithmetic mean 25.3 minutes) and was around 30 min and longer for subjects with rocuronium re-use time points from 22 minutes (N=7) onwards.

Table 3 Individual Onset Times of NMB to Rocuronium Administration and NMB Duration (Lowest T1-25% recovery), All-Subject Evaluable group (Per Protocol)

| Relative re-use time-points ¹ [mm:ss] | Subject Number | Relative NMB onset time ² [min] | Clinical duration of NMB ³ [min] |
|---|---------------------|---|--|
| 59:59 | 101001 | 1.32 | 43.6 |
| 45:00 | 101007 | 1.23 | 46.0 |
| 30:00 | 101002 | 1.43 | 29.9 |
| 27:30 | 101012 | 2.60 | 34.4 |
| 25:00 | 101006 | 2.05 | 37.3 |
| 22:30 | 101011 | 3.83 | 29.1 |
| 20:00 | 101003 | 3.15 | 21.4 |
| 15:00 | 101008 | 2.80 | 26.6 |
| 09:57 | 101004 | 3.48 | 19.7 |
| 07:30 | 101010 | 2.35 | 24.6 |
| 05:00 | 101005 | 3.57 | 17.8 |
| 05:00 | 101013 | 2.73 | 22.7 |
| 05:00 | 101014 ⁴ | 2.75 | 41.0 |
| 05:00 | 101016 | 1.92 | 22.4 |
| 05:00 | 101017 | 2.68 | 17.7 |
| 04:59 | 101015 | 4.72 | 30.0 |

Note: Subject 101009 was not dosed with sugammadex due to technical issues with the monitoring of neuromuscular transmission, which prevented adequate timing of sugammadex dosing. Subsequently, no rocuronium re-use took place.

¹ relative to start of sugammadex administration

² relative to start of rocuronium administration

³ time to recovery to T₁=25%

⁴ Subject 101014 received a second i.v. dose of sugammadex (2 mg/kg) because recovery times after re-use of rocuronium exceeded 2 hours.

Source: Table 14.3.7-1

Source: Table 14, Dr. Nallani's review p. 54 of 59

Simulations showed that if re-use of 1.2 mg/kg rocuronium is initiated >25 minutes after 4 mg/kg sugammadex reversal, NMB onset times are achieved which are with 95% confidence below 4 minutes. Moreover, if in this setting re-use of 1.2 mg/kg rocuronium is initiated <25 minutes after reversal of sugammadex, NMB onset times are with 95% confidence below 4.25 minutes. The estimated geometric mean duration of NMB was 24.1 minutes and the lower limit of the 95% C.I. was 17.2 minutes for subjects receiving 1.2 mg/kg rocuronium 5 minutes after reversal with 4 mg/kg sugammadex.

Vecuronium re-use: In Part 2, six subjects received the second dose of vecuronium with re use time points between 2 hours and 5 hours after sugammadex administration. A complete neuromuscular block with onset times below 3 minutes was only observed for vecuronium re use times from 3.5 hours onwards. No complete NMB occurred after vecuronium re-use at 2 hours and 2.5 hours after sugammadex administration. Therefore, it was decided not to proceed with earlier time-points of re-use of vecuronium. Onset times of neuromuscular block at re-use times ≥3.5 hours ranged from 1.68 minutes (re-use at 3.5 h) to 3.15 minutes (re-use at 4 h) with NMB durations between 24.2 minutes (reuse at 4 h) and 31.4 minutes.

Table 4 Individual Onset Times of NMB to Rocuronium Administration and NMB Duration (Lowest T1-25% recovery), All-Subject Evaluable group (Per Protocol)

NDA 22225

(b) (4)

13

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

| Relative re-use time-points ¹ [hh:mm] | Subject Number | Relative NMB onset time-point ² [min] | Duration of NMB ³ [min] |
|--|----------------|---|---------------------------------------|
| 05:00 | 101101 | 2.03 | 31.3 |
| 04:00 | 101104 | 3.15 | 24.2 |
| 03:30 | 101105 | 1.68 | 31.4 |
| 03:00 | 101103 | 7.35 | 20.6 |
| Subjects excluded from the Per-Protocol group (no complete neuromuscular block appeared) | | | |
| 02:30 | 101106 | 5.68 | Not possible |
| 02:00 | 101102 | 5.45 | 10.5 |

Subjects 101102 and Subject 101106 were excluded from the Per-Protocol (PP) group because no complete neuromuscular block ($T_1=0\%$) occurred after re-use of vecuronium.

¹ relative to start of sugammadex administration

² relative to start of vecuronium administration

³ time to recovery to $T_1=25\%$

Source: Table 14.3.7-1

Source: Table 15, Dr. Nallani's review, p. 55 of 59

This study examines a clinically relevant question that was raised at the ALSDAC meeting during the first review cycle, that is, can NMBs be reused after sugammadex. The data suggest that rocuronium may be reused fairly soon after sugammadex administration and a normal duration of block may be achieved. However, 4 minutes for onset is a considerable time to onset if the NMB is being used at the time of anesthesia induction, particularly if it is a rapid sequence induction, including intubation in the emergent intubation setting. The data from Part 2 (using vecuronium as the NMB) seems quite preliminary considering the few subjects at any time point and the variability of results. Nonetheless, this is important information that should be conveyed in the labeling. The exact wording should be reflective of the relatively small amount of evidence provided.

9. PK study of sugammadex in male and female Chinese subjects (Study P05997). This was an open-label single-dose pharmacokinetic study.
 - a. Results – Pharmacokinetics of sugammadex was similar in Chinese subjects compared to Caucasian subjects. In addition, there were no gender-related differences in the pharmacokinetics of sugammadex in Chinese subjects.

- Overall Assessment

1. The Clinical Pharmacology group recommends that from the clinical pharmacology perspective, the application for use of sugammadex in the adult population may be approved.
2. The Clinical Pharmacology group further finds that the Applicant has appropriately addressed the clinical pharmacology issues and recommendations raised in the Not Approvable letter to support dosing and labeling.
3. Outstanding issues
 - a. The label will be finalized in a subsequent cycle due to deficiencies identified by other disciplines and so specific labeling language will not be described until that time.

NDA 22225

(b) (4)

14

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

While the Applicant had demonstrated the efficacy of sugammadex for the reversal of moderate to deep NMB in the original application, and no additional efficacy studies in adults were required or requested in the NAL, they included a number of new studies in this submission. The following summary of the data from those studies has been reproduced from pages 22 through 25 of Dr. Breder's review:

In the NDA resubmission, the Applicant has included a number of new clinical studies that contained efficacy data (**Table 8**). These trials evaluated only the lower doses of sugammadex proposed for clinical use, and the findings were consistent with those of the pivotal studies conducted for the original NDA submission.

Table 5 Efficacy Trials included in the Resubmission

| Study | Design / Population | Sugammadex dose(s) | Comparator | Primary Endpoint |
|---|---|--------------------|-------------------------|---|
| Phase 3 Studies with sugammadex administered at the reappearance of T2 | | | | |
| P05768 | randomized, active, parallel-group, multisite, safety-assessor-blinded trial of sugammadex of 291 adult, ASA-PS 1-3, Chinese and Caucasian subjects | 2 mg/kg | neostigmine (50 mcg/kg) | time to recovery of the T4/T1 ratio to 0.9. |
| P06101 | randomized, active-controlled, parallel group, multi-site, safety-assessor-blinded study of 128 adult, ASA-PS 1-3, Korean subjects | 2 mg/kg | neostigmine (50 mcg/kg) | time to recovery of the T4/T1 ratio to 0.9. |
| Phase 3 studies with sugammadex administered at 1-2 PTCs | | | | |
| P05767 | multi-center, randomized, parallel-group, comparative, placebo-controlled, safety-assessor blinded in 140, adult, ASA-PS 1-3 subjects undergoing profound neuromuscular blockade. | 4.0 mg/kg | Pbo | time to return of the T4/T1 ratio to 0.9. |
| P05699 | multi-center, randomized, parallel-group, active-controlled, safety-assessor blinded trial of 133 adult ASA-PS 1-3 subjects | 4.0 mg/kg | neostigmine (50 mcg/kg) | time to return of the T4/T1 ratio to 0.9. |

NDA 22225

(b) (4)

15

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

| Study | Design / Population | Sugammadex dose(s) | Comparator | Primary Endpoint |
|----------------------------|---|---|--|--|
| P05774 | multi-center, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded, anesthesiologist- TOF-Watch® SX-blinded trial of 100 adult, ASA-PS 1-3 subjects | 4.0 mg/kg ◊ | Neostigmine (50 mcg/kg) ◊ | T4/T1 ratio at the time of tracheal extubation |
| Special populations | | | | |
| P05769 | open-label, multicenter, parallel-group, comparative study in 68 adult, ASA-PS 1-3 subjects with normal and severely impaired renal function | 4.0 mg/kg at a target depth of neuromuscular blockade of 1-2 PTCs | None | time to return of the T4/T1 ratio to 0.9 |
| P05773 | single center, exploratory, open label trial in 6 ASA-PS 1-4 subjects with severe renal impairment (creatinine clearance < 30 mL/min and a clinical indication for dialysis) who were hospitalized in an ICU scheduled for a surgical procedure | 4 mg/kg 15 minutes after administration of rocuronium | None | time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9, 0.8, and 0.7 Exploratory endpoint to evaluate the dialysability of the sugammadex / rocuronium complex |
| Other | | | | |
| P05698 | multi-center, randomized, peripheral nerve stimulator (PNS)-assessor-blinded, parallel-group, active, within-subject controlled trial of 91 adult, ASA-PS 1-3 subjects | 1:2 ratio to receive either a single dose of 1.0 or 4.0 mg/kg sugammadex administered at 15 minutes after the last dose of rocuronium, respectively, and in a 1:1 ratio to having the TOF-Watch® SX affixed to either the dominant or the non-dominant forearm. | | the time from start administration of 4.0 mg/kg of sugammadex to reappearance of T4 as detected manually with PNS monitoring. |
| P05700 | multicenter, randomized, safety-assessor blinded, parallel group, active-controlled, comparative trial in 161 adult, ASA-PS 1-3 subjects | 4 mg/kg bolus dose of sugammadex for reversal at a target depth of blockade of 1-2 PTCs | 1 mg/kg bolus dose of succinylcholine followed by spontaneous recovery | time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9. The time from start of administration of succinylcholine to T1 reaching 90% of baseline was a secondary endpoint. |
| P05775 | open-label, single-dose, multi-site trial in 115 Chinese Asians living in China and 36 European Caucasians living in Europe. | 4 mg/kg at a target depth of blockade of 1-2 PTCs, | None | time to return of the T4/T1 ratio to 0.9 |

◊ = administered “per standard of care” knowing whether spontaneous recover had already reached 1-2 post tetanic contractions (PTCs) or better

Source: created from information in Dr. Simone’s review, Section 6.1.1

Of these studies, Dr. Simone provided a more detailed review of Study P05774 (see the italicized text below) (b) (4)

The primary endpoint of P05774 was to compare the incidence of residual neuromuscular blockade at the time of tracheal extubation after reversal of rocuronium bromide-induced neuromuscular blockade with 4 mg.kg⁻¹ sugammadex compared with 50 µg/kg⁻¹ neostigmine. Residual paralysis was defined as T4/T1 ratio of <0.9.

NDA 22225

(b) (4)

16

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

Although it was not a pivotal study, [REDACTED] (b) (4). Although the findings may be accurate and the study appropriately designed to assess the primary endpoint, the study does not demonstrate the efficacy of sugammadex. The study does appear to show that when patients are not monitored with PNS [PNS = peripheral nerve stimulator] following administration of a reversal agent they are more likely to extubate a patient at a T4/T1 = 0.9 with sugammadex than neostigmine. The implication is that patients are "more" reversed with sugammadex than neostigmine and therefore, less likely to risk morbidity associated with inadequate reversal. However, the study was not designed to demonstrate such a benefit, and the exclusion of PNS monitoring from the assessments made prior to determining whether it was safe to extubate a patient is inconsistent with the current standard of care. [REDACTED] (b) (4).

I concur with his assessment of this trial.

Dr. Zhou, the statistical reviewer, analyzed the primary and secondary endpoints from this study. She verified that the same statistical results were achieved as the Applicant...

While the outcome was statistically significant, [REDACTED] (b) (4). The data seem to only demonstrate that certain investigators were willing to extubate the patient well before the standard of care of a T4/T1 of > 0.9. The range extends as low as 0.38 which is closer to a threshold when the reversal agent would just be given (e.g., T4/T1 = 0.2) than the point of extubation. I am also concerned about the reliability of the data and possibility of technical error in the conduct of this study since the range for T4/T1 in the sugammadex data extends to 1.41 while the maximum theoretical physiological value for T4/T1 is 1.

I concur with the review team that there are no outstanding concerns regarding the efficacy of sugammadex that would preclude approval of the product for use in adult patients.

8. Safety

The following summary of the current extent of exposure data has been reproduced from pages 27 and 28 of Dr. Breder's review:

Since the Not Approvable action was taken, the Applicant has completed 20 new clinical trials and in the process has doubled the size of the safety database. In the original NDA submission, there were a total of 2,369 subject exposures to intravenous sugammadex in 2,054 unique subjects. The new clinical trials add 2,547 subject exposures to IV sugammadex in 1,967 unique subjects. In addition, sugammadex was approved in the European Union on July 25, 2008, and is currently registered in 71 countries and marketed in 41 countries. The Applicant reports the distribution of over [REDACTED] (b) (4) vials for use in patients through June, 2012. Therefore, the secondary focus of this review was whether the new safety database or the postmarketing adverse event data present a risk profile that is similar to that characterized in the original NDA submission or whether any new safety signals exist.

³ A table similar to the Complete Cases (left side) of Table 10 from my review

⁴ Dr. Simone's review, p. 35 of 303 (PDF Version)

NDA 22225

[REDACTED] (b) (4)

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

Dr. Simone noted⁵ that the safety data seemed adequate for most of the populations of interest for the 2 and 4 mg/kg doses however there are limited data for older (> 65 years) and sicker (ASA-PS 3-4) subjects given the highest proposed sugammadex dose, 16 mg/kg.

In general, there were no new major or unexpected safety concerns identified in the safety data collected from the time of the original NDA submission to the lockout date for this submission.

The following summary of the data generated to address the specific safety concerns related to hypersensitivity and anaphylaxis has been reproduced from pages 36 through 39 of Dr. Breder's review:

To address the hypersensitivity issue raised by the FDA, the Applicant conducted the following a studies and analyses:

- A dedicated trial in healthy volunteers (Trial P06042) on possible effects of hypersensitivity and/or anaphylaxis after repeated administration of routine doses of sugammadex (4 mg/kg), high doses of sugammadex (16 mg/kg), or placebo in healthy subjects with independent blinded adjudication of hypersensitivity cases. Additional work proposed by the FDA to further elucidate the mechanism of action of these hypersensitivity reactions based on the results of the biomarkers (skin testing, anti sugammadex IgE/IgG assay, basophil histamine release testing, such as Basophil HR-Testing, activation of contact and complement system, parameters of neutrophil or cytokine activation) was also included in Trial P06042.

P06042 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects age 18 to 55. A total of 480 subjects received a single-blind, saline placebo test dose at Week 0, and patients who experienced a reaction to the placebo dose were screened out. Of the 480 subjects enrolled, 448 were randomized in a 1:1:1 ratio to receive the following doses intravenously on Day 8 (Week 1), Day 36 (Week 5), and Day 78 (Week 11):

- sugammadex 4 mg/kg (n=148)
- sugammadex 16 mg/kg (n=150)
- Saline placebo (n=150)

On a scheduled inspection of one of the sites (site #2) from this trial, OSI inspectors found that the investigators had been unblinded, calling into question the integrity of data. Furthermore, on multiple occasions, a dosing investigator evaluated adverse events in violation of the protocol, potentially affecting six (6) cohorts (approximately 53 of the 95 randomized subjects from this site). This is described more fully in **Section 12.C. Clinical Site Inspections**.

In healthy volunteers in Trial P06042, a dose-related risk for hypersensitivity including anaphylaxis was identified, with the greatest risk being associated with the 16-mg/kg dose of sugammadex (a dose recommended only for immediate reversal in emergency interventions). Clinical signs and symptoms of hypersensitivity and/or anaphylaxis occurred soon after sugammadex administration (i.e., between "immediately" and 3.5 hours after sugammadex administration). The more severe reactions (including 3 reactions fulfilling any of the Sampson and/or Brighton anaphylaxis criteria) started within 1 minute after dosing. Symptoms and signs that did occur resolved quickly and spontaneously or responded to usual treatment. The following table summarizes the disposition of subjects from this trial.

⁵ Dr. Simone's review, p. 49 of 303 (PDF Version)

NDA 22225

(b) (4)

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

Table 6 Patient Disposition - Study P06042

| | Placebo (N=150) | sugammadex 4mg/kg (N=150) | sugammadex 16mg/kg (N=150) |
|--|----------------------------|--|---|
| | n (%) | | |
| Patients who completed the study | 135 (90) | 135 (91.2) | 127 (84.7) |
| Patients who withdrew early | 15 (10) | 13 (8.8) | 23 (15.3) |
| Reasons for withdrawal | | | |
| <i>Hypersensitivity Adverse Events</i> | 2 (1.3) | 4 (2.7) | 10 (6.7) |
| Swollen tongue | 1 (0.7) | 0 | 0 |
| Anaphylactic Shock | 0 | 0 | 1 (0.7) |
| Hypotension | 0 | 0 | 1 (0.7) |
| Urticaria | 0 | 0 | 3 (2.0) |
| <i>Lost to Follow Up</i> | 2 (1.3) | 1 (0.7) | 2 (1.3) |
| <i>Consent Withdrawn</i> | 2 (1.3) | 3 (2.0) | 5 (3.3) |
| <i>Non-Compliance</i> | 9 (6.0) | 5 (3.4) | 6 (4) |
| Source: Table 5, p. 79, Clinical Study Report P06042 Module 5.3.5.4 (10.1) and Section 16.2.7.5, p. 576-578, Clinical Study Report P06042, Module 5.3.5.4 (16.2.7.5) . | | | |

Source: Table 1 from DPARP consult response, June 19, 2013

Overall 10 subjects in the study discontinued treatment after experiencing suspected hypersensitivity symptoms: 7 were from the sugammadex 16mg/kg group, 2 were from sugammadex 4mg/kg, and 1 from the placebo group. The reason for withdrawal for some of the subjects who experienced hypersensitivity symptoms were captured under categories other than adverse events, such as consent withdrawn and noncompliance.

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms, the Applicant identified 68 cases of suspected hypersensitivity in 49 subjects. These were sent by the Applicant to an Adjudication Committee comprised of independent allergist / immunologists and anesthesiologists for review. The committee classified 8 subjects as having had a hypersensitivity reaction.

The consulting Division, DPARP has reviewed each of the suspected cases resulting from the Applicant's search. Those listings which included adverse events that were consistent with anaphylaxis were then crosschecked with case narratives. A final determination of anaphylaxis for these cases was made using NIAID/FAAN criterion #1 (as outlined in **Section 15.A. NIAID/FAAN Criteria for Anaphylaxis**). Using this method, DPARP identified 3 cases of anaphylaxis among the 68 potential hypersensitivity cases in 49 subjects.

Based on this case review, DPARP concluded that there are at least 3 clear cases of anaphylaxis in healthy subjects in this repeat dose clinical trial. Study P06042 consisted of 298 unique healthy volunteer subjects who received sugammadex. As a result, a frequency of anaphylaxis of 1.0% (3/298) in a healthy volunteer population we calculated. It is of note that all three cases of anaphylaxis occurred in the sugammadex 16 mg/kg group, and with the initial dose.

Among the 5 additional subjects adjudicated by the Applicant's Committee as having a hypersensitivity reaction, 4 subjects were in the sugammadex 16 mg/kg group, and 1 subject in the

NDA 22225

(b) (4)

19

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

4 mg/kg group. With the exception of 1 subject in the 16 mg/kg group who experienced urticaria with the 2nd dose, all hypersensitivity reactions occurred with initial administration. One subject in the 16 mg/kg experienced urticaria on all three administrations of sugammadex, while one subject in the 4 mg/kg group experienced pruritic rash on the first two administrations, and no reaction with the third administration. In general, signs and symptoms of hypersensitivity in these patients were immediate in onset (within minutes), with the exception of one patient who experienced urticaria ~3 hours post-dose, and were characterized by urticaria and flushing.

Results from assessment of tryptase levels, skin testing, assessment for sugammadex-specific IgE/IgG, as well as results from additional mechanistic studies exploring potential underlying mechanisms do not support basophil/mast cell-mediated hypersensitivity either via an IgE-mediated or direct non-IgE-mediated mechanism, nor a role for contact/complement activation, neutrophil activation, or cytokine release.

In addition to Trial P06042, the Applicant characterized the cumulative safety in the Phase 1-3 database and Postmarketing data.

Based on the analyses of the cumulative safety database from Phase 1-3 trials, in which suspected cases of anaphylaxis were adjudicated by the same Adjudication Committee, as in Trial P06042, no additional cases of anaphylaxis were identified. In the clinical setting of Phase 2 to 3 trials, the incidence of adjudicated hypersensitivity-related cases was calculated by the Applicant to be 0.1%.

The Applicant's pharmacovigilance database Global Pharmacovigilance Corporate Adverse Events Reporting and Evaluation System was searched by the Applicant on July 3, 2012 for postmarketing reports of anaphylaxis and serious hypersensitivity received from healthcare providers, cumulatively from market introduction through June 15, 2012 in patients administered sugammadex. Anaphylaxis reports were identified by querying the narrow Anaphylaxis Standard MedDRA Query (SMQ), along with narrow terms from the "Anaphylactic/ anaphylactoid shock" sub-SMQ in the Shock SMQ. Serious hypersensitivity reports were identified by querying the broad Anaphylaxis SMQ, along with the preferred term "hypersensitivity". A total of 144 reports were identified in this query: 87 reports of anaphylaxis and 57 reports of serious hypersensitivity.

The Applicant suggested from their review of sugammadex's postmarketing experience that cases of anaphylaxis with serious clinical signs were rare and generally manageable in the clinical setting of the operating room. Based on their assumptions about reporting and exposure, the Applicant suggested the risk for sugammadex-associated anaphylaxis in the postmarketing surveillance reports appeared similar in magnitude to background rates for established agents routinely used in the peri-operative setting.

While the Applicant has sought adjudication of these reports by an external committee, DPARP contends that due to the nature of post-market reporting (limited/missing information) and characteristics of the surgical patients to whom the drug was administered (polypharmacy, multiple comorbidities, the effects of surgery), it is difficult to interpret/adjudicate these cases definitively. Therefore, DPARP has considered these post-marketing reports only as a means of further characterizing the types of hypersensitivity reactions that have been observed with use of sugammadex in the controlled clinical studies.

The following summary of the data generated to address the specific safety concerns related to coagulation has been reproduced from pages 39 through 43 of Dr. Breder's review:

NDA 22225

(b) (4)

20

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

The Applicant's response to the FDA's request for additional information [regarding coagulation safety concerns] included the following components:

- The conduct and analysis of a clinical trial (Trial P07038) to assess events of bleeding and coagulation parameters in surgical subjects
- The conduct of a pooled analysis of serious/major events of bleeding from the Phase 2 to 3 development program (including the proposed clinical trial [Trial P07038])
- The conduct of a clinical study (P07044) in healthy subjects to assess Sugammadex -anticoagulant interaction
- The conduct of a clinical study (P07025) in healthy subjects to assess Sugammadex-aspirin interaction
- A summary of serious postmarketing events of bleeding.

As previously noted, DAAAP consulted the Division of Hematology and Oncology Products (DHOP) to review the Applicant's submission with respect to this issue.

The Trial P07038 evaluated the risk for bleeding in a high risk population of surgical subjects concomitantly treated with anticoagulants prior to major orthopedic surgery. The primary endpoint was the proportion of subjects with at least one, adjudicated, major or non-major but unanticipated event of bleeding within 24 hours after trial drug administration summarized in the following table, reproduced from the Applicant's submission (**Table 18**). The primary outcome endpoint was met by 2.9% of subjects randomized to the sugammadex arm compared to 4.1% in the control arm, identified by the Applicant as the "usual care" arm. These events included both major bleeding (2.0% vs. 3.4% in the SU and usual care arms, respectively) as defined in the protocol and unexpected non-major bleeding (0.9% vs. 0.7% in the sugammadex and usual care arms, respectively) as determined by the Adjudication Committee. For the majority of events, the relationship between the trial drug and bleeding was determined to be "possible."

Table 7 Incidence of Subjects with at Least One Suspected Unanticipated Adverse Event of Bleeding

Protocol No. P07038

| Onset | Maximum Relationship ^b | Sugammadex (N=596) | | Usual Care (N=588) | |
|---------------------------------------|-----------------------------------|--------------------|-------------------------|--------------------|-------------------------|
| | | Major | Total (Major+Non-major) | Major | Total (Major+Non-Major) |
| Within 24 hours | Unlikely | 0 | 1 (0.2) | 2 (0.3) | 3 (0.5) |
| | Possible | 12 (2.0) | 16 (2.7) | 18 (3.1) | 21 (3.6) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 12 (2.0) | 17 (2.9) | 20 (3.4) | 24 (4.1) |
| Total ^a (Up to 14 days) | Unlikely | 5 (0.8) | 7 (1.2) | 4 (0.7) | 5 (0.9) |
| | Possible | 13 (2.2) | 17 (2.9) | 19 (3.2) | 22 (3.7) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 18 (3.0) | 24 (4.0) | 23 (3.9) | 27 (4.6) |

SUAEB=suspected unanticipated adverse event of bleeding

^a Only events with an onset on or before Day 14 were included. Note that each subject is counted only once.

^b Maximum relationship (by adjudicator) implies that if a subject experienced, for example, 2 major adjudicated events, one unlikely and one possible related, the subject was counted in the 'possible' row, and not in the 'unlikely' row.

Source: [Section 14.2.1.1.1.1.1](#)

Source: Table 11-1, Dr. Shashaty's (DHOP) May 2, 2013 consult response

NDA 22225

(b) (4)

21

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

A secondary endpoint for the trial extended the time of observation for the bleeding from the first 24 hours after surgery to 14 days after surgery. There was an increase in the incidence of major and unexpected non-major bleeding events in both arms, but slightly more so with sugammadex. Most of those events were considered unlikely to be related to trial-drug administration. Although there was a proportionally greater number of bleeding episodes after the 24 hour period, it is increased in both arms and is not statistically different. In addition, they would not be expected to be related to the administration of sugammadex because of the short duration of the effects of sugammadex on the clotting times.

At 10 minutes after trial drug administration, there was a small, but statistically significant increase in the aPTT in subjects in the 4 mg/kg sugammadex arm compared to baseline [4.7% (CI, 3.4%, 5.9%)] and in subjects in the sugammadex arm compared to the usual care arm [5.5% (CI, 3.7%, 7.3%)] summarized in the following table, reproduced from the Applicant's submission (Table 19). Similar comparative increases were noted in the PT measurements [4.5% (CI, 3.3%, 5.8%) and 3.0% (CI, 1.3%, 4.7%)], respectively. At 60 minutes after trial drug administration, the laboratory findings had resolved.

Table 8 Change in Coagulation Parameters for Sugammadex and Usual Care

Protocol No. P07038

| | | Sugammadex (vs Baseline) | | Usual Care (vs Baseline) | | Sugammadex vs Usual Care | |
|------------------------|--------|-----------------------------|---------------------|-----------------------------|---------------------|-----------------------------|---------------------|
| | | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a |
| aPTT ^b | 10 min | 4.7% | (3.4%, 5.9%) | -0.8% | (-2.0%, 0.4%) | 5.5% | (3.7%, 7.3%) |
| | 60 min | -1.9% | (-3.2%, -0.6%) | -2.8% | (-4.1%, -1.5%) | 0.9% | (-0.9%, 2.8%) |
| PT(INR) ^{b,c} | 10 min | 4.5% | (3.3%, 5.8%) | 1.5% | (0.3%, 2.7%) | 3.0% | (1.3%, 4.7%) |
| | 60 min | 2.7% | (1.2%, 4.1%) | 1.7% | (0.3%, 3.2%) | 0.9% | (-1.0%, 2.9%) |

aPTT=activated partial thromboplastin time; CI=confidence interval; PT(INR)=prothrombin time (international normalized ratio).

^a Estimates and confidence intervals are geometric means, adjusted for trial center, usual care group (active reversal versus spontaneous recovery), renal function (< or ≥ 60 mL/min), antithrombotic therapy (LWMH/UFH vs. other), surgical procedure (hip fracture, hip or knee replacement/revision, or hip or knee stage 1 revision [total or partial]), and treatment-by-time interaction.

^b A total of 567 subjects treated with sugammadex and 548 treated with usual care contributed to the cLDA analyses with a valid parameter value, both for aPTT as well as for PT(INR).

^c Estimates for PT and INR are identical; values for PT were used in analysis since these were provided with higher precision.

Source: Table 11-4, Dr. Shashaty's (DHOP) May 2, 2013 consult response

The Applicant concluded that treatment with 4 mg/kg sugammadex was not associated with an increased bleeding risk in comparison to usual care. This conclusion was made based on their analysis of the primary endpoint as well as a number of secondary bleeding endpoints irrespective of the definition or onset of the bleeding event. This finding was also consistent with the observation that there was no difference between sugammadex-treated subjects and subjects treated with usual care regarding endpoints of anemia, bleeding index, drainage volume, need for postoperative transfusion, and associated transfusion volume. With regard to the laboratory coagulation parameters aPTT and PT(INR), a small (5.5% and 3.3%, respectively) and transient increase (within 1 hour after administration) was associated with sugammadex treatment, which did not seem associated with any increase in the clinical risk for bleeding or blood loss. The incidences of treatment emergent adverse events are summarized in the following table, reproduced from the Applicant's submission (Table 20).

NDA 22225

(b) (4)

22

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

Table 9 Number of Subjects with at Least One Treatment Emergent Adverse Event

| | Number (%) of Subjects | | Difference Estimate (95% CI) ^a |
|---|------------------------|-----------------------|--|
| | Treatment Groups | | |
| | Sugammadex n = 564 | Usual Care n = 560 | |
| Subjects with Treatment-Emergent AEs ^b | 551 (92.4%) | 549 (93.4%) | -0.9 [-3.9; 2.0] |
| Subjects with SAEs | 39 (6.5%) | 40 (6.8%) | -0.3 [-3.2; 2.6] |
| Subjects with Treatment-Related AEs ^c | 64 (10.7%) | 72 (12.2%) | -1.5 [-5.2; 2.1] |
| Subjects with Treatment-Related SAEs ^c | 4 (0.7%) | 2 (0.3%) | 0.3 [-0.6; 1.4] |
| Deaths ^d | 0 (0.0%) | 3 (0.5%) | -0.5 [-1.5; 0.1] |

AE= adverse event; CI = Confidence interval; SAE = serious adverse event

^a Risk difference and associated 95% confidence interval according to Miettinen-Nurminen method.

^b A treatment-emergent AE is defined as an AE occurring during or after trial medication administration up to and including 14 days after trial administration.

^c A treatment-related AE is defined as a treatment-emergent AE considered “possibly” or “probably” related to the medication by the investigator.

^d Any death occurring during or after trial administration. A total of 4 subjects assigned to usual care group died during the trial, but one subject (Subject 1/00144) was discontinued before administration of trial medication due to a pulmonary embolism (Section 16.2.72) and is not accounted for in the table.

Source: Table 12-2, Dr. Shashaty’s (DHOP) May 2, 2013 consult response

Additional in vitro PK and PK-PD models investigating the possible mechanism of action suggested the effects of Sugammadex on coagulation parameters aPTT and PT (INR) were likely to be mediated via an effect on Factor Xa activity/generation and were consistently found to be transient and of limited magnitude similar to the effects described in Trial P07038.

A drug-drug interaction study in healthy volunteers did not suggest a clinically relevant additive effect of sugammadex (4 mg/kg) and aspirin (75 mg) on relevant coagulation parameters such as platelet aggregation, aPTT, PT (INR), or anti-Factor Xa activity. Similar results were observed in a similar study of healthy volunteers exposed to sugammadex (4 mg/kg or 16 mg/kg) and enoxaparin (40 mg subcutaneous) or unfractionated heparin (5,000 IU subcutaneous). These studies further showed that sugammadex doses up to 16 mg/kg were associated with limited (\leq 25%) and transient (\leq 1 hour) increases in aPTT and PT (INR).

The DHOP review of pooled data from the data base containing studies from Phase 1 to 3 (surgical subjects) noted that treatment with sugammadex did not seem associated with a significantly higher risk of events of bleeding in comparison to control treatments (placebo or neostigmine).

The Applicant also provided reports of postmarketing cases of hemorrhage events cumulative to June 15, 2012. There were a total of 5 incidents. The reports included the following:

- Two patients had postoperative bleeding at the surgical sites, i.e., following parotid resection and tonsillectomy. It was not possible to determine the extent, if any, to which sugammadex, inadequate wound closure, or inadequate hemostasis at the time of wound closure contributed to the bleeding.
- One patient developed bradycardia and cardiac arrest one minute following sugammadex administration following abdominal surgery for ovarian cancer. She required insertion of an intra-aortic balloon pump and anticoagulation for life support, but died 19 days later. At autopsy, she was found to have intra-abdominal hemorrhage and a lacerated aorta.

NDA 22225

(b) (4)

23

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

- One patient received sugammadex following total gastrectomy and experienced hypotension with no detectable pulse related to anaphylactoid shock followed by cardiac arrest. The patient went on to develop disseminated intravascular coagulation and intra-abdominal hemorrhage from bleeding at the surgical sites. The patient went on to develop multiorgan failure and died on postoperative Day 3.
- One patient received sugammadex following orthopedic surgery involving her femur. Later on the day of surgery, she experienced bradycardia, hypotension, increased “vascular permeability” and hemorrhagic shock. Inadequate information was captured in the report, including the time to onset of shock relative to sugammadex administration, to assess the role of sugammadex in this case.

In summary, both the Applicant and the DHOP consulting reviewer concluded that, based on clinical trials in at-risk subjects being treated with antithrombotic prophylaxis, the clinical safety database, and postmarketing surveillance data, the limited and transient effects of sugammadex on aPTT and PT (INR), which appear to be mediated mainly by a reversible inhibition of Factor Xa activity, are not associated with an increased bleeding risk in surgical subjects. I agree with these conclusions.

The following summary of the data generated to address the specific safety concerns related to cardiovascular adverse events has been reproduced from pages 43 through 48 of Dr. Breder’s review:

a - QT

In post-action discussions with the Applicant, the Agency agreed that, based on the data available and an additional analysis of ECG data for arrhythmias, there was no increased risk of QTc prolongation or arrhythmias associated with sugammadex use, and the Applicant need not conduct the study recommended in the Not Approvable letter. Nonetheless, the Applicant conducted a third QTc study (see **Section 6**), this time examining the risk of QTc prolongation when sugammadex was administered either propofol-induced or sevoflurane-induced general anesthesia. This study demonstrated no increased risk of QTc prolongation with sugammadex with either of these anesthetics. The previous studies showed the same for sugammadex administered alone and for sugammadex administered concurrently with rocuronium or vecuronium. Evaluation of the updated safety database indicated no increased risk of QTc prolongation or arrhythmias with sugammadex compared to placebo and neostigmine.

b - Arrhythmias

As part of the resubmission of the NDA, the Applicant was instructed to analyze both the clinical trial data and the postmarketing data evaluating the occurrence of all arrhythmias.

Clinical Trial Safety Database

To compare the incidence of arrhythmias across treatment groups, the Applicant performed Broad and Narrow Standardized MedDRA Query (SMQ) analyses for “Cardiac Arrhythmias” in both the pooled placebo-controlled trials and the pooled neostigmine-controlled trials. They reported no significant differences between sugammadex and its comparators for any of the SMQs in either the broad or narrow searches or in its component terms for the placebo-controlled trials (c.f., Table 21 of Dr. Simone’s review).

Additional analyses included evaluated the pooled Phase 1-3 trials for the percentage of exposures in subjects with treatment-emergent markedly abnormal pulse rate values, i.e., a heart rate outside the range of 50-120 bpm that was also a change from baseline ≥ 15 bpm. The percentage and range of abnormal values were similar for sugammadex and placebo subjects.

NDA 22225

(b) (4)

24

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

The Applicant also reported that no time point trends were observed for the percent of exposures in subjects with markedly abnormal values. However, a dose trend for markedly decreased pulse rate was present as was a dose trend for the bradycardia AEs exhibited in **Table 21** of my Review. In the dose-pooled analysis, the rate of bradycardia for sugammadex was 1.1% versus 0.7% for Pbo.

Table 10 Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group

| MedDRA Preferred Term | Placebo (N=544) | Sugammadex | | | |
|-----------------------|-----------------|-----------------|------------------|-----------------|-----------------------------|
| | | 2 mg/kg (n=838) | 4 mg/kg (n=1798) | 16 mg/kg (n=98) | Total ^A (N=3407) |
| At least one AE | 8 (1.5) | 12 (1.4) | 29 (1.6) | 6 (6.1) | 58 (1.7) |
| Tachycardia | 3 (0.6) | 9 (1.1) | 18 (1.0) | 3 (3.1) | 32 (0.9) |
| Bradycardia | 4 (0.7) | 2 (0.2) | 7 (0.4) | 2 (2.0) | 17 (0.5) |
| Heart rate increased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 1 (1.0) | 4 (0.1) |
| Heart rate decreased | 1 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Heart rate irregular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |

Source: Table 23, p 108 of 303 of Dr. Simone's review

In shift table analyses, there were a greater proportion of patients who were not bradycardic (>50 beats/minute) at baseline that experienced a decrease in heart rate below 50 beats/minutes compared with those in the placebo group. A small increase in the proportion of subjects with a marked reduction (>20 bpm) was observed that seemed dose responsive in the sugammadex group⁶, however the numbers having this event were small so the significance of this finding is unclear. The Applicant also compared the incidence of atropine administration one hour after study drug and found a slightly higher incidence with rocuronium (0.8%) than vecuronium (0.2%) use.

The Applicant made the following conclusions regarding the cardiovascular safety in their updated database:

- Sugammadex is not associated with QT/QTc prolongation beyond the level of regulatory concern when 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.
- Sugammadex does not demonstrate any clinically relevant QT/QTc prolongation, or an increase in the incidence of categorical or change-from baseline outliers when compared to placebo in a meta-analysis of QTc data across the clinical development program
- Sugammadex is not associated with an increase in the incidence of AEs of QTc prolongation compared to placebo, when the QT interval is appropriately corrected for HR using the Fridericia formula, in an analysis of reported AEs of the integrated clinical development database.
- 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.
- For bradycardia in particular, there appears to be a small mean overall effect on heart rate when sugammadex is administered for the reversal of some NMBAs. This effect seems to be dependent on the choice of background NMBA and more consistently observable with rocuronium than in the setting of vecuronium. Furthermore, this effect seems to translate in rare bradycardic events

⁶ Table 26, p 110 of 303 of Dr. Simone's review (PDF Version)

NDA 22225

(b) (4)

that are easily detected. The clinical trial database did not suggest a risk for clinically important bradycardia.

In his own analysis of cardiac SAEs, Dr. Simone noted that the only SAE that occurred with a frequency greater than 1% in any sugammadex dose group was QTc prolongation. With a doubling of the size of the safety database compared to the original NDA submission, only three additional incidents of QT prolongation have been reported as SAEs: two more in the 4 mg/kg dose group and one more in the 16 mg/kg dose group. Overall, this represents a decrease in frequency from 1.4% to 0.7% for SAEs of QTc prolongation with sugammadex treatment, which is not substantially different than that observed with placebo treatment, i.e., 0.2%.

Dr. Simone noted that the more commonly occurring adverse events in the resubmission database are, as it was with the original NDA submission, bradycardia, QTc prolongation, and tachycardia. With the resubmission, there were 29 new AEs of bradycardia; a single new AE of QTc prolongation and 28 new AEs for tachycardia. The overall incidence of each of these AEs has decreased since the original NDA submission such that they do not differ substantially from neostigmine or placebo treatments. For each of these AEs, there is no indication of dose dependence with sugammadex treatment.

Table 11 Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|--|-----------|--------------------|----------|-----------|-----------|----------|-----------|-----------|-----------|----------|------------|----------------------|-----------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | Total | 50 | 70 |
| N | 1318 | 137 | 220 | 856 | 2198 | 29 | 156 | 39 | 348 | 164 | 4147 | 814 | 42 |
| Adverse Event | | | | | | | | | | | | | |
| Acute myocardial infarction | 2 | | | | 1 | | | | | | 1 | 2 | |
| Atrial fibrillation | 2 | 1 | | 7 | 5 | | | | | | 13 | 4 | |
| Atrial flutter | | | | | 2 | | | | | | 2 | | |
| Atrioventricular block (1°) | 1 | | | | | | | | | | 0 | | |
| Atrioventricular block (2°) | 1 | | | | | | | | | 1 | 1 | | |
| Bradycardia | 9 | 1 | 1 | 14 | 30 | 1 | 6 | 1 | 8 | | 62 | 65 | |
| % | 1 | 1 | 0 | 2 | 1 | 3 | 4 | 3 | 2 | 0 | 1 | 8 | 0 |
| Cardiac arrest | | | | | | | | | | | 0 | 1 | |
| T wave abnormality | 1 | | | | | | | | | | 0 | 1 | |
| PR interval prolonged | | | | | | | | | | | 0 | | |
| QTc interval prolonged | 3 | | 1 | 13 | 6 | | 2 | 3 | 4 | | 29 | | 2 |
| % | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 8 | 1 | 0 | 1 | 0 | 5 |
| Supraventricular and Ventricular extrasystoles | 1 | | | 1 | 2 | | | | | 1 | 3 | 4 | |
| Tachycardia | 7 | | 5 | 26 | 47 | 1 | 2 | | 11 | 1 | 93 | 21 | 2 |
| % | 1 | 0 | 2 | 3 | 2 | 3 | 1 | 0 | 3 | 1 | 2 | 3 | 5 |
| Ventricular fibrillation | 1 | | | | | | | | | | | | |
| Ventricular tachycardia | | | | 1 | | | | | | 1 | | 1 | |
| WPW | | | | 1 | | | | | | | | | |
| Total | 28 | 2 | 7 | 63 | 93 | 2 | 10 | 4 | 23 | 4 | 208 | 99 | 4 |
| % of N | 2 | 1 | 3 | 7 | 4 | 7 | 6 | 10 | 7 | 2 | 5 | 12 | 10 |

Source: Table 31, p. 116 of 303 from Dr. Simone's review

Dr. Simone concluded the following based on the additional QT study conducted by the Applicant and the analyses of the safety database from the clinical trials:

1. Appropriately designed and conducted thorough QT studies have demonstrated that sugammadex, at doses intended for clinical use, does not prolong the QTc interval when administered:
 - a. Alone, i.e., not in the presence of anesthetic agents or neuromuscular blocking agents (NMBAs)
 - b. In combination with rocuronium or vecuronium but not in the presence of anesthetic agents

NDA 22225

(b) (4)

26

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

- c. In the presence of anesthetic agents but not in combination with an NMBA
2. The risk of QTc prolongation with sugammadex does not exceed the risk with placebo or neostigmine to a clinically relevant extent.
 3. QTc prolongation that was observed in the clinical trials was not associated with any episodes of Torsades de Pointes.
 4. The risk of cardiac arrhythmias and acute myocardial infarction were not increased to a clinically significant degree by treatment with sugammadex compared to treatment with placebo or neostigmine.
 5. Episodes of tachycardia and bradycardia that qualified as adverse events occurred following administration of sugammadex but not at frequencies that substantially differed from neostigmine or that exceeded that from placebo by a clinically relevant amount.

Based on the information provided in the NDA submission, the Applicant has sufficiently characterized the risk of cardiac arrhythmias and QTc prolongation to allow an informed benefit: risk assessment and appropriate labeling of the product without the need for further clinical studies.

Postmarketing Findings

Since the first approval of sugammadex in the European Union on July 25, 2008, the Applicant reports the distribution of over (b) (4) vials for use in adult and pediatric patients as of June 15, 2012.

The following table reflects the arrhythmia-related postmarketing cases provided by the Applicant in this submission.

Table 12 Postmarketing arrhythmia-related adverse events

| Preferred Term | Number of Events (Serious) | Life Threatening | Non-Life Threatening |
|--------------------------------|-----------------------------------|-------------------------|-----------------------------|
| Tachycardia | 18 (15) | 14 | 4 |
| Bradycardia | 18 (10) | 8 | 10 |
| Cardiac arrest | 9 (9) | 7 | 2 |
| Heart rate increased | 8 (4) | 6 | 2 |
| Heart rate decreased | 5 (3) | 0 | 5 |
| Sinus bradycardia | 2 (2) | 0 | 2 |
| Sinus tachycardia | 2 (2) | 0 | 2 |
| Supraventricular tachycardia | 2 (2) | 0 | 2 |
| Arrhythmia | 1 (1) | 0 | 1 |
| Atrioventricular block | 1 (1) | 1 | 0 |
| Cardio-respiratory arrest | 2 (2) | 1 | 1 |
| Supraventricular extrasystoles | 1 (1) | 0 | 1 |
| Total Events | 69 (52) | 37 | 32 |

Source: Table 34 , p 120 of 303 of Dr. Simone’s review

The most frequently reported arrhythmia-related events (55 of 69 events) were increases in ventricular rate (30 of 69 events reported as tachycardia, heart rate increases, sinus tachycardia) or decreases in ventricular rate (25 of 69 events reported as bradycardia, heart rate decreases, sinus bradycardia).

NDA 22225

(b) (4)

In their calculations regarding the incidence of postmarketing events, the Applicant used assumptions that only 90% of the product had been administered as of the cutoff date and 10% of the cases were reported. Based on these assumptions, the Applicant estimated the incidence of arrhythmias and cardiac arrest to be 21.7 per 100,000 operations [95% CI: 20.0; 23.4]. They considered this estimated arrhythmia incidence of 0.022% to be very low compared to the background incidence of arrhythmias in the range of 14-22%, as reported in the epidemiologic literature. The Applicant provided other rationale as to why these numbers were not clinically concerning:

- The cases were confounded by other medications.
- Tachyphylaxis was noted in the context of anaphylaxis, where it seemed to occur most often.
- Of the bradycardia cases (N=25), 10/25 did not have enough detail 12 occurred in the setting of anaphylaxis, and 13/25 occurred in otherwise stable pts...Overall, it seemed to them to be a rare event.
- There were 7 Cardiac arrests with 3 being fatalities, all had comorbid conditions.
- Patients in the OR are well monitored.

Upon review of the individual event reports and the Applicant's summary, Dr. Simone noted that :

- The majority of ventricular/supraventricular tachyarrhythmias were reported in the context of anaphylaxis (ie, 25 events out of the 30 events reported as tachycardia, etc) and appear to be related to that event.
- A total of 6 of 25 events of bradyarrhythmias occurred during anaphylaxis. A total of 8 of 25 cases were confounded by use of propofol (listing 'bradycardia' as an expected AE in the prescribing information).
- One patient with the reported term of Bradycardia had a fatal outcome.
- One additional case (2009SP039392) was reported as "cardiac arrest" and included a description of a slowed heart rate in the report narrative, but bradycardia/heart rate decreased was not specifically coded as an AE.
- Ten reports (with 11 events) of cardiac or cardio-pulmonary arrest were identified. In total, 6 of the 10 cases were non-fatal, and 4 cases were fatal.
- For 55 of the 64 reports, a medical outcome was provided, and 51 of the 55 patients recovered. The 4 fatal cases were caused by cardiac or cardio-pulmonary arrest. These fatal cases were all patients with serious co-morbid medical conditions, and most patients had multiple concurrent medications at the time of the cardiac arrest.

Dr. Simone further commented that

- The incidence of adverse events for tachycardia and bradycardia in the clinical development program was 1.6% and 0.3%, respectively, which are orders of magnitude greater than the Applicant's estimate of 0.022% based on postmarketing information.
- Regardless of the actual incidence for tachycardia and bradycardia, their association with anaphylactic reactions striking: 80% and 12%, respectively.
- At the time sugammadex is administered and for the 30 minutes thereafter, the patient is being continuously monitored in the operating room or post-anesthesia care unit by clinicians and nurses trained to detect and treat arrhythmias and cardiac arrest and who have the equipment and medications to do so expeditiously.
- The product's label should include the warning stated above (the currently proposed label lacks that warning) as well as a statement describing the associated with anaphylaxis.
- Clinicians need to monitor patients carefully for the relatively small risks of bradycardia and tachycardia and the risks of anaphylaxis and cardiac arrest with which they have been associated

NDA 22225

(b) (4)

28

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

I concur with Dr. Simone's findings on the cardiac safety.

I concur with the clinical review team's conclusions regarding the safety profile of sugammadex.

9. Advisory Committee Meeting

See my first cycle review for a discussion of the ALSDAC meeting held during that cycle. As noted above, the meeting of the AADPAC that was scheduled for this review cycle was canceled pending resolution of the data integrity concerns.

10. Pediatrics

A proposed Pediatric Study Plan was submitted during this review cycle. Drs. Simone and Breder have discussed that plan in their reviews. However, further internal discussion will be necessary prior to reaching any agreement with the Applicant. Therefore, I will not further address the plan in this review.

11. Other Relevant Regulatory Issues

There were two important regulatory issues that impacted our ability to carefully and thoroughly assess the data in this submission. The first involved data quality concerns that resulted in a 3-month clock extension; and the second involved data integrity concerns. The evaluation resulting from the data integrity concerns remains ongoing at this time.

The following summary of the data quality issues that resulted in the clock extension has been reproduced from pages 52 and 53 of Dr. Breder's review:

We sent information requests to Merck regarding two issues related to the datasets between February 7th and 25th, 2013. The final submission on March 1, 2013, was determined to be adequate.

The first issue pertained to our need for Demography datasets (DM) with only one row per subject for each study and integrated summary. A properly formatted DM is needed to analyze most other datasets (e.g., AES, Conmeds) with our reviewer tools because of the need to join demographic and treatment information to datasets. We particularly were concerned about those associated with the ISS, since the previously identified Cardiac safety signal is going to be analyzed with these data. We had at least 3 to 4 rounds of communications with Merck, including emails and phone calls. During the phone calls, they seemed to understand what we needed but the datasets they submitted still had the issue of multiple rows for many subjects until their final submission on 3/1/13.

The second issue was our request for a treatment variable to be added to each dataset with events related in time to the treatment such as AEs and concomitant meds. This was determined to be needed when both we and Merck realized that only the treatment sequence could be added to DM, since this file could only contain one row per subject. After one unacceptable proposal from

NDA 22225

(b) (4)

29

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

Merck, I consulted (b) (4) and we determined a strategy which was ultimately relayed to Merck and successfully incorporated.

The following summary of the current data integrity concerns has been reproduced from pages 53 to 55 of Dr. Breder's review:

An Interim Summary of Inspectional Findings was provided by Dr. Cynthia F. Kleppinger, M.D. of the Good Clinical Practice Assessment Branch (GCPAB), Division of Good Clinical Practice Compliance (DGPCPC) in the Office of Scientific Investigation (OSI) on August 20, 2013 because the inspection of the study sites and materials is ongoing.

A Request for Clinical Inspections was submitted to the Division of Good Clinical Practice Compliance in the OSI on January 31, 2013. Site inspections were requested for two sites, one each for Study P07038, the orthopedic surgery study assessing postoperative bleeding and coagulation issues and Study P06042, the main study addressing the issue of Anaphylaxis / Hypersensitivity.

For Study P07038, the site of Dr. Walter Klimscha, an Austrian site was inspected on May 27-31, 2013. There were only minor deviations noted and overall the inspection was considered No Action Indicated (NAI).

For Study P06042 the site of Dr. Lawrence Galitz was selected based on the large proportion of randomized subjects (129 of the 448 randomized in the study). On (b) (4), the Division notified the Applicant that the OSI group was not able to access the records. The site was initially owned by the contract research organization (CRO) (b) (4) which went out of business (b) (4). Our Office of Regulatory Affairs (ORA) inspector called the (b) (4) point of contact who informed her that the business was closing. The Applicant confirmed the (b) (4) and noted that the records for the study would not likely be released without approval from the (b) (4).

A contractor for the Applicant has located the study records at an (b) (4) facility in (b) (4). The Applicant agreed on a protocol with the contractor to retrieve and transfer the records to the Principal Investigator, Dr. Galitz, to hold until the inspection. Merck has also identified a CRO to host the inspection. Some logistics are still being worked out but the inspection is tentatively scheduled for the second week in September. A formal request was also sent to the Applicant to submit the site trial master file to the application for review.

Another P06042 site, Dr. Ulrike Lorch, an investigator in the UK who had randomized 127 subjects, was selected on 4/16/13 by the Review Team for inspection. The inspection was conducted June 10-21, 2013 and had several objectionable conditions were observed that resulted in a Form FDA 483-Inspectional Observations. The inspectional results were communicated to OSI on July 12, 2013.

The following observations were made:

- The protocol contained the following procedures related to blinding:

"This study will be performed as a double-blind study. The syringes used for the intravenous administration of trial medication(s) will be blinded to ensure that the light color difference between sugammadex and placebo will not be revealed. Moreover, the investigator who evaluates the adverse events will not be involved in dosing of the subjects."

NDA 22225

(b) (4)

30

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

A Note to File signed by the PI on 25 June 2010 was found by the FDA inspector which acknowledged that the protocol had not been followed. A transparent colored foil was placed on the syringe and the PI assumed that that was enough for blinding. The sub-investigator, Dr. Vedran Pavlovic, was dosing the study product and also evaluating the subjects for adverse events. This continued for approximately 8 weeks and potentially affected six (6) cohorts (approximately 53 randomized subjects). On October 20, 2009, Dr. Pavlovic notified Applicant personnel that he noticed increased viscosity between the treatments (saline, 4 mg sugammadex, and 16 mg sugammadex) upon manual administration. It was at this point that the practice of a single sub-investigator administering the medication and evaluating for adverse events was discovered and this practice ceased. In the review of 35 case report forms during the FDA inspection, several subjects were observed to have been impacted by being dosed by a sub-investigator who attended an adverse event for the same subject (e.g., Subjects 007, 206, 213, 230). The incident was not reported as a protocol deviation in the clinical study report nor was there any discussion of the issue. The Note to File contained a footer that documented that this incident was considered a protocol deviation.

- The site had a practice of migrating Applicant information to its own templates. The site used its own case report form template, “Signs and Symptoms of Hypersensitivity”, which did not contain all the elements of the protocol’s such as the “Gastrointestinal” section, which elicited subject information associated with “Diarrhea, Abdominal Pain, Nausea, and Vomiting”. The incorrect version was used from the study’s start until, on or about October 1, 2009, affecting at least eight (8) randomized study subjects and all screening subjects having achieved Visit 2 (Day 1) by that date. Furthermore, all subjects were affected by missing information required by the Applicant to be on the form after October 13, 2010 concerning laboratory mast cell tryptase elevation. This protocol deviation was not reported to the FDA. A deviation note at the site contained a footer that documented that this incident was considered a protocol deviation.

Other minor issues are noted in the DGPC Summary Review. Because of the above issues, the last two remaining sites for protocol P06042 will be inspected.

The following summary of the inspection findings to date has been reproduced from pages 2 through 7 of Dr. Kleppinger’s review:

The P07038 study began on Oct 30, 2011 and was completed on September 26, 2012. There was enrollment at 22 sites located in Austria, Belgium, and Germany. The primary objective was to assess the effect of reversal of rocuronium- or vecuronium-induced neuromuscular blockade (NMB) with 4 mg/kg sugammadex compared with reversal according to usual care (neostigmine or spontaneous reversal) on the incidence of adjudicated events of bleeding with onset within 24 hours in subjects receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip/knee) replacement. In total, 1198 subjects were randomized in this trial, and 1184 subjects were treated, 596 subjects with sugammadex and 588 subjects with usual care.

For study P7038, one site in Austria was chosen due to high enrollment and no previous history of inspection.

The P6042 study began on August 24, 2009 and was completed on April 13, 2010. This was a non-IND Phase 1 clinical study conducted in Germany, the Netherlands and the United Kingdom. There was one site in the United States that was conducted under IND. The primary objective of this study was to determine the number and percentage of subjects with adjudicated signs/symptoms of hypersensitivity for each dose of sugammadex (4 mg/kg and 16 mg/kg

NDA 22225

(b) (4)

31

Division Director’s Review and Recommendation for Complete Response Action
September 10, 2013

intravenous and placebo bolus injection on Days 8, 36, and 78). A total of 480 subjects received the single-blind placebo dose on Day 1, and 448 of these subjects were assigned to randomized treatment (148 subjects in the sugammadex 4 mg/kg group, 150 subjects in the sugammadex 16 mg/kg group, and 150 subjects in the placebo group).

For study P6042, one domestic US site was initially chosen for inspection:
Lawrence Galitz, M.D.

(b) (4)

This site was chosen based on the large number of subjects enrolled (129 subjects). The site also underwent a For-Cause inspection in December 2011 based on two complaints. The final classification of that inspection was a downgrade to Voluntary Action Indicated (VAI).

During the planning of the inspection, it was discovered that the site is no longer in existence. The site was initially owned by the contract research organisation (CRO) (b) (4)

(b) (4). The inspection was to begin in (b) (4) at a satellite location owned by (b) (4). The sponsor has continued to work towards release of the site records for inspection.

An alternative site in the United Kingdom was chosen for inspection. At the conclusion of the inspection, the data from this site were considered unreliable (discussed further below).

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 22225 in accordance with Compliance Program 7348.811. General instructions were also provided with the assignments.

In consultation with the review division, it was decided to arrange to inspect the final two sites in the PO6042 study, Dr. Yelka Koster in Utrecht, Netherlands and Dr. Doris Neuenhofer in Monchengladbach, Germany, and the sponsor.

I. RESULTS (by Site)

| Name of CI/ Site # | Protocol # and # of Subjects Randomized | Inspection Date | Final Classification |
|---|---|----------------------|----------------------|
| Dr. Walter Klimscha Vienna, Austria Site #302 | Protocol: P07038 158 Subjects | May 27-31 2013 | Preliminary NAI |
| Dr. Ulrike Lorch Surrey, United Kingdom Site #02 | Protocol: P06042 127 Subjects | June 10- 21, 2013 | Preliminary OAI |
| Dr. Lawrence Galitz (b) (4) | Protocol: P06042 129 Subjects | Pending | Pending |

NDA 22225

(b) (4)

32

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

| | | | |
|---|-------------------------------------|---------|---------|
| Dr. Yelka Koster* Utrecht, Netherlands Site #03 | Protocol: P06042 111 Subjects | Pending | Pending |
| Dr. Doris Neuenhofer Monchengladbach, Germany Site #04 | Protocol: P06042 81 Subjects | Pending | Pending |

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Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Dr. Walter Klimscha

Langobardenstrasse 122

Abteilung für Anesthesiologie und Intensivmedizin

Wien A-1220 Austria

- a. **What was inspected:** A total of 70 subject records were reviewed. Also available were the subjects' medical records. Reviewed were case report forms, laboratory results, ECG results, anesthesiology records, concomitant medication logs, and adverse event logs. Regulatory records containing laboratory accreditations, medical personnel qualifications, and laboratory reference ranges were reviewed. Records containing all communications with the Ethics Committee were reviewed. All signed consent forms were reviewed. All financial disclosure forms were reviewed. Drug accountability records were reviewed.
- b. **General observations/commentary:** The first subject was screened on 12/4/2011 and randomized on 12/5/2011. The study was officially closed at the site on 9/26/2012. The site screened 163 subjects, enrolled/randomized 158 subjects; 155 subjects completed the study. One subject withdrew consent prior to investigational medicinal product (IMP) administration (Subject 100888); one subject was removed due to an adverse event prior to IMP administration (Subject 100895); one subject withdrew due to administrative reasons prior to IMP administration (Subject 100520). Overall, the records were adequate and well organized. No deficiencies were noted with respect to the informed consent process. The study file records showed timely review and approval by delegated staff personnel. The regulatory records contained the appropriate information. Subject 100020 did not meet inclusion/exclusion criteria for thrombocytes and was enrolled due to oversight. This deviation had been previously documented by the sponsor. There were four subjects (100874, 100371, 100304, and 200100) randomized prior to completion of all Visit 1 study-specific procedures. Central blood samples were collected after randomization; however, local blood samples were collected and reviewed prior to randomization. Contraceptive use was not recorded in the files. There was no evidence of under-reporting of adverse events. There was no indication that any of the subjects or Blinded Safety Assessors were unblinded.
- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Ulrike Lorch

Richmond Pharmacology Limited

NDA 22225

(b) (4)

33

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

530 London Road Mayday
University Hospital\Croydon,
Surrey, CR7 7YE
United Kingdom

- a. **What was inspected:** Approximately 34 subject charts and case report forms (CRFs) were reviewed during the current inspection. All nine CRFs of subjects receiving hypersensitivity adjudication were reviewed. All consent forms were reviewed. Financial disclosures were reviewed. Drug accountability records were reviewed.
- b. **General observations/commentary:** Approximately 616 subjects were screened, 127 were randomized, and 115 completed the study. The study records were unorganized and difficult to maneuver efficiently. Binders were overflowing with open clamps and papers without adequate identification. There were a significant number of instances where hand-written information was covered by firm identification stickers, obstructing the ability to view the original information. Several objectionable conditions were observed. The inspection resulted in a Form FDA 483-Inspectional Observations. The inspectional results were communicated to OSI on July 12, 2013. Of critical significance was the observation that protocol specific blinding procedures were not followed.

Observation 1

An investigation was not conducted according to the investigational plan.

Protocol P06042, section 7.4.1.4, "Management of Blinding of Study Treatments," requires, in part that, *"This study will be performed as a double-blind study. The syringes used for the intravenous administration of trial medication(s) will be blinded to ensure that the light color difference between sugammadex and placebo will not be revealed. Moreover, the investigator who evaluates the adverse events will not be involved in dosing of the subjects."*

On multiple occasions, a dosing investigator evaluated adverse events, potentially affecting six (6) cohorts (approximately 53 randomized subjects).

OSI Comment: A Note to File signed by the PI on 25 June 2010 was found by the FDA inspector which acknowledged that the protocol had not been followed. A transparent colored foil was placed on the syringe and the PI assumed that that was enough for blinding. The sub-investigator was dosing the study product and also evaluating the subjects for adverse events. This continued for approximately 8 weeks. On October 20, 2009, Dr. Pavlovic notified sponsor personnel that he noticed increased viscosity between the IMP (saline, 4 mg sugammadex, and 16 mg sugammadex) upon manual administration. It was at this point that the practice of a single sub-investigator administering the medication and evaluating for adverse events was discovered and this practice ceased. In the review of 34 case report forms during the FDA inspection, several subjects were observed to have been impacted by being dosed by a sub-investigator who attended an adverse event for the same subject (e.g., Subjects 007, 206, 213, and 230).

The incident was not reported as a protocol deviation in the clinical study report nor was there any discussion of the issue. There is a footnote on the document showing evidence that the sponsor considered the breach a protocol deviation. It has also been confirmed that the Data and Safety Monitoring Board overseeing the study was not made aware of this breach.

The PI acknowledged during the inspection that the protocol had not been followed as she did not think it was necessary, and it was also impractical to have separation of the duties of drug administration and adverse event evaluation since the syringes were covered.

NDA 22225

(b) (4)

34

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

Observation 2

Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent.

The firm's case report form (CRF) template associated with Protocol PO6042 Appendix IV "Signs and Symptoms of Hypersensitivity" did not contain all of the elements of Appendix IV, including the "Gastrointestinal" section, which elicited subject information associated with "Diarrhea, Abdominal Pain, Nausea, and Vomiting".

OSI Comment: The site had a practice of migrating sponsor information to its own templates. The site used its own case report form template, "Signs and Symptoms of Hypersensitivity", which did not contain all the elements of the protocol's such as the "Gastrointestinal" section, which elicited subject information associated with "Diarrhea, Abdominal Pain, Nausea, and Vomiting". The incorrect version was used from the study's start until on or about October 1, 2009, affecting at least 8 randomized study subjects and all screening subjects having achieved Visit 2 (Day 1) by that date. Furthermore, all subjects were affected by missing information required by the sponsor to be on the form after October 13, 2010 concerning laboratory mast cell tryptase elevation.

These protocol deviations were not reported to the FDA.

Other issues found during the inspection included no signed informed consent for screened Subject 2427, no signed Pharmacogenetic informed consent for screened Subject 2055, and three separate instances of duplicated screening numbers were observed (S02004, S02128, S02185).

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. Due to the PI's decision not to follow the blinding procedures outlined in the protocol, there was significant unblinding at the site. Data from this inspection are considered not reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA included one planned foreign site inspection of Dr. Klimscha's site for Study PO7038. There were only minor deviations noted and overall the inspection was considered satisfactory and the data are considered reliable. The planned domestic site inspection of Dr. Galitz's site for Study PO6042 has not been possible because of the inability to inspect the files. In an attempt to adjust inspectional coverage, an alternative site, Dr. Lorch in the United Kingdom, was chosen. Data from that inspection are considered not reliable.

Because of the above issues, in consultation with the review team, the three remaining sites for Study P06042 (Drs. Galitz, Koster, and Neuenhofer) and the sponsor will be inspected.

Observations noted above for Drs. Klimscha and Lorch are based on the review of the Establishment Inspection Reports, 483 Observations, and communications with the FDA field investigators. A final clinical inspection summary will be generated once the additional inspections have been completed.

NDA 22225

(b) (4)

35

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

12. Labeling

Labeling changes recommended by the review team are still being negotiated with the Applicant. Continuation of these discussions will occur during the next review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
Complete Response
- Risk Benefit Assessment

The Applicant has provided sufficient data to support the efficacy and safety of sugammadex when it is used according to the proposed labeling. However, the integrity of the data has been brought into question due to protocol violations found during the inspection at one of the clinical study sites. Not only was the blinding at that site compromised due to the fact that an investigator both administered the study drug and assessed adverse events, but he was also able to tell the difference between the lower and higher doses of study drug due to differences in their viscosity and the fact that the syringes were not adequately masked. Perhaps of even greater concern, these protocol violations (and others) were noted in the site's records, and were communicated to the sponsor at that time (2009), but not to the Agency. I agree with the review team that the inspection findings raise concerns regarding the potential for systemic data integrity problems. As such, OSI will be undertaking inspections of the remaining study sites and the Applicant's Trial Master File, especially focusing on all data transfer and storage from the previous sponsor, as well as all deviations regarding unblinding.

It is true that hypersensitivity reactions, anaphylaxis and cardiac arrhythmias could potentially be managed in the operating room or ICU setting where sugammadex would primarily be used. However, the critical deficiencies that resulted in our initial decision not to approve this application were a lack of data to assess the potential for delayed onset of anaphylaxis that might occur after discharge from a surgical center or after the patient had been moved to a non-monitored ward, and a lack of data to assess the potential for anaphylaxis upon re-exposure to sugammadex. While the studies undertaken to address these concerns did appear to demonstrate a minimal incidence of delayed reactions or reactions upon re-exposure, the integrity of the data from those studies is now in question. Until we have reassurance that the data are sufficiently reliable to allow us to accurately assess the efficacy and safety of the product, we cannot reschedule the advisory committee meeting or finalize

NDA 22225

(b) (4)

36

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

our conclusions regarding the approvability of the application. Therefore, I am recommending a Complete Response action.

NDA 22225

(b) (4)

37

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

APPENDIX

15 pages of this Appendix have been withheld in full immediately following this page as a duplicate copy of the "Summary Review for Regulatory Action" dated 7/30/2008 which can be found in this review.

NDA 22225

(b) (4)

38

Division Director's Review and Recommendation for Complete Response Action
September 10, 2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
09/11/2013

Cross-Discipline Team Leader Review
 Division of Anesthesia, Analgesia, and Addiction Products

| | |
|--|--|
| Date | 8/30/13 |
| From | Christopher D. Breder, MD PhD Clinical Team Leader, Anesthesia Products |
| Subject | Cross-Discipline Team Leader Review |
| NDA / Supp Doc # | 22225 / 51 |
| Applicant | Merck/Organon USA |
| Date of Submission | 12/21/12 |
| PDUFA Goal Date | 9/20/13 (after 3-month calendar extension) |
| Original NDA Submission / Action, Action Date | October 31, 2007 / Not Approvable, July 31, 2008 |
| Proprietary Name / Established (USAN) names | (b) (4) / Sugammadex sodium injection |
| Dosage forms / Strength | IV Injection; 100 mg/mL |
| Proposed Indications | <ol style="list-style-type: none"> 1. Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium 2. Immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Recommended Action: | Complete Response |

1. Introduction

Sugammadex, also known as Org 25969, is a new molecular entity of the γ -cyclodextrin class. The Applicant is seeking approval for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium. The proposed dosing regimens are to be administered as a single bolus injection for:

Routine Reversal

A dose of 4.0 mg/kg Sugammadex is recommended if recovery has reached 1 to 2 post tetanic counts (PTC) (“profound blockade”) following administration of rocuronium or vecuronium induced blockade.

A dose of 2.0 mg/kg Sugammadex is only recommended if spontaneous recovery has reached the reappearance of T2 (“shallow blockade”) following rocuronium or vecuronium induced blockade.

Immediate reversal

If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg Sugammadex is recommended.

This document will highlight the Applicant's Complete Response to and the Division's review of the issues raised in the first review cycle that resulted in the July 31, 2008 Not Approvable letter. The Not Approvable issues were hypersensitivity/anaphylaxis and coagulation disorders and a recommendation for studies related to cardiac arrhythmias was included as well. Several new studies and trials have been completed since the submission of the last NDA and these are reviewed for their contribution to the safety database and their support of labeling clinical, clinical pharmacology, nonclinical, and chemistry labeling.

The original PDUFA date for this submission was June 20, 2013. On March 1, 2013, we received a solicited major amendment from the Applicant to this application and the goal date was extended by three months to September 20, 2013. Further details of this and other important amendments are described in **Section 12. Other Relevant Regulatory Issues**.

2. Background

A. Preliminary Findings from NDA 022225 prior to the March 2008 Meeting of the Anesthetic and Life Support Drug Advisory Committee (ALSDAC)

NDA 022225 was originally submitted by Organon USA, Inc. on October 31, 2007. The clinical development program at that time consisted of 28 studies, which included bioanalytical, clinical pharmacology, and safety/efficacy studies in healthy volunteers and in patients. There were four primary clinical trials submitted in support of efficacy for the proposed indications. Three of the studies 19.4.301 (Study 301), 19.4.302 (Study 302), and 19.4.310 (Study 310), were of similar design; Study 19.4.303 (Study 303) differed extensively from the others. The key features of these studies are summarized in the table below (**Table 1**).

Table 1 Primary Supportive Studies for Efficacy in NDA 022225

| | Study 301 | Study 302 | Study 310 | Study 303 |
|----------------------------------|---|--|---|--|
| Location | Europe | United States | Europe | United States and Canada |
| Study Period | November 2005 to March 2006 | November 2005 to March 2006 | November 2005 to March 2006 | February 2006 to August 2006 |
| Clinical Scenario | "shallow" neuromuscular block, defined as the return of T2 (second twitch in the ToF stimulation) | "profound" neuromuscular block, defined as 1-2 post titanic counts | "shallow" neuromuscular block, defined as the return of T2 (second twitch in the ToF stimulation) | "immediate" reversal defined as 3 minutes post rocuronium administration |
| Dose | 2 mg/kg | 4 mg/kg | 2 mg/kg | 16 mg/kg |
| Treatment groups | a. Roc/Org25969 b. Roc/Neo c. Vec/Org25969 d. Vec/Neo | a. Roc/Org25969 b. Roc/Neo c. Vec/Org25969 d. Vec/Neo | a. Roc/Org25969 b. Cis-atr/Neo | a. Roc/Org25969 b. Succinylcholine /No reversal |
| Number of patients | 196 randomized patients | 182 randomized patients | 84 randomized patients | 115 randomized patients |
| Primary efficacy endpoint | $T_4/T_1 = 0.9$ | $T_4/T_1 = 0.9$ | $T_4/T_1 = 0.9$ | $T_1 = 0.1$ |

Abbreviations – Cis-atr = Cis-Atracurium, Neo = Neostigmine, Roc = Rocuronium, T4/T1 = the ratio of response for twitch 4 to twitch 1 in a ToF stimulation, T1 = the recovery of twitch 1 in a ToF stimulation, Vec = Vecuronium.

Source: Dr. Shibuya's review of June 24, 2008

The results of the studies are summarized in the table below (**Table 2**). While DAAAP agreed with the Applicant that they had demonstrated efficacy for routine reversal of neuromuscular blockade, we had concerns regarding the design of the study supporting the “immediate reversal” indication, and those concerns were discussed at the advisory committee meeting (See discussion of this issue in **Section B. Findings from the Advisory Committee**).

Table 2 Summary Table of Efficacy for Original 022225 NDA Submission

| Study # | NMB | Time to ToF = 0.9 (m:sec) | | p-value |
|---------|------------------------------------|---------------------------|-------------|---------|
| | | Sugammadex | Neostigmine | |
| 301 | Roc | 1:29 | 18:30 | <0.0001 |
| | Vec | 2:48 | 16:48 | |
| 302 | Roc | 2:50 | 50:22 | <0.0001 |
| | Vec | 4:28 | 66:12 | |
| 310 | Roc | 2:02 | - | <0.0001 |
| | Cis-Atr | - | 8:46 | |
| 303 | Roc | 4:22 | - | <0.0001 |
| | Succinylcholine - (no reversal) | 7:04 | - | |

Abbreviations – Cis-atr = Cis-Atracurium, m:sec = time in minutes:seconds to primary outcome was achieved, NMB = neuromuscular blocking agent, Roc = Rocuronium, Vec = Vecuronium.

Source: Dr. Shibuya's review of June 24, 2008

The safety database consisted of data collected from 28 clinical studies with approximately 2000 subjects, and analyzed in comparison to placebo and to neostigmine. A total of 182 Serious Adverse Events (SAEs) experienced by 126 adult subjects were reported for the development program, which included 2708 exposures to sugammadex. One hundred fifty one of these SAEs occurred in 106 of the 1845 subjects who were treated with sugammadex. The table below summarizes the overall occurrences of SAEs by drug and dose (**Table 3**).

Table 3 Incidence of Serious Adverse Events in N022225 by Dose

| Tx | Pbo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|-------|-----|--------------------|-----|-----|----|-----|----|-----|----|-----|-----|----------------------|----|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Dose | N/A | | | | | | | | | | | | |
| N | 336 | 124 | 178 | 613 | 9 | 729 | 28 | 154 | 39 | 127 | 164 | 135 | 74 |
| Exps. | 418 | 124 | 178 | 613 | 9 | 813 | 28 | 154 | 39 | 131 | 578 | 136 | 74 |
| SAEs | 10 | 13 | 7 | 73 | 1 | 41 | 2 | 4 | 3 | 6 | 1 | 6 | 6 |
| % | 3 | 10 | 4 | 12 | 11 | 6 | 7 | 3 | 8 | 5 | 1 | 4 | 8 |

Source: Slide 22 of the FDA Presentation of the ALSDAC March 11, 2008

The most frequent adverse events (preferred terms) in pooled placebo-controlled Phase 1 to 3 studies where the incidence was greater than 2% and more than placebo were: vomiting, anesthetic complication, pain, procedural hypotension, chills, back pain, electrocardiogram QT corrected interval prolonged, and abdominal pain.

The safety issues that were most concerning to the Division based on our review of the NDA *prior* to the Advisory Committee meeting were:

- Cardiac adverse events, including QT prolongation and other serious events
- Hypersensitivity / Anaphylaxis

Cardiac adverse events

The occurrence of the SAEs associated with QTc prolongation in the clinical studies represented a discrepancy between the studies and the results from the two well-designed and conducted thorough QT studies, which only demonstrated prolongation times of < 10 msec. In the NDA safety database there was a three-fold greater incidence of QTc prolongation in sugammadex-treated subjects than in placebo-treated subjects, 3% versus 1%, respectively. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects. These included atrial fibrillation, cardiac arrest, cardiogenic shock, electro-mechanical dissociation, myocardial infarction and ventricular tachycardia. The incidence of these events did not appear to be dose-related.

Hypersensitivity/Anaphylaxis

Five subjects in the safety database experienced reactions to sugammadex that were consistent with anaphylaxis. The Applicant identified these events as hypersensitivity reactions.

B. Findings from the Advisory Committee

A meeting of the ALSDAC was held on March 11, 2008, during which the applicant presented their rationale for development of the product and the safety and efficacy data. The Agency presented the clinical efficacy with an emphasis on the outliers, the clinical safety focusing on the hypersensitivity reactions, and the nonclinical data.

The following are some of the key points from the discussion at that meeting:

- The committee felt that the endpoint in Study 303 (T1 = 0.1) was of minimal clinical use, but felt that it supported the conclusion that sugammadex reversal of paralysis from rocuronium was faster than spontaneous recovery from succinylcholine. The committee felt that more meaningful information to be included in the label would be the time from injection to the response time of most (e.g., 95%) of the patients.
- The committee felt that the combination of rocuronium followed by sugammadex could not replace succinylcholine for rapid sequence induction, particularly because succinylcholine would be necessary if re-intubation was required. The committee felt that

sugammadex was an important product that could be useful in the “cannot intubate/cannot ventilate” scenario although it opposed the use of the words “immediate reversal” or claims that sugammadex was effective in the “cannot intubate/cannot ventilate” scenario. The following is from the Minutes of the 2008 ALSDAC :

The committee agreed that sugammadex does offer some advantages in comparison to other neuromuscular blockade reversal agents, but other factors must be considered (in the approach to the “cannot intubate / cannot ventilate scenario”), including the induction agent and other concomitant medications used, and whether these were likely to interfere with spontaneous ventilation. The presence of co-morbidities such as upper airway anatomical abnormalities or pulmonary insufficiency would also be relevant. In addition, new technologies such as the LMA and combitube have been demonstrated to be useful in emergency settings such as the CICV scenario. It was noted that the Applicant did not address the obstetric patient population, where failed tracheal intubation is more likely, or those with renal insufficiency, where succinylcholine remains a necessary agent (since sugammadex would not be used to reverse this depolarizing neuromuscular blocker).

- The committee would have liked to have seen more data in the obstetric population.
- The committee felt that non-clinical findings discussed regarding the potential accumulation of sugammadex in the bone and teeth were of no concern to adults, and that the current data would support a single-dose study in pediatric patients.
- The committee felt that more data would be required for multiple-dose pediatric studies and that nonclinical studies must be conducted to assess safety in neonates or premature infants. The committee also felt that assessments of bone strength in juvenile animal models were necessary.

DAAAP agreed with the finding from ALSDAC that efficacy for routine reversal had been demonstrated. The Division further agreed that words such as “immediate reversal” or claims that Org 25969 was effective in the “cannot intubate/cannot ventilate” clinical scenario should not be included in the indication, although it may be appropriate to describe the results in labeling.

The ALSDAC unanimously recommended approval of sugammadex. However, a detailed review of the drug hypersensitivity data was not available for discussion at the time of the March 11, 2008, meeting. The preliminary nature of the available data analysis limited our ability to engage the panel members in a more detailed discussion of the spectrum of anaphylaxis and the resultant clinical implications of this safety signal. Notably, no repeat-dose data were available in the original submission and the potential risk of hypersensitivity reactions upon re-exposure had not been evaluated. This issue was ultimately raised in the July 31, 2008 Not Approvable letter.

C. Division's Final Review of the Original 2007 NDA Submission

This section describes events following the ALSDAC meeting related to the two main safety issues described above, as well as the issue related to a potential coagulation disorder that was identified during the first review cycle, but after the ALSDAC meeting, and therefore not discussed at the ALSDAC meeting.

Hypersensitivity/Anaphylaxis

Additional investigation of the adverse events suggestive of anaphylaxis and hypersensitivity reported during the clinical development program for sugammadex was undertaken in consultation with the Division of Pulmonary and Allergy Products (now the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)). At that point, of the 1973 adults and 51 children exposed to the drug during the initial development program, 7 subjects with adverse events suspicious for drug hypersensitivity reaction were identified by the Applicant. Out of 7 potential cases identified by the Applicant, 2 subjects in the database met the diagnostic NIAID/FAAN¹ criteria for anaphylaxis (see **Section 15 Appendix A.NIAID/FAAN Criteria for Anaphylaxis** for the criteria), indicating a rate of anaphylaxis at approximately 0.1%.

The Applicant conducted a clinical study (Study 19.4.110) to evaluate skin prick testing (SPT) and intradermal skin testing (IDT) in healthy volunteers with no prior sugammadex exposure and in patients with prior exposure with and without symptoms of hypersensitivity reactions. Of the 12 subjects who were previously exposed to sugammadex, 2 had positive skin tests – one who had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. No unexposed subjects had a positive skin test, suggesting that sugammadex does not produce a non-specific irritant reaction. The results of the skin test study suggested that exposure to sugammadex may induce sensitization. While the underlying mechanism remained uncertain, the possibility of the production of sugammadex-specific IgE and an increased risk of reaction upon re-exposure could not be ruled out and this raised concern, particularly in the absence of any clinical repeat-dose experience.

The Applicant also organized a panel of experts to review the results of the SPT study, the 7 suspected cases from the safety database, as well as 5 subsequently identified cases. All four consultants agreed on the classification of 11 of the 12 possible cases as drug hypersensitivity related to sugammadex administration. The consultants also agreed that the most likely mechanism would be shown to be non-immunologic, non-IgE mediated histamine release from tissue mast cells or basophils. Each consultant recommended an in vitro examination of histamine release from cultured human basophils, as the most relevant initial test of mechanism.

DPARP reviewed the 12 potential cases of anaphylaxis identified by the Applicant. Of these cases, DPARP concluded that at least 3 cases in healthy volunteers met diagnostic criteria for anaphylaxis. Three other cases among healthy subjects were also notable. Although not

¹The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network;

meeting full criteria for anaphylaxis, these cases were notable for the immediate occurrence of symptoms suggestive of mediator-release and drug hypersensitivity following sugammadex administration in otherwise healthy volunteers. Two additional healthy subjects experienced rash with pruritus and isolated rash, but the rashes appeared several hours after infusion, making the association with sugammadex less clear. However, DPARP remained concerned that these were healthy subjects with no other apparent cause for rash or pruritus, and that these limited dermatological manifestations may be markers of sugammadex sensitization, which could render such patients at risk for multi-system allergic reactions, including anaphylaxis on re-exposure. The remaining 4 cases involved subjects who received sugammadex in the setting of various surgical procedures. At least 2 of these 4 cases met diagnostic criteria for anaphylaxis, although the evaluation of these cases was confounded by polypharmacy, co-morbid conditions, and expected effect of surgery.

DPARP concluded from their case reviews that there were at least 3 cases of anaphylaxis in healthy volunteers with another 2 possible cases in surgical patients identified from the overall sugammadex clinical database. At the time of the original NDA submission, the safety database consisted of 2024 unique adult and pediatric patients who had been exposed to sugammadex; 209 of the 2024 were healthy volunteers enrolled in Phase 1 studies. If one were to consider the entire database of $n=2024$, the rate of anaphylaxis was calculated to be between 0.1 to 0.3% depending on whether the two surgical cases were included in the numerator (e.g., 3/2024 or 5/2024).

In the calculation of the anaphylaxis rate, DPARP excluded Phase 2 and 3 data due to the number of confounding factors that made adjudication of these cases difficult. As a result, DPARP calculated a frequency of anaphylaxis of 1.4% (3/209) in the healthy volunteer population of the sugammadex safety database. DPARP thought this was a relatively high frequency of anaphylaxis, but expressed concern that this might be an underestimate still, since the clinical development program did not evaluate the safety of repeated exposures.

The Not Approvable letter (July 31, 2008) outlined the following information needed to address the hypersensitivity-related deficiencies:

- 1) Characterize the safety of sugammadex on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions,
- 2) Define the frequency/time course of events related to sugammadex administration, and other characteristics of the adverse reactions, and
- 3) Attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium.

The Applicant's Complete Response to this issue and Dr. Simone's review are discussed in **Section 9.I.1** of my review.

Coagulation Parameters

Another issue arising from the first review cycle, but after the meeting of the Anesthetic Life Support Drugs Advisory Committee (ALSDAC), was related to coagulation parameters. The Applicant did not assess coagulation parameters as part of the clinical laboratory investigations in their clinical development program. In the two *in vitro* studies that were conducted, it was noted that sugammadex caused statistically significant increases in the mean measured values of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the international normalized ratio for PT (INR). The Applicant indicated that the *in vitro* values were increased for concentrations of sugammadex comparable to peak plasma concentrations associated with a 16 mg/kg dose. However, changes for concentrations comparable for the other proposed doses were not reported.

In the safety database, the reported rate of hemorrhagic adverse events for all doses of sugammadex was 6% compared to 3% for placebo-treated subjects, yet concurrent assessments of the coagulation parameters were not made. The *in vitro* findings combined with the differences in hemorrhage rates from the clinical studies warranted a formal investigation as to the effects of sugammadex on coagulation in patients undergoing a variety of surgical procedures.

The Not Approvable letter (July 31, 2008) outlined the following information needed to address the coagulation deficiencies:

1. [Provide] studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting.

The Applicant's Complete Response to this issue and Dr. Simone's review are discussed in **Section 9.I.2** of my review.

Cardiac adverse events

Although not required for approval, the following was recommended in the July 31, 2008, Not Approvable letter:

A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

Following this request, the results of a meta-analysis of the placebo-controlled studies with an ECG assessment were provided by the Applicant. Based on the information at that time, the Division concurred with the Applicant's position that sugammadex sodium is not likely to

pose an increased risk for QT prolongation or arrhythmias in the surgical setting. If sugammadex were to be approved, cardiac adverse events observed in the clinical studies would be included in the label and monitoring for these events in the post-marketing period will be continued. These comments were conveyed to the Applicant on July 23, 2009.

Following this communication, the Division noted that a substantial number of cardiac arrhythmias had been reported to the IND. A meeting in preparation for the resubmission was held between DAAAP and the Applicant on June 14, 2012. In this meeting, the Division requested that a combined safety dataset related to these adverse events be submitted in the Integrated Summary of Safety of the Complete Response. All types of arrhythmias were to be included and the analysis was also to include an evaluation of those arrhythmias that were considered life threatening versus non-life-threatening, and those arrhythmias requiring treatment versus those arrhythmias where no treatment was needed.

The Applicant's Complete Response to this issue and Dr. Simone's review are discussed in **Section 9.I.3)** of my review.

D. Applicant's Complete Response

The updated sugammadex clinical development program submitted in the Complete Response on December 20, 2012, consisted of 52 studies: 32 studies summarized in the original NDA submission, and 20 new clinical studies (9 Phase 1 and 11 Phase 3 trials) conducted since the original NDA submission. The cumulative database for sugammadex contains a total of 7531 subject exposures to IV sugammadex in 5536 unique subjects. The integration of subjects from the original NDA with those from studies completed after the original NDA filing provides an increase of 5162 additional subject exposures to IV sugammadex in 3482 additional unique subjects. Across the clinical program, the majority of IV subject exposures occurred at the 2- and 4-mg/kg doses of sugammadex, which are the proposed recommended doses for routine reversal of NMB, and a smaller proportion of subjects were exposed to the 16-mg/kg dose of sugammadex, which is the proposed dose for immediate reversal of rocuronium.

Since my recommendation will be a Complete Response, labeling is not discussed in detail in the CDTL review for this cycle.

3. CMC

At the conclusion of the Division's review of the NDA in the first cycle, there were no outstanding concerns (except potential labeling) that would preclude approval from a CMC perspective².

During the review of this Complete Response the following issues were addressed:

- General product quality considerations
 1. The applicant has fulfilled the following agreements with respect to specifications in this resubmission:

² Dr. Rappaport's Summary Review for Regulatory Action, July 30, 2008.

- An agreement to tighten the impurity specifications for the drug substance once the applicant has manufactured drug substance at full scale using at least 10 different production lots of the (b) (4).
- An agreement to tighten the specifications for degradants in the drug product following additional experience with the commercial manufacturing process.

It should be noted that both CMC and Pharmacology/Toxicology accepted the impurities acceptance criteria in the original NDA during the last review cycle. In the resubmission, the applicant tightened the acceptance criteria for the impurities.

2. In this resubmission, the long term stability data was updated to support 36 months shelf life at room temperature.
3. A comparability protocol was submitted in this resubmission but retracted after the review team identified several deficiencies related to sterility assurance³. The 12/19/2012 submission also included a comparability protocol for an alternate manufacturing location. After review of the comparability protocol and subsequent teleconference on 4/24/2013 between members of the FDA review team (CMC team, New Drug Microbiology Staff, and the Office of Compliance) and the Applicant, the applicant submitted a formal request dated 5/8/2013 to the NDA to withdraw the comparability protocol.

- Facilities review/inspection

The manufacturing facility is Organon (Ireland) Limited in Swords, Ireland. The recommendation from the Office of Compliance for this establishment is “Acceptable” with a recommendation date of 8/21/2013.

The Office of Compliance’s overall recommendation, made on August 27, 2013 in EES, is “Acceptable” for this NDA.

- Other notable issues (resolved or outstanding)

1. During the labeling review for NDA 22-225, the CMC team identified the following issues that need to be addressed to label the product consistent with current Agency policies.
 - The current USP policy is to name and designate the strength of drug products according to the neutral, active moiety unless the salt ion contributes substantively to the desired ADME profile. In those cases where the salt form contributes to the desired ADME profile, the salt form may be used in the name provided the strength designation matches the salt form. The labels currently use the non-proprietary established name "sugammadex sodium".
 - The labeled strength (100 mg/mL) of the drug product is based on the combined concentration of the free acids of Org 25969 (sugammadex sodium) and Org 48302 (sodium salt). Since the assay accounts for both Org 25969 and Org 48302, the non-proprietary name should reflect the inclusion of Org 48302.

³ Primary CMC Review of Yung Hu, pp. 73 of 78

- The USAN entry currently lists "sugammadex sodium", which aside from listing the salt, does not include (b) (4) Org 48302 (the related (b) (4)).
- The code names need to be updated or revised to reflect the correct status of the molecule (neutral species or sodium salt and designate strength accordingly) and current ownership of the application (e.g., Org 25969 to Mrk 25969).

A teleconference was conducted between members of the Review team and the Applicant on August 27, 2013 and an email summarizing the issues was sent later that day.

2. This NDA is recommended by Drs. Hu and Peri for Approval pending satisfactory labeling revision by the applicant.
3. There were no Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

I concur with the findings and conclusion of the CMC team.

4. Nonclinical Pharmacology/Toxicology

The nonclinical part of the original NDA submission was reviewed by Dr. Zengjun Xu (primary reviewer) and Dr. Adam Wasserman (Supervisory Review) in June 2008. A consult for this review was obtained from Dr. Gemma Kuijpers from the Division of Reproductive and Urologic Products⁴. At that time, they concurred that the application may be approved for the adult population without further nonclinical evaluation.

The same team, including the consultant is the reviewers for this Complete Response submission.

- General Considerations

Further nonclinical studies were also not required to initiate single-dose clinical trials in pediatric patients. However, several nonclinical evaluations were deemed necessary prior to any multiple-dose pediatric trials, approval of a pediatric indication, or inclusion of pediatric data in the label. The following five comments were communicated in the Not Approvable letter:

1. *Provide an evaluation of sugammadex in a nonclinical model of bone fracture to examine potential effects of the drug on bone healing. You are encouraged to submit protocols of such studies to the Agency for comment prior to their conduct.*

A. Applicant Response - The effect of Org 25969 on bone repair was evaluated in adult animals (Study number: 090319). The results of the data did not show evidence of adverse

⁴ Now the Division of Bone, Reproductive and Urologic Products.

change on bone healing in animals with pre-fracture treatment in any Org 25969 dosing group as compared to control as assessed by pQCT scan, μ CT scan, bone strength test, and histopathology examination. With post-fracture treatment, statistically significant changes in some of the bone healing indices were observed at 500 mg/kg groups as compared to the concurrent control. Specifically, histopathology examination revealed an increase in callus formation, a decrease in bone formation, and decrease in the extent of bridging at the fracture site by new bone at 500 mg/kg.

B. Nonclinical Assessment - These data suggest a slight delay in bone healing process. The NOAEL in post-fracture treated animals is identified to be 120 mg/kg, while in pre-fracture treated animals the NOAEL is 500 mg/kg. The post fracture findings are not considered to be clinically concerning because

- The dose level and dosing regimen are well above the anticipated use, and
- Other parameters of bone strength and density were not changed.

The safety margins (**Table 4**) are calculated based on the AUC and bone concentration comparison between animals in this bone repair study and human.

Table 4 Safety margin for multiple-dose administration at 4 mg/kg in adult and pediatric patients with bone fracture

| | | Rat | Human | Safety margin |
|--------------------|------------------|-----------|-------------------|---------------|
| Young adult rat | Dose | 120 NOAEL | 4 | |
| (Fx healing study) | AUC (ug*h/mL) | 230 | 40 | 5.8x |
| | Bone conc (ug/g) | 235 | 9 (adult) | 26x |
| | | | 18 (child 10 yrs) | 13x |
| | | | 24 (child 4 yrs) | 10x |
| | Dose | 500 NOAEL | 4 | |
| | AUC (ug*h/mL) | 1101 | 40 | 28x |
| | Bone conc (ug/g) | 480 | 9 (adult) | 53x |
| | | | 18 (child 10 yrs) | 27x |
| | | | 24 (child 4 yrs) | 20x |

Source: Table from Dr. Xu's review, p. 10 of 60

The Study was considered supportive of dosing 4 and 16 mg/kg in (b) (4) adults (b) (4), since the bone growth process is continuous in rats during adulthood.

2. Provide data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study.

A. Applicant Response / Division assessment – This is addressed in Non-Approvable Letter Issue #3 below.

3. Provide a repeat-dose study of sugammadex in the juvenile rat with an extended period of recovery, such that bone length, material properties, and integrity at full skeletal maturity may be evaluated in order to clarify the observation of slight but lasting decreased bone length and body weight observed in the 28-day juvenile toxicity study. Within this study, micro-computed tomography (μ CT), bone turnover markers, and bone strength assessment should be obtained and evaluated. Also, the study should incorporate positive control arms

to verify assay sensitivity. Lastly, though not required, the inclusion of vertebral evaluation would be helpful to interpret bone effects since vertebrae have a more homogenous trabecular structure than long bones such as femur. You are encouraged to consider an alternative, intermittent dosing paradigm in order to minimize effects of sugammadex on body weight while allowing for significant drug accumulation in the skeleton.

In the previously submitted 28-day juvenile rat toxicity study in the original NDA (Study 063592), minor decrease in ulna length ($\leq 5\%$), femur length ($\leq 3.5\%$) and weight ($\leq 6.5\%$) were observed at 120 and 500 mg/kg Org 25969 after 28-day daily dosing. The Applicant indicated that the minor change was due to smaller size of the animals in Org 25969 treated groups likely due to decreased food consumption, and thus did not represent bone effect of Org 25969. The Division did not agree with this conclusion because the bone length decrease was not coincident with the body weight decrease and thus requested more information to clarify this finding.

Further the NOAEL was identified to be 30 mg/kg which corresponds to approximately 22 $\mu\text{g}\cdot\text{hr}/\text{ml}$ in plasma AUC and 150 $\mu\text{g}/\text{g}$ bone Org 25969. By plasma AUC comparison, exposure at NOAEL in juvenile rats, the NOAEL (22 $\mu\text{g}\cdot\text{hr}/\text{ml}$) did not cover human exposure at 4 mg/kg (40 $\mu\text{g}\cdot\text{hr}/\text{ml}$). Although estimated bone concentration provided sufficient coverage, it is uncertain whether AUC level or local bone concentration level shall be used for safety margin calculation since the bone effect in juvenile rats has not been well characterized from the nonclinical data in the original NDA submission.

A. Applicant Response – The Applicant responded by providing a reanalysis of the previous 28-week study to evaluate the contribution of body weight to the observed effects and by conducting an 8-week intermittent dosing toxicity in juvenile rats (Study 080229).

Data for femur length from the 4-week juvenile rat study were re-analyzed using ANCOVA analysis with body weight as the covariate. The results showed that the minor bone length decrease was still statistically significant, further suggesting that the decreased bone length following Org 25969 administration in juvenile rats might not be associated with body weight change.

In the new 8-week study, juvenile rats were dosed weekly from postnatal day (PND) 7 for 8 doses at 0, 7.5, 30, and 120 mg/kg Org 25969, and the animals were sacrificed the second day after last dosing and at the end of 8-week recovery. Bone effects of Org 25969 were evaluated by in vivo ulna length measurement, blood concentration analysis of bone turnover markers including osteocalcin and C-telopeptide crosslinks (CTx), histopathology examination of the bone, postmortem measurement of femur and terminal ulna length, μCT evaluation, and bone strength tests. The results of the study did not show significant changes in the parameters tested except a statistically significant decrease (15%) of osteocalcin at the end of 8-week recovery period but not at the end of dosing.

B. Nonclinical Assessment – The significance of this finding was unclear since there were no effects on bone density or strength.

In order to determine the sufficiency of the 8-week weekly dosing juvenile rat study to support the safety of future clinical trial in pediatrics, safety margins (**Table 5**) were calculated based on AUC and estimated bone concentration comparison between animals and human

Table 5 Safety Margin for sugammadex multiple-dose treatment at 4 mg/kg in pediatric subjects

| | | Rat | Human | Safety Margin |
|--------------|------------------|-----------|-------------------|---------------|
| Juvenile rat | Dose | 120 NOAEL | 4 | |
| | AUC (ug x h/mL) | 254 | 40 | 6.4x |
| | Bone conc (ug/g) | 400 | 18 (child 10 yrs) | 22x |
| | | | 24 (child 4 yrs) | 16.5x |

Source: Table from Dr. Xu's review, pp. 7-8 of 60

As shown above, the 8-week intermittent bone study in juvenile provide 6.4-fold and \geq 16.5-fold safety margin for pediatric use at 4 mg/kg with weekly administration up to the same duration (8 weekly dosing) based on AUC and bone concentration comparison. Assuming a linear increase of plasma exposure (AUC) and bone concentration, which is the worst scenario for bone concentration estimation because bone deposition of Org 25969 was found to be less than dose proportional, the 8-week toxicity study in juvenile provides sufficient margin for 8-week weekly dosing clinical study in pediatric patients based on plasma AUC ($6.4/4 = 1.6$ -fold) and bone concentration ($\geq 16.5/4 = 4$ -fold).

This juvenile rat study successfully fulfills the nonclinical request 3 list in the Non-Approvable letter. In addition, this study also fulfills the request 2 because growth plate morphology was included in this study.

4. *Provide definitive information on the binding site of sugammadex in bone as well as a reevaluation of bone localization of sugammadex as presentation of the data on bone localization was not clear and errors in descriptions were noted in the submitted materials.*

A. Applicant Response – An in vitro [14C]-Org 25969 binding study (Study number 090085) and a microautoradiography study in rats were included in this submission (Study 090071). While initially radiolabel was present in the metaphysis directly adjacent to the growth plate and only at trabecular and cortical bone surfaces, label was located more distally in the diaphysis and more centrally inside the cortical and trabecular bone compartments at the later 3- and 12-week observation times.

B. Nonclinical Assessment - The data showed that Org 25969 did not bind in growth plate in the bone. The redistribution or movement of the compound to hydroxyapatite sites elsewhere in the bone does not represent a safety concern. These studies fulfill the nonclinical request 4 listed in the Non-Approvable letter.

5. *Provide data, which may be derived from published literature, in vitro studies, and/or in vivo studies, along with a persuasive, well-supported rationale, to show that the risk of administration and long-term retention of sugammadex in the bones of pediatric patients*

will not confer a risk for bone tumor development in this population. Otherwise, an evaluation of the carcinogenic potential of sugammadex may be required. Although plasma levels of sugammadex rapidly decline with acute administration, the long retention of sugammadex in skeletal bone may be considered to be chronic exposure (i.e., greater than six months) and raises concern regarding the potential for development of tumors of this tissue, especially in the pediatric population, which is known to develop primary bone tumors at rates that exceed those in the adult population.

In a meeting with the Applicant on December 1st, 2008, the Agency indicated demonstration of binding to hydroxyapatite as well as submission of bone metabolism and histopathology data from the requested juvenile rat study with extended duration of follow-up would address the carcinogenicity concern.

A. Applicant Response – In this submission, the Applicant submitted an in vitro study clearly demonstrating that Org 25969 binds with hydroxyapatite, a component of bone extracellular matrix, at the same site for bisphosphonate binding. In addition, a microautoradiography study indicated that Org 25969 does not deposit in the growth plate of long bones, the area responsible for bone growth and elongation. In addition, histopathology examination did not show signs of carcinogenicity such as hyperplasia or hypertrophy of bone cells after 16-week Org 25969 exposure in the bone. Furthermore, bisphosphonate which binds the same site at hydroxyapatite does not cause bone-related cancer after long-term exposure (Whitaker et al., 2012).

B. Nonclinical Assessment – The Applicant’s response suggests that Org 25969 may not be associated with significant risk for bone tumor development. Therefore, the request 5 in the Non-Approvable letter is considered to be sufficiently fulfilled.

- Overall Assessment

1. The Nonclinical group (Dr. Xu and Wasserman) recommend that from the nonclinical standpoint, the application for use of sugammadex in the adult population may be approved.

2. (b) (4)

3. Outstanding issues

- a. The label will be finalized in a subsequent cycle due to deficiencies identified by other disciplines and so specific labeling language will not be described until that time. The following issues identified in this review cycle will need to be addressed.

- i. It will be necessary to define the Established Pharmacologic Class for the label: the proposed (b) (4) is not considered acceptable to the Division. Others, such as (b) (4) are being considered and will be finalized for the next cycle.

- ii. The revision of the proposed label in order to be in conformance with the Pregnancy and Lactation Labeling Rule will be negotiated with members of the Pediatric and Maternal Health Staff as well.
- iii. The extent to which nonclinical data will be described in the Animal Toxicology section remains to be decided.

I concur with the findings and conclusion of the Nonclinical team.

6. Clinical Pharmacology/Biopharmaceutics

Clinical Pharmacology was reviewed by Dr. Lei Zhang in the first review cycle. From a Clinical Pharmacology point of view, the application was considered acceptable, providing agreement was reached on the labeling. No Clinical Pharmacology studies were required in the Not Approvable Letter of July 31, 2008. However, as part of the Applicant's response to the deficiency in the Not Approvable Letter related to coagulation (see **Section C. Division's Final Review of the Original 2007 NDA Submission**), the following studies were conducted:

1. Clinical Study (P07044) in healthy subjects to assess sugammadex-anticoagulant (enoxaparin or heparin) interaction.
 - a. Results – There was no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin.
2. Clinical Study (P07025) in healthy subjects to assess sugammadex-aspirin interaction.
 - a. Result – There was no effect of 4 mg/kg of platelet aggregation effects of aspirin.

Several studies were recommended in the Not Approvable letter:

3. A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

As part of the response to this request, Study 19.4.116 (or P06315), a TQT study, was conducted to evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers.

- a. Result – No significant QTc prolongation effect of sugammadex was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/sugammadex were below 10 ms, the threshold for regulatory concern as

described in ICH E14 guidelines. The overall summary of findings is presented in the table below:

| Treatment | Time (min) | $\Delta\Delta QTcF$ (ms) | 90% CI (ms) |
|------------------------|------------|--------------------------|-------------|
| Propofol/Sugammadex | 120 | 2.7 | (-3.1, 8.5) |
| Sevoflurane/Sugammadex | 30 | 2.0 | (-1.6, 5.7) |

Source: Table from Dr. Nallani's review, p. 7 of 59

There was no significant concentration-QT relationship observed for the studied sugammadex dose of 4 mg/kg. In addition, there was no suprathreshold dose evaluated in this study, and the evaluated dose is not sufficient to address the high exposure scenario (e.g., elderly subject with moderate renal impairment treated with 16 mg/kg for immediate reversal), which would result in an 8.8-fold increase in AUC compared to sugammadex 4 mg/kg. However, Study 19.4.109 from the previous submission, evaluated a suprathreshold dose of sugammadex 32 mg/kg, and the mean QT prolongation was less than 10 ms. The combination of the previous study results where an appropriate suprathreshold dose was evaluated and the current study results, which demonstrate no significant concentration-QT relationship support that substantial QT prolongation under the high exposure scenario is unlikely with the proposed maintenance regimens.

4. A study to assess clearance of sugammadex-rocuronium complexes in patients with renal failure who undergo hemodialysis using high flux filtration.

Related to this comment, the following studies were conducted:

- Clinical study to evaluate the dialyzability of the sugammadex-rocuronium complex in vivo in subjects with renal impairment (Study 19.4.333 or P05773).
 - a. Result – In Study 19.4.333 (or P05773), over an average six hours of dialysis episode a mean reduction in plasma sugammadex and rocuronium concentration was about 70% and 75% during the first episode and about 50% during the sequential episodes.
- Clinical study evaluating effectiveness of sugammadex in subjects with normal or severely impaired renal function (Study 19.4.328 or P05769).
 - b. Results – In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment), the median reduction in sugammadex plasma concentrations after a 3 to 4 hours of dialysis for the high-flux filter (n=5) was 70.2% and for the low-flux filter (n=5) the reduction was only 29.8%.
- Clinical study evaluating effectiveness, PK, and safety of sugammadex after rocuronium in subjects with normal or impaired renal function (updated Study 19.4.304 or P05948, previously reviewed by Dr. Zhang in 2008).

- c. Results – In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment. Using high-flux dialysis filter, compared to low-flux filter, results in a more efficient clearance of sugammadex (and sugammadex+ rocuronium) from plasma.

The PK of sugammadex was not been evaluated in patients with renal impairment whose NMB are induced by vecuronium. Because vecuronium or rocuronium show little effect on sugammadex PK, the studies conducted with rocuronium-induced NMB was felt by the reviewer⁵ to be extrapolated to vecuronium-induced NMB.

5. Studies to assess safety, efficacy, and dosing requirements for sugammadex when used in patients with hepatic impairment. The studies should characterize the pharmacokinetics and pharmacodynamics of rocuronium and vecuronium in these patients following the administration of sugammadex.

- a. Result – The applicant does not plan to propose specific recovery times of T4/T1 ratio to 0.9 in the label in patients with hepatic impairment. Therefore, a dedicated PK-PD trial in subjects with hepatic impairment has not been conducted. The Applicant states that hepatic impairment is unlikely to affect PK of sugammadex, as it is predominantly, if not exclusively, eliminated via renal excretion of the unchanged product. The Applicant also states that it cannot be entirely excluded that in some individuals with severe hepatic impairment (especially in cases of ascites or general edema in severe hepatic impairment with significantly impaired protein synthesis function) the time of distribution of sugammadex and/or rocuronium/vecuronium may be altered, potentially resulting in some delay in the recovery time from NMBA effects. Therefore, the Applicant proposes a general statement in the label stating that sugammadex should be used with caution in subjects with severe hepatic impairment with coagulopathy or severe edema.

This was deemed as an acceptable approach by the Clinical Pharmacology reviewer. This is acceptable from my perspective as well, pending a review of the proposed labeling.

6. Studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. Such studies should not be started until the safety issues for the adult population have been fully vetted by the Agency.

- a. Results – This is discussed in **Section 11**.

Several other Clinical Pharmacology studies were included in this resubmission

⁵ Dr. Zhang's 2008 review, pp. 5-6

7. Clinical study to assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by IV diclofenac or IV flucloxacillin 5 minutes after reversal of NMB by sugammadex (Study 19.4.112 or P05861).
 - a. Results – Diclofenac or flucloxacillin did not alter pharmacokinetic disposition of rocuronium or vecuronium in plasma. No reoccurrence of neuromuscular block was observed after the administration of the administration of IV diclofenac or IV flucloxacillin based on TOF Watch SX monitoring during anesthesia. At this time, IV formulations of diclofenac or flucloxacillin are not available in the United States and hence this study has not impact on labeling.

8. Clinical study to evaluate re-use of rocuronium and vecuronium after NMB with Sugammadex (Study 19.4.113 or P05861). This was an open-label study to assess the safety and evaluate the onset of neuromuscular blockade at variable times of re-use of 1.2 mg/kg rocuronium (Part 1) and 0.1 mg/kg vecuronium (Part 2) after reversal of neuromuscular blockade by 4 mg/kg sugammadex in anesthetized healthy volunteers. The concern leading to this study was that use of sugammadex would preclude use of certain aminosteroid NMBs immediately thereafter.
 - a. Results – Subjects were given rocuronium in Part 1 in decreasing intervals from the time of sugammadex administration (see Table 6). For the 6 subjects with rocuronium re-use at 5 min, NMB onset time ranged from 1.92 to 4.72 min (arithmetic mean: 3.06). For longer re-use time points (30 min onwards) NMB onset times decreased, ranging between 1.23 and 1.43 min. Clinical duration of the NMB among the 6 subjects with rocuronium re-use time-point at 5 minutes, ranged from 17.8- 41.0 min (arithmetic mean 25.3 minutes) and was around 30 min and longer for subjects with rocuronium re-use time points from 22 minutes (N=7) onwards.

Table 6 Individual Onset Times of NMB to Rocuronium Administration and NMB Duration (Lowest T1-25% recovery), All-Subject Evaluable group (Per Protocol)

| Relative re-use time-points ¹ [mm:ss] | Subject Number | Relative NMB onset time ² [min] | Clinical duration of NMB ³ [min] |
|---|---------------------|---|--|
| 59:59 | 101001 | 1.32 | 43.6 |
| 45:00 | 101007 | 1.23 | 46.0 |
| 30:00 | 101002 | 1.43 | 29.9 |
| 27:30 | 101012 | 2.60 | 34.4 |
| 25:00 | 101006 | 2.05 | 37.3 |
| 22:30 | 101011 | 3.83 | 29.1 |
| 20:00 | 101003 | 3.15 | 21.4 |
| 15:00 | 101008 | 2.80 | 26.6 |
| 09:57 | 101004 | 3.48 | 19.7 |
| 07:30 | 101010 | 2.35 | 24.6 |
| 05:00 | 101005 | 3.57 | 17.8 |
| 05:00 | 101013 | 2.73 | 22.7 |
| 05:00 | 101014 ⁴ | 2.75 | 41.0 |
| 05:00 | 101016 | 1.92 | 22.4 |
| 05:00 | 101017 | 2.68 | 17.7 |
| 04:59 | 101015 | 4.72 | 30.0 |

Note: Subject 101009 was not dosed with sugammadex due to technical issues with the monitoring of neuromuscular transmission, which prevented adequate timing of sugammadex dosing. Subsequently, no rocuronium re-use took place.

¹ relative to start of sugammadex administration

² relative to start of rocuronium administration

³ time to recovery to T₁=25%

⁴ Subject 101014 received a second i.v. dose of sugammadex (2 mg/kg) because recovery times after re-use of rocuronium exceeded 2 hours.

Source: Table 14.3.7-1

Source: Table 14, Dr. Nallani's review p. 54 of 59

Simulations showed that if re-use of 1.2 mg/kg rocuronium is initiated >25 minutes after 4 mg/kg sugammadex reversal, NMB onset times are achieved which are with 95% confidence below 4 minutes. Moreover, if in this setting re-use of 1.2 mg/kg rocuronium is initiated <25 minutes after reversal of sugammadex, NMB onset times are with 95% confidence below 4.25 minutes. The estimated geometric mean duration of NMB was 24.1 minutes and the lower limit of the 95% C.I. was 17.2 minutes for subjects receiving 1.2 mg/kg rocuronium 5 minutes after reversal with 4 mg/kg sugammadex.

Vecuronium re-use: In Part 2, six subjects received the second dose of vecuronium with re use time points between 2 hours and 5 hours after sugammadex administration. A complete neuromuscular block with onset times below 3 minutes was only observed for vecuronium re use times from 3.5 hours onwards. No complete NMB occurred after vecuronium re-use at 2 hours and 2.5 hours after sugammadex administration. Therefore, it was decided not to proceed with earlier time-points of re-use of vecuronium. Onset times of neuromuscular block at re-use times ≥ 3.5 hours ranged from 1.68 minutes (re-use at 3.5 h) to 3.15 minutes (re-use at 4 h) with NMB durations between 24.2 minutes (reuse at 4 h) and 31.4 minutes.

Table 7 Individual Onset Times of NMB to Rocuronium Administration and NMB Duration (Lowest T1-25% recovery), All-Subject Evaluable group (Per Protocol)

| Relative re-use time-points ¹ [hh:mm] | Subject Number | Relative NMB onset time-point ² [min] | Duration of NMB ³ [min] |
|--|----------------|---|---------------------------------------|
| 05:00 | 101101 | 2.03 | 31.3 |
| 04:00 | 101104 | 3.15 | 24.2 |
| 03:30 | 101105 | 1.68 | 31.4 |
| 03:00 | 101103 | 7.35 | 20.6 |
| Subjects excluded from the Per-Protocol group (no complete neuromuscular block appeared) | | | |
| 02:30 | 101106 | 5.68 | Not possible |
| 02:00 | 101102 | 5.45 | 10.5 |

Subjects 101102 and Subject 101106 were excluded from the Per-Protocol (PP) group because no complete neuromuscular block (T₁=0%) occurred after re-use of vecuronium.

¹ relative to start of sugammadex administration

² relative to start of vecuronium administration

³ time to recovery to T₁=25%

Source: Table 14.3.7-1

Source: Table 15, Dr. Nallani's review, p. 55 of 59

This study examines a clinically relevant question that was raised at the ALSDAC meeting during the first review cycle, that is, can NMBs be reused after sugammadex. The data suggest that rocuronium may be reused fairly soon after sugammadex administration and a normal duration of block may be achieved. However, 4 minutes for onset is a considerable time to onset if the NMB is being used at the time of anesthesia induction, particularly if it is a rapid sequence induction, including intubation in the emergent intubation setting. The data from Part 2 (using vecuronium as the NMB) seems quite preliminary considering the few subjects at any time point and the variability of results. Nonetheless, this is important information that should be conveyed in the labeling. The exact wording should be reflective of the relatively small amount of evidence provided.

9. PK study of sugammadex in male and female Chinese subjects (Study P05997). This was an open-label single-dose pharmacokinetic study.

a. Results – Pharmacokinetics of sugammadex was similar in Chinese subjects compared to Caucasian subjects. In addition, there were no gender-related differences in the pharmacokinetics of sugammadex in Chinese subjects.

- Overall Assessment

1. The Clinical Pharmacology group recommends that from the clinical pharmacology perspective, the application for use of sugammadex in the adult population may be approved.

2. The Clinical Pharmacology group further finds that the Applicant has appropriately addressed the clinical pharmacology issues and recommendations raised in the Not Approvable letter to support dosing and labeling.
3. Outstanding issues
 - a. The label will be finalized in a subsequent cycle due to deficiencies identified by other disciplines and so specific labeling language will not be described until that time.
 - b. Pediatrics is discussed in **Section (b) (4) Pediatrics.**

I concur with the findings and conclusion of the Clinical Pharmacology.

7. Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application.

8. Clinical/Statistical- Efficacy

The clinical efficacy of sugammadex was reviewed by Dr. Robert Shabuya on 6/24/2008. He found that based on the clinical trials reported in the original NDA submission, sugammadex was found to be effective for reversing rocuronium- and vecuronium-induced neuromuscular blockade under two clinical conditions:

1. With the return of the second twitch (T2) when a train-of-four (TOF) stimulus is applied to the ulnar nerve and the response of the abductor pollicis muscle is assessed,
2. With the presence of one to two post-tetanic contractions following a tetanic electrical stimulus applied to the ulnar nerve and assessed by the adductor pollicis longus muscle response.

Sugammadex (16 mg) was also found to be effective for reversing the neuromuscular blockade resulting from a 1.2 mg/kg dose of rocuronium when it is given at three minutes following rocuronium administration, the time when the maximal pharmacodynamic effect of rocuronium is expected.

In the NDA resubmission, the Applicant has included a number of new clinical studies that contained efficacy data (**Table 8**). These trials evaluated only the lower doses of sugammadex proposed for clinical use, and the findings were consistent with those of the pivotal studies conducted for the original NDA submission.

Table 8 Efficacy Trials included in the Resubmission

| Study | Design / Population | Sugammadex dose(s) | Comparator | Primary Endpoint |
|---|--|--------------------|-------------------------|--|
| Phase 3 Studies with sugammadex administered at the reappearance of T2 | | | | |
| P05768 | randomized, active, parallel-group, multisite, safety-assessor-blinded | 2 mg/kg | neostigmine (50 mcg/kg) | time to recovery of the T4/T1 ratio to |

| Study | Design / Population | Sugammadex dose(s) | Comparator | Primary Endpoint |
|---|---|---|---------------------------|--|
| | trial of sugammadex of 291 adult, ASA-PS 1-3, Chinese and Caucasian subjects | | | 0.9. |
| P06101 | randomized, active-controlled, parallel group, multi-site, safety-assessor-blinded study of 128 adult, ASA-PS 1-3, Korean subjects | 2 mg/kg | neostigmine (50 mcg/kg) | time to recovery of the T4/T1 ratio to 0.9. |
| Phase 3 studies with sugammadex administered at 1-2 PTCs | | | | |
| P05767 | multi-center, randomized, parallel-group, comparative, placebo-controlled, safety-assessor blinded in 140, adult, ASA-PS 1-3 subjects undergoing profound neuromuscular blockade. | 4.0 mg/kg | Pbo | time to return of the T4/T1 ratio to 0.9. |
| P05699 | multi-center, randomized, parallel-group, active-controlled, safety-assessor blinded trial of 133 adult ASA-PS 1-3 subjects | 4.0 mg/kg | neostigmine (50 mcg/kg) | time to return of the T4/T1 ratio to 0.9 |
| P05774 | multi-center, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded, anesthesiologist-TOF-Watch® SX-blinded trial of 100 adult, ASA-PS 1-3 subjects | 4.0 mg/kg ◊ | Neostigmine (50 mcg/kg) ◊ | T4/T1 ratio at the time of tracheal extubation |
| Special populations | | | | |
| P05769 | open-label, multicenter, parallel-group, comparative study in 68 adult, ASA-PS 1-3 subjects with normal and severely impaired renal function | 4.0 mg/kg at a target depth of neuromuscular blockade of 1-2 PTCs | None | time to return of the T4/T1 ratio to 0.9 |
| P05773 | single center, exploratory, open label trial in 6 ASA-PS 1-4 subjects with severe renal impairment (creatinine clearance < 30 mL/min and a clinical indication for dialysis) who were hospitalized in an ICU scheduled for a surgical procedure | 4 mg/kg 15 minutes after administration of rocuronium | None | time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9, 0.8, and 0.7 Exploratory endpoint to evaluate the dialysability of |

| Study | Design / Population | Sugammadex dose(s) | Comparator | Primary Endpoint |
|--------------|--|---|--|--|
| | | | | the sugammadex / rocuronium complex |
| Other | | | | |
| P05698 | multi-center, randomized, peripheral nerve stimulator (PNS)-assessor-blinded, parallel-group, active, within-subject controlled trial of 91 adult, ASA-PS 1-3 subjects | 1:2 ratio to receive either a single dose of 1.0 or 4.0 mg/kg sugammadex administered at 15 minutes after the last dose of rocuronium, respectively, and in a 1:1 ratio to having the TOF-Watch® SX affixed to either the dominant or the non-dominant forearm. | | the time from start administration of 4.0 mg/kg of sugammadex to reappearance of T4 as detected manually with PNS monitoring. |
| P05700 | multicenter, randomized, safety-assessor blinded, parallel group, active-controlled, comparative trial in 161 adult, ASA-PS 1-3 subjects | 4 mg/kg bolus dose of sugammadex for reversal at a target depth of blockade of 1-2 PTCs | 1 mg/kg bolus dose of succinylcholine followed by spontaneous recovery | time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9. The time from start of administration of succinylcholine to T1 reaching 90% of baseline was a secondary endpoint. |
| P05775 | open-label, single-dose, multi-site trial in 115 Chinese Asians living in China and 36 European Caucasians living in Europe. | 4 mg/kg at a target depth of blockade of 1-2 PTCs, | None | time to return of the T4/T1 ratio to 0.9 |

◇ = administered “per standard of care” knowing whether spontaneous recover had already reached 1-2 post tetanic contractions (PTCs) or better

Source: created from information in Dr. Simone’s review, Section 6.1.1

Of these studies, Dr. Simone provided a more detailed review of Study P05774 (see the italicized text below) (b) (4)

The primary endpoint of P05774 was to compare the incidence of residual neuromuscular blockade at the time of tracheal extubation after reversal of rocuronium bromide-induced neuromuscular blockade with 4 mg.kg⁻¹ sugammadex compared with 50 µg/kg⁻¹ neostigmine. Residual paralysis was defined as T4/T1 ratio of <0.9.

(b) (4)

Although the findings may be accurate and the study appropriately designed to assess the primary endpoint, the study does not demonstrate the efficacy of sugammadex. The study does appear to show that when patients are not monitored with PNS [PNS = peripheral nerve stimulator] following administration of a reversal agent they are more likely to extubate a patient at a T4/T1 = 0.9 with sugammadex than neostigmine. The implication is that patients are “more” reversed with sugammadex than neostigmine and therefore, less likely to risk morbidity associated with inadequate reversal. However, the study was not designed to demonstrate such a benefit, and the exclusion of PNS monitoring from the assessments made prior to determining whether it was safe to extubate a patient is inconsistent with the current standard of care (b) (4)

I concur with his assessment of this trial.

Dr. Zhou, the statistical reviewer, analyzed the primary and secondary endpoints from this study. She verified that the same statistical results were achieved as the Applicant (**Table 9 - Table 12**).

While the outcome was statistically significant, I agree with Dr. Simone, (b) (4)

The data seem to only demonstrate that certain investigators were willing to extubate the patient well before the standard of care of a T4/T1 of > 0.9. The range extends as low as 0.38 which is closer to a threshold when the reversal agent would just be given (e.g., T4/T1 = 0.2) than the point of extubation. I am also concerned about the reliability of the data and possibility of technical error in the conduct of this study since the range for T4/T1 in the sugammadex data extends to 1.41 while the maximum theoretical physiological value for T4/T1 is 1.

Table 9 Summary Statistics of the T4/T1 ratio at tracheal extubation.

Table 3: Summary statistics of the T₄/T₁ ratio at tracheal extubation

| | Complete Cases | | Including imputed data | |
|------------------|----------------|-------------|------------------------|-------------|
| | Sugammadex | Neostigmine | Sugammadex | Neostigmine |
| N | 43 | 38 | 51 | 46 |
| Mean (SD) | 1.03 (0.15) | 0.73 (0.24) | 1.02 (0.15) | 0.78 (0.24) |
| Median | 1.03 | 0.76 | 1.00 | 0.87 |
| Min - Max | 0.38 - 1.41 | 0.13 - 1.06 | 0.38 - 1.41 | 0.13 - 1.06 |

Source: Clinical Study Report Table 10 and Reviewer's Analyses

Source: Table 3 of Dr. Zhou's review, p. 9

⁶ A table similar to the Complete Cases (left side) of **Table 10** from my review

⁷ Dr. Simone's review, p. 35 of 303 (PDF Version)

Table 10 Frequency of the T4/T1 ratio at Tracheal Extubation**Table 4: frequency table of the T₄/T₁ ratio at tracheal extubation**

| | Complete Cases | | Including imputed data | |
|-------------------|----------------|-------------|------------------------|-------------|
| | Sugammadex | Neostigmine | Sugammadex | Neostigmine |
| N | 43 | 38 | 51 | 46 |
| <= 0.6 | 1 (2%) | 10 (26%) | 1 (2%) | 10 (22%) |
| (0.6, 0.7] | 0 (0%) | 5 (13%) | 0 (0%) | 5 (11%) |
| (0.7, 0.8] | 0 (0%) | 5 (15%) | 0 (0%) | 5 (11%) |
| (0.8, 0.9) | 1 (2%) | 6 (16%) | 1 (2%) | 6 (13%) |
| >= 0.9 | 41 (95%) | 12 (32%) | 49 (96%) | 20 (43%) |

Source: Clinical Study Report Table 11 and Reviewer's Analyses

Source: Table 4 of Dr. Zhou's review, p. 9

Table 11 Primary Analysis Results**Table 5: Primary analysis results**

| | Including imputed data | |
|------------------|------------------------|-------------|
| | Sugammadex | Neostigmine |
| N | 51 | 46 |
| < 0.9 | 2 (4%) | 26 (57%) |
| >= 0.9 | 49 (96%) | 20 (43%) |

Source: Reviewer's Analysis

Note: P-value < 0.0001 using Fisher-exact test

Source: Table 5 of Dr. Zhou's review, p. 9

I do find the secondary outcome of the recovery time of T4/T1 to 0.9 (Table 12) supportive of the efficacy of sugammadex for routine reversal.

Table 12 Recovery time of the T4 / T1 variable to 0.9 (minute:second)**Table 6: For secondary efficacy variable: recovery time of the T4/T1 ratio to 0.9 (minute: second)**

| | Complete Cases | | Including imputed data | |
|----------------------|----------------|--------------|------------------------|--------------|
| | Sugammadex | Neostigmine | Sugammadex | Neostigmine |
| N | 49 | 19 | 51 | 46 |
| Mean (SD) | 2:28 (1:09) | 9:36 (6:44) | 2:32 (1:11) | 7:57 (6:55) |
| Median | 2:02 | 6:48 | 2:05 | 5:43 |
| Min - Max | 0:44 – 5:21 | 1:17 – 23:11 | 0:44 – 5: 21 | 1:17 – 23:11 |
| LS Means (SE) | - | - | 2:54 (0:45) | 8:27 (0:47) |
| P-value | - | - | | < 0.0001 |

Source: Clinical Study Report Table 16 and Reviewer's Analysis

Source: Table 6 of Dr. Zhou's review, p. 10

While this Review will not discuss the issues in labeling for efficacy of sugammadex, I will highlight some of the most important concepts elaborated by Dr. Simone⁸ in this regard that should be considered when selecting information to include in the final labeling.

⁸ Here I am discussing Section 6.1.4 of Dr. Simone's review (PDF Version).

- The previous evidence (i.e., Studies 301, 302, and 303) supporting the efficacy of sugammadex in terms of the doses and timing (i.e., level of spontaneous recovery from NMB) for reversal is consistent with the wording in their proposed indication, “Routine reversal...of neuromuscular blockade induced by rocuronium or vecuronium.”
- Some patients in the sugammadex group take notably longer than the mean value to recover.⁹ This finding indicates that not all patients are going to respond similarly to sugammadex, just as they do not respond similarly to neostigmine, and therefore, it is imperative that patients be monitored until full reversal is assured.
- With respect to the Study 303 (the “Immediate Reversal” study), the following points were discussed:
 - The applicant selected an endpoint of T1 = 0.1 of baseline. The justification for not using the more established T4/T1 ratio was that the comparator was succinylcholine, which is a depolarizing NMBA and therefore, does not produce fade in twitch responses to the TOF stimulus. The applicant did not provide any references to support the clinical significance of the cutoff, i.e., 0.1, for this endpoint, but is clear that for recovery from rocuronium, T1 = 0.1 will not be sufficient for a patient to either maintain a patent airway or adequately ventilate without assistance. Therefore, while the return of some strength is considered evidence of reversal of blockade or offset of action, for both succinylcholine and rocuronium, the clinical significance of this particular endpoint is subject to debate.
 -  (b) (4)

9. Safety

A. Adequacy of the Database

Since the Not Approvable action was taken, the Applicant has completed 20 new clinical trials and in the process has doubled the size of the safety database. In the original NDA submission, there were a total of 2,369 subject exposures to intravenous sugammadex in 2,054 unique subjects. The new clinical trials add 2,547 subject exposures to IV sugammadex in 1,967 unique subjects. In addition, sugammadex was approved in the European Union on July 25, 2008, and is currently registered in 71 countries and marketed in 41 countries. The Applicant reports the distribution of over  (b) (4) vials for use in patients through June, 2012. Therefore, the secondary focus of this review was whether the new safety database or the postmarketing adverse event data present a risk profile that is

⁹ Dr. Simone’s review, p. 32 of 303 (PDF Version)

similar to that characterized in the original NDA submission or whether any new safety signals exist.

Dr. Simone noted¹⁰ that the safety data seemed adequate for most of the populations of interest for the 2 and 4 mg/kg doses however there are limited data for older (> 65 years) and sicker (ASA-PS 3-4) subjects given the highest proposed sugammadex dose, 16 mg/kg.

B. Deaths

In the overall sugammadex clinical development program, eight deaths have been reported, including three deaths reported in the original NDA submission. Four deaths followed sugammadex treatments (one subject for the 0.5 mg/kg dose and 2 mg/kg dose and four subjects for the 4 mg/kg dose); one death occurred following neostigmine treatment and three deaths followed placebo treatment. The Applicant notes that all of the deaths occurred after the trial was completed, and that none of them were considered drug-related according to the reporting investigators. In the safety review of the original NDA submission, Dr. Simone concurred that two of the deaths were unlikely to be drug related, but felt that sugammadex may have contributed, in part, to at least one of the deaths. All eight cases are described and discussed in his review¹¹.

C. Nonfatal SAEs

There were 411 Nonfatal SAEs involving 219 Preferred Terms (PTs).

In their analysis of serious adverse events (SAEs), the Applicant used their pooled Phase 1-3 trials and considered treatment-emergent events that occurred within 7 days of study drug administration. They also compared the events as tabulated in the safety database for the original NDA submission (2007) and compared those to the cumulative safety database for the resubmission (2012). Based on these data the Applicant concluded that:

Overall the incidences were considered to be comparable between the two treatment groups. Between the doses of sugammadex and the two datasets (2007 and 2012), there were no clinically relevant differences in SAE incidence rate in the various SOC.

Based on this analysis of the SAE data, Dr. Simone concurred with the Applicant's observation; however, Dr. Simone also noted that SAE data from the active-controlled, i.e., neostigmine-controlled studies are not included in this analysis, nor are data from studies in which no anesthetic or NMBA were administered. Therefore, he created a table¹² that includes all SAEs reported for intravenous injections or infusions of sugammadex grouped by SOC and compared to those of subjects treated with either placebo or neostigmine, regardless of whether an anesthetic or an NMBA was administered. The data in the table indicated to Dr. Simone that overall and for each individual SOC there are no substantial differences between

¹⁰ Dr. Simone's review, p. 49 of 303 (PDF Version)

¹¹ Dr. Simone's review, pp. 54-57 of 303 (PDF Version)

¹² Dr. Simone's review, Table 13 from pp. 60-62 of 303 (PDF Version)

sugammadex and either placebo or neostigmine and that there is no dose-dependency for SAEs.

I concur with his interpretation of the data.

Dr. Simone also did an analysis by SAE PTs related to the three major issues included in the Complete Response e.g., hypersensitivity/anaphylaxis and coagulation, and cardiac arrhythmias. For peri-operative bleeding events, he did an analysis grouping similar terms since these were divided into 17 different PTs. He also grouped the cardiac AEs for analysis, though these were of different types (e.g., arrhythmias, vs. myocardial infarction). Results from these PTs are found in (Table 13).

Table 13 Clinical Reviewer Analysis of the Nonfatal Serious Adverse Events Related to Bleeding and Cardiac Events

| SAE Types | placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine | |
|-------------------------------------|---------|--------------------|---|----|---|----|---|---|----|----|-------|-------------|--|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | Total | | |
| All hemorrhage and hematomas | | | | | | | | | | | | | |
| n | 11 | 4 | 1 | 10 | 0 | 16 | 0 | 1 | 0 | 2 | 34 | 5 | |
| % | 3 | 3 | 1 | 2 | 0 | 2 | 0 | 1 | 0 | 2 | 2 | 1 | |
| All cardiac-rhythm | | | | | | | | | | | | | |
| n | 6 | 2 | 0 | 18 | 0 | 11 | 0 | 1 | 3 | 6 | 41 | 1 | |
| % | 2 | 2 | 0 | 3 | 0 | 2 | 0 | 1 | 8 | 5 | 2 | 0 | |

Source: Dr. Simone's review, p 66

Dr. Simone noted that SAEs related to bleeding occur no more frequently with sugammadex than for placebo, and that bleeding events are not dose-related for sugammadex treatment. He also commented that for cardiac events overall, there were events were no more frequent following sugammadex treatment than for placebo and that the higher doses of sugammadex, i.e., 12 and 16 mg/kg, were associated with an increased frequency of these events. He expressed that the clinical significance of this finding is uncertain due to the limited number of subjects in these treatment groups.

Upon my own review, I found that most of the SAE events to be associated with QTc prolongation. Most were reported because of relative changes from baseline versus the QTc being greater than 500 msec. None had Torsades de Pointes associated with the event. In light of the results from the 3 QT studies performed by the Applicant, these results do not present a signal of concern.

For the third issue of Hypersensitivity/Anaphylaxis, there was only one SAE with the preferred term anaphylactic shock, which occurred following the administration of 16 mg/kg of sugammadex.

D. Discontinuations due to AEs

Since sugammadex is administered as an intravenous bolus, discontinuations of administration were possible only in the trials where the study drug was infused or in crossover trials where a subject did not proceed to a subsequent period. Trials 19.4.108 and 19.4.109 involved infusions of study drugs over 4-minute periods; trial 19.4.109 was also a crossover study. The

Applicant reported that the infusion of sugammadex was not discontinued in any subject in these two trials. Therefore, there were only subject withdrawals from the trials due to an adverse event (AE) rather than discontinuations of treatment per se. This summary was limited to the pooled Phase 1-3 placebo-controlled studies (**Table 14**). Two discontinuation events occurred in active-controlled trials resulting in a total of 8 discontinuation events in the sugammadex group (see the (2012) column for Discontinued due to adverse event).

Table 14 Subject disposition for placebo-controlled studies

| | 0 mg/kg (Placebo) | | 2 mg/kg | | 4 mg/kg | | 16 mg/kg | | Total ^a sugammadex x | |
|-----------------------------------|----------------------|-------------|-------------|-------------|-------------|--------------|------------|------------|---------------------------------------|--------------|
| | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 |
| Total number of subjects exposed | 140 | 544 | 605 | 838 | 580 | 1798 | 98 | 98 | 1926 | 3407 |
| Completed study | 137 (98) | 534 (98) | 597 (99) | 830 (99) | 574 (99) | 1764 (98) | 95 (97) | 95 (97) | 1891 (98) | 3343 (98) |
| Discontinued due to adverse event | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 3 (0) | 1 (1) | 1 (1) | 4 (0) | 6 (0) |
| Discontinued due to other reason | 3 (2) | 9 (2) | 8 (1) | 8 (1) | 5 (1) | 31 (2) | 2 (2) | 2 (2) | 31 (2) | 58 (2) |

^a Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20, 32 mg/kg). There were no new subjects since the 2007 submission exposed to doses of sugammadex that are not displayed.

Source: Dr. Simone's review, p. 67 of 303

In the Pooled Neostigmine-controlled trials, one subject in the neostigmine group discontinued the trial due to AEs of gastric perforation and "procedural complications." These AEs were considered to be unrelated to trial medication by the investigator. No subjects in the sugammadex group discontinued from a trial due to an AE in this pooled group.

The discontinuations that occurred during the development program were few in number due to the acute use of sugammadex in the controlled setting of the operating room or clinical research facility. Given the limitations associated with eight events that occurred with sugammadex and single events that occurred with neostigmine and placebo treatments, it was not possible to determine whether there were any trends in the findings or differences between the treatment groups.

E. General AEs

1) Common Adverse Events

The Applicant reported a total of 22,961 adverse events (AEs) categorized under 1,146 preferred terms for their entire clinical development program. To identify common AEs for the purposes of evaluating the safety of sugammadex for its intended use and product labeling, an analysis was performed after refining¹³ the AE database. Dr. Simone first produced **Table 26** (see **Appendices, Section 15.B**) that had AEs with an incidence greater than 0.5%. After further combining like terms and including only AEs with an incidence of $\geq 1\%$ for sugammadex, he produced the results in **Table 15** below.

Table 15 Adverse Event Counts For AEs Occurring With A Greater Frequency For Sugammadex Than Placebo And With A Frequency $> 1\%$ For Sugammadex

| System Organ Class | Preferred Term | Placebo (N=1759) | | Sugammadex (N=4914) | | Neostigmine (N=804) | |
|--|----------------------------|------------------|----|---------------------|----|---------------------|----|
| | | n | % | n | % | n | % |
| Cardiac disorders | Hypertension | 39 | 2 | 177 | 4 | 34 | 4 |
| | Hypotension | 18 | 1 | 173 | 4 | 60 | 7 |
| | Constipation | 73 | 4 | 264 | 5 | 113 | 14 |
| | Nausea | 145 | 8 | 960 | 20 | 274 | 34 |
| | Vomiting | 71 | 4 | 419 | 9 | 118 | 15 |
| General disorders and administration site conditions | Chills | 15 | 1 | 91 | 2 | 12 | 1 |
| | Edema peripheral | 25 | 1 | 91 | 2 | 32 | 4 |
| | Pyrexia | 18 | 1 | 209 | 4 | 45 | 6 |
| | Anesthetic complication | 1 | 0 | 62 | 1 | 1 | 0 |
| | Incision site complication | 0 | 0 | 87 | 2 | 16 | 2 |
| | Pain | 402 | 23 | 2362 | 48 | 747 | 93 |
| | Procedural complication | 6 | 0 | 77 | 2 | 34 | 4 |
| Nervous system disorders | Dizziness | 30 | 2 | 213 | 4 | 84 | 10 |
| | Dysgeusia | 7 | 0 | 193 | 4 | 5 | 1 |
| | Insomnia | 24 | 1 | 145 | 3 | 57 | 7 |
| Skin and subcutaneous tissue disorders | Erythema | 7 | 0 | 50 | 1 | 39 | 5 |
| | Pruritus | 9 | 1 | 89 | 2 | 27 | 3 |

Source: Table 36 from Dr. Simone's review, p. 136 of 303

Those which occurred with sugammadex at rates greater than 3 percentage points over placebo included:

- Nausea

¹³ e.g., removing AEs that occurred before sugammadex treatment, during sugammadex treatments that were not by the intravenous route; see Dr. Simone's review, p. 133 (PDF Version) for a full description of his methodology

- Vomiting
- Pain (including: arthralgia, back pain, musculoskeletal pain, myalgia, pain in extremity, oropharyngeal pain, pharyngolaryngeal pain, procedural pain, post procedural pain, abdominal pain, and incision site pain)
- Dysgeusia

Of the four AEs above, only dysgeusia appears to be sugammadex-dose dependent¹⁴.

No AEs occurred with a frequency difference¹⁵ of greater than 1 percentage point for sugammadex compared to neostigmine treatment with the exception of dysgeusia. For nausea, vomiting and pain, the AEs having a greater frequency with sugammadex treatment compared to placebo treatment, the frequency of these AEs was more than 5 percentage points higher in the neostigmine treatment group than in the sugammadex-treatment group.

The Applicant used a different method of AE analysis, not integrating the Phase 1 studies in which no neuromuscular blocking agent or anesthetic were administered. Dr. Simone noted that this analysis resembled his own (see **Table 26** of this review) in that nausea and dysgeusia occur substantially more often with sugammadex than with placebo, the only two specific AEs to do so, and the two which comprise approximately half the total AEs reported for those SOC. These AEs also appear to be sugammadex-dose dependent in the Applicant's analysis.

While the labeling will not be discussed in detail in this review cycle, Dr. Simone noted that the Applicant's proposed table for common adverse events does not appear to be adequate; although it accurately reflects the data that met the criteria for the pooled Phase 1-3 placebo-controlled studies. His Table 36 (**Table 15** from this review) provides a more comprehensive list of AEs likely to be observed in clinical practice, in particular, the occurrence of dysgeusia.

2) Significant Adverse Events

Dr. Simone's analysis of the severe adverse events occurring for the three treatment groups and various dose groups of sugammadex indicate that sugammadex was not associated with greater risk for SAEs compared to placebo or neostigmine or that the risk for such events was greater with increased doses of sugammadex. These findings were consistent across SOC and preferred terms for the events occurring most frequently.

I concur with his interpretation overall, however, the incidence of severe AEs (not subdivided) seemed slightly higher in the sugammadex group (20%) than the Pbo (13%) or neostigmine group (14%).¹⁶ This is, however, not likely to be clinically relevant since there were no notable differences in the incidence of any of SOC that would have suggested a specific clinical issue.

F. Laboratory Tests

The Applicant summarized lab data in terms of descriptive statistics (mean values, change from baseline, etc), shift analyses, markedly significant changes, and lab-related adverse

¹⁴ See Table 37 from Dr. Simone's review, p.138 (PDF Version)

¹⁵ Incidence of AE for sugammadex minus neostigmine

¹⁶ From Table 16 of Dr. Simone's review, p. 75 of 303 (PDF Version).

events. The Applicant has provided an adequate assessment of the effects of sugammadex on hematological, biochemical and urological laboratory parameters.

The only hematology-related AEs that occurred in more than 1.0% of the total sugammadex group were anemia (3.6%) and anemia postoperative (2.1%). There was no dose trend and the values for these two AEs were higher in the placebo group than the values for the total sugammadex group. The incidence of these AEs was lower for sugammadex treated patients than the neostigmine-treated patients as well.

The Applicant noted that, in the pooled placebo-controlled trials, the percent of subjects with markedly abnormal post-baseline values for elevated fasting glucose which was 6% higher in the sugammadex treatment group than the placebo-treatment group. Dr. Simone did not feel this result was clinically significant because of the following considerations:

- Based on the study site, the cutoff for abnormally high glucose level ranged from 6.66-7.32 mmol/L, which was a range of 10%. Thus, subjects with the same glucose level could be considered not markedly abnormal at one site but markedly abnormal at another site.
- The difference was not observed for neostigmine versus sugammadex treatments.
- There were no differences between placebo and sugammadex treatments for AEs related to blood glucose increased.

The only biochemistry-related AE that occurred in more than 1% of the total sugammadex group was hypokalemia (2.0%).

The Applicant reported that the treatment groups in the pooled Phase 1-3 trials showed no dose trends for the percent of exposures in subjects with markedly abnormal post-baseline urinalysis values that met their pre-specified criteria. In the sugammadex group, there were markedly abnormal increased post-baseline values for beta-2-microglobulin, microalbumin (creatinine-dependent), microalbumin (non-creatinine-dependent) and N acetylglucosaminidase. In addition, there were markedly abnormal decreased post-baseline values for urine creatinine.

The assessment contained in the original NDA submission was considered adequate with the exception of coagulation parameters, which were not evaluated at all in the subjects participating in any of the clinical studies. For those parameters that were evaluated, none were considered to have been altered to a clinically significant extent by the administration of sugammadex, based on comparisons to placebo and neostigmine treatments.

G. Vitals Signs

In the Phase 1-3 trials where a neuromuscular blocking agent (NMBA) was administered, vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and central body temperature. Blood pressure and pulse rate data were summarized by the Applicant according to the following time intervals:

- Baseline (i.e., last measurement before the administration of study drug)
- Post-baseline (2, 5, 10, 30, 60, and 120 min and 3 hours)
- Minimum and maximum values (from start of study drug to 6 hours later)

- Final visit (last measurement after study drug till 6 hours later).
- Post-anesthetic visit (from 6 hours after study drug until 48 hours after study drug, or Day 2)
- Follow-up visit (from Day 4 onwards)

In the pooled Phase 1 dataset of non-anesthetized healthy volunteers who did not receive an NMBA, vital signs included blood pressure, pulse rate, respiratory rate, temperature, and body weight. Blood pressure and pulse rate data were summarized according to the following time intervals:

- Baseline (i.e., before the administration of the trial medication)
- At 2 min, 10 min, 15 min, 30 min, 35 min, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-baseline

Body temperature, body weight, and respiratory rate data were summarized for the pooled Phase 1 population only at baseline and follow-up. Similarly, body weight, height, and body temperature data were summarized for screening and follow-up.

The Applicant used descriptive statistics, including the mean, Standard Deviation (SD), median, minimum, and maximum observed values, and absolute and percent mean (SD), median, minimum, and maximum changes from baseline to characterize the effects on vital signs that were observed with the various treatment groups. The number and percent of subjects with markedly abnormal values, according to the pre-defined safety ranges, were also summarized by treatment group. The subjects with markedly abnormal values (**Table 16**) are identified as were adverse events (AEs) that were considered related to vital signs abnormalities.

Table 16 Absolute value cutoffs and changes for blood pressure and heart rate that were used to determine “markedly abnormal values”

| Parameter | Safety Range | | Criteria Value | |
|---------------------------------|--------------|------|----------------|----------|
| | Low | High | Decrease | Increase |
| Systolic blood pressure (mmHg) | 90 | 160 | 20 | 20 |
| Diastolic blood pressure (mmHg) | 45 | 95 | 15 | 15 |
| Heart rate (bpm) | 50 | 120 | 15 | 15 |

Source: Table 47, p. 160 of Dr. Simone’s review

Systolic Blood Pressure

For Placebo-controlled trials, the largest difference between the two groups was observed at 30 min post-baseline (median increase 7 mmHg for sugammadex; 0 mmHg for placebo).

Interpretation of these results is difficult because of the differences in the timing for turning off the anesthetic with different doses of sugammadex and also with placebo. The Applicant noted that in the pooled placebo-controlled Phase 1-3 trials, there were more markedly abnormal decreases in SBP that met the pre-specified criteria than markedly abnormal increases. They also observed that there was a dose-related trend for decreased SBP and for the AE “procedural hypotension” in the sugammadex-treated subjects which was higher than that for

Pbo-treated subjects (3.2 vs. 1.5%), with incidences generally higher in the 16 mg/kg dose group. The number of markedly abnormal SBP values was low and about the same between sugammadex and placebo-treated subjects.

For the pooled neostigmine-controlled trials, the Applicant stated that the descriptive statistics for SBP in the sugammadex treatment group were similar to the neostigmine treatment group. The incidence of AEs related to abnormalities of SBP was low overall, and the differences in incidence between the sugammadex group and the neostigmine group were not considered clinically relevant by the Applicant. The only BP-related AE that was greater in the sugammadex relative to the neostigmine group was that of “Hypertension” (2.9% vs. 1.4%). The Applicant noted that in the pooled neostigmine-controlled trials, the percent of subjects with markedly abnormal post-baseline SBP values was small and comparable between the sugammadex and neostigmine groups.

The Applicant also did an analysis of the mean % change in mmHG for the SBP at 2, 5, and 30 minutes from baseline. The changes are consistent with what is seen with Pbo and neostigmine.

Overall, Dr. Simone felt that these analyses of SBP indicate that the doses of sugammadex proposed for marketing do not alter SBP in a clinically meaningful way either at the end of surgery or during the early stages of anesthetic recovery.

Diastolic Blood Pressure (DBP)

The Applicant reported that the overall percentage of subjects in the both the placebo-and neostigmine controlled trials, with treatment-emergent markedly abnormal DBP values was small and similar between the two treatment groups regardless of timepoint. The incidence of AEs related to abnormalities of DBP was low overall, and the differences in incidence between the sugammadex group and the placebo group were not clinically relevant.

The Applicant did a similar analysis of the mean % change in mmHG for the DBP at 2, 5, and 30 minutes from baseline. The changes are consistent with what is seen with Pbo and neostigmine.

Heart Rate

Safety related to heart rate is discussed in **Section** Error! Reference source not found.

Respiratory Rate

The Applicant reported that for the pooled Phase 1-3 placebo and neostigmine-controlled trials, in the total sugammadex group mean and median changes from baseline to the final visit were small, and no dose trend was apparent for change from baseline. There were also no dose trends apparent for the AEs related to abnormalities of respiratory rate.

Dr. Simone felt the data showed that Sugammadex had no apparent clinically relevant effect on respiratory rate and was no different in this regard than placebo or neostigmine.

Body Temperature

The Applicant reported that there were no apparent dose trends for the AEs related to abnormalities of core body temperature (CBT) in the pooled Phase 1-3 clinical trials.

The incidence of Pyrexia (6% vs. 3.1%) and postoperative fever (0.4% vs. 0.2%) in placebo-controlled trials was higher in the Total sugammadex group than in the Pbo group, however the numbers were small overall. There did not seem to be a dose dependency for this effect.

Overall Impression of Vital Signs

Despite a near doubling of the safety database, Dr. Simone felt that the updated vital signs data analyses did not indicate any substantial changes in the overall safety of sugammadex compared to that observed with the data contained in the original NDA submission. The various analyses of the vital signs data related to blood pressure, respiratory rate and core body temperature do not indicate that sugammadex, at the doses proposed for clinical use, poses a clinically relevant risk that would affect any of these parameters.

H. Immunogenicity

The occurrence of anaphylactic reactions in several of the clinical trials led to the product being investigated for potential immunogenic properties. The findings of those investigations are summarized in **Section 9.I.1**).

I. Special Safety Concerns

1) Hypersensitivity / Anaphylaxis

To address the hypersensitivity issue raised by the FDA, the Applicant conducted the following studies and analyses:

- A dedicated trial in healthy volunteers (Trial P06042) on possible effects of hypersensitivity and/or anaphylaxis after repeated administration of routine doses of sugammadex (4 mg/kg), high doses of sugammadex (16 mg/kg), or placebo in healthy subjects with independent blinded adjudication of hypersensitivity cases. Additional work proposed by the FDA to further elucidate the mechanism of action of these hypersensitivity reactions based on the results of the biomarkers (skin testing, anti sugammadex IgE/IgG assay, basophil histamine release testing, such as Basophil HR-Testing, activation of contact and complement system, parameters of neutrophil or cytokine activation) was also included in Trial P06042.

P06042 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects age 18 to 55. A total of 480 subjects received a single-blind, saline placebo test dose at Week 0, and patients who experienced a reaction to the placebo dose were screened out. Of the 480 subjects enrolled, 448 were randomized in a 1:1:1 ratio to receive the following doses intravenously on Day 8 (Week 1), Day 36 (Week 5), and Day 78 (Week 11):

- sugammadex 4 mg/kg (n=148)

- sugammadex 16 mg/kg (n=150)
- Saline placebo (n=150)

On a scheduled inspection of one of the sites (site #2) from this trial, OSI inspectors found that the investigators had been unblinded, calling into question the integrity of data. Furthermore, on multiple occasions, a dosing investigator evaluated adverse events in violation of the protocol, potentially affecting six (6) cohorts (approximately 53 of the 95 randomized subjects from this site). This is described more fully in **Section 12.C. Clinical Site Inspections**.

In healthy volunteers in Trial P06042, a dose-related risk for hypersensitivity including anaphylaxis was identified, with the greatest risk being associated with the 16-mg/kg dose of sugammadex (a dose recommended only for immediate reversal in emergency interventions). Clinical signs and symptoms of hypersensitivity and/or anaphylaxis occurred soon after sugammadex administration (i.e., between “immediately” and 3.5 hours after sugammadex administration). The more severe reactions (including 3 reactions fulfilling any of the Sampson and/or Brighton anaphylaxis criteria) started within 1 minute after dosing. Symptoms and signs that did occur resolved quickly and spontaneously or responded to usual treatment. The following table summarizes the disposition of subjects from this trial.

Table 17 Patient Disposition - Study P06042

| | Placebo (N=150) | sugammadex 4mg/kg (N=150) | sugammadex 16mg/kg (N=150) |
|--|----------------------------|--|---|
| | n (%) | | |
| Patients who completed the study | 135 (90) | 135 (91.2) | 127 (84.7) |
| Patients who withdrew early | 15 (10) | 13 (8.8) | 23 (15.3) |
| Reasons for withdrawal | | | |
| <i>Hypersensitivity Adverse Events</i> | 2 (1.3) | 4 (2.7) | 10 (6.7) |
| Swollen tongue | 1 (0.7) | 0 | 0 |
| Anaphylactic Shock | 0 | 0 | 1 (0.7) |
| Hypotension | 0 | 0 | 1 (0.7) |
| Urticaria | 0 | 0 | 3 (2.0) |
| <i>Lost to Follow Up</i> | 2 (1.3) | 1 (0.7) | 2 (1.3) |
| <i>Consent Withdrawn</i> | 2 (1.3) | 3 (2.0) | 5 (3.3) |
| <i>Non-Compliance</i> | 9 (6.0) | 5 (3.4) | 6 (4) |
| Source: Table 5, p. 79, Clinical Study Report P06042 Module 5.3.5.4 (10.1) and Section 16.2.7.5, p. 576-578, Clinical Study Report P06042, Module 5.3.5.4 (16.2.7.5) . | | | |

Source: Table 1 from DPARP consult response, June 19, 2013

Overall 10 subjects in the study discontinued treatment after experiencing suspected hypersensitivity symptoms: 7 were from the sugammadex 16mg/kg group, 2 were from sugammadex 4mg/kg, and 1 from the placebo group. The reason for withdrawal for some of

the subjects who experienced hypersensitivity symptoms were captured under categories other than adverse events, such as consent withdrawn and noncompliance.

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms, the Applicant identified 68 cases of suspected hypersensitivity in 49 subjects. These were sent by the Applicant to an Adjudication Committee comprised of independent allergist / immunologists and anesthesiologists for review. The committee classified 8 subjects as having had a hypersensitivity reaction.

The consulting Division, DPARP has reviewed each of the suspected cases resulting from the Applicant's search. Those listings which included adverse events that were consistent with anaphylaxis were then crosschecked with case narratives. A final determination of anaphylaxis for these cases was made using NIAID/FAAN criterion #1 (as outlined in **Section 15.A. NIAID/FAAN Criteria for Anaphylaxis**). Using this method, DPARP identified 3 cases of anaphylaxis among the 68 potential hypersensitivity cases in 49 subjects.

Based on this case review, DPARP concluded that there are at least 3 clear cases of anaphylaxis in healthy subjects in this repeat dose clinical trial. Study P06042 consisted of 298 unique healthy volunteer subjects who received sugammadex. As a result, a frequency of anaphylaxis of 1.0% (3/298) in a healthy volunteer population we calculated. It is of note that all three cases of anaphylaxis occurred in the sugammadex 16 mg/kg group, and with the initial dose.

Among the 5 additional subjects adjudicated by the Applicant's Committee as having a hypersensitivity reaction, 4 subjects were in the sugammadex 16 mg/kg group, and 1 subject in the 4 mg/kg group. With the exception of 1 subject in the 16 mg/kg group who experienced urticaria with the 2nd dose, all hypersensitivity reactions occurred with initial administration. One subject in the 16 mg/kg experienced urticaria on all three administrations of sugammadex, while one subject in the 4 mg/kg group experienced pruritic rash on the first two administrations, and no reaction with the third administration. In general, signs and symptoms of hypersensitivity in these patients were immediate in onset (within minutes), with the exception of one patient who experienced urticaria ~3 hours post-dose, and were characterized by urticaria and flushing.

Results from assessment of tryptase levels, skin testing, assessment for sugammadex-specific IgE/IgG, as well as results from additional mechanistic studies exploring potential underlying mechanisms do not support basophil/mast cell-mediated hypersensitivity either via an IgE-mediated or direct non-IgE-mediated mechanism, nor a role for contact/complement activation, neutrophil activation, or cytokine release.

In addition to Trial P06042, the Applicant characterized the cumulative safety in the Phase 1-3 database and Postmarketing data.

Based on the analyses of the cumulative safety database from Phase 1-3 trials, in which suspected cases of anaphylaxis were adjudicated by the same Adjudication Committee, as in Trial P06042, no additional cases of anaphylaxis were identified. In the clinical setting

of Phase 2 to 3 trials, the incidence of adjudicated hypersensitivity-related cases was calculated by the Applicant to be 0.1%.

The Applicant's pharmacovigilance database Global Pharmacovigilance Corporate Adverse Events Reporting and Evaluation System was searched by the Applicant on July 3, 2012 for postmarketing reports of anaphylaxis and serious hypersensitivity received from healthcare providers, cumulatively from market introduction through June 15, 2012 in patients administered sugammadex. Anaphylaxis reports were identified by querying the narrow Anaphylaxis Standard MedDRA Query (SMQ), along with narrow terms from the "Anaphylactic/ anaphylactoid shock" sub-SMQ in the Shock SMQ. Serious hypersensitivity reports were identified by querying the broad Anaphylaxis SMQ, along with the preferred term "hypersensitivity". A total of 144 reports were identified in this query: 87 reports of anaphylaxis and 57 reports of serious hypersensitivity.

The Applicant suggested from their review of sugammadex's postmarketing experience that cases of anaphylaxis with serious clinical signs were rare and generally manageable in the clinical setting of the operating room. Based on their assumptions about reporting and exposure, the Applicant suggested the risk for sugammadex-associated anaphylaxis in the postmarketing surveillance reports appeared similar in magnitude to background rates for established agents routinely used in the peri-operative setting.

While the Applicant has sought adjudication of these reports by an external committee, DPARP contends that due to the nature of post-market reporting (limited/missing information) and characteristics of the surgical patients to whom the drug was administered (polypharmacy, multiple comorbidities, the effects of surgery), it is difficult to interpret/adjudicate these cases definitively. Therefore, DPARP has considered these post-marketing reports only as a means of further characterizing the types of hypersensitivity reactions that have been observed with use of sugammadex in the controlled clinical studies.

2) Coagulation

The Applicant's response to the FDA's request for additional information included the following components:

- The conduct and analysis of a clinical trial (Trial P07038) to assess events of bleeding and coagulation parameters in surgical subjects
- The conduct of a pooled analysis of serious/major events of bleeding from the Phase 2 to 3 development program (including the proposed clinical trial [Trial P07038])
- The conduct of a clinical study (P07044) in healthy subjects to assess Sugammadex -anticoagulant interaction
- The conduct of a clinical study (P07025) in healthy subjects to assess Sugammadex-aspirin interaction
- A summary of serious postmarketing events of bleeding.

As previously noted, DAAAP consulted the Division of Hematology and Oncology Products (DHOP) to review the Applicant's submission with respect to this issue.

The Trial P07038 evaluated the risk for bleeding in a high risk population of surgical subjects concomitantly treated with anticoagulants prior to major orthopedic surgery. The primary endpoint was the proportion of subjects with at least one, adjudicated, major or non-major but unanticipated event of bleeding within 24 hours after trial drug administration summarized in the following table, reproduced from the Applicant's submission (**Table 18**). The primary outcome endpoint was met by 2.9% of subjects randomized to the sugammadex arm compared to 4.1% in the control arm, identified by the Applicant as the "usual care" arm. These events included both major bleeding (2.0% vs. 3.4% in the SU and usual care arms, respectively) as defined in the protocol and unexpected non-major bleeding (0.9% vs. 0.7% in the sugammadex and usual care arms, respectively) as determined by the Adjudication Committee. For the majority of events, the relationship between the trial drug and bleeding was determined to be "possible."

Table 18 Incidence of Subjects with at Least One Suspected Unanticipated Adverse Event of Bleeding

Protocol No. P07038

| Onset | Maximum Relationship ^b | Sugammadex (N=596) | | Usual Care (N=588) | |
|---------------------------------------|-----------------------------------|--------------------|-------------------------|--------------------|-------------------------|
| | | Major | Total (Major+Non-major) | Major | Total (Major+Non-Major) |
| Within 24 hours | Unlikely | 0 | 1 (0.2) | 2 (0.3) | 3 (0.5) |
| | Possible | 12 (2.0) | 16 (2.7) | 18 (3.1) | 21 (3.6) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 12 (2.0) | 17 (2.9) | 20 (3.4) | 24 (4.1) |
| Total ^a (Up to 14 days) | Unlikely | 5 (0.8) | 7 (1.2) | 4 (0.7) | 5 (0.9) |
| | Possible | 13 (2.2) | 17 (2.9) | 19 (3.2) | 22 (3.7) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 18 (3.0) | 24 (4.0) | 23 (3.9) | 27 (4.6) |

SUAEB=suspected unanticipated adverse event of bleeding

^a Only events with an onset on or before Day 14 were included. Note that each subject is counted only once.

^b Maximum relationship (by adjudicator) implies that if a subject experienced, for example, 2 major adjudicated events, one unlikely and one possible related, the subject was counted in the 'possible' row, and not in the 'unlikely' row.

Source: [Section 14.2.1.1.1.1.1](#)

Source: Table 11-1, Dr. Shashaty's (DHOP) May 2, 2013 consult response

A secondary endpoint for the trial extended the time of observation for the bleeding from the first 24 hours after surgery to 14 days after surgery. There was an increase in the incidence of major and unexpected non-major bleeding events in both arms, but slightly more so with sugammadex. Most of those events were considered unlikely to be related to trial-drug administration. Although there was a proportionally greater number of bleeding episodes after the 24 hour period, it is increased in both arms and is not statistically different. In addition,

they would not be expected to be related to the administration of sugammadex because of the short duration of the effects of sugammadex on the clotting times.

At 10 minutes after trial drug administration, there was a small, but statistically significant increase in the aPTT in subjects in the 4 mg/kg sugammadex arm compared to baseline [4.7% (CI, 3.4%, 5.9%)] and in subjects in the sugammadex arm compared to the usual care arm [5.5% (CI, 3.7%, 7.3%)] summarized in the following table, reproduced from the Applicant's submission (**Table 19**). Similar comparative increases were noted in the PT measurements [4.5% (CI, 3.3%, 5.8%) and 3.0% (CI, 1.3%, 4.7%)], respectively. At 60 minutes after trial drug administration, the laboratory findings had resolved.

Table 19 Change in Coagulation Parameters for Sugammadex and Usual Care

Protocol No. P07038

| | | Sugammadex (vs Baseline) | | Usual Care (vs Baseline) | | Sugammadex vs Usual Care | |
|------------------------|--------|-----------------------------|---------------------|-----------------------------|---------------------|-----------------------------|---------------------|
| | | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a |
| aPTT ^b | 10 min | 4.7% | (3.4%, 5.9%) | -0.8% | (-2.0%, 0.4%) | 5.5% | (3.7%, 7.3%) |
| | 60 min | -1.9% | (-3.2%, -0.6%) | -2.8% | (-4.1%, -1.5%) | 0.9% | (-0.9%, 2.8%) |
| PT(INR) ^{b,c} | 10 min | 4.5% | (3.3% , 5.8%) | 1.5% | (0.3%, 2.7%) | 3.0% | (1.3%, 4.7%) |
| | 60 min | 2.7% | (1.2%, 4.1%) | 1.7% | (0.3%, 3.2%) | 0.9% | (-1.0%, 2.9%) |

aPTT=activated partial thromboplastin time; CI=confidence interval; PT(INR)=prothrombin time (international normalized ratio).

^a Estimates and confidence intervals are geometric means, adjusted for trial center, usual care group (active reversal versus spontaneous recovery), renal function (< or ≥ 60 mL/min), antithrombotic therapy (LWMH/UFH vs. other), surgical procedure (hip fracture, hip or knee replacement/revision, or hip or knee stage 1 revision [total or partial]), and treatment-by-time interaction.

^b A total of 567 subjects treated with sugammadex and 548 treated with usual care contributed to the cLDA analyses with a valid parameter value, both for aPTT as well as for PT(INR).

^c Estimates for PT and INR are identical; values for PT were used in analysis since these were provided with higher precision.

Source: Table 11-4, Dr. Shashaty's (DHOP) May 2, 2013 consult response

The Applicant concluded that treatment with 4 mg/kg sugammadex was not associated with an increased bleeding risk in comparison to usual care. This conclusion was made based on their analysis of the primary endpoint as well as a number of secondary bleeding endpoints irrespective of the definition or onset of the bleeding event. This finding was also consistent with the observation that there was no difference between sugammadex-treated subjects and subjects treated with usual care regarding endpoints of anemia, bleeding index, drainage volume, need for postoperative transfusion, and associated transfusion volume. With regard to the laboratory coagulation parameters aPTT and PT(INR), a small (5.5% and 3.3%, respectively) and transient increase (within 1 hour after administration) was associated with sugammadex treatment, which did not seem associated with any increase in the clinical risk for bleeding or blood loss. The incidences of treatment emergent adverse events are summarized in the following table, reproduced from the Applicant's submission (**Table 20**).

Table 20 Number of Subjects with at Least One Treatment Emergent Adverse Event

| | Number (%) of Subjects |
|--|------------------------|
|--|------------------------|

| | Treatment Groups | | Difference Estimate (95% CI) ^a |
|---|-----------------------|-----------------------|--|
| | Sugammadex n = 564 | Usual Care n = 560 | |
| Subjects with Treatment-Emergent AEs ^b | 551 (92.4%) | 549 (93.4%) | -0.9 [-3.9; 2.0] |
| Subjects with SAEs | 39 (6.5%) | 40 (6.8%) | -0.3 [-3.2; 2.6] |
| Subjects with Treatment-Related AEs ^c | 64 (10.7%) | 72 (12.2%) | -1.5 [-5.2; 2.1] |
| Subjects with Treatment-Related SAEs ^c | 4 (0.7%) | 2 (0.3%) | 0.3 [-0.6; 1.4] |
| Deaths ^d | 0 (0.0%) | 3 (0.5%) | -0.5 [-1.5; 0.1] |

AE= adverse event; CI = Confidence interval; SAE = serious adverse event

^a Risk difference and associated 95% confidence interval according to Miettinen-Nurminen method.

^b A treatment-emergent AE is defined as an AE occurring during or after trial medication administration up to and including 14 days after trial administration.

^c A treatment-related AE is defined as a treatment-emergent AE considered “possibly” or “probably” related to the medication by the investigator.

^d Any death occurring during or after trial administration. A total of 4 subjects assigned to usual care group died during the trial, but one subject (Subject 1/00144) was discontinued before administration of trial medication due to a pulmonary embolism (Section 16.2.72) and is not accounted for in the table.

Source: Table 12-2, Dr. Shashaty’s (DHOP) May 2, 2013 consult response

Additional in vitro PK and PK-PD models investigating the possible mechanism of action suggested the effects of Sugammadex on coagulation parameters aPTT and PT (INR) were likely to be mediated via an effect on Factor Xa activity/generation and were consistently found to be transient and of limited magnitude similar to the effects described in Trial P07038.

A drug-drug interaction study in healthy volunteers did not suggest a clinically relevant additive effect of sugammadex (4 mg/kg) and aspirin (75 mg) on relevant coagulation parameters such as platelet aggregation, aPTT, PT (INR), or anti-Factor Xa activity. Similar results were observed in a similar study of healthy volunteers exposed to sugammadex (4 mg/kg or 16 mg/kg) and enoxaparin (40 mg subcutaneous) or unfractionated heparin (5,000 IU subcutaneous). These studies further showed that sugammadex doses up to 16 mg/kg were associated with limited ($\leq 25\%$) and transient (≤ 1 hour) increases in aPTT and PT (INR).

The DHOP review of pooled data from the data base containing studies from Phase 1 to 3 (surgical subjects) noted that treatment with sugammadex did not seem associated with a significantly higher risk of events of bleeding in comparison to control treatments (placebo or neostigmine).

The Applicant also provided reports of postmarketing cases of hemorrhage events cumulative to June 15, 2012. There were a total of 5 incidents. The reports included the following:

- Two patients had postoperative bleeding at the surgical sites, i.e., following parotid resection and tonsillectomy. It was not possible to determine the extent, if any, to which sugammadex, inadequate wound closure, or inadequate hemostasis at the time of wound closure contributed to the bleeding.
- One patient developed bradycardia and cardiac arrest one minute following sugammadex administration following abdominal surgery for ovarian cancer. She required insertion of an intra-aortic balloon pump and anticoagulation for life support, but died 19 days later. At autopsy, she was found to have intra-abdominal hemorrhage and a lacerated aorta.

- One patient received sugammadex following total gastrectomy and experienced hypotension with no detectable pulse related to anaphylactoid shock followed by cardiac arrest. The patient went on to develop disseminated intravascular coagulation and intra-abdominal hemorrhage from bleeding at the surgical sites. The patient went on to develop multiorgan failure and died on postoperative Day 3.
- One patient received sugammadex following orthopedic surgery involving her femur. Later on the day of surgery, she experienced bradycardia, hypotension, increased “vascular permeability” and hemorrhagic shock. Inadequate information was captured in the report, including the time to onset of shock relative to sugammadex administration, to assess the role of sugammadex in this case.

In summary, both the Applicant and the DHOP consulting reviewer concluded that, based on clinical trials in at-risk subjects being treated with antithrombotic prophylaxis, the clinical safety database, and postmarketing surveillance data, the limited and transient effects of sugammadex on aPTT and PT (INR), which appear to be mediated mainly by a reversible inhibition of Factor Xa activity, are not associated with an increased bleeding risk in surgical subjects. I agree with these conclusions.

3) Cardiovascular

a - QT

In post-action discussions with the Applicant, the Agency agreed that, based on the data available and an additional analysis of ECG data for arrhythmias, there was no increased risk of QTc prolongation or arrhythmias associated with sugammadex use, and the Applicant need not conduct the study recommended in the Not Approvable letter. Nonetheless, the Applicant conducted a third QTc study (see **Section 6**), this time examining the risk of QTc prolongation when sugammadex was administered either propofol-induced or sevoflurane-induced general anesthesia. This study demonstrated no increased risk of QTc prolongation with sugammadex with either of these anesthetics. The previous studies showed the same for sugammadex administered alone and for sugammadex administered concurrently with rocuronium or vecuronium. Evaluation of the updated safety database indicated no increased risk of QTc prolongation or arrhythmias with sugammadex compared to placebo and neostigmine.

b - Arrhythmias

As part of the resubmission of the NDA, the Applicant was instructed to analyze both the clinical trial data and the postmarketing data evaluating the occurrence of all arrhythmias.

Clinical Trial Safety Database

To compare the incidence of arrhythmias across treatment groups, the Applicant performed Broad and Narrow Standardized MedDRA Query (SMQ) analyses for “Cardiac Arrhythmias” in both the pooled placebo-controlled trials and the pooled neostigmine-controlled trials. They reported no significant differences between sugammadex and its comparators for any of the SMQs in either the broad or narrow searches or in its component terms for the placebo-controlled trials (c.f., Table 21 of Dr. Simone’s review).

Additional analyses included evaluated the pooled Phase 1-3 trials for the percentage of exposures in subjects with treatment-emergent markedly abnormal pulse rate values, i.e., a heart rate outside the range of 50-120 bpm that was also a change from baseline ≥ 15 bpm. The percentage and range of abnormal values were similar for sugammadex and placebo subjects.

The Applicant also reported that no time point trends were observed for the percent of exposures in subjects with markedly abnormal values. However, a dose trend for markedly decreased pulse rate was present as was a dose trend for the bradycardia AEs exhibited in **Table 21** of my Review. In the dose-pooled analysis, the rate of bradycardia for sugammadex was 1.1% versus 0.7% for Pbo.

Table 21 Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group

| MedDRA Preferred Term | Placebo (N=544) | Sugammadex | | | |
|-----------------------|-----------------|-----------------|------------------|-----------------|-----------------------------|
| | | 2 mg/kg (n=838) | 4 mg/kg (n=1798) | 16 mg/kg (n=98) | Total ^A (N=3407) |
| At least one AE | 8 (1.5) | 12 (1.4) | 29 (1.6) | 6 (6.1) | 58 (1.7) |
| Tachycardia | 3 (0.6) | 9 (1.1) | 18 (1.0) | 3 (3.1) | 32 (0.9) |
| Bradycardia | 4 (0.7) | 2 (0.2) | 7 (0.4) | 2 (2.0) | 17 (0.5) |
| Heart rate increased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 1 (1.0) | 4 (0.1) |
| Heart rate decreased | 1 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Heart rate irregular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |

Source: Table 23, p 108 of 303 of Dr. Simone's review

In shift table analyses, there were a greater proportion of patients who were not bradycardic (>50 beats/minute) at baseline that experienced a decrease in heart rate below 50 beats/minutes compared with those in the placebo group. A small increase in the proportion of subjects with a marked reduction (>20 bpm) was observed that seemed dose responsive in the sugammadex group¹⁷, however the numbers having this event were small so the significance of this finding is unclear. The Applicant also compared the incidence of atropine administration one hour after study drug and found a slightly higher incidence with rocuronium (0.8%) than vecuronium (0.2%) use.

The Applicant made the following conclusions regarding the cardiovascular safety in their updated database:

- Sugammadex is not associated with QT/QTc prolongation beyond the level of regulatory concern when 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.

¹⁷ Table 26, p 110 of 303 of Dr. Simone's review (PDF Version)

- Sugammadex does not demonstrate any clinically relevant QT/QTc prolongation, or an increase in the incidence of categorical or change-from baseline outliers when compared to placebo in a meta-analysis of QTc data across the clinical development program
- Sugammadex is not associated with an increase in the incidence of AEs of QTc prolongation compared to placebo, when the QT interval is appropriately corrected for HR using the Fridericia formula, in an analysis of reported AEs of the integrated clinical development database.
- 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.
- For bradycardia in particular, there appears to be a small mean overall effect on heart rate when sugammadex is administered for the reversal of some NMBA. This effect seems to be dependent on the choice of background NMBA and more consistently observable with rocuronium than in the setting of vecuronium. Furthermore, this effect seems to translate in rare bradycardic events that are easily detected. The clinical trial database did not suggest a risk for clinically important bradycardia.

In his own analysis of cardiac SAEs, Dr. Simone noted that the only SAE that occurred with a frequency greater than 1% in any sugammadex dose group was QTc prolongation. With a doubling of the size of the safety database compared to the original NDA submission, only three additional incidents of QT prolongation have been reported as SAEs: two more in the 4 mg/kg dose group and one more in the 16 mg/kg dose group. Overall, this represents a decrease in frequency from 1.4% to 0.7% for SAEs of QTc prolongation with sugammadex treatment, which is not substantially different than that observed with placebo treatment, i.e., 0.2%.

Dr. Simone noted that the more commonly occurring adverse events in the resubmission database are, as it was with the original NDA submission, bradycardia, QTc prolongation, and tachycardia. With the resubmission, there were 29 new AEs of bradycardia; a single new AE of QTc prolongation and 28 new AEs for tachycardia. The overall incidence of each of these AEs has decreased since the original NDA submission such that they do not differ substantially from neostigmine or placebo treatments. For each of these AEs, there is no indication of dose dependence with sugammadex treatment.

Table 22 Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|--|-----------|--------------------|----------|-----------|-----------|----------|-----------|-----------|-----------|----------|------------|----------------------|-----------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | Total | 50 | 70 |
| N | 1318 | 137 | 220 | 856 | 2198 | 29 | 156 | 39 | 348 | 164 | 4147 | 814 | 42 |
| Adverse Event | | | | | | | | | | | | | |
| Acute myocardial infarction | 2 | | | | 1 | | | | | | 1 | 2 | |
| Atrial fibrillation | 2 | 1 | | 7 | 5 | | | | | | 13 | 4 | |
| Atrial flutter | | | | | 2 | | | | | | 2 | | |
| Atrioventricular block (1°) | 1 | | | | | | | | | | 0 | | |
| Atrioventricular block (2°) | 1 | | | | | | | | | 1 | 1 | | |
| Bradycardia | 9 | 1 | 1 | 14 | 30 | 1 | 6 | 1 | 8 | | 62 | 65 | |
| % | 1 | 1 | 0 | 2 | 1 | 3 | 4 | 3 | 2 | 0 | 1 | 8 | 0 |
| Cardiac arrest | | | | | | | | | | | 0 | 1 | |
| T wave abnormality | 1 | | | | | | | | | | 0 | 1 | |
| PR interval prolonged | | | | | | | | | | | 0 | | |
| QTc interval prolonged | 3 | | 1 | 13 | 6 | | 2 | 3 | 4 | | 29 | | 2 |
| % | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 8 | 1 | 0 | 1 | 0 | 5 |
| Supraventricular and Ventricular extrasystoles | 1 | | | 1 | 2 | | | | | 1 | 3 | 4 | |
| Tachycardia | 7 | | 5 | 26 | 47 | 1 | 2 | | 11 | 1 | 93 | 21 | 2 |
| % | 1 | 0 | 2 | 3 | 2 | 3 | 1 | 0 | 3 | 1 | 2 | 3 | 5 |
| Ventricular fibrillation | 1 | | | | | | | | | | | | |
| Ventricular tachycardia | | | | 1 | | | | | | 1 | | 1 | |
| WPW | | | | 1 | | | | | | | | | |
| Total | 28 | 2 | 7 | 63 | 93 | 2 | 10 | 4 | 23 | 4 | 208 | 99 | 4 |
| % of N | 2 | 1 | 3 | 7 | 4 | 7 | 6 | 10 | 7 | 2 | 5 | 12 | 10 |

Source: Table 31, p. 116 of 303 from Dr. Simone's review

Dr. Simone concluded the following based on the additional QT study conducted by the Applicant and the analyses of the safety database from the clinical trials:

1. Appropriately designed and conducted thorough QT studies have demonstrated that sugammadex, at doses intended for clinical use, does not prolong the QTc interval when administered:
 - a. Alone, i.e., not in the presence of anesthetic agents or neuromuscular blocking agents (NMBAs)
 - b. In combination with rocuronium or vecuronium but not in the presence of anesthetic agents
 - c. In the presence of anesthetic agents but not in combination with an NMBA
2. The risk of QTc prolongation with sugammadex does not exceed the risk with placebo or neostigmine to a clinically relevant extent.
3. QTc prolongation that was observed in the clinical trials was not associated with any episodes of Torsades de Pointes.
4. The risk of cardiac arrhythmias and acute myocardial infarction were not increased to a clinically significant degree by treatment with sugammadex compared to treatment with placebo or neostigmine.
5. Episodes of tachycardia and bradycardia that qualified as adverse events occurred following administration of sugammadex but not at frequencies that substantially differed from neostigmine or that exceeded that from placebo by a clinically relevant amount.

Based on the information provided in the NDA submission, the Applicant has sufficiently characterized the risk of cardiac arrhythmias and QTc prolongation to allow an informed

benefit:risk assessment and appropriate labeling of the product without the need for further clinical studies.

Postmarketing Findings

Since the first approval of sugammadex in the European Union on July 25, 2008, the Applicant reports the distribution of over (b) (4) vials for use in adult and pediatric patients as of June 15, 2012.

The following table reflects the arrhythmia-related postmarketing cases provided by the Applicant in this submission.

Table 23 Postmarketing arrhythmia-related adverse events

| Preferred Term | Number of Events (Serious) | Life Threatening | Non-Life Threatening |
|--------------------------------|-----------------------------------|-------------------------|-----------------------------|
| Tachycardia | 18 (15) | 14 | 4 |
| Bradycardia | 18 (10) | 8 | 10 |
| Cardiac arrest | 9 (9) | 7 | 2 |
| Heart rate increased | 8 (4) | 6 | 2 |
| Heart rate decreased | 5 (3) | 0 | 5 |
| Sinus bradycardia | 2 (2) | 0 | 2 |
| Sinus tachycardia | 2 (2) | 0 | 2 |
| Supraventricular tachycardia | 2 (2) | 0 | 2 |
| Arrhythmia | 1 (1) | 0 | 1 |
| Atrioventricular block | 1 (1) | 1 | 0 |
| Cardio-respiratory arrest | 2 (2) | 1 | 1 |
| Supraventricular extrasystoles | 1 (1) | 0 | 1 |
| Total Events | 69 (52) | 37 | 32 |

Source: Table 34 , p 120 of 303 of Dr. Simone's review

The most frequently reported arrhythmia-related events (55 of 69 events) were increases in ventricular rate (30 of 69 events reported as tachycardia, heart rate increases, sinus tachycardia) or decreases in ventricular rate (25 of 69 events reported as bradycardia, heart rate decreases, sinus bradycardia).

In their calculations regarding the incidence of postmarketing events, the Applicant used assumptions that only 90% of the product had been administered as of the cutoff date and 10% of the cases were reported. Based on these assumptions, the Applicant estimated the incidence of arrhythmias and cardiac arrest to be 21.7 per 100,000 operations [95% CI: 20.0; 23.4]. They considered this estimated arrhythmia incidence of 0.022% to be very low compared to the background incidence of arrhythmias in the range of 14-22%, as reported in the epidemiologic literature. The Applicant provided other rationale as to why these numbers were not clinically concerning:

- The cases were confounded by other medications.
- Tachyphylaxis was noted in the context of anaphylaxis, where it seemed to occur most often.
- Of the bradycardia cases (N=25), 10/25 did not have enough detail 12 occurred in the setting of anaphylaxis, and 13/25 occurred in otherwise stable pts...Overall, it seemed to them to be a rare event.
- There were 7 Cardiac arrests with 3 being fatalities, all had comorbid conditions.
- Patients in the OR are well monitored.

Upon review of the individual event reports and the Applicant's summary, Dr. Simone noted that :

- The majority of ventricular/supraventricular tachyarrhythmias were reported in the context of anaphylaxis (ie, 25 events out of the 30 events reported as tachycardia, etc) and appear to be related to that event.
- A total of 6 of 25 events of bradyarrhythmias occurred during anaphylaxis. A total of 8 of 25 cases were confounded by use of propofol (listing 'bradycardia' as an expected AE in the prescribing information).
- One patient with the reported term of Bradycardia had a fatal outcome.
- One additional case (2009SP039392) was reported as "cardiac arrest" and included a description of a slowed heart rate in the report narrative, but bradycardia/heart rate decreased was not specifically coded as an AE.
- Ten reports (with 11 events) of cardiac or cardio-pulmonary arrest were identified. In total, 6 of the 10 cases were non-fatal, and 4 cases were fatal.
- For 55 of the 64 reports, a medical outcome was provided, and 51 of the 55 patients recovered. The 4 fatal cases were caused by cardiac or cardio-pulmonary arrest. These fatal cases were all patients with serious co-morbid medical conditions, and most patients had multiple concurrent medications at the time of the cardiac arrest.

Dr. Simone further commented that

- The incidence of adverse events for tachycardia and bradycardia in the clinical development program was 1.6% and 0.3%, respectively, which are orders of magnitude greater than the Applicant's estimate of 0.022% based on postmarketing information.
- Regardless of the actual incidence for tachycardia and bradycardia, their association with anaphylactic reactions striking: 80% and 12%, respectively.
- At the time sugammadex is administered and for the 30 minutes thereafter, the patient is being continuously monitored in the operating room or post-anesthesia care unit by clinicians and nurses trained to detect and treat arrhythmias and cardiac arrest and who have the equipment and medications to do so expeditiously.
- The product's label should include the warning stated above (b) (4) as well as a statement describing the associated with anaphylaxis.
- Clinicians need to monitor patients carefully for the relatively small risks of bradycardia and tachycardia and the risks of anaphylaxis and cardiac arrest with which they have been associated

I concur with Dr. Simone's findings on the cardiac safety.

J. Major Safety Signals

No additional major safety signals were identified

K. Special Studies

Special safety studies are described in **Section I Special Safety Concerns**

L. Foreign Marketing Experience

On 6/17/13, DAAAP asked the Applicant to send a copy of all of postmarketing reports/CIOMS forms that they had received. The Applicant provided DAAAP the CIOMS forms (data locked to 5/31/13) on 6/21/13. The Applicant's submission of sugammadex reports safety reports to FDA is voluntary because to date, sugammadex has no U.S. approval. Therefore, the Applicant's CIOMS submission is considered to be more complete than what is in FAERS.

It should be noted that the Applicant submitted only serious unlabeled event reports to the IND and in this submission. A request for all postmarketing reports resulted in 654 reports being submitted. The Applicant indicated that it was not possible to provide the reports in a searchable data format.

A manual review of the reports indicated that the largest percentage related to anaphylactic reactions with cardiovascular changes occurring second most frequently; although the difference was substantial for the two. Given the limitations of postmarketing reports in terms of the data submitted, the rates at which they are under reported, and the lack of accurate numbers of exposures, a qualitative assessment was the best that could be made. In that regard, the postmarketing reports were consistent with adverse events reported in the clinical trails, with the exception that bradycardia, sometimes severe and leading to cardiac arrest was reported in the postmarketing safety database but not in the clinical trial database. Otherwise, there was no indication of a new safety signal in the review of these events.

Dr. Martin Pollock provided an analysis of the safety reports for sugammadex in FAERS. The time period of the search was from 1969 to 6/29/13, though the first approval was in 2008. Eighty-eight (88) cases were retrieved; those representing more than 2% of the cases are presented in **Table 24**. While these reports are most likely only a small fraction of adverse events in the postmarketing experience, they provide an indication of the relative type and proportion of postmarketing adverse events. Most of these events are consistent with the type of safety issues evaluated in the Complete Response, i.e., Arrhythmias, Anaphylaxis/Hypersensitivity, and Coagulation, suggesting that the premarketing analyses are able to reasonably inform about the postmarketing safety profile.

Table 24 Preferred Terms Occurring in Greater than 2% of Reports Ranked by Incidence

| Preferred Term | Count Of Events | Percent Of Total Cases |
|--------------------------------------|-----------------|------------------------|
| BLOOD PRESSURE DECREASED | 15 | 17.05% |
| RESPIRATORY ARREST | 11 | 12.50% |
| ANAPHYLACTIC SHOCK | 10 | 11.38% |
| CARDIAC ARREST | 9 | 10.23% |
| RECURRENCE OF NEUROMUSCULAR BLOCKADE | 9 | 10.23% |
| ANAPHYLACTIC REACTION | 8 | 9.06% |
| ERYTHEMA | 7 | 7.95% |
| TACHYCARDIA | 7 | 7.95% |
| BRONCHOSPASM | 6 | 6.82% |
| OXYGEN SATURATION DECREASED | 6 | 6.82% |
| URTICARIA | 6 | 6.82% |
| BRADYCARDIA | 5 | 5.68% |
| DYSPNOEA | 5 | 5.68% |
| POST PROCEDURAL HAEMORRHAGE | 5 | 5.68% |
| WHEEZING | 5 | 5.68% |
| HYPOXIA | 4 | 4.55% |
| PULMONARY OEDEMA | 4 | 4.55% |
| RASH | 4 | 4.55% |
| AIRWAY PEAK PRESSURE INCREASED | 3 | 3.41% |
| ANAPHYLACTOID REACTION | 3 | 3.41% |
| CARDIO-RESPIRATORY ARREST | 3 | 3.41% |
| FLUSHING | 3 | 3.41% |
| GENERALISED ERYTHEMA | 3 | 3.41% |
| SWELLING FACE | 2 | 2.27% |

Source: data supplied by Dr. Pollock

10. Advisory Committee Meeting

A meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) was scheduled for July 18, 2003. This meeting had to be cancelled on about July 16th because of the OSI findings described in **Section 12**.

11. Pediatrics

A proposal for the Pediatric Study Plan was submitted during the course of the NDA review. (b) (4)

[Redacted text block]

(b) (4)



(b) (4)



The pediatric studies should include each of the three timepoints for administration of sugammadex labeled for the adult population, i.e., at the reappearance of T2, at 1-2 PTCs, and at three minutes after a dose of 1.2 mg/kg of rocuronium. The studies should also evaluate safety and efficacy and appropriate dosing regimens for vecuronium as well as rocuronium for the first two timepoints of administration, i.e., at the reappearance of T2 and at 1-2 PTCs. The pediatric studies should not be started until the remaining safety issues for the adult population have been fully vetted by the Agency, and the appropriate juvenile animal studies have been conducted and reviewed by the Division.

12. Other Relevant Regulatory Issues

A. Calendar Extension

We sent information requests to Merck regarding two issues related to the datasets between February 7th and 25th, 2013. The final submission on March 1, 2013, was determined to be adequate.

The first issue pertained to our need for Demography datasets (DM) with only one row per subject for each study and integrated summary. A properly formatted DM is needed to analyze most other datasets (e.g., AES, Conmeds) with our reviewer tools because of the need to join demographic and treatment information to datasets. We particularly were concerned about those associated with the ISS, since the previously identified Cardiac safety signal is going to be analyzed with these data. We had at least 3 to 4 rounds of communications with Merck, including emails and phone calls. During the phone calls, they seemed to understand what we needed but the datasets they submitted still had the issue of multiple rows for many subjects until their final submission on 3/1/13.

The second issue was our request for a treatment variable to be added to each dataset with events related in time to the treatment such as AEs and concomitant meds. This was determined to be needed when both we and Merck realized that only the treatment sequence could be added to DM, since this file could only contain one row per subject. After one unacceptable proposal from Merck, I consulted (b) (4) and we determined a strategy which was ultimately relayed to Merck and successfully incorporated.

B. Other Significant Amendments

On May 6, 2013 the Applicant notified the Review team that it was discovered that a coding convention of adverse events in the clinical trial data base led to a situation where a number of cases of bradycardia and tachycardia were not selected for analyses as presented in the NDA. This coding convention applied to cases of bradycardia and tachycardia that were either observed during the surgical procedure or related specifically to anesthesia, and distinguished them from cases observed outside the surgical setting. Cases reported during the procedure were by convention coded as Procedural complication; cases which contained a reference to anesthesia were coded as Anaesthetic complication cardiac. In cases of bradycardia or tachycardia that occurred outside the setting of the surgical procedure and/or general anesthesia, the coding was defined simply as Bradycardia or Tachycardia. This convention had been applied throughout the clinical program, and was used for the original submission in 2007 as well.

After submitting revised dataset on May 24th, 2013. I discovered that the Applicant had made corrections to an old version of the dataset that did not incorporate the changes that were the subject of the extension described in **Section 12.A**. A teleconference was held on May 30, 2013, wherein I reminded the Applicant that for every row it was previously understood that the treatment be added, and that each have a unique subject ID. I could not find these in the new dataset, and asked the Applicant to explain and clarify. The Statistician on the phone call discovered upon my pointing this out that they had inadvertently made the modification on the original dataset, and not the most recent dataset. The Applicant agreed to fix this and ultimately sent a revised ISS AE dataset on May 31, 2013.

C. Clinical Site Inspections

An Interim Summary of Inspectional Findings was provided by Dr. Cynthia F. Kleppinger, M.D. of the Good Clinical Practice Assessment Branch (GCPAB), Division of Good Clinical Practice Compliance (DGCPC) in the Office of Scientific Investigation (OSI) on August 20, 2013 because the inspection of the study sites and materials is ongoing.

A Request for Clinical Inspections was submitted to the Division of Good Clinical Practice Compliance in the OSI on January 31, 2013. Site inspections were requested for two sites, one each for Study P07038, the orthopedic surgery study assessing postoperative bleeding and coagulation issues and Study P06042, the main study addressing the issue of Anaphylaxis / Hypersensitivity.

For Study P07038, the site of Dr. Walter Klimscha, an Austrian site was inspected on May 27-31, 2013. There were only minor deviations noted and overall the inspection was considered No Action Indicated (NAI).

For Study P06042 the site of Dr. Lawrence Galitz was selected based on the large proportion of randomized subjects (129 of the 448 randomized in the study). On 3/25/13, the Division notified the Applicant that the OSI group was not able to access the records. The site was initially owned by the contract research organization (CRO) (b) (4) which went out of business and was (b) (4). Our Office of Regulatory Affairs (ORA) inspector called the (b) (4) point of contact who informed her that the business was closing. The Applicant confirmed the

(b) (4) and noted that the records for the study would not likely be released without approval from the (b) (4)

A contractor for the Applicant has located the study records at an (b) (4) facility in (b) (4). The Applicant agreed on a protocol with the contractor to retrieve and transfer the records to the Principal Investigator, Dr. Galitz, to hold until the inspection. Merck has also identified a CRO to host the inspection. Some logistics are still being worked out but the inspection is tentatively scheduled for the second week in September. A formal request was also sent to the Applicant to submit the site trial master file to the application for review.

Another P06042 site, Dr. Ulrike Lorch, an investigator in the UK who had randomized 127 subjects, was selected on 4/16/13 by the Review Team for inspection. The inspection was conducted June 10-21, 2013 and had several objectionable conditions were observed that resulted in a Form FDA 483-Inspectional Observations. The inspectional results were communicated to OSI on July 12, 2013.

The following observations were made:

- The protocol contained the following procedures related to blinding:

“This study will be performed as a double-blind study. The syringes used for the intravenous administration of trial medication(s) will be blinded to ensure that the light color difference between sugammadex and placebo will not be revealed. Moreover, the investigator who evaluates the adverse events will not be involved in dosing of the subjects.”

A Note to File signed by the PI on 25 June 2010 was found by the FDA inspector which acknowledged that the protocol had not been followed. A transparent colored foil was placed on the syringe and the PI assumed that that was enough for blinding. The sub-investigator, Dr. Vedran Pavlovic, was dosing the study product and also evaluating the subjects for adverse events. This continued for approximately 8 weeks and potentially affected six (6) cohorts (approximately 53 randomized subjects). On October 20, 2009, Dr. Pavlovic notified Applicant personnel that he noticed increased viscosity between the treatments (saline, 4 mg sugammadex, and 16 mg sugammadex) upon manual administration. It was at this point that the practice of a single sub-investigator administering the medication and evaluating for adverse events was discovered and this practice ceased. In the review of 35 case report forms during the FDA inspection, several subjects were observed to have been impacted by being dosed by a sub-investigator who attended an adverse event for the same subject (e.g., Subjects 007, 206, 213, 230). The incident was not reported as a protocol deviation in the clinical study report nor was there any discussion of the issue. The Note to File contained a footer that documented that this incident was considered a protocol deviation.

- The site had a practice of migrating Applicant information to its own templates. The site used its own case report form template, “Signs and Symptoms of Hypersensitivity”, which did not contain all the elements of the protocol’s such as the “Gastrointestinal” section, which elicited subject information associated with “Diarrhea, Abdominal Pain, Nausea,

and Vomiting”. The incorrect version was used from the study’s start until, on or about October 1, 2009, affecting at least eight (8) randomized study subjects and all screening subjects having achieved Visit 2 (Day 1) by that date. Furthermore, all subjects were affected by missing information required by the Applicant to be on the form after October 13, 2010 concerning laboratory mast cell tryptase elevation. This protocol deviation was not reported to the FDA. A deviation note at the site contained a footer that documented that this incident was considered a protocol deviation.

Other minor issues are noted in the DGPC Summary Review. Because of the above issues, the last two remaining sites for protocol P06042 will be inspected..

13. Labeling

- Proprietary Name Review: DMEPA previously reviewed the proposed name, (b) (4) submitted to NDA 022225 on February 19, 2008, and found the name acceptable on May 23, 2008. In Europe, the product was approved by the EMEA in 2008 with the proprietary name, Bridion. Three years following Bridion’s approval in the European market, the Applicant withdrew the proposed name (b) (4) from NDA 022225, on December 20, 2011 and submitted the proposed name Bridion to IND 68029 on December 15, 2011. DMEPA completed an evaluation of the proprietary name Bridion in OSE review #2011-4588 dated June 7, 2012. The name, Bridion, was determined to be unacceptable. Six months later, the Applicant submitted a proprietary name request proposing the name (b) (4) (submitted to NDA 022225 on December 21, 2012). (b) (4) contains the (b) (4) and thus was unacceptable. On January 14, 2013, the Applicant withdrew the proposed proprietary name (b) (4) from NDA 022225 and submitted a Request to reconsider the proposed proprietary name, Bridion. On April 15, 2013, DMEPA concluded that the data submitted was insufficient to support the use of the proposed name for this product and continued to find the use of the proposed proprietary name, Bridion, unacceptable. On April 17, 2013, the Applicant submitted the proprietary name (b) (4) to NDA 022225. The proposed proprietary name was determined to be acceptable from both a promotional and safety perspective.

14. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

A Complete Response action is recommended.

I agree with Dr. Simone’s recommendation (italicized text) that to address the deficiency associated with the conduct of the P06042 study, the Applicant should be required to do one of the following:

- 1. Perform sensitivity analyses on Study P06042 and provide your rationale as to why the results are acceptable support for your conclusions, as follows:*
 - a. Identify all subjects whose treatment was not blinded from the investigators.*

I would add to the population proposed by Dr. Simone to be omitted from the sensitivity analysis, the subjects whose data was potentially affected because the site used its own case report form template, “Signs and Symptoms of Hypersensitivity”, which did not contain all the elements of the protocol’s (see p. 54 of my Review).

- b. Remove those subjects from the database and perform the protocol specified analyses on the remainder of the subjects.*
- c. Provide the results of the new analyses to the Agency along with a rationale for why the reduced number of subjects, based on the power calculations for the study, is adequate to address the deficiency in the Not Approvable letter.*
- d. Provide the Agency with necessary source documents to determine the validity of the data used in the reanalyses.*

OR

- 2. Repeat Study P06042 and submit the clinical study report to the Agency.*

- Risk Benefit Assessment

The benefits of a reversal agent for neuromuscular blockers must be interpreted in light of the fact that pharmacological reversal is not usually mandatory from a clinical perspective, with the exception of certain procedures where the patient needs some form of testing immediately after surgery (e.g., certain neurosurgical procedures). However, it is considered standard practice because it allows for faster exit from the operating room and decreases the period of residual weakness, which could affect ventilatory effort. This is said to put the benefit and risk into perspective.

The benefit of this product for the routine reversal of neuromuscular blockade by vecuronium and rocuronium was demonstrated in clinical trials 301, 302, 303, 310 and through the secondary endpoint of P05774. These studies characterized the time required for the endpoint of the ratio for T4/T1 to become greater than 0.9 in an adequate and well-controlled manner. These will allow for description of the dosing regimen and expected timing for onset for the claimed effect.

Dr. Simone and I have extensively documented rationale supporting the position that the data from the 303 study is not adequate for an indication of Immediate Reversal or a claim for use in the “Cannot Intubate / Cannot Ventilate scenario.” Most notably, the 303 endpoint of time to T1 = 1 is not clinically meaningful, since this level of reversal will not be sufficient for a patient to either maintain a patent airway or adequately ventilate without assistance. Furthermore, the Applicant provided no evidence that sugammadex has such an effect e.g., the endpoint of time to successful recovery of a patent airway and spontaneous ventilation.

An updated safety database and an evaluation of specific risks of hypersensitivity / anaphylaxis, coagulation, and cardiac arrhythmias associated with sugammadex use

were to be studied in this Complete Response. The updated safety profile, including adverse events, labs, vitals and the special studies focusing on the cardiovascular and hematologic issues were satisfactorily completed to characterize their component of the risk profile of sugammadex. Findings from the inspection of the Lorch site from the hypersensitivity / anaphylaxis study cast the integrity of the data into question since 53 of 448 subjects may have been unblinded. Since the hypersensitivity / anaphylaxis issue was one of the most important for review of the Complete Response and potentially, for the final labeling of safety for the drug, the risk:benefit profile cannot be fully characterized at this time.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

At present there is no need for any postmarketing risk evaluation and mitigation strategies.

- Recommendation for other Postmarketing Requirements and Commitments

The Applicant should conduct studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. The pediatric studies should include each of the three timepoints for administration of sugammadex labeled for the adult population, i.e., at the reappearance of T2, at 1-2 PTCs, and at three minutes after a dose of 1.2 mg/kg of rocuronium. The studies should also evaluate safety and efficacy and appropriate dosing regimens for vecuronium as well as rocuronium for the first two timepoints of administration, i.e., at the reappearance of T2 and at 1-2 PTCs. The pediatric studies should not be started until the remaining safety issues for the adult population have been fully vetted by the Agency, and the appropriate juvenile animal studies have been conducted and reviewed by the Division.

- Recommended Comments to Applicant

Deficiency:

The P06042 study was conducted to evaluate, in part, the safety of sugammadex sodium on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. The validity of those results have been called into question due to protocol violations that unblinded the safety assessor to the treatments administered and potentially biased the assessment of adverse events that were subjective in nature. These were violations documented by the site and known to the Applicant well in advance of the CR submission.

Without the support of the findings in Study P06042, it is not possible to determine the risk of anaphylaxis occurring with repeat exposure to sugammadex, and it is, therefore, not possible to determine whether the benefits of faster recovery from neuromuscular blockade at the end of surgery outweigh the risk of a potentially life-threatening reaction in a substantial segment of the population that presents for multiple surgical procedures over the course of a lifetime.

Furthermore, the scheduled Advisory Committee was cancelled because of this data integrity issue from Study P06042. Until the impact of the violation is fully evaluated, the Advisory Committee can not consider the risk:benefit of sugammadex.

Information needed:

1. Perform sensitivity analyses on Study P06042 and provide your rationale as to why the results are acceptable support for your conclusions, as follows:

a. Identify all subjects whose treatment was not blinded from the investigators and all subjects whose data was potentially affected because the site used its own case report form template, "Signs and Symptoms of Hypersensitivity", which did not contain all the elements of the protocol.

b. Perform the protocol specified analyses on the remainder of the subjects.

c. Provide the results of the new analyses to the Agency along with a rationale for why the reduced number of subjects, based on the power calculations for the study, is adequate to address the deficiency in the Not Approvable letter.

d. Provide the Agency with necessary source documents to determine the validity of the data used in the reanalyses.

OR

2. Repeat Study P06042 and submit the clinical study report to the Agency.

15. Appendices

A. NIAID/FAAN Criteria for Anaphylaxis

The three recommended NIAID/FAAN diagnostic criteria are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

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)
2. Two or more of the following that occur rapidly after exposure to a **likely** allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to **known** allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

B. Common Adverse Events¹⁸

Table 26 AEs occurring with a frequency greater than 0.5% in sugammadex-treated subjects

| System Organ Class | Preferred Term | Placebo (N=1759) | | Sugammadex (N=4914) | | Neostigmine (N=804) | |
|--|----------------------------------|---------------------|---|------------------------|----|------------------------|----|
| | | n | % | n | % | n | % |
| Blood and lymphatic system disorders | Anaemia | 49 | 3 | 125 | 3 | 38 | 5 |
| Body as a whole - general disorders | Therapeutic response decreased | 1 | 0 | 28 | 1 | 0 | 0 |
| Cardiac disorders | Tachycardia | 4 | 0 | 37 | 1 | 11 | 1 |
| Ear and labyrinth disorders | Vertigo | 9 | 1 | 41 | 1 | 22 | 3 |
| Gastrointestinal disorders | Abdominal distension | 2 | 0 | 29 | 1 | 7 | 1 |
| | Abdominal pain | 13 | 1 | 90 | 2 | 22 | 3 |
| | Abdominal pain upper | 6 | 0 | 25 | 1 | 14 | 2 |
| | Constipation | 73 | 4 | 264 | 5 | 113 | 14 |
| | Diarrhoea | 30 | 2 | 97 | 2 | 20 | 2 |
| | Dry mouth | 1 | 0 | 34 | 1 | 20 | 2 |
| | Dyspepsia | 5 | 0 | 26 | 1 | 9 | 1 |
| | Flatulence | 11 | 1 | 71 | 1 | 12 | 1 |
| | Nausea | 112 | 6 | 854 | 17 | 236 | 29 |
| | Vomiting | 59 | 3 | 384 | 8 | 104 | 13 |
| General disorders and administration site conditions | Chills | 15 | 1 | 91 | 2 | 12 | 1 |
| | Fatigue | 8 | 0 | 29 | 1 | 4 | 0 |
| | Oedema peripheral | 25 | 1 | 91 | 2 | 32 | 4 |
| | Pain | 17 | 1 | 199 | 4 | 131 | 16 |
| | Pyrexia | 18 | 1 | 209 | 4 | 45 | 6 |
| Infections and infestations | Naso-pharyngitis | 33 | 2 | 48 | 1 | 6 | 1 |
| | Urinary tract infection | 13 | 1 | 37 | 1 | 20 | 2 |
| Injury, poisoning and procedural complications | Anaemia postoperative | 52 | 3 | 76 | 2 | 19 | 2 |
| | Anaesthetic complication | 1 | 0 | 62 | 1 | 1 | 0 |
| | Incision site complication | 0 | 0 | 87 | 2 | 16 | 2 |
| | Incision site pain | 6 | 0 | 116 | 2 | 64 | 8 |
| | Post procedural complication | 22 | 1 | 58 | 1 | 12 | 1 |
| | Post procedural haemorrhage | 7 | 0 | 35 | 1 | 12 | 1 |
| | Post procedural nausea | 6 | 0 | 53 | 1 | 14 | 2 |
| | Post procedural pain | 0 | 0 | 33 | 1 | 0 | 0 |
| | Postoperative wound complication | 3 | 0 | 42 | 1 | 1 | 0 |
| | Procedural complication | 6 | 0 | 77 | 2 | 34 | 4 |
| | Procedural hypertension | 23 | 1 | 103 | 2 | 23 | 3 |

¹⁸ See Section 9.E.1)

| | | | | | | | |
|---|---|-----|----|------|----|-----|----|
| | Procedural hypotension | 8 | 0 | 115 | 2 | 24 | 3 |
| | Procedural nausea | 27 | 2 | 53 | 1 | 24 | 3 |
| | Procedural pain | 199 | 11 | 1398 | 28 | 426 | 53 |
| | Procedural vomiting | 12 | 1 | 35 | 1 | 14 | 2 |
| | Seroma | 1 | 0 | 25 | 1 | 22 | 3 |
| | Wound complication | 14 | 1 | 42 | 1 | 17 | 2 |
| | Wound haemorrhage | 8 | 0 | 31 | 1 | 18 | 2 |
| | Wound secretion | 19 | 1 | 27 | 1 | 5 | 1 |
| Investigations | Blood creatine phosphokinase increased | 1 | 0 | 32 | 1 | 3 | 0 |
| | Electrocardiogram QT corrected interval prolonged | 2 | 0 | 25 | 1 | 0 | 0 |
| | Haemoglobin decreased | 2 | 0 | 31 | 1 | 13 | 2 |
| | Oxygen saturation decreased | 0 | 0 | 25 | 1 | 4 | 0 |
| Metabolism and nutrition disorders | Hypocalcaemia | 4 | 0 | 30 | 1 | 4 | 0 |
| | Hypokalaemia | 28 | 2 | 69 | 1 | 28 | 3 |
| Musculoskeletal and connective tissue disorders | Arthralgia | 64 | 4 | 108 | 2 | 7 | 1 |
| | Back pain | 25 | 1 | 117 | 2 | 19 | 2 |
| | Musculoskeletal pain | 6 | 0 | 33 | 1 | 11 | 1 |
| | Myalgia | 8 | 0 | 31 | 1 | 8 | 1 |
| | Pain in extremity | 16 | 1 | 61 | 1 | 15 | 2 |
| Nervous system disorders | Dizziness | 21 | 1 | 172 | 4 | 62 | 8 |
| | Dysgeusia | 7 | 0 | 193 | 4 | 5 | 1 |
| Nervous system disorders | Headache | 98 | 6 | 287 | 6 | 58 | 7 |
| | Hypoaesthesia | 9 | 1 | 54 | 1 | 6 | 1 |
| | Paraesthesia | 9 | 1 | 47 | 1 | 7 | 1 |
| | Somnolence | 8 | 0 | 25 | 1 | 4 | 0 |
| Psychiatric disorders | Anxiety | 1 | 0 | 43 | 1 | 15 | 2 |
| | Insomnia | 24 | 1 | 145 | 3 | 57 | 7 |
| | Sleep disorder | 57 | 3 | 118 | 2 | 43 | 5 |
| Renal and urinary disorders | Bladder spasm | 1 | 0 | 29 | 1 | 5 | 1 |
| | Oliguria | 9 | 1 | 29 | 1 | 17 | 2 |
| | Urinary retention | 12 | 1 | 41 | 1 | 6 | 1 |
| Respiratory, thoracic and mediastinal disorders | Cough | 17 | 1 | 57 | 1 | 24 | 3 |
| | Dyspnoea | 9 | 1 | 45 | 1 | 11 | 1 |
| | Oropharyngeal pain | 31 | 2 | 36 | 1 | 10 | 1 |
| | Pharyngolaryngeal pain | 11 | 1 | 115 | 2 | 20 | 2 |
| Skin and subcutaneous tissue disorders | Erythema | 7 | 0 | 50 | 1 | 39 | 5 |
| | Hyperhidrosis | 3 | 0 | 25 | 1 | 7 | 1 |
| | Pruritus | 9 | 1 | 89 | 2 | 27 | 3 |
| | Rash | 11 | 1 | 40 | 1 | 14 | 2 |
| Vascular disorders | Haematoma | 26 | 1 | 72 | 1 | 34 | 4 |
| | Hypertension | 16 | 1 | 74 | 2 | 11 | 1 |
| | Hypotension | 10 | 1 | 58 | 1 | 36 | 4 |

Source: Table 35 from Dr. Simone's review, pp. 133-4.

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/s/

CHRISTOPHER D BREDER
08/30/2013

CLINICAL REVIEW

| | |
|--------------------------|---|
| Application Type | NDA - Complete Response |
| Application Number(s) | 022225 |
| Priority or Standard | Standard |
| Submit Date(s) | December 20, 2012 |
| Received Date(s) | December 20, 2012 |
| PDUFA Goal Date | September 20, 2013 |
| Division / Office | DAAAP/ODE 2 |
| Reviewer Name(s) | Arthur Simone, MD, PhD |
| Review Completion Date | August 23, 2013 |
| Established Name | Sugammadex sodium |
| (Proposed) Trade Name | (b) (4) |
| Therapeutic Class | Neuromuscular blockade reversal agent |
| Applicant | Organon USA Inc. |
| Formulation(s) | Injectable |
| Dosing Regimen | Single-dose |
| (Proposed) Indication(s) | Routine reversal of moderate or deep NMB by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium |
| Intended Population(s) | Adults |

Table of Contents

| | | |
|----------|--|-----------|
| 1 | RECOMMENDATIONS/RISK BENEFIT ASSESSMENT | 8 |
| 1.1 | Recommendation on Regulatory Action..... | 8 |
| 1.2 | Risk Benefit Assessment | 8 |
| 1.3 | Recommendations for Postmarket Risk Evaluation and Mitigation Strategies | 10 |
| 1.4 | Recommendations for Postmarket Requirements and Commitments..... | 10 |
| 2 | INTRODUCTION AND REGULATORY BACKGROUND..... | 11 |
| 2.1 | Product Information..... | 11 |
| 2.2 | Currently Available Treatments for Proposed Indications | 11 |
| 2.3 | Availability of Proposed Active Ingredient in the United States | 11 |
| 2.4 | Important Safety Issues with Consideration to Related Drugs | 12 |
| 2.5 | Summary of Presubmission Regulatory Activity Related to Submission..... | 12 |
| 2.6 | Other Relevant Background Information | 13 |
| 3 | ETHICS AND GOOD CLINICAL PRACTICES..... | 14 |
| 3.1 | Submission Quality and Integrity | 14 |
| 3.2 | Compliance with Good Clinical Practices | 14 |
| 3.3 | Financial Disclosures..... | 14 |
| 4 | SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES..... | 16 |
| 4.1 | Chemistry Manufacturing and Controls | 16 |
| 4.2 | Clinical Microbiology | 16 |
| 4.3 | Preclinical Pharmacology/Toxicology..... | 16 |
| 4.4 | Clinical Pharmacology | 16 |
| 4.4.1 | Mechanism of Action..... | 16 |
| 4.4.2 | Pharmacodynamics | 17 |
| 4.4.3 | Pharmacokinetics | 17 |
| 5 | SOURCES OF CLINICAL DATA | 18 |
| 5.1 | Tables of Studies/Clinical Trials | 18 |
| 5.2 | Review Strategy..... | 19 |
| 5.3 | Discussion of Individual Studies/Clinical Trials | 19 |
| 6 | REVIEW OF EFFICACY | 20 |
| | Efficacy Summary | 20 |
| 6.1 | Indication..... | 22 |
| 6.1.1 | Methods | 22 |
| 6.1.2 | Demographics | 27 |
| 6.1.3 | Subject Disposition | 29 |
| 6.1.4 | Analysis of Primary Endpoints | 29 |
| 6.1.5 | Analysis of Secondary Endpoints(s) | 36 |
| 6.1.6 | Other Endpoints | 38 |
| 6.1.7 | Subpopulations..... | 38 |
| 6.1.8 | Analysis of Clinical Information Relevant to Dosing Recommendations..... | 39 |
| 6.1.9 | Discussion of Persistence of Efficacy and/or Tolerance Effects..... | 39 |
| 6.1.10 | Additional Efficacy Issues/Analyses..... | 39 |
| 7 | REVIEW OF SAFETY..... | 40 |
| | Safety Summary | 40 |
| 7.1 | Methods..... | 44 |
| 7.1.1 | Studies/Clinical Trials Used to Evaluate Safety..... | 44 |

| | | |
|----------|---|------------|
| 7.1.2 | Categorization of Adverse Events..... | 46 |
| 7.1.3 | Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence..... | 47 |
| 7.2 | Adequacy of Safety Assessments..... | 49 |
| 7.2.1 | Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations..... | 49 |
| 7.2.2 | Explorations for Dose Response..... | 51 |
| 7.2.3 | Special Animal and/or In Vitro Testing..... | 51 |
| 7.2.4 | Routine Clinical Testing..... | 52 |
| 7.2.5 | Metabolic, Clearance, and Interaction Workup..... | 52 |
| 7.2.6 | Evaluation for Potential Adverse Events for Similar Drugs in Drug Class..... | 53 |
| 7.3 | Major Safety Results..... | 54 |
| 7.3.1 | Deaths..... | 54 |
| 7.3.2 | Nonfatal Serious Adverse Events..... | 57 |
| 7.3.3 | Dropouts and/or Discontinuations..... | 67 |
| 7.3.4 | Significant Adverse Events..... | 73 |
| 7.3.5 | Submission Specific Primary Safety Concerns..... | 78 |
| 7.4 | Supportive Safety Results..... | 133 |
| 7.4.1 | Common Adverse Events..... | 133 |
| 7.4.2 | Laboratory Findings..... | 144 |
| 7.4.3 | Vital Signs..... | 159 |
| 7.4.4 | Electrocardiograms (ECGs)..... | 173 |
| 7.4.5 | Special Safety Studies/Clinical Trials..... | 173 |
| 7.4.6 | Immunogenicity..... | 174 |
| 7.5 | Other Safety Explorations..... | 175 |
| 7.5.1 | Dose Dependency for Adverse Events..... | 175 |
| 7.5.2 | Time Dependency for Adverse Events..... | 175 |
| 7.5.3 | Drug-Demographic Interactions..... | 175 |
| 7.5.4 | Drug-Disease Interactions..... | 176 |
| 7.5.5 | Drug-Drug Interactions..... | 177 |
| 7.6 | Additional Safety Evaluations..... | 178 |
| 7.6.1 | Human Carcinogenicity..... | 178 |
| 7.6.2 | Human Reproduction and Pregnancy Data..... | 178 |
| 7.6.3 | Pediatrics and Assessment of Effects on Growth..... | 178 |
| 7.6.4 | Overdose, Drug Abuse Potential, Withdrawal and Rebound..... | 178 |
| 7.7 | Additional Submissions / Safety Issues..... | 180 |
| 8 | POSTMARKET EXPERIENCE..... | 181 |
| 9 | APPENDICES..... | 182 |
| 9.1 | Literature Review/References..... | 182 |
| 9.2 | Labeling Recommendations..... | 182 |
| 9.3 | Advisory Committee Meeting..... | 182 |
| 9.4 | Reviews of Individual Clinical Studies..... | 182 |
| 9.5 | Post Marketing Safety Reports Received Since the Original NDA Submission..... | 182 |
| 9.6 | Consultations..... | 183 |
| 9.6.1 | Consultations Related to Anaphylaxis and Hypersensitivity..... | 183 |
| 9.6.2 | Consultations Related to Coagulation and Bleeding..... | 16 |

Table of Tables

| | |
|---|-----|
| Table 1. Clinical studies not included in the original NDA submission. | 18 |
| Table 2. Study 301 treatment groups..... | 22 |
| Table 3. Demographics for subjects in the integrated summary of efficacy database | 28 |
| Table 4. Subject disposition for efficacy studies of the proposed indication. (Based on data from Table 2-2.1 on p. 323, Table 2-2.1 on p. 335, and Table 2-3.1 on p. 346 of Section 2.5 in the NDA resubmission) | 29 |
| Table 5. Summary of results from Studies 301 and 302..... | 32 |
| Table 6. Summary of the results from Study 303..... | 35 |
| Table 7. (b) (4) | 36 |
| Table 8. Comparisons of the findings for Studies 301, 302 and 303 for reversal of rocuronium..... | 38 |
| Table 9. Studies used for the analyses of safety (derived from data contained in Table 54 pp 175-178 and Table A-1 pp 232-259 of Section 2.5 in the NDA resubmission) | 44 |
| Table 10. Key demographic components of the safety database | 50 |
| Table 11. Adult subject exposures to sugammadex or placebo in the pooled Phase 1-3 studies (Table 4 on p. 43 of section 5.3.5.3 in the NDA resubmission) | 51 |
| Table 12. Number (%) of exposures for adult subjects who received anesthesia and/or NMBA and placebo or sugammadex in pooled Phase 1-3 Trials with at least one SAE (Table 34, p. 102 in section 5.3.5.3 of the NDA resubmission)..... | 58 |
| Table 13. Serious adverse event counts for all subjects who received intravenous study drug..... | 60 |
| Table 14. Serious adverse events related to bleeding and cardiac rhythm abnormalities. | 66 |
| Table 15. Subject disposition for placebo-controlled studies (from Table 18 on p. 71 of section 5.3.5.3 of the resubmission)..... | 67 |
| Table 16. Summary of severe adverse events N(%) by type of event and system organ class..... | 75 |
| Table 17. Summary of cardiac arrhythmia and acute myocardial infarction adverse events from the original NDA safety database..... | 99 |
| Table 18. Bradycardia, QTc prolongation, and tachycardia AEs from the original NDA safety database.. | 99 |
| Table 19. Summary of cardiac arrhythmia and acute myocardial infarction SAE data from the original NDA safety database..... | 100 |
| Table 20. Number (%) of subject exposures with AEs within Cardiac Arrhythmias related SMQs during the treatment period (combined data from Tables 69 and 70 on pp. 197-198 and 200-201 in Section 5.3.5.3 of the resubmission)..... | 104 |
| Table 21. Arrhythmia-related Investigations (signs and symptoms) (Broad SMQ) in pooled Phase 1-3 placebo-controlled studies (Table 67 on p. 193 of Section 5.3.5.3 of the resubmission)..... | 106 |
| Table 22. Markedly Abnormal pulse rates at any In-Treatment post-baseline timepoint in pooled Phase 1-3 placebo-controlled studies (Table 113 on p. 300 of Section 5.3.5.3 of the NDA resubmission) | 107 |
| Table 23. Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 112 on p. 299 of Section 5.3.5.3 in the NDA resubmission)..... | 107 |
| Table 24. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled placebo-controlled trials in order of decreasing incidence in the total sugammadex group (Table 114 on p. 300 in Section 5.3.5.3 of the NDA resubmission)..... | 108 |
| Table 25. Number (%) of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline for exposures in pooled Phase 1-3 studies by time point (Table 77 on p. 208 of Section 5.3.5.3 of the NDA resubmission) | 110 |
| Table 26. Number (%) of subject exposures for subjects with a decrease ≥ 20 bpm resulting in a heart rate ≤ 50 bpm for exposures pooled Phase 1-3 trials by time point (Table 78 on p. 210 of Section 5.3.5.3 of the NDA resubmission) | 110 |
| Table 27. Number of exposures for adult subjects who received NMBA and placebo or sugammadex in pooled Phase 2-3 studies who were administered atropine within one hour after study drug, by NMBA (Table 79 on p. 212 of Section 5.3.5.3 of the NDA resubmission)..... | 111 |

| | |
|---|-----|
| Table 28. Markedly abnormal values at any in-treatment timepoint and minimum and maximum pulse rate values in pooled Phase 3 neostigmine-controlled studies (Table 115 on p. 301 of Section 5.3.5.3 of the NDA resubmission)..... | 112 |
| Table 29. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled neostigmine-controlled trials in order of decreasing incidence in the total sugammadex group (Table 116 on p. 302 in Section 5.3.5.3 in the NDA resubmission) | 112 |
| Table 30. Summary of serious adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database..... | 114 |
| Table 31. Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database..... | 116 |
| Table 32. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13) | 117 |
| Table 33. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13) | 117 |
| Table 34. Postmarketing arrhythmia-related adverse events (Table 80 on p. 217 in Section 5.3.5.3 of the NDA resubmission)..... | 120 |
| Table 35. Adverse event counts for AEs occurring with a frequency of greater than 0.5% in sugammadex-treated subjects..... | 134 |
| Table 36. Adverse event counts for AEs occurring with a greater frequency for sugammadex than placebo and with a frequency > 1% for sugammadex..... | 136 |
| Table 37. Incidence of adverse events for nausea, vomiting, pain and dysgeusia by study drug and dose of sugammadex..... | 138 |
| Table 38. Number (%) of adverse events in pooled placebo-controlled trials for AEs with incidence for sugammadex of at least 1% and at least twice of that for placebo (Table 28 on p. 89 of Section 5.3.5.3 of the NDA resubmission)..... | 139 |
| Table 39. Number (%) of subject exposures associated with adverse events in pooled neostigmine-controlled trials (incidence $\geq 2\%$ in one or more treatment groups) (Table 30 on p. 94 of Section 5.3.5.3 in the NDA resubmission)..... | 140 |
| Table 40. Number (%) of subject exposures associated with adverse events in pooled Phase 1 trials in descending incidence by total sugammadex (incidence $\geq 2\%$ in one or more treatment groups) (Table 32 on p. 96 in Section 5.3.5.3 of the NDA resubmission)..... | 140 |
| Table 41. Notable shift categories (Table 89 on p. 258 in Section 5.3.5.3 of the NDA resubmission) | 145 |
| Table 42. Number (%) of exposures associated with adverse events in pooled Phase 1-3 Trials in order of decreasing incidence in the total sugammadex group (Table 90 on pp. 260-261 in Section 5.3.5.3 of the NDA resubmission)..... | 148 |
| Table 43. Number (%) of exposures associated with adverse events in pooled neostigmine-controlled trials in order of decreasing incidence in the total sugammadex group (Table 96 on p. 266 of Section 5.3.5.3 in the NDA resubmission)..... | 149 |
| Table 44. Number (%) of exposures associated with adverse events in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (Table 97 on pp. 268-269 in Section 5.3.5.3 of the NDA resubmission)..... | 152 |
| Table 45. Incidence of Markedly High Biochemistry Values at any In-treatment Post-baseline Timepoint and Corresponding Maximum Observed Values in Adult Subjects in Pooled Neostigmine-controlled Trials (Table 101 on p. 275 in Section 5.3.5.3 of the NDA resubmission) | 154 |
| Table 46. Number (%) of exposures associated with adverse events for urinalysis abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (Table 104 on pp. 280-281 in Section 5.3.5.3 of the NDA resubmission)..... | 156 |
| Table 47. Absolute value cutoffs and changes for blood pressure and heart rate that were used to determine “markedly abnormal values” (from Table 138 on p. 4317 in Appendix A of Section 5.3.5.3 in the NDA resubmission)..... | 160 |
| Table 48. Number (%) of exposures associated with blood pressure related adverse events in pooled Phase 1-3 placebo-controlled studies (Table 105 on p. 208 in section 5.3.5.3 of the NDA resubmission) | 163 |

| | |
|---|-----|
| Table 49. Summary of markedly abnormal, post-baseline, systolic blood pressure values in pooled placebo-controlled trials (Table 106 on p. 291 in Section 5.3.5.3 of the NDA resubmission) ... | 164 |
| Table 50. Number (%) of exposures associated with blood pressure related adverse events in pooled Phase 1-3 neostigmine-controlled studies (Table 109 on p. 294 in section 5.3.5.3 of the NDA resubmission) | 164 |
| Table 51. Summary of markedly abnormal, post-baseline, systolic blood pressure values in pooled neostigmine-controlled trials (Table 108 on p. 293 in Section 5.3.5.3 of the NDA resubmission) | 165 |
| Table 52. Mean % changes (absolute changes in mmHg) in systolic blood pressure from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)..... | 166 |
| Table 53. Mean % changes (absolute changes in mmHg) in systolic blood pressure from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13) | 166 |
| Table 54. Summary of markedly abnormal, post-baseline, diastolic blood pressure values in pooled placebo-controlled trials (Table 110 on p. 296 in Section 5.3.5.3 of the NDA resubmission) ... | 168 |
| Table 55. Summary of markedly abnormal, post-baseline, diastolic blood pressure values in pooled neostigmine-controlled trials (Table 111 on p. 297 in Section 5.3.5.3 of the NDA resubmission) | 168 |
| Table 56. Mean % changes (absolute changes in mmHg) in diastolic blood pressure from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)..... | 169 |
| Table 57. Mean % changes (absolute changes in mmHg) in diastolic blood pressure from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13) | 169 |
| Table 58. Number (%) of Exposures Associated with Adverse Events for Respiratory Rate Abnormalities in Pooled Phase 1-3 Trials by PT in Order of Decreasing Incidence in the Total Sugammadex Group (Table 117 on p. 303 in Section 5.3.5.3 of the NDA resubmission) | 170 |
| Table 59. Number (%) of exposures associated with adverse events in pooled neostigmine-controlled trials by pt in order of decreasing incidence in the total sugammadex group (from Table 119 on p. 305 in Section 5.3.5.3 of the NDA resubmission) | 171 |
| Table 60. Number (%) of exposures associated with adverse events in pooled phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 120 on p.306 in section 5.3.5.3 of the NDA resubmission)..... | 172 |
| Table 61. Number (%) of exposures associated with adverse events for body temperature abnormalities in pooled neostigmine-controlled trials by preferred term in order of decreasing incidence in the total sugammadex group (Table 122 on p. 308 of Section 5.3.5.3 in the NDA resubmission).. | 172 |

Table of Figures

Figure 1. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at the reappearance of T_2 by treatment group and NMBA (Figure 5 on p. 44 of Section 2.5 of the NDA resubmission)33

Figure 2. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at 1-2 PTCs by treatment group and NMBA (Figure 8 on p. 48 of Section 2.5 of the NDA resubmission)34

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A Complete Response action is recommended.

In the Not Approvable letter issued on July 31, 2008, the Applicant was required to characterize the safety of sugammadex sodium on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. To this end, the Applicant has submitted the results of study P06042. However, the validity of those results have been called into question due to protocol violations that unblinded the safety assessor to the treatments administered and potentially biased the assessment of adverse events that were subjective in nature. The violations were not reported to the Agency at the time the Applicant was informed of them or in the final study report when it was submitted in the NDA. Whether the violations were limited to only one of the four study sites is unknown at the time this review was completed. Without the support of the findings in study P06042, it is not possible to determine the risk of anaphylaxis occurring with repeat exposure to sugammadex, and it is, therefore, not possible to determine whether the benefits of faster recovery from neuromuscular blockade at the end of surgery outweigh the risk of a potentially life-threatening reaction in a substantial segment of the population that presents for multiple surgical procedures over the course of a lifetime.

To address this deficiency, the Applicant should be required to do one of the following:

1. Amend study P06042 as follows:
 - a. Identify all subjects whose treatment was not blinded from the investigators.
 - b. Remove those subjects from the database and perform the protocol-specified analyses on the remainder of the subjects.
 - c. Provide the results of the new analyses to the Agency along with a rationale for why the reduced number of subjects, based on the power calculations for the study, is adequate to address the deficiency in the Not Approvable letter.
 - d. Provide the Agency with necessary source documents to determine the validity of the data used in the reanalyses.
2. Repeat study P06042 and submit the clinical study report to the Agency.

1.2 Risk Benefit Assessment

The studies conducted to assess the efficacy of sugammadex consistently shown it to be superior to neostigmine reducing recovery times from rocuronium by 15 to 45

minutes when administered after spontaneous recovery has begun, i.e., at the reappearance of T₂ and at 1-2 PTCs, respectively, and from vecuronium by 10 to 60 minutes when administered at the same timepoints into spontaneous recovery. Additionally, sugammadex has been shown to be effective at reversing even the maximum labeled dose of rocuronium when its effects are at their peak. While the Applicant has not conducted any studies to show a clinical benefit associated with these reductions in reversal times, the benefits of sugammadex may be predicated on its ability to reliably and substantially hasten the recovery from paralysis induced by nondepolarizing neuromuscular blocking agents. Specifically, recovery from neuromuscular blockade may reduce anesthetic and surgical risks to patients by allowing earlier:

- cessation of exposure to anesthetic agents required to maintain unconsciousness
- return of spontaneous ventilation and maintenance of a patent airway, permitting discontinuation of mechanical ventilation and extubation of the trachea
- evaluation of neurological function, e.g., assess patients' ability to move extremities, peripheral sensation, speech and cognitive function, following surgical procedures that can affect the nervous system, e.g., spine surgery, carotid endarterectomy

The extent of the benefit depends on an individual patient's medical condition, surgical procedure, type of anesthesia and the difference in recovery time, which for sugammadex has been shown to be substantial.

The risks associated have not been fully characterized. With the exception of anaphylaxis, the risks are generally no worse than those for neostigmine, and often less. The risks with the greatest potential for morbidity and mortality, i.e., bradycardia, hemodynamic changes, and anaphylaxis generally occurred shortly after the administration of sugammadex, while patients are in a clinical setting where they are continuously monitored for such events and the staff and facilities needed to treat them are readily available. Although the anaphylactic events were typically reported as mild to moderate in severity, the frequency with which they have been observed, up to 1% in two clinical trials, raises the concern over the possibility of increased risk with repeat exposure, which would likely occur in a large segment of the population. Therefore, to be able to complete the risk benefit assessment, it is imperative that the Applicant resolve the issues surrounding the repeat-dose anaphylaxis study discussed in Section 1.1.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

At present there is no need for any postmarketing risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant should be required to conduct studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. The pediatric studies should include each of the three timepoints for administration of sugammadex labeled for the adult population, i.e., at the reappearance of T_2 , at 1-2 PTCs, and at three minutes after a dose of 1.2 mg/kg of rocuronium. The studies should also evaluate safety and efficacy and appropriate dosing regimens for vecuronium as well as rocuronium for the first two timepoints of administration, i.e., at the reappearance of T_2 and at 1-2 PTCs. The pediatric studies should not be started until the remaining safety issues for the adult population have been fully vetted by the Agency, and the appropriate juvenile animal studies have been conducted and reviewed by the Division.

2 Introduction and Regulatory Background

2.1 Product Information

Sugammadex, Org 25969, is a modified γ -cyclodextran in which all eight primary alcohols have been substituted by thiopropionate groups. The drug product contains (b) (4) Org 48302, which is also a modified γ -cyclodextran, (b) (4) Org 48302 is a (b) (4) It can comprise up to (b) (4) of the drug substance, and it has pharmacological activity and a pharmacokinetic profile that are similar to those of Org 25969. For the purposes of this review, sugammadex is used refer to the final drug product, i.e., both the Org 25969 and (b) (4) Org 48302.

2.2 Currently Available Treatments for Proposed Indications

Three products, pyridostigmine (NDA 17-398), edrophonium (NDA 7-959), and neostigmine (NDA 204078) are approved as reversal agents for the neuromuscular blocking effects of all available nondepolarizing muscle relaxants. In the United States, neostigmine is the most commonly used reversal agent; it is preferred in clinical practice because of its more rapid onset of action. An anticholinergic agent is frequently co-administered to counter the cholinergic effects of these agents. One formulation of edrophonium, Enlon-Plus (NDA 19-678), is a combination product containing atropine as the anticholinergic.

2.3 Availability of Proposed Active Ingredient in the United States

Sugammadex is a new molecular entity not currently marketed in the United States. Sugammadex was approved in the European Union on July 25, 2008, for use in adult patients and children and adolescents (2-17 years). As of July 2012, sugammadex has been registered in 71 countries and marketed in 41 countries. The Applicant reports the distribution of over (b) (4) vials for use in adult and pediatric patients through June, 2012.

2.4 Important Safety Issues with Consideration to Related Drugs

Sugammadex is a new molecular entity and the first in its class as a new type of reversal agent for neuromuscular blocking agents. Therefore, there are no related drugs and no known safety issues to consider in this context.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On July 31, 2008, the Agency issued an NDA Not Approvable letter identifying two clinical deficiencies that needed to be addressed before the product could again be considered for approval. The letter also included five additional recommendations for studies, that were not required for approval, and a list of the nonclinical evaluations that would be required before any multiple-dose pediatric trials could be initiated. A copy of the letter is included in the appendices to this review.

After the regulatory action was taken, multiple interactions between the Applicant and the Agency occurred to address the issues in the Not Approvable letter. The outcomes of these interactions are summarized here; those related to anaphylaxis/hypersensitivity, coagulation/bleeding, and cardiac arrhythmias are described in more detail in Section 7.3.5 below and consultations from the Division of Pulmonary, Allergy, and Rheumatology Products and the Division of Hematology Products that are included in the appendices.

On December 1, 2008, a post action meeting was held during which the Agency responded to the Applicant's questions regarding the regulatory decision and the rationale behind the deficiencies cited in the Not Approvable letter. After that meeting, the subsequent key interactions are listed below, grouped by the content.

Cardiac Arrhythmias

July 22, 2009: The Agency concurred with the Applicant that sugammadex is not likely to pose an increased risk for QT prolongation or arrhythmias. Therefore, it was not necessary to conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation as described in the "Not Approvable" letter list of recommendations.

Anaphylaxis and Hypersensitivity

February 26, 2009: The Applicant submitted to the IND, for Agency review their draft protocol for a repeat-exposure hypersensitivity study in healthy subjects.

November 19, 2009: the Agency indicated to the Applicant that the proposed study, as amended to address the Agency's concerns, was acceptable

January 19, 2011: The Agency advised the Applicant that a preliminary review of the results for the hypersensitivity study indicated that it appeared to adequately assess the risk of clinical anaphylaxis/hypersensitivity reactions with repeat exposure to

sugammadex. The Agency also stated that a formal determination would be made after a thorough review of the study and the safety data.

Coagulation and Bleeding

April 30, 2009: The Applicant submitted to the IND for Agency review the work that had been completed to address the effects of sugammadex on coagulation parameters.

January 25, 2010: The Agency informed that Applicant that two clinical studies would be needed: one assessing the bleeding risk in surgical patients treated with sugammadex and one evaluating the potential drug-drug interaction between sugammadex and anticoagulant/antiplatelet therapies commonly used in the perioperative period.

June 14, 2010: A Type A meeting was held to discuss whether the coagulation study precluded the need for the bleeding study. The Applicant was to submit a new protocol to include a primary endpoint with a clinical assessment of bleeding. The protocol would include a population administered different types of anticoagulation agents, a rationale for powering the study, and detailed explanations of the assays to be used.

January 19, 2011: The Agency advised the Applicant that completion of Study P07038 along with the results of in vitro work to characterize the mechanism of action by which sugammadex impacts the coagulation cascade, may provide sufficient clinical data to characterize the effect of clinical doses of sugammadex on bleeding and coagulation and to address the requirement to conduct a clinical study in surgical patients to support the resubmission of the sugammadex NDA.

June 29, 2012: The Applicant provided the Agency with its justification for shortening the follow-up period in the surgical patient bleeding study, which was later considered acceptable by the Agency.

Pre-NDA resubmission

June 14, 2012: A Type C meeting was held to discuss the resubmission of the NDA. The Agency noted the number of safety reports received regarding cardiac arrhythmias, the doubling of the safety database, and the number of new efficacy studies conducted. The Applicant was required to reintegrate the safety and efficacy findings to allow a benefit:risk analysis of all the available data to date. The Applicant was informed that another advisory committee meeting would be held.

August 24, 2012: The Agency notified the Applicant that their plans for updating the clinical sections in the NDA resubmission were acceptable.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was organized and complete in terms of locating the clinical information necessary to complete this review. There were issues related to the adverse event database that required multiple interactions with the Applicant before the issues were addressed and the safety analysis could begin. Specifically, the demography datasets had to be revised to include only one row per subject, unique subject identifiers had to be incorporated into the database, and the adverse event database needed to be revised to indicate the treatment and dose that were associated with the adverse event. When the revisions were finally made and submitted, it was considered a major amendment and the PDUFA deadline for the review was extended accordingly. An additional issue that impeded review was the submission of only those postmarketing reports that were considered serious and unlabeled; those that were consistent with the labeling in foreign countries were not submitted initially. There were a total of 654 reports that were ultimately submitted, but another request had to be made to receive them in a spreadsheet format.

Lastly, an inspection by the Office of Scientific Investigations revealed a number of protocol violations at one of four sites responsible for performing the study to address the anaphylaxis related deficiency in the Not Approvable letter. The failure of the Applicant to note the violations in the final study report and to notify the Agency of the situation when it occurred raised concern for the validity of the findings of the study overall and is the basis for a recommendation for a Complete Response to the NDA resubmission.

3.2 Compliance with Good Clinical Practices

The Applicant has stated that all clinical trials were conducted in compliance with Good Clinical Practices.

3.3 Financial Disclosures

In the original NDA submission, the Financial Certification and Disclosure document indicated that two investigators received significant payments:

1. (b) (6) served on the adjudication committee, acted as a consultant, and received an institutional grant. He was an investigator in Study 301.
2. (b) (6) received an educational grant and served as a investigator for Studies (b) (6).

In the resubmission, the Applicant made the following disclosures:

1. (b) (6), study P07038, site (b) (6), disclosed that he received an unrestricted educational grant for 100,000.00 €. (b) (6) received (part of) this grant, for his contribution as a Scientific Advisory Committee member for a study that is not the subject of this application.

The Applicant otherwise certified that none of the clinical investigators, from whom information was obtainable, disclosed a proprietary interest in the product or a significant equity in the sponsor. The Applicant further certified none of the investigators was the recipient of significant payments of other sorts. Some of the financial disclosure information under Schering Plough's ownership of the product was listed as "not available" primarily for study P05768 (>30) and P055775 (>20), but some were also listed this way in studies P05769, P05773, and P06101. In each of these cases, disclosure information was listed as "available" under Merck's ownership.

Based on the blinded design of the key clinical studies, the limited number of disclosures reported, and the availability of all disclosures during Merck ownership of the NDA, the missing disclosures under Schering Plough's ownership is not expected to have a significant impact on the overall assessment of safety or efficacy.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The review team included Drs. Yong Hu and Prasad Peri. They had identified no issues that would preclude approval of sugammadex at this time.

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

The review team included Drs. Alex Xu and Adam Wasserman. They had identified no issues that would preclude approval of sugammadex at this time.

4.4 Clinical Pharmacology

The review team included Drs. Srikanth Nallani, Atul Bhattaram and Yun Xu. They had identified no issues that would preclude approval of sugammadex at this time.

4.4.1 Mechanism of Action

Its mechanism of action consists of forming inclusion complexes with various drug molecules. With its lipophilic core it attracts the lipophilic steroidal parts of the neuromuscular blocking agents (NMBAs) rocuronium and vecuronium. These two neuromuscular blocking agents NMBAs are then retained in the core of the sugammadex molecule by the 8 side-chains connected to it, each with a negatively charged group on its end that are attracted to the positively charged ammonium group of rocuronium and vecuronium.

While sugammadex is especially able to bind rocuronium and, to a lesser degree, vecuronium, (b) (4)

4.4.2 Pharmacodynamics

The pharmacodynamic effects of sugammadex were previously evaluated in Phase 2 and 3. The drug appears to have no other effect except binding rocuronium and vecuronium. As the NMBAs are bound to the sugammadex molecules, the amount of NMBA available to bind to receptors in the neuromuscular junction is reduced, resulting in the reversal of the blockade. The rate at which reversal of neuromuscular blockade occurs has been demonstrated to be dependent on the extent to which receptors at the neuromuscular junction are bound to NMBA and the amount of sugammadex administered.

4.4.3 Pharmacokinetics

Key clinical pharmacology data include:

- The volume of distribution is 12-15 liters.
- The terminal half-life is 1-4 hours.
- The drug is not appreciably metabolized but is renally excreted unchanged.
- The clearance rate of sugammadex is similar to the glomerular filtration rate in healthy humans.
- PK parameters did not vary by gender, race (Caucasian versus Asian), or under general anesthesia.
- Severe renal impairment increases exposure 8 fold and terminal half-life by up the 13 fold compared to normal controls.
- Using high-flux dialysis filter, compared to low-flux filter, results in a more efficient clearance of sugammadex and the sugammadex-rocuronium complex from plasma.
- The product is dose proportional within the planned dose range.
- Pharmacokinetic modeling was used to predict the behavior of the drug in hepatically impaired patients
- Sugammadex has no effect of 4 mg/kg of platelet aggregation effects of aspirin.
- Sugammadex has no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 provides a list of the studies completed since the time of the original NDA submission. To the extent possible the Applicant was to have incorporated the safety data from these studies into an updated safety database and reassess safety. The same was to have been done with the efficacy data generated by these studies.

Table 1. Clinical studies not included in the original NDA submission.

| Study Number | Type of Study |
|-----------------|--|
| 19.4.110/P05854 | Skin prick and intradermal skin testing in volunteers not previously exposed to sugammadex; to investigate hypersensitivity |
| 19.4.112/P05860 | To assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by diflofenac or flucloxacillin 5 minutes after reversal of NMB by sugammadex |
| 19.4.113/P05861 | Assess the safety of re-use of rocuronium and vecuronium after reversal of NMB by sugammadex |
| 19.4.114/P05997 | Safety, PK in Chinese volunteers |
| 19.4.115/P05810 | Investigate the effect of sugammadex on hemostasis parameters |
| 19.4.116/P06315 | To evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers |
| 19.4.117/P06042 | Evaluate the incidence of hypersensitivity for each dose of sugammadex and placebo |
| 19.4.313/P05698 | To compare the T4/T1 ratio measured by the TOF-Watch® with the reappearance of T4 measured by a peripheral nerve stimulator within a subject |
| 19.4.316/P05767 | To demonstrate faster recovery from profound NMB with Org 25696 compared to placebo |
| 19.4.318/P05699 | To compare recovery from NMB by sugammadex and neostigmine |
| 19.4.324/P05768 | To show the recovery time from NMB induced by rocuronium after reversal by sugammadex is faster than by neostigmine |
| 19.4.326/P06101 | To compare recovery from NMB between sugammadex and neostigmine in Korean subjects |
| 19.4.328/P05769 | To show equivalent efficacy of sugammadex in subjects with normal or severely impaired renal function |
| 19.4.333/P05773 | To evaluate the dialysability of the sugammadex-rocuronium complex in vivo in subjects with renal impairment |
| 19.4.335/P05775 | To show the recovery time from NMB induced by rocuronium after reversal at a target depth of blockade of 1-2 PTCs by sugammadex is within 10 minutes in 95% of Caucasian subjects; and to show equivalence in the time to recovery in Chinese and Caucasian subjects |
| P07025 | To investigate the potential of an interaction between sugammadex and aspirin on platelet aggregation |
| P07044 | To evaluate the potential interaction effect between sugammadex and |

| Study Number | Type of Study |
|--------------------------------------|--|
| | enoxaparin or unfractionated heparin on anticoagulant activity |
| P07038 | To assess the effect of reversal of NMB with sugammadex compared with reversal according to usual care |
| INT00103441 (Heuman et al., 2009) | Assessment of possible effect of Org 25969 on the incidence of bleeding complications in patients; an analysis of adverse events |
| 19.4.319/(P05700) | To evaluate changes in plasma potassium levels after treatment with rocuronium followed by sugammadex or succinylcholine |
| 19.4.334/P05774 | To compare the incidence of residual NMB at time of tracheal extubation with sugammadex and neostigmine |

5.2 Review Strategy

The focus of this review was on the clinical studies conducted to address the two deficiencies identified in the Complete Response letter for the original NDA submission, specifically, the risk of anaphylaxis and hypersensitivity following exposure and repeat exposure to sugammadex and the effects of sugammadex on coagulation and bleeding. Additional focus was also placed on the new QTc study submitted by the Applicant and on cardiac arrhythmias associated with sugammadex use as reported in the updated safety database. The postmarketing data for all three of these safety issues was also evaluated.

As the Applicant has doubled the size of the safety database and conducted over 20 clinical trials since the original NDA submission, safety and efficacy data have been re-evaluated to determine whether any new safety signals exist, the safety profile has changed in a clinically relevant way, or the previous efficacy findings for the proposed dosing regimen and indications have been modified.

5.3 Discussion of Individual Studies/Clinical Trials

The studies conducted by the Applicant to address the issues in the Complete Response letter are discussed in Sections 7.5.3.1 and 7.5.3.1 and described in detail in the consultations from the Division of Pulmonary, Allergy and Rheumatology Products and the Division of Hematology Products, which are included in the appendices of this review.

6 Review of Efficacy

Efficacy Summary

Based on the clinical trials reported in the original NDA submission, sugammadex was found to be effective for reversing rocuronium- and vecuronium-induced neuromuscular blockade under two clinical conditions:

1. With the return of the second twitch (T_2) when a train-of-four (TOF) stimulus is applied to the ulnar nerve and the response of the abductor pollicis muscle is assessed
2. With the presence of one to two post-tetanic contractions following a tetanic electrical stimulus applied to the ulnar nerve and assessed by the adductor pollicis longus muscle response

Sugammadex was also found to be effective for reversing the neuromuscular blockade resulting from a 1.2 mg/kg dose of rocuronium when it is given at three minutes following rocuronium administration, the time when the maximal pharmacodynamic effect of rocuronium is expected.

For the first two clinical scenarios above, sugammadex provided a more rapid return of the ratio of the intensity of the fourth twitch (T_4) in a TOF stimulus to that of the first twitch (T_1) to 90% ($T_4/T_1 = 0.9$) compared to placebo or neostigmine, the anticholinesterase agent most commonly used in clinical practice for the reversal of nondepolarizing neuromuscular blocking agents (NMBAs).

For the third clinical scenario, sugammadex was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied in this scenario was the return of T_1 in a TOF stimulus to 10% of its baseline value. Sugammadex reversed the neuromuscular blockade induced by rocuronium in less time than it took for the effects of succinylcholine to spontaneously resolve. However, the clinical relevance of this level of recovery was not demonstrated in the clinical study and not otherwise provided by the Applicant. In this study, the Applicant evaluated the time to $T_4/T_1 = 0.9$ for the rocuronium/sugammadex treatment group as a secondary endpoint. The recovery time from this level of blockade took less than one tenth of the time it took for the highest labeled dose (by weight) of neostigmine to reverse a partially recovered rocuronium-induced blockade. These findings strongly support the efficacy of this dose and timing of administration of sugammadex.

The Applicant has indicated that the ability to reverse the highest labeled dose of rocuronium at the time of its maximum effect has the potential to reduce the morbidity and mortality that are associated with the inability to intubate or ventilate a paralyzed patient. However, they provided no evidence that such a claim is valid.

In the NDA resubmission, the Applicant has included a number of new clinical studies that contained efficacy data. These trials evaluated only the lower doses of sugammadex proposed for clinical use, and the findings were consistent with those of the pivotal studies conducted for the original NDA submission.

One new study warrants special note. Study P05774 evaluate the T₄/T₁ values for subjects on extubation after sugammadex was administered, per proposed labeling, at 1-2 PTCs and neostigmine was administered per standard of care; however, twitch monitoring was not used following administration of study drug to assess the level of recovery from neuromuscular blockade as part of overall evaluation of a patient's readiness to be extubated. The study showed that more subjects were extubated with T₄/T₁ < 0.9 when treated with neostigmine than with sugammadex. (b) (4)

(b) (4)

(b) (4)

(b) (4)

An additional efficacy-related labeling point also needs to be considered. The Applicant has applied the terms "routine" and "immediate" to the reversal from neuromuscular blockade. The term "immediate" has implications related to the Applicant's suggestion that this type of reversal has a safety benefit in emergency situations. The data do not suggest that the reversal is immediate: the drug must be given at 3 minutes after rocuronium is administered, and reversal to T₄/T₁ does not occur for several minutes more. (b) (4). Based on the efficacy data, it is recommended that the product be approved for the reversal of rocuronium at the three time points following rocuronium administration that were studied and for the reversal of vecuronium for the two timepoints following its administration that were studied. For the high dose of sugammadex, the label should be modified to indicate that doses of rocuronium up to 1.2 mg/kg can be reversed after 3 minutes with a 16 mg/kg dose of sugammadex.

In summary, the efficacy studies conducted over the entire development program support the finding that sugammadex is superior to neostigmine for reversing rocuronium and vecuronium when administered as proposed. The additional studies of the 16 mg/kg dose of sugammadex demonstrated that it is effective at reversing doses of rocuronium up to 1.2 mg/kg after 3 minutes. The studies did not show the need for dose adjustments based on age, gender, race, renal impairment, or hepatic impairment.

[N.B.: In the sections that follow, the tables, interpretations of the data, and comments contained therein are those of this reviewer unless they are specifically attributed to the Applicant or other entity.]

6.1 Indication

The Applicant has proposed the following indications for sugammadex:

For routine reversal:

- A dose of 4 mg/kg sugammadex 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 sugammadex is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.

For immediate reversal:

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16 mg/kg sugammadex is recommended.

6.1.1 Methods

In the original NDA submission, the Applicant submitted data from 23 clinical trials evaluating the efficacy of sugammadex four of which they considered to be pivotal. These were reviewed by Dr. Robert Shibuya in the first review cycle and are summarized here.

Three of the pivotal trials were similar in design and evaluated the efficacy of sugammadex when used for, what the Applicant termed, “routine reversal.” These included Studies 19.4.301 (Study 301), 19.4.302 (Study 302), and 19.4.310 (Study 310) each of which is described briefly below.

Study 301

In this study, subjects included healthy adults without renal disease [American Society of Anesthesiologists – Physical Status (ASA-PS) 1-3] who were scheduled for surgery requiring general anesthesia in the supine position. Following screening, patients were randomized 1:1:1:1 to one of the treatment groups in Table 2.

Table 2. Study 301 treatment groups

| GroupNumber | Neuromuscular Blocking Agent (NMBA) | Reversal Agent |
|-------------|-------------------------------------|----------------|
| 1 | Rocuronium | sugammadex |
| 2 | Rocuronium | neostigmine |
| 3 | Vecuronium | sugammadex |
| 4 | Vecuronium | neostigmine |

General anesthesia was induced with a standardized intravenous sequence followed by paralysis with the specified NMBA. Anesthesia was maintained with sevoflurane and parenteral agents, and the level of neuromuscular blockade was monitored with a Train-Of-Four (TOF) nerve stimulator. At the return of the second twitch response to a train-of-four stimulation, T2, the reversal agent was administered. This level of blockade was referred to as “shallow” blockade by the Applicant. The dose of sugammadex was 2 mg/kg; the dose of neostigmine was 50 mcg/kg.

The primary endpoint was the elapsed time between the start of administration of the reversal agent and the recovery of the T4/T1 ratio to 0.9, as measured by acceleromyography. Other clinical measures of recovery included a 5-second head lift and an assessment of general weakness. Safety was assessed from the induction of anesthesia through recovery by a safety assessor who was blinded to the treatment used.

Study 302

This study was similar in design to Study 301 but differed in two key aspects:

1. The reversal agent was administered when 1-2 twitches were detected following a tetanic stimulation, i.e., at 1-2 Post-Tetanic-Counts (PTCs). This level of blockade was referred to by the Applicant as “profound” blockade.
2. The dose of sugammadex was 4 mg/kg and the dose of neostigmine was 70 mcg/kg.

Study 310

This study differed from Study 301 and 302 in that there were two treatment groups:

1. Rocuronium reversed with sugammadex
2. Cisatracurium reversed with neostigmine

Dr. Shibuya did not consider this study to be properly designed to evaluate efficacy because the comparator neuromuscular blocking agent used was cisatracurium, to rocuronium. The study was therefore considered to be supportive rather than pivotal.

Study 303

This study was designed to assess the efficacy of sugammadex when used for “immediate reversal” of rocuronium. The Applicant considered this use of sugammadex as having the potential to reduce morbidity and mortality in the clinical situation where an unconscious, paralyzed patient can neither be ventilated nor intubated and a rapid return to spontaneous ventilation desirable. Currently, in anesthesia practice, the shortest acting NMBA is succinylcholine, a depolarizing NMBA whose effect diminishes as the drug diffuses away from the neuromuscular junction and is broken down by

plasma cholinesterase; at present, it cannot be reversed pharmacologically. The Applicant chose to compare the reversal of rocuronium, which has an onset of action similar to succinylcholine when a 1.2 mg/kg dose is administered, with sugammadex to the spontaneous recovery from succinylcholine to evaluate the possibility of a more rapid return to normal neuromuscular function. Thus, Study 303 differed substantially from Studies 301, 302, and 310. The following were the key differences:

1. Patient population
 - a. Subjects were healthier, i.e., only ASA-PS 1 and 2 patients were enrolled.
 - b. Subjects had to be undergoing surgical procedures for which a short period of neuromuscular blockade was appropriate.
2. Treatment arms
 - a. Rocuronium (1.2 mg/kg dose) followed by sugammadex (16 mg/kg dose) after three minutes had elapsed (the time point of maximal blockade)
 - b. Succinylcholine (1 mg/kg)
3. Primary endpoint

Since patients treated with succinylcholine do not demonstrate fade on TOF stimulation, and therefore, T_4/T_1 does not vary with recovery, the primary efficacy endpoint was the elapsed time from the injection of NBMA to recovery of T_1 to 10% of the baseline value.

In the NDA resubmission, the Applicant has included the study reports for 10 additional efficacy trials, none of which they classified as pivotal. These studies are listed below with a brief description of their efficacy assessments. Only the first four of the studies were randomized, controlled, had a single method for administering the study drugs, and had a primary endpoint that assessed the efficacy of sugammadex as a reversal agent for neuromuscular blockade (versus assessed the level of neuromuscular blockade at the time of extubation). The other studies provided efficacy data for patients with renal impairment and for assessing recovery using accelerometry versus manual evaluation of TOF twitch responses.

1. Phase 3 Studies with sugammadex administered at the reappearance of T_2
 - a. P05768 (19.4.324): This was a randomized, active, parallel-group, multi-site, safety-assessor-blinded trial of sugammadex of 291 adult, ASA-PS 1-3, Chinese and Caucasian subjects undergoing elective surgery under propofol anesthesia. It compared the recovery from rocuronium using either sugammadex (2 mg/kg) or neostigmine (50 mcg/kg) administered at the reappearance of T_2 . Neuromuscular functioning was monitored using a TOF-Watch® SX at the adductor pollicis. The primary efficacy endpoint was the time from study drug administration to recovery of the T_4/T_1 ratio to 0.9.
 - b. P06101 (19.4.326): This was a randomized, active-controlled, parallel-group, multi-site, safety-assessor-blinded study of 128 adult, ASA-PS 1-3, Korean subjects undergoing elective surgical procedures under general

anesthesia requiring the administration of rocuronium and requiring reversal of neuromuscular blockade. Subjects were randomly assigned to sugammadex (2 mg/kg) or neostigmine (50 mcg/kg) administered at the reappearance of T₂. Neuromuscular functioning was monitored using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was the time to recovery of the T₄/T₁ ratio to 0.9.

2. Phase 3 studies with sugammadex administered at 1-2 PTCs
 - a. P05767 (19.4.316): This was a multi-center, randomized, parallel-group, comparative, placebo-controlled, safety-assessor blinded trial of 4.0 mg/kg sugammadex in 140, adult, ASA-PS 1-3 subjects undergoing profound neuromuscular blockade. Sugammadex or placebo was administered as a single bolus dose at the end of surgery when 1-2 PTCs were detected. Neuromuscular functioning was monitored with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was time to return of the T₄/T₁ ratio to 0.9.
 - b. P05699 (19.4.318): This was a multi-center, randomized, parallel-group, active-controlled, safety-assessor blinded trial of 133 adult ASA-PS 1-3 subjects scheduled to undergo a laparoscopic cholecystectomy or appendectomy under general anesthesia requiring neuromuscular relaxation with rocuronium. Subjects were randomized to either sugammadex (4 mg/kg) or neostigmine (50 mcg/kg) administered as a single bolus dose at the end of surgery when 1-2 PTCs were detected. Neuromuscular functioning was monitored with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. The primary efficacy endpoint for the study was the time from administration of study drug to the recovery of the T₄/T₁ ratio to 0.9.
 - c. P05774 (19.4.334): This was a multi-center, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded, anesthesiologist-TOF-Watch® SX-blinded trial of 100 adult, ASA-PS 1-3 subjects scheduled to undergo an elective, open-abdominal, surgical procedure expected to last ≤ 4 hours under general anesthesia requiring reversal of neuromuscular blockade. Neuromuscular functioning was monitored continuously with acceleromyography using a TOF-Watch® SX at the adductor pollicis muscle. Study drugs included sugammadex (4 mg/kg) administered when 1-2 PTCs, or better, were detected and neostigmine (50 mcg/kg), which was administered “per standard of care” knowing whether spontaneous recover had already reached 1-2 PTCs or better. The primary efficacy endpoint was the T₄/T₁ ratio at the time of tracheal extubation.
3. Special populations
 - a. P05769 (19.4.328): This was an open-label, multicenter, parallel-group, comparative study in 68 adult, ASA-PS 1-3 subjects with normal and severely impaired renal function scheduled for a surgical procedure in the

supine position under general anesthesia with propofol requiring neuromuscular relaxation with the use of rocuronium. Subjects received a single bolus dose of 4.0 mg/kg of sugammadex at a target depth of neuromuscular blockade of 1-2 PTCs. Neuromuscular monitoring was performed using a TOF-Watch® SX at the adductor pollicis muscle. The primary endpoint was the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9.

- b. P05773 (19.4.333): This was a single center, exploratory, open label trial. It was designed to evaluate the dialysability of the sugammadex-rocuronium complex *in vivo* in 6 ASA-PS 1-4 subjects with severe renal impairment (creatinine clearance < 30 mL/min and a clinical indication for dialysis) who were hospitalized in an ICU scheduled for a surgical procedure in the supine position under general anesthesia requiring neuromuscular relaxation with the use of rocuronium. Subjects received a single 4 mg/kg dose of sugammadex at 15 minutes after administration of rocuronium after which, the dialysability of the sugammadex-rocuronium complex was evaluated for dialysis using the Fresenius 4008H hemodialyzer, with a hemodiafilter standard helixone membrane FX 600. Neuromuscular monitoring was performed using a TOF-Watch® SX at the adductor pollicis muscle. The primary efficacy endpoints for the trial were the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9, 0.8, and 0.7

4. Other

- a. P05698 (19.4.313): This was a multi-center, randomized, peripheral nerve stimulator (PNS)-assessor-blinded, parallel-group, active, within-subject controlled trial of 91 adult, ASA-PS 1-3 subjects scheduled for a surgical procedure in the supine position under general anesthesia requiring neuromuscular relaxation with the use of rocuronium. Subjects were randomly allocated in a 1:2 ratio to receive either a single dose of 1.0 or 4.0 mg/kg sugammadex, respectively, and in a 1:1 ratio to having the TOF-Watch® SX affixed to either the dominant or the non-dominant forearm. The study drug was administered at 15 minutes after the last dose of rocuronium. The primary endpoints were the time from start administration of 4.0 mg/kg of sugammadex to recovery of the T_4/T_1 ratio to 0.9 for TOF-Watch® SX monitoring and the time from start administration of 4.0 mg/kg of sugammadex to reappearance of T_4 as detected manually with PNS monitoring.
- b. P05700 (19.4.319): This was a multicenter, randomized, safety-assessor blinded, parallel group, active-controlled, comparative trial in 161 adult, ASA-PS 1-3 subjects scheduled for short (≤ 1.5 hours) surgical procedures in out-patient surgicenters. Subjects were randomly assigned to receive either rocuronium followed by a 4 mg/kg bolus dose of sugammadex for reversal at a target depth of blockade of 1-2 PTCs, or a 1

mg/kg bolus dose of succinylcholine followed by spontaneous recovery. Neuromuscular functioning was monitored using a TOF-Watch® SX device at the adductor pollicis muscle. The primary efficacy endpoint was the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9. The time from start of administration of succinylcholine to T_1 reaching 90% of baseline was a secondary endpoint.

- c. P05775 (19.4.335): This was an open-label, single-dose, multi-site trial to evaluate the time to recovery following administration of 4.0 mg/kg sugammadex at a target depth of 1-2 PTCs following rocuronium-induced neuromuscular blockade in 115 Chinese Asians living in China and 36 European Caucasians living in Europe. The subjects were ASA-PS 1-3 adults undergoing elective surgery under general anesthesia with rocuronium. Neuromuscular functioning was monitored using a TOF-Watch® SX at the adductor pollicis muscle. After the last dose of rocuronium, at a target depth of blockade of 1-2 PTCs, a single 4.0 mg/kg dose of sugammadex was administered. The primary efficacy endpoint is the time from start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9.

6.1.2 Demographics

Overall, subjects in the clinical trials were most often Caucasian, female, between 18 and 65 years of age, and relatively healthy, i.e., ASA-PS 1-2. Table 3 provides a demographic breakdown for study drug exposures by dose. The only major change since the original NDA submission is the increase in representation of Asian subjects due primarily to studies specifically directed at this population.

Table 3. Demographics for subjects in the integrated summary of efficacy database

| Parameter | Placebo | Sugammadex (mg/kg) | | | | | | | | | | | Neostigmine (mcg/kg) | | Succinylcholine (Spontaneous Recovery)) |
|------------|---------|--------------------|-----|-----|----|------|-----|-----|----|----|-----|-----|----------------------|----|---|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 50 | 70 | |
| N | 479 | 132 | 184 | 824 | 12 | 1723 | 29 | 122 | 39 | 93 | 2 | 1 | 801 | 42 | 134 |
| Gender (%) | | | | | | | | | | | | | | | |
| F | 48 | 48 | 42 | 51 | 25 | 55 | 10 | 41 | 38 | 61 | 100 | 0 | 60 | 60 | 63 |
| M | 52 | 52 | 58 | 49 | 75 | 45 | 90 | 59 | 62 | 39 | 0 | 100 | 40 | 40 | 37 |
| Race (%) | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asian | 5 | 30 | 21 | 27 | 8 | 10 | 0 | 16 | 0 | 4 | 0 | 0 | 22 | 12 | 3 |
| Black | 0 | 0 | 0 | 4 | 0 | 3 | 0 | 0 | 0 | 13 | 0 | 0 | 0 | 2 | 10 |
| Caucasian | 9 | 70 | 79 | 68 | 92 | 86 | 100 | 84 | 95 | 83 | 100 | 100 | 77 | 86 | 84 |
| Other | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 3 |
| | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ASA-PS (%) | | 0 | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 20 | 59 | 59 | 43 | 58 | 26 | 72 | 53 | 49 | 42 | 50 | 100 | 34 | 12 | 32 |
| 2 | 62 | 39 | 36 | 41 | 42 | 59 | 24 | 43 | 38 | 53 | 50 | 0 | 55 | 69 | 62 |
| 3 | 18 | 2 | 4 | 16 | 0 | 15 | 3 | 3 | 13 | 5 | 0 | 0 | 11 | 19 | 6 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Age (%) | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ≤ 65 y | 61 | 92 | 97 | 77 | 83 | 70 | 83 | 95 | 85 | 91 | 50 | 100 | 72 | 76 | 94 |
| > 65 y | 39 | 58 | 3 | 23 | 17 | 30 | 17 | 5 | 15 | 9 | 50 | 0 | 28 | 24 | 6 |

6.1.3 Subject Disposition

With a single administration of study drug in a confined setting such as the operating room, it would be expected that most subjects treated would complete the study. This was the situation that occurred with the sugammadex trials related to the proposed indication as shown in Table 4. For each method of administering sugammadex, more than 90% of subjects randomized received the study drug, and 99% of treated subjects completed the study.

Table 4. Subject disposition for efficacy studies of the proposed indication. (Based on data from Table 2-2.1 on p. 323, Table 2-2.1 on p. 335, and Table 2-3.1 on p. 346 of Section 2.5 in the NDA resubmission)

| Timing of Treatment | Randomized n | Treated ^A n (%) | Completed ^B n (%) | ITT ^C N (%) |
|--------------------------------|-----------------|-------------------------------|---------------------------------|---------------------------|
| Reappearance of T ₂ | 1577 | 1494 (95) | 1479 (99) | 1471 (93) |
| 1-2 PTCs | 953 | 885 (93) | 873 (99) | 845 (89) |
| 3 min. after rocuronium | 233 | 228 (98) | 226 (99) | 227 (97) |

^A Percent of randomized subjects who received study drug

^B Percent of treated subjects who completed the trial

^C Percent of randomized subjects

6.1.4 Analysis of Primary Endpoints

In general, the goal in reversing a neuromuscular blocking agent (NMBA) is to expedite and assure the return of neuromuscular function to the extent that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. In the clinical practice of anesthesia, a number of assessments may be made to evaluate a patient's ability to carry out both of these functions. These assessments include:

1. Mechanical responses of muscles to electrical stimulation of the motor nerves supplying them
2. Grip strength, which requires a level of consciousness that permits the patient to follow commands
3. Sustained head lift, for 5 or more seconds, which requires a level of consciousness that either allows the patient to follow commands or is associated with a return of the gag reflex
4. Spontaneous ventilation parameters, such as
 - a. Negative inspiratory force > -20 cm H₂O
 - b. Tidal volume > 5 mL/kg
 - c. Vital capacity > 10 mL/kg
 - d. Respiratory rate < 30 breaths/min
 - e. Appropriate oxygen saturation and end-tidal CO₂ levels

Often, the decision whether a patient is adequately recovered from the NMBA is based on a combination of these assessments; however, the standard of care includes the use of a peripheral nerve stimulator (PNS) to apply electric stimuli and permit an assessment of motor response.

The peripheral nerve stimulator has been used in clinical research as part of the development program for NMBAs, specifically, to characterize their pharmacodynamics as part of NDAs and to support the efficacy findings and dosing requirements. In addition, and more apropos to this NDA, the device has been used to generate pharmacodynamic and dosing and administration data for Enlon (edrophonium), Enlon-Plus (edrophonium and atropine), and Neoversa (neostigmine) which are approved for the same indication sought for sugammadex, i.e. reversal of NMBAs. In this regard, the technology is used to determine whether use of a reversal agent is appropriate, the dose of the agent and extent of recovery of neuromuscular function following administration of the reversal agent. This method of monitoring the level of neuromuscular blockade most often involves evaluating the responses of the abductor pollicis longus to varying types of electrical stimulation applied to the ulnar nerve. It should be noted that there is no evidence-based support that distinguishes a particular type of electrical stimulus as the most predictive of full recovery of neuromuscular function or that identifies a specific response to electrical stimulation as indicative that normal function has been fully restored. The types of electrical stimulation patterns used by the Applicant are those typically used in clinical practice and clinical research:

1. Train-of-Four (TOF) ratio – Four electrical impulses of equal amplitude and duration (between 0.1 and 0.5 msec) are applied at 2 Hz (i.e., 0.5 sec intervals); the ratio of the twitch response to the fourth impulse to that of the first impulse defines the TOF ratio. Prior to administration of an NMBA, all four twitch responses are (ideally) identical and the TOF ratio is 1.0. With increasing nondepolarizing blockade, the ratio decreases (fades) and the TOF ratio is < 1.0; with recovery, the TOF ratio increases until it returns to 1.0.
2. Post-tetanic stimulation – A tetanic stimulation at 50 Hz for five seconds is applied followed 3 sec later by single twitch stimulation at 1 Hz. The number of evoked post tetanic twitches detected is called the post tetanic count (PTC). This method is useful when there is no response to single twitch, TOF or tetanic stimulations. A PTC of ≥ 8 generally indicates the imminent return of TOF responses.

While the method of stimulating nerves to elicit a response has been well established in anesthesia practice, the methods for assessing the responses have not and range from manual evaluation of twitch strength to mechanomyography, which measures the force of contraction, and acceleromyography, which measures the acceleration of muscle contraction that in turn is proportional to the force. Early in the clinical development program, the Applicant argued that mechanomyography, the gold standard to quantitate the strength of contraction of the adductor pollicis, was not feasible because the equipment is no longer manufactured and the technique is too complex. They instead proposed the use of an acceleromyograph. The Division concurred with the proposal.

For Studies 301, 302, and 310, the applicant selected the return of the T_4 to T_1 ratio (T_4/T_1) to 0.9 as the primary endpoint. There is a substantial body of evidence in the literature that supports $T_4/T_1 = 0.9$ as an indication that sufficient neuromuscular function has returned for the patient to maintain a patent airway ventilate adequately without assistance. While this is the current standard, data in the literature up until the mid-1970s suggested that a $T_4/T_1 = 0.7$ was associated with clinically acceptable values for vital capacity, inspiratory force, and peak expiratory flow rates making this value often used as the standard cut-off point for adequate reversal of an NMBA. It should also be noted that other factors play a role in adequate ventilation in the immediate postoperative period, e.g., diminished respiratory drive due to sedatives and narcotics and muscle weakness related to inhaled anesthetics, which cannot be monitored with PNS.

For Study 303, the “immediate” reversal study, the applicant selected an endpoint of $T_1 = 0.1$ of baseline. The justification for not using the more established T_4/T_1 ratio was that the comparator was succinylcholine, which is a depolarizing NMBA and therefore, does not produce fade in twitch responses to the TOF stimulus. The applicant did not provide any references to support the clinical significance of the cutoff, i.e., 0.1, for this endpoint, but is clear that for recovery from rocuronium, $T_1 = 0.1$ will not be sufficient for a patient to either maintain a patent airway or adequately ventilate without assistance. Therefore, while the return of some strength is considered evidence of reversal of blockade or offset of action, for both succinylcholine and rocuronium, the clinical significance of this particular endpoint is subject to debate.

In this section, the efficacy studies will be considered based on their design and, therefore, the portion of the indication they support.

For the pivotal studies, 301 and 302, the results are summarized in Table 5. The recovery from neuromuscular blockade induced with either rocuronium or vecuronium was markedly reduced with sugammadex compared to neostigmine. The differences were not only statistically significant, but clinically relevant as well.

The reductions in recovery time, from 15 to 60 minutes, have important safety implications for patients in that it can reduce their exposure to and the risks from anesthetic agents and mechanical ventilation. The substantial reductions in recovery times also indicate that it is possible to maintain the paralysis to the end of the surgical procedure, thereby minimizing the risk of a surgical complication secondary to patient movement, without delaying recovery from the anesthetic and tracheal extubation, or alternatively, without beginning the recovery from the anesthetic and NMBA while the surgical procedure is still in progress in order to minimize the time to tracheal extubation once the procedure has ended. These potential benefits would need to be demonstrated in clinical outcome studies for the purposes of making a claim, but the incidence of adverse events related to intraoperative patient movement, exposures to

anesthetic agents for periods up to an hour, and mechanical ventilation for an hour are low making a clinical study difficult due to the number of subjects needed.

Table 5. Summary of results from Studies 301 and 302

| Study # | Sugammadex/ Neostigmine Dose | Timing of Administration | N | Geometric Mean Time to $T_4/T_1 = 0.9$ (mm:ss) | | p-value |
|---------|------------------------------------|--------------------------------|----|--|-------------|---------|
| | | | | Sugammadex | Neostigmine | |
| 301 | 2 mg/kg 50 mcg/kg | Reappearance of T ₂ | 96 | 01:29 (R) | 18:30 | <0.0001 |
| | | | 93 | 02:48 (V) | 16:48 | |
| 302 | 4 mg/kg 70 mcg/kg | 1-2 PTCs | 74 | 02:52 (R) | 50:22 | <0.0001 |
| | | | 83 | 04:28 (V) | 66:12 | |

R = rocuronium
 V = vecuronium

Although sugammadex has been clearly demonstrated to be superior to neostigmine for reversing rocuronium and vecuronium at the two time points of spontaneous recovery used in studies 301 and 302, there are two issues that need to be considered when weighing the product's benefits. First, some patients required substantially longer, than the mean value, to recover. For sugammadex, these outliers recovered sooner than the outliers associated with neostigmine treatment. This occurred for reversal administered at the reappearance of T₂ and at 1-2 PTCs. The Kaplan-Meier curves in Figure 1 and Figure 2 demonstrate this issue. The figures below were taken from the NDA submission and combine the efficacy data from all the trials (not Studies 301 and 302 alone) where study drug was administered at these time points in recovery. This finding indicates that not all patients are going to respond similarly to sugammadex, just as they do not respond similarly to neostigmine, and therefore, it is imperative that patients be monitored until full reversal is assured. This segues to the second issue that needs to be considered. The T₄/T₁ ratio is only an indicator of recovery from neuromuscular blockade, it does not indicate that a patient is able to maintain a patent airway or ventilate adequately without assistance. Therefore, it is important that clinicians take appropriate precautions in assessing patients prior to and after discontinuation of mechanical ventilation and tracheal extubation, as they have done in the past.

The two figures also indicate that the data from the new studies support the initial findings in the pivotal studies, 301 and 302, in that the Kaplan-Meier curves from those studies, not shown here but contained in Dr. Shibuya's review, are almost superimposable on the updated curves.

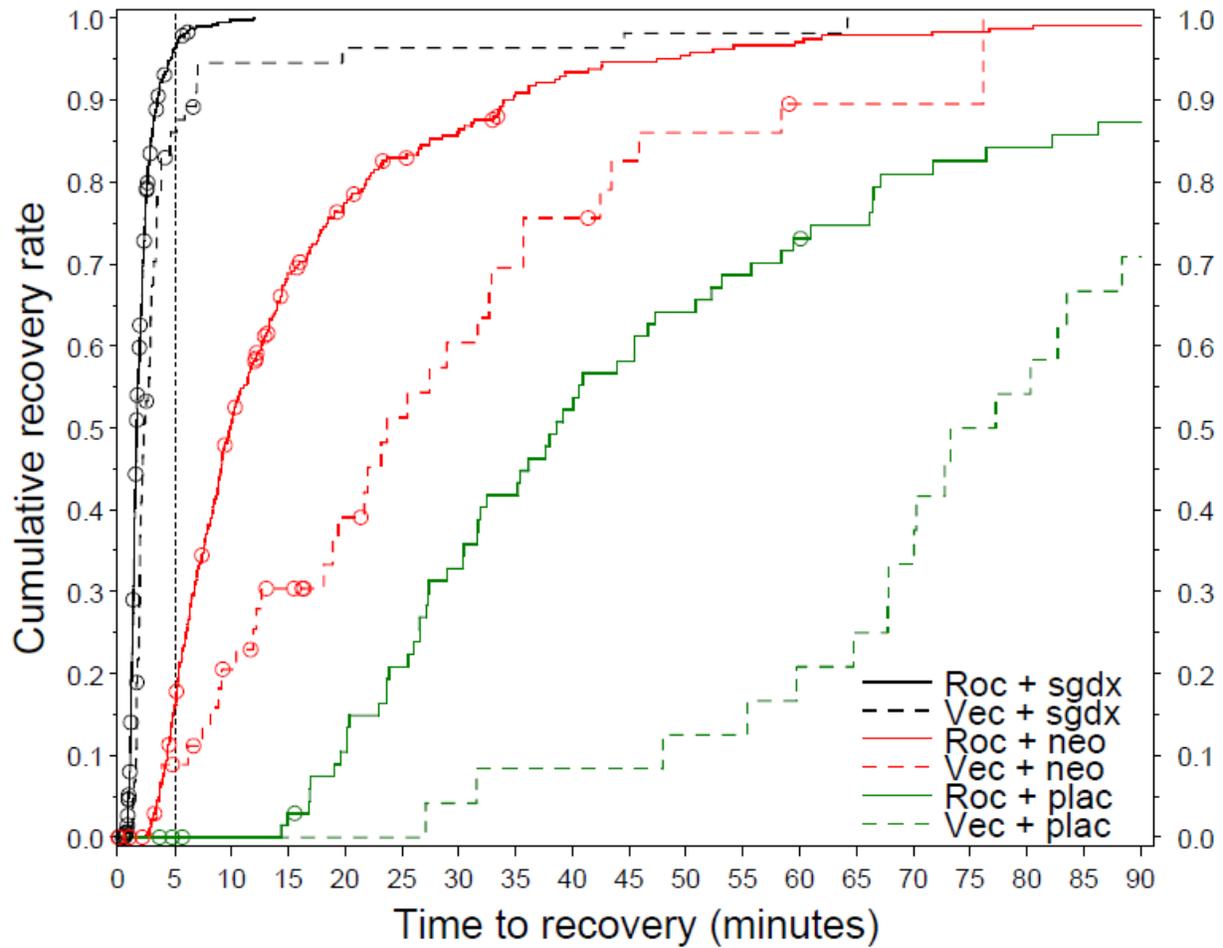


Figure 1. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at the reappearance of T_2 by treatment group and NMBA (Figure 5 on p. 44 of Section 2.5 of the NDA resubmission)

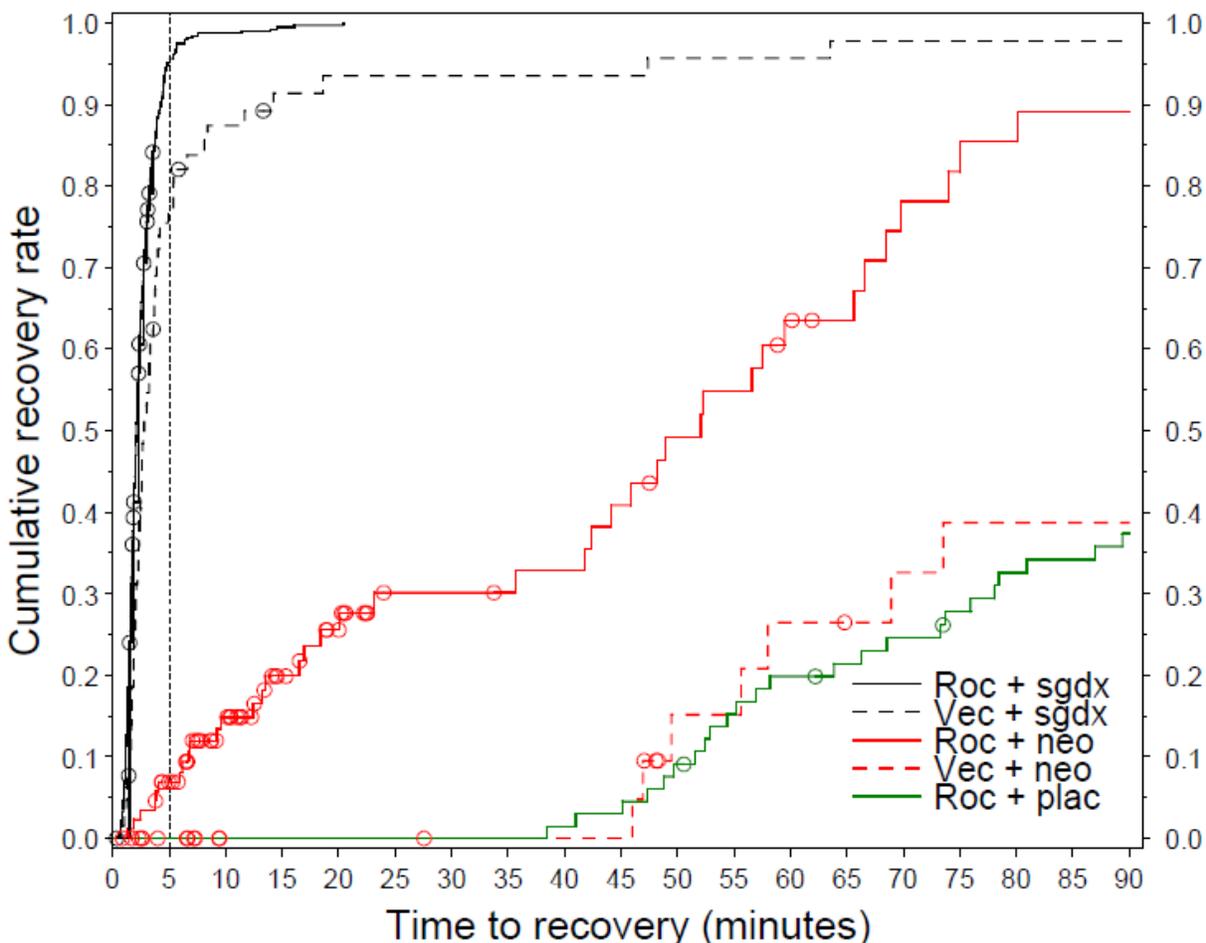


Figure 2. Kaplan-Meier curves for recovery times to $T_4/T_1 = 0.9$ with reversal administered at 1-2 PTCs by treatment group and NMBA (Figure 8 on p. 48 of Section 2.5 of the NDA resubmission)

The results for the primary endpoint in Study 303 are summarized in Table 6. In this study, recovery with sugammadex was significantly faster than spontaneous recovery from succinylcholine – at least to the point where $T_1 = 0.1$. The Applicant has not provided any evidence that sugammadex would provide a faster recovery to the point that a patient is capable of maintaining a patent airway and an adequate level of ventilation so that mechanical ventilation can be discontinued and the trachea extubated. Nonetheless, the level of recovery observed with sugammadex at this timepoint is remarkable for three reasons:

1. This is the same point following rocuronium administration that the NMBA would be expected to have its maximal effect.
2. The maximum recommended dose of rocuronium was used, and sugammadex reliably reversed its effect.
3. None of the approved reversal agents would likely have any efficacy when administered at this time point. Although none were used as comparators, the

extent of recovery with neostigmine in Studies 301 and 302, and the superiority of sugammadex in those studies, strongly suggest the sugammadex would be superior when administered in this setting as well.

Table 6. Summary of the results from Study 303

| Statistical Parameter | Recovery Time for $T_1 = 0.1$ [complete cases only] (mm:ss) | |
|-----------------------|---|---------------------------|
| | Rocuronium + Sugammadex (N=54) | Succinylcholine (N=53) |
| Mean (SD) | 4:21 (0:43) | 7:09 (1:33) |
| Median | 4:11 | 7:11 |
| Min. – Max. | 3:28 – 7:43 | 3:45 – 10:28 |

The precautionary comments made above regarding the use of sugammadex for reversal at reoccurrence of T_2 and at 1-2 PTCs apply in this setting as well. The Applicant has suggested that the level of reversal observed in Study 303 would make the combination of rocuronium and sugammadex a safer choice for patients than succinylcholine alone in the setting where a patient could not be ventilated or intubated after an NMBA was administered. That claim was not supported by any safety studies conducted to evaluate such a benefit, and the study design did not include the endpoint of time to successful recovery of a patent airway and spontaneous ventilation such that a comparison could be made to the duration of apnea that has been associated with morbidity or mortality.

The Applicant did not conduct any new studies of the reversal of rocuronium at 3 minutes following its administration.

(b) (4)
 . Although the findings may be accurate and the study appropriately designed to assess the primary endpoint, the study does not demonstrate the efficacy of sugammadex. The study does appear to show that when patients are not monitored with PNS following administration of a reversal agent they are more likely to extubate a patient at a $T_4/T_1 = 0.9$ with sugammadex than neostigmine. The implication is that patients are “more” reversed with sugammadex than neostigmine and therefore, less likely to risk morbidity associated with inadequate reversal. However, the study was not designed to demonstrate such a benefit, and the exclusion of PNS monitoring from the assessments made prior to determining whether it was safe to extubate a patient is inconsistent with the current standard of care. (b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

Generally, the secondary endpoints in the majority of the efficacy studies were the time to reaching a T4/T1 of 0.8 and 0.7. The findings for the secondary endpoints were consistent with the findings for the primary endpoint.

For pivotal Study 303, recovery to T4/T1=0.9 for sugammadex (16 mg/kg) was evaluated as a secondary endpoint, but was not compared to any other assessments in study. However, comparing Study 303 to Studies 301 and 302, it is noted that:

- The populations were similar.
- The neostigmine treatments were administered after spontaneous recovery had begun – giving them an advantage over the sugammadex treatment in Study 303.
- The 70 mcg/kg dose of neostigmine is the highest labeled dose (by weight) for that product.

Therefore, it may be possible to compare the recovery times with sugammadex to recover times with neostigmine in the other two studies noting that the highest labeled dose (by weight) of neostigmine was administered in Study 302 at a time when spontaneous recovery from rocuronium had occurred, in essence, giving neostigmine a head start in the comparison to sugammadex given before spontaneous recovery had begun. Recognizing that caution is needed in making comparisons of data from different studies, this approach was taken to gain an appreciation of whether sugammadex would have been found to be superior to neostigmine had a neostigmine-treatment arm been incorporated into Study 303.

Table 8 compares the data for the three studies.

Table 8. Comparisons of the findings for Studies 301, 302 and 303 for reversal of rocuronium

| | Study 303 | Study 301 | Study 302 |
|---------------------------|--|-------------------------|-------------------------|
| Treatment | Sugammadex (16 mg/kg) | Neostigmine (50 mcg/kg) | Neostigmine (70 mcg/kg) |
| N | 54 | 45 | 22 |
| Time of Administration | 3 minutes after administration of rocuronium | Reappearance of T2 | 1-2 PTCs |
| Time to T4/T1=0.9 [mm:ss] | | | |
| Mean (SD) | 5:23 (2:11) | 27:18 (25:12) | 60:57 (25:03) |
| Median | 4:50 | 18:31 | 57:04 |
| Range | 3:29-17:21 | 3:40 - 106:53 | 13:16 - 133:28 |

The data indicate that the 16 mg/kg dose of sugammadex can reverse the highest labeled dose of rocuronium, at the time of its peak effect, in a tenth of the time it took the highest dose of neostigmine to reverse a lesser level of rocuronium induced blockade. In fact, the longest time for a subject to achieve T4/T1 = 0.9 with the 16 mg/kg dose of sugammadex (17 minutes) was not much longer than the shortest time to reach the same level of reversal with the high dose of neostigmine (13 minutes). In short, it appears that had a 70 mcg/kg neostigmine-treatment arm been included in Study 303, it is highly likely that sugammadex would have been found superior to an extent that it was determined to be in Studies 301 and 302.

6.1.6 Other Endpoints

Other exploratory or experimental efficacy endpoints were not included in studies contain in either the original NDA submission or the resubmission.

6.1.7 Subpopulations

The data from pooled analyses across the different efficacy trials indicated that the proposed dosing recommendations based on the initial dose-response trials for each time point of administration and both of the NMBA's were appropriate for all subpopulations evaluated. Special studies of dose requirements for patients with renal or hepatic impairment and patients with cardiac and pulmonary disease were also conducted. These indicated there was no need to adjust the dose in any of these populations.

A limited number of elderly subjects were enrolled in the clinical trials. In all, there were 62 subjects who were 65-74 years of age and 40 subjects who were ≥ 75 years of age. For these subjects there was no indication that the dose of sugammadex needed to be adjusted. It should be noted that the safety and efficacy of sugammadex has not be fully evaluated in pediatric patients at this point in time.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the pivotal studies submitted in the original NDA, the Applicant provided sufficient evidence to support each of the three components of its dosing regimen for sugammadex. The additional efficacy studies that were completed since the original NDA submission and were included in the resubmission supported the dosing recommendations and did not raise any concerns for the suitability of those recommendations in the general population or in any particular subpopulation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Sugammadex is administered acutely; therefore, there is no concern for its persistence of efficacy or tolerance of its effects.

6.1.10 Additional Efficacy Issues/Analyses

There were no additional efficacy issues that were identified and no addition analyses performed.

7 Review of Safety

Safety Summary

On July 31, 2008, a Not Approvable action was taken on the original NDA submission. The bases of the action were two clinical deficiencies:

1. The sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug. Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure. As widespread use of sugammadex sodium is expected, an individual patient may be exposed to the drug multiple times. This expected pattern of use is of concern because the risk of Type I hypersensitivity, including anaphylaxis, is likely to increase on repeat exposure.
2. The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program. The in vitro assessment indicated that sugammadex increased activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and the International Normalized Ratio (INR). In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol-specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined. The mechanism and the clinical significance of the effects of sugammadex on coagulation are not known.

In addition, it was recommended that the Applicant conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

The primary focus of this review was on the actions taken by the Applicant to address the two deficiencies and the information provided regarding QT prolongation and arrhythmias.

Since the Not Approvable action was taken, the Applicant has completed 20 new clinical trials and in the process has doubled the size of the safety database. In the original NDA submission, there were a total of 2,369 subject exposures to intravenous

sugammadex in 2,054 unique subjects. The new clinical trials add 2,547 subject exposures to IV sugammadex in 1,967 unique subjects. In addition, sugammadex was approved in the European Union on July 25, 2008, and is currently registered in 71 countries and marketed in 41 countries. The Applicant reports the distribution of over (b) (4) vials for use in patients through June, 2012. Therefore, the secondary focus of this review was whether the new safety database or the postmarketing adverse event data present a risk profile that is similar to that characterized in the original NDA submission or whether any new safety signals exist.

To assess the risk of hypersensitivity reactions to sugammadex with repeat exposure, the Applicant conducted a single clinical study, P06042, at four sites. The Agency concurred with the design of the study. Its results indicated a frequency of anaphylaxis for sugammadex of 1.0% (3/298) all occurring with the first dose, which was 16 mg/kg. The risk did not appear to increase with repeat exposure. While the results provided the necessary information to address the deficiency, the validity of the study was called into question when the Office of Scientific Investigations discovered that the safety assessor at one of the sites was not treatment blinded when evaluating a substantial number of subjects. Furthermore, the protocol violation was not described in the final study report, and the Agency was not informed of the situation. The only U.S. site was closed due to bankruptcy proceedings and the source document for the site was, therefore, not available for inspection. With the validity of the study in doubt and no other source of information available to address the deficiency, it is not possible to adequately characterize the risk of anaphylaxis, and therefore, not possible to make a recommendation for the product to be approved.

To assess the effects of sugammadex on coagulation and bleeding, the Applicant performed several studies. The results of the studies indicated that sugammadex causes a significant increase in aPTT, PT, and INR within minutes following its administration. The changes observed tended to be dose dependent, resolved within an hour, were not associated with any increase in bleeding, and were not considered clinically relevant. Study P07044, examined the effects of sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity in healthy volunteers; they found there was no clinically relevant effect of sugammadex on the anti-Xa activity of enoxaparin, and while sugammadex induced a dose-dependent prolongation of both the PT and the aPTT, it did not appear to affect the extent of changes induced by heparin. Study P 07038 evaluated the risk of bleeding in surgical patients following the use of sugammadex. Despite the use of anticoagulants in all of these patients, there did not appear to be a synergistic effect on post-operative bleeding. In fact, all bleeding endpoints occurred less frequently with sugammadex treatment than with "usual care" treatment, although the differences were not statistically significant. In addition, there were no significant differences between sugammadex and usual care treatments for incidence of postoperative anemia or venous thromboembolic events. With these studies, the Applicant demonstrated that there is a brief increase in aPTT, PT and INR following sugammadex treatment, but this increase is not associated with increased incidents of bleeding. Furthermore, they demonstrated that sugammadex dose not

adversely affect the perioperative use of anticoagulants and does not pose a risk for increased bleeding. These studies have fully addressed the second deficiency.

In post-action discussions with the Applicant, the Agency agreed that, based on the data available and an additional analysis of ECG data for arrhythmias, there was no increased risk of QTc prolongation or arrhythmias associated with sugammadex use, and the Applicant need not conduct the study recommended in the Not Approvable letter. Nonetheless, the Applicant conducted a third QTc study, this time examining the risk of QTc prolongation when sugammadex was administered either propofol-induced or sevoflurane-induced general anesthesia. This study demonstrated no increased risk of QTc prolongation with sugammadex with either of these anesthetics. The previous studies showed the same for sugammadex administered alone and for sugammadex administered concurrently with rocuronium or vecuronium. Evaluation of the updated safety database indicated no increased risk of QTc prolongation or arrhythmias with sugammadex compared to placebo and neostigmine, but did reveal that bradycardia was not uncommon and was not uncommonly associated with anaphylactic reactions. The postmarketing data also showed that bradycardia, sometimes leading to cardiac arrest, and sometimes associated with anaphylaxis, occurs in the surgical population. Based on the postmarketing data, the Applicant has updated their labels to include a warning on the risk. In summary, the risk of QTc prolongation and cardiac arrhythmias are not increased with sugammadex; however, bradycardia, when it occurs, can be life threatening and may be associated with anaphylaxis.

The analyses of common adverse events in the updated safety database demonstrated that sugammadex had a safety profile that, in general, posed only minimal additional risk compared to placebo and somewhat less risk than neostigmine. The most common adverse events were nausea, vomiting, pain and dysgeusia, with only dysgeusia being sugammadex-dose related. Similarly, the analysis of SAEs reported in the clinical trials indicated that, overall, the safety profile for sugammadex was not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm related adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it was only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appeared to differ substantially from placebo and neostigmine. Review of the postmarketing data, produced similar findings.

The review of the updated safety database indicated that there were no subpopulations at greater risk from sugammadex or for whom the dose of sugammadex needed to be adjusted.

The review of the postmarketing data indicated that anaphylactic reactions were the most frequently reported adverse events followed by changes in heart rate and blood pressure. There was no indication of a new safety signal in the database.

In summary, the safety profile for sugammadex has been well characterized with the exception of the risk of anaphylaxis following repeat exposure. The overall safety of sugammadex did not differ substantially from placebo in the clinical trials where it also appeared to pose slightly less risk than neostigmine. With the findings of anaphylaxis in the clinical trial database and the reports in the postmarketing database, it is critical that the deficiency for this reaction that was included in the Not Approvable letter be fully addressed before the product can be considered for approval.

[N.B.: In the sections that follow, the tables, interpretations of the data, and comments contained therein are those of this reviewer unless they are specifically attributed to the Applicant or other entity.]

7.1 Methods

The Applicant has indicated that the sugammadex clinical development program at the time of this resubmission consisted of 52 trials. Of these trials, 32 were included in the original NDA submission. The 20 clinical trials conducted since that time include 9 Phase 1 and 11 Phase 3 trials. The safety database in the original submission consisted of 2369 exposures to intravenous (IV) sugammadex in 2054 subjects. The Applicant notes that the more recent trials provide 2547 additional exposures to IV sugammadex in an additional 1967 unique subjects. The Applicant has integrated the safety data from the newer studies into the original safety database thereby providing a total of 4916 IV exposures to sugammadex in 4021 unique subjects. This database of 52 clinical trials also contains safety data from a total of 2615 exposures to neostigmine or placebo in a total of 1515 unique subjects. The current safety database forms the basis for the analyses conducted by the Applicant, and this reviewer, to characterize the risk profile of sugammadex for the proposed indications. The Applicant has noted that data from Trial P07981, which was ongoing within three months of the NDA resubmission, were not included in the safety database or analyses.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Data from the studies listed in the table below formed the basis for the review of safety by the Applicant. For the purposes of this review, only the studies involving the intravenous administration of sugammadex were considered for the evaluation of safety; this approach, therefore, excluded the safety data from study 19.4.110.

Table 9. Studies used for the analyses of safety (derived from data contained in Table 54 pp 175-178 and Table A-1 pp 232-259 of Section 2.5 in the NDA resubmission)

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---------------------------------|--|---------------------------------|
| 19.4.101 | placebo | 29 | first in human study |
| 19.4.102 | placebo | 28 | Japanese vs. Caucasian PK study |
| 19.4.105 | placebo/moxifloxacin | 62 | QT study |
| 19.4.106 | placebo | 19 | high-dose PK study |
| 19.4.107 | none | 6 | ADME study |
| 19.4.108 | none | 16 | Pre QT pilot study |
| 19.4.109 | placebo/moxifloxacin | 83 | QT study |

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---|--|---|
| 19.4.110 | histamine/histamine dihydrochloride | 23 | skin-prick testing |
| 19.4.112 | none | 24 | drug-drug interaction study |
| 19.4.113 | none | 22 | use of NMBA after sugammadex |
| 19.4.115 | placebo | 8 | assess effects on aPTT, PT and INR |
| 19.4.201 | placebo | 27 | dose-finding study |
| 19.4.202 | placebo | 98 | dose-finding study |
| 19.4.203 | none | 28 | dose-finding study |
| 19.4.204 | none | 36 | dose-finding study |
| 19.4.205 | placebo | 35 | dose-finding study |
| 19.4.206 | placebo | 171 | dose-finding study |
| 19.4.207 | placebo | 106 | dose-finding study |
| 19.4.208 | placebo | 191 | dose-finding study |
| 19.4.209 | none | 199 | dose-finding study |
| 19.4.210 | none | 42 | use with propofol vs. sevoflurane |
| 19.4.301 | neostigmine | 185 | pivotal efficacy study |
| 19.4.302 | neostigmine | 155 | pivotal efficacy study |
| 19.4.303 | spontaneous recovery from succinylcholine | 108 | pivotal efficacy study |
| 19.4.304 | none | 30 | renal impairment study |
| 19.4.305 | none | 159 | elderly vs. adult patients (61 subjects: 65-75 yrs and 40 subjects: >75 yrs) |
| 19.4.306 | placebo | 90 | adult and pediatric patients (27 adults and 63 pediatric subjects 28 days - 17 yrs) |
| 19.4.308 | none | 77 | patients with pulmonary disease |
| 19.4.309 | placebo | 116 | patients with cardiac disease |
| 19.4.310 | Cis-atracurium reversed with neostigmine | 72 | Cis-atracurium study |
| 19.4.311 | none | 192 | open-label efficacy study |
| 19.4.312 | none | 51 | use with propofol vs. sevoflurane |
| 19.4.313 | none | 89 | manual detection of T4 vs. device detection |
| 19.4.316 | placebo | 136 | efficacy study |
| 19.4.318 | neostigmine | 132 | efficacy study |
| 19.4.319 | spontaneous recovery from | 132 | assess changes in K ⁺ levels |

| Trial Number | Study Drug Comparator(s) | N (subjects completing the study) | Comments |
|---------------------|---------------------------------|--|---|
| | succinylcholine | | |
| 19.4.328 | none | 67 | severe renal impairment study |
| 19.4.333 | none | 4 | dialysis study |
| 19.4.334 | neostigmine | 100 | residual blockade at time of extubation |
| P05768 | neostigmine | 291 | Chinese vs. Caucasian efficacy assessment |
| P05775 | none | 151 | Chinese vs. Caucasian efficacy assessment |
| P05997 | none | 12 | Chinese PK study |
| P06042 | placebo | 397 | assess anaphylaxis/hypersensitivity with repeat doses |
| P06101 | neostigmine | 120 | Korean vs. Caucasian efficacy assessment |
| P06315 | placebo | 132 | QT study in presence of propofol or sevoflurane |
| P07025 | placebo | 26 | assessment of sugammadex and aspirin on platelet aggregation and clotting |
| P07038 | placebo and neostigmine | 1137 | dedicated bleeding study |
| P07044 | placebo | 51 | effects of sugammadex and enoxaparin or unfractionated heparin on anticoagulation |

In addition to the clinical studies, the Applicant searched their pharmacovigilance database for adverse events reported up to June 15, 2012. They have submitted all of these postmarketing reports and have analyzed those adverse events related to anaphylaxis, hypersensitivity, cardiac arrhythmias, or post-operative bleeding events. For this review, the entire postmarketing database was analyzed for both safety concerns identified in the Complete Response letter and for safety signals not observed in the clinical studies.

7.1.2 Categorization of Adverse Events

The Applicant used MedDRA version 15.0 to code the adverse events (AEs) reported in the integrated safety database. They noted that some of the trials conducted early on in

the development program used other versions of MedDRA for coding the AEs; these events were recoded for the integrated database.

All of the AEs reported in the safety database were treatment emergent, defined as having an onset time after the start of study drug administration and within the 7 days following treatment with some exceptions for cross-over studies when the next treatment was administered on Day 7.

The system organ classification (SOC) used for individual AEs was variable among studies based on whether an event was considered possibly related to the surgical procedure or the anesthetic, e.g., reports of bradycardia occurring within minutes of sugammadex administration were sometimes coded as “injury, poisoning and procedural complications” and attributed to anesthetic agents used prior to the administration of sugammadex. In addition, some AEs were tabulated under the heading of “investigations” if they occurred in studies not involving surgical procedures, e.g., QTc prolongation occurring in one of the thorough QT studies. For the purposes of this review, AEs reported under these two SOCs were tabulated with those reported under the biological system involved, e.g., reports of bradycardia listed under “injury, poisoning and procedural complications” were counted with those listed under “cardiac disorders.”

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant analyzed safety data by pooling trials in multiple categories. These included the following:

1. Pooled Phase 1 Trials: these included healthy subjects treated with sugammadex or placebo but were not administered a neuromuscular blocking agent (NMBA) or an anesthetic. This group consisted of 11 trials
2. Pooled Phase 1-3 Trials: these included healthy volunteers and surgical patients who were administered an anesthetic and/or an NMBA, and who were treated with sugammadex, placebo, or an active comparator. This group consisted of 40 trials; it was further subdivided into two groups:
 - a. Pooled Placebo-Controlled Trials: 13 trials that compared sugammadex to placebo
 - b. Pooled Neostigmine-Controlled Trials: 7 trials that compared sugammadex to neostigmine

This approach to evaluating safety is useful for discerning AEs that may be related to the anesthetic or surgical procedure from those due to sugammadex and also allows an assessment as to whether the sugammadex-rocuronium or sugammadex-vecuronium complex has a different risk profile than sugammadex alone.

As the demographics of the subjects were similar in most of the clinical trials, the safety data were considered ensemble for the purposes of this review in addition to being considered by the pooling methods used by the Applicant.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the original NDA submission, the Applicant was considered to have had a sufficient number of exposures and broad enough target populations to adequately characterize the risk profile for sugammadex, with the exceptions of the issues raised in the Complete Response letter. The Applicant has doubled the size of the safety database with the studies conducted since the time of the complete response.

In the 52 clinical trials that were conducted, a total of 4,021 subjects were exposed to sugammadex. The safety database includes 3,531 unique subjects exposed to intravenous (IV) sugammadex, 1,102 subjects who received placebo, and 856 subjects who received neostigmine (50 or 70 mcg/kg). The table below provides the key demographic data for the database. The table shows that number of exposures for the proposed doses should be sufficient to characterize the safety of sugammadex, based on age, gender, and the American Society of Anesthesiologists – Physical Status (ASA-PS) category, for younger (≤ 65 years) healthier (ASA-PS 1 and 2) patients. There are limited data for older (> 65 years) and sicker (ASA-PS 3-4) subjects given the highest proposed sugammadex dose, 16 mg/kg. This limitation is not compensated by safety data for these populations exposed to higher doses of sugammadex. Exposure to the proposed lower doses of sugammadex, i.e., 2 mg/kg and 4 mg/kg, was adequate to evaluate the risks for both of these more vulnerable populations, the elderly and sicker.

Table 10. Key demographic components of the safety database

| Parameter | | Placebo | Sugammadex Dose (mg/kg) | | | | | | | | | | | Neostigmine (mcg/kg) | | |
|-----------------|------|----------|-------------------------|----------|----------|----------|---------|-----------|---------|----------|---------|----------|--------|----------------------|----------|---------|
| | | | 0.1 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 50 | 70 |
| N | | 1102 | 4 | 133 | 213 | 849 | 12 | 1872 | 29 | 127 | 39 | 135 | 6 | 112 | 814 | 42 |
| Age (years) [%] | ≤ 65 | 916 [83] | 4 [100] | 123 [92] | 208 [98] | 663 [78] | 10 [83] | 1347 [72] | 24 [83] | 121 [95] | 33 [85] | 127 [94] | 5 [83] | 112 [100] | 591 [73] | 32 [76] |
| | > 65 | 186 [17] | 0 [0] | 10 [8] | 5 [2] | 186 [22] | 2 [17] | 525 [28] | 5 [17] | 6 [5] | 6 [15] | 8 [6] | 1 [17] | 0 [0] | 223 [27] | 10 [24] |
| M/F (%) | | 53/47 | 100/0 | 53/47 | 58/42 | 49/51 | 75/25 | 46/54 | 90/10 | 60/40 | 62/38 | 50/50 | 67/33 | 53/47 | 40/60 | 40/59 |
| ASA-PS | 1-2 | 1018 | 4 | 131 | 205 | 716 | 12 | 1609 | 28 | 123 | 34 | 130 | 6 | 112 | 725 | 34 |
| | 3-4 | 84 | 0 | 2 | 8 | 133 | 0 | 263 | 1 | 4 | 5 | 5 | 0 | 0 | 89 | 8 |

7.2.2 Explorations for Dose Response

During the development program, over 10 doses of sugammadex were evaluated in adult subjects. The majority of these exposures occurred in placebo-controlled studies. The table below summarizes these exposures and indicates that they were adequate to allow meaningful assessments of whether adverse events were dose dependent.

Table 11. Adult subject exposures to sugammadex or placebo in the pooled Phase 1-3 studies (Table 4 on p. 43 of section 5.3.5.3 in the NDA resubmission)

| Study Phase | Placebo (mg/kg) | Sugammadex (mg/kg) | | | | | | | | | | |
|--------------|-----------------|--------------------|-----|----|------|----|-----|----|----|----|-----|------|
| | | 0 | <2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 |
| | N | n | n | n | n | n | n | n | n | n | n | N |
| Phase 1 | 77 | 4 | 26 | 0 | 89 | 0 | 3 | 0 | 5 | 4 | 168 | 299 |
| Phase 2 | 84 | 250 | 212 | 9 | 167 | 28 | 122 | 39 | 38 | 0 | 1 | 866 |
| Phase 3 | 383 | 40 | 600 | 3 | 1542 | 0 | 0 | 0 | 55 | 2 | 0 | 2242 |
| Total | 544 | 294 | 838 | 12 | 1798 | 28 | 125 | 39 | 98 | 6 | 169 | 3407 |

n= number of subject exposures at each dose

N=total number of exposures per treatment group and phase

^a Total Sugammadex = number of subject exposures to IV sugammadex across all doses.

Dose-response exploration comparing sugammadex to neostigmine are much more limited. For the seven pooled neostigmine-controlled Phase 1-3 studies, the Applicant reported a total of 797 adult subjects exposed to sugammadex and 804 subjects exposed to neostigmine. The sugammadex doses evaluated in these studies were limited to 2, 3, and 4 mg/kg.

7.2.3 Special Animal and/or In Vitro Testing

The Applicant's preclinical information in the original NDA submission was evaluated by Drs. Zengjun Xu and Adam Wasserman of the Pharmacology-Toxicology review team. In their review of that data, they noted (in Dr. Wasserman's addendum dated July 7, 2008) that because "of the deposition of sugammadex into bone and the demonstration of an extended duration of retention with single administration (bone $t_{1/2(\beta)}$ mean of 172 days), an evaluation of the potential for bone carcinogenicity should be considered. This concern is especially relevant for the pediatric population in comparison to the adult population due to the higher concentration of drug which is believed will be retained in this tissue as well as the intrinsically high level of growth in this tissue prior to skeletal maturation and closure of the epiphyseal plates." In the Complete Response letter, additional nonclinical studies were considered as necessary prior to any multiple-dose

pediatric trials, approval of a pediatric indication, or inclusion of pediatric data in the label. The Applicant has addressed those issues in the resubmission, and they have been reviewed by Drs. Xu and Wasserman. Summaries of their reviews are included in Section 4.3 of this review.

The Applicant conducted *in-vitro* testing of the effects of sugammadex on coagulation parameters in the original NDA submission. Those studies indicated that sugammadex can prolong activated partial thromboplastin time (aPTT), prothrombin time (PT), and the international normalized ratio (INR). The findings of those studies were further described in the clinical safety review of that submission. Those findings, in part, led to the requirement in the Complete Response letter for studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures.

No additional nonclinical or *in-vitro* study information requiring clinical evaluation was included in the NDA resubmission.

7.2.4 Routine Clinical Testing

The routine testing of subjects was adequate in terms of assessing biochemistry and hematologic laboratory parameters and for monitoring of vital signs and ECG. The lack of evaluations of coagulation parameters in any of the clinical trials in the original NDA submission was addressed by the Applicant in the resubmission in a clinical study comparing the effects of sugammadex versus neostigmine or spontaneous recovery on these parameters.

7.2.5 Metabolic, Clearance, and Interaction Workup

Sugammadex was found to have no metabolites in both nonclinical and clinical studies. Only renal excretion of unchanged product was observed as the means of elimination. In adults with normal renal function, the elimination half-life is 2 hours. More than 90% of the product is excreted within 24 hours. The Applicant has conducted studies that examined the safety and efficacy of sugammadex in surgical patients with moderate and severe renal impairment.

Sugammadex does not induce or inhibit drug metabolizing enzymes, and therefore, “classical” drug-drug interaction studies were not conducted. The Applicant conducted various pharmacokinetic simulations to assess the potential for other medications to displace rocuronium from sugammadex, and thereby increase the level of neuromuscular blockade, and the potential for the sugammadex-rocuronium complex to bind another medication. The displacement of rocuronium from sugammadex by flucloxacillin or diclofenac was evaluated in a clinical study. In addition, the effects of sugammadex on the anticoagulant activity of enoxaparin and unfractionated heparin and the anti-platelet-aggregation activity of aspirin were evaluated in clinical studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Sugammadex is unique in its mechanism of action compared as a reversal agent for neuromuscular blocking agents (NMBAs). Sugammadex directly binds to rocuronium and vecuronium removing them from the systemic circulation and the neuromuscular junction. The alternative reversal agents, neostigmine and edrophonium, are anticholinesterases and have risk profiles that reflect the physiological effects of excess acetylcholine. Seven of the clinical studies compared sugammadex to neostigmine and provide for a comparison of the adverse events associated with use of each of these agents under similar clinical settings.

7.3 Major Safety Results

7.3.1 Deaths

In the overall sugammadex clinical development program, eight deaths have been reported, including three deaths reported in the original NDA submission. The Applicant notes that all of the deaths occurred after the trial was completed, and that none of them were considered drug-related according to the reporting investigators. In the safety review of the original NDA submission, this reviewer concurred that two of the deaths were unlikely to be drug related, but felt that sugammadex may have contributed, in part, to at least one of the deaths. All eight cases are described and discussed below. Four deaths followed sugammadex treatments (one subject for the 0.5 mg/kg dose and 2 mg/kg dose and four subjects for the 4 mg/kg dose); one death occurred following neostigmine treatment and three deaths followed placebo treatment.

Deaths following treatment with sugammadex

Subject 203104007 (reported in the original NDA submission) participated in trial 19.4.203 (sugammadex 0.5 mg/kg dose group) and was a 65-year-old Caucasian female who died 42 days after surgery and the administration of sugammadex. She presented for an anterior resection of carcinoma of the large intestine. Her past medical history was significant only for hypertension, peptic ulcer and rheumatoid arthritis. From the data in her Case Report Form (CRF), it appears there were no surgical complications and the procedure lasted approximately 3 hours. At approximately 23 hours following the end of surgery, the patient experienced atrial fibrillation and respiratory failure. She was reported to have “recovered with sequelae” from these events. The list of concomitant medications administered following surgery included therapies for post-operative pain (including epidural infusions of fentanyl and levobupivacaine) and nausea, prophylaxis for deep vein thrombosis, and treatment of adrenal suppression (dexamethasone 5 mg IV administered 3 hours after the sugammadex); no medications for the treatment of either atrial fibrillation or respiratory failure were listed. Her death was attributed to a combination of factors, including myocardial infarction, cardiogenic shock, and pulmonary edema. According to the investigator, these post-trial SAEs were unlikely related to the trial medication. The Investigator and the Applicant judged the subject’s death as not related to the trial medication; however, this reviewer believes that sugammadex cannot be ruled out for having contributed to the subject’s demise. This belief is based on the lack of data between 3 and 23 hours postdose during which time the subject began to experience atrial fibrillation and respiratory failure. As she experienced sequelae from these events, to the extent that Sugammadex contributed to the occurrence of either adverse event, it was related to the outcome.

Subject 208107008 (reported in the original NDA submission) in trial 19.4.208B (sugammadex 2 mg/kg dose group), a 61-year-old male Caucasian, died 18 days after surgery and the administration of sugammadex due to a pulmonary embolus. The subject had no previous medical history except for his diagnosis of prostate cancer. He underwent a radical prostatectomy with radical iliacal lymphadenectomy that were complicated by an intraoperative 1-cm perforation of the colon. The perforation was surgically repaired and the patient was prophylactically treated with antibiotics. The patient was discharged 6 days following surgery with a surgical drain *in situ*. The drain was reported to have been removed a “few days” after surgery. The subject was reported to have “felt tired” 11 or 12 days post-operatively and was ultimately hospitalized on post-operative day 15, at which time he was diagnosed as having a pulmonary embolus. Due to his recent surgery, he was considered to have unacceptable risks for thrombolytic therapy and was, therefore, treated with low molecular weight heparin. The subject died two days later. According to the Investigator, thrombosis and embolus were complications of the subject’s surgical procedure, and pelvic thrombosis was a known complication of surgery of the lower abdomen. Given the nature of the surgery and the reported time sequence, the causal relationship for this SAE and death were assessed as “not related” by the Applicant. This reviewer concurs with the Applicant’s assessment.

Subject 333101006, in trial 19.4.333 (sugammadex 4 mg/kg dose group), was a 77-year-old male with a medical history that included cardiovascular disease, renal failure, diabetes, and coagulopathy. He underwent a thoracic artery endoprosthesis and esophageal stent placement due to “thoracic fissures” on (b) (6). His condition deteriorated in the weeks following surgery with signs of sepsis, pneumonia and free air around the thoracic endoprosthesis reported. On (b) (6), the endoprosthesis was replaced with a homograft during uneventful surgery. On (b) (6), he underwent bronchoscopy following which he received 4 mg/kg of sugammadex. On (b) (6) the subject experienced an acute pulmonary hemorrhage with blood entering the endotracheal tube. It was not possible to ventilate the subject, and he died about 1.5 hours later. The Investigator and the Applicant considered the hemorrhagic SAE and the subject’s subsequent death as unrelated to the use of sugammadex. This reviewer concurs with their assessment.

Subject 333101007, in trial 19.4.333 (sugammadex 4 mg/kg dose group), was a 63-year-old male with a history of cardiovascular disease, renal failure, cirrhosis, diabetes, and alcohol abuse. He underwent a mitral valvuloplasty, an aortic valve replacement, and a coronary artery bypass graft on (b) (6), after which he was required inotropic support. On (b) (6) he underwent transesophageal echocardiography to evaluate ongoing heart failure. After the procedure, he received 4 mg/kg of sugammadex. Over the next two days he experienced worsening hypotension, bowel ischemia, and liver insufficiency. The subject died on (b) (6). The Investigator and the Applicant did not consider his SAEs of bowel ischemia, worsening heart failure and liver insufficiency or his death as related to the sugammadex. Of note, the outcome for the SAEs “worsening of heart failure” and “liver insufficiency” were changed from

“fatal” to “not recovered.” Although hypotension has been observed within minutes following the administration of sugammadex, this subject’s hypotension was first reported more than 12 hours following treatment. Given the severity of his underlying medical conditions, including cardiac disease, and the timing of onset of the events leading to his demise, this reviewer concurs with the Applicant’s assessment that the subject’s death was not related to sugammadex.

Deaths following treatment with placebo

Subject 309107003 (reported in the original NDA submission) in trial 19.4.309 (placebo group) was a 73-year-old male Caucasian who died 12 days after surgery and the administration of the trial medication. He had undergone a craniotomy for resection of a cerebral meningioma. His past medical history was significant for myocardial infarction, post-infarction angina pectoris, status post CABG, hypertension, meningioma with visual deficits, headache, and reduced cognitive functioning. On postoperative day 1, the patient was reported to have had a > 60 msec prolongation of QTc, which was not treated. CT scans performed at 2, 5, 9 and 10 days post-operatively showed edema, intraventricular and subarachnoidal blood, and midline shifts which worsened to the point of suspected subfalx and transtentorial herniation. He died on post-operative day 11; the cause of death was listed as cerebral edema and ventricular bleeding with hydrocephalus. Autopsy results showed a lesion in the left middle cerebral artery that had been caused by the surgery during removal of a meningioma. The Investigator and the Applicant judged the subject’s death as not related to the trial medication. This reviewer concurs with the Applicant’s assessment.

Subject P07038-96004, in trial P07038, was a 67 year old male with a history of cardiovascular disease, renal cell carcinoma, lung “neoplasm,” and metastasis. He underwent knee surgery on (b) (6), with a combination of epidural and general anesthesia. He received a placebo treatment at the end of his surgery. He was discharged from the hospital 6 days after surgery and died on (b) (6), reportedly due to the metastatic renal cell carcinoma. His death was not considered to be due to the study drug; this reviewer concurs with that assessment.

Subject P07038-31832, in trial P07038, was a 65 year old male with a history of atrial fibrillation, bradycardia-tachycardia syndrome, hypertension and hyperuricemia. He underwent total hip arthroplasty on (b) (6), under general anesthesia. He received a placebo treatment at the end of his procedure. On (b) (6), he was found unconscious in asystole with pacemaker spikes. Cardiopulmonary resuscitation was begun but was not successful and discontinued after 24 minutes at which time the patient was pronounced dead. His death was not attributed to study drug treatment by the Investigator; this reviewer concurs with that assessment.

Deaths following treatment with neostigmine

Subject P07038-3021796, in trial P07038, was a 90 year old male with a history of cardiac disease and deep vein thrombosis who presented for internal fixation of a hip fracture. He had his surgery on (b) (6) under general anesthesia. At the end of surgery he received treatment with neostigmine 0.05 mg/kg. He died in his sleep 43 days after surgery; the cause of death was listed as cardiac arrest. The Investigator considered the subject's death as unlikely related to the study drug; this reviewer concurs with that assessment.

In summary, the analysis of the deaths that occurred in the clinical development program do not indicate that sugammadex poses any greater risk than either placebo or neostigmine. There was a single death reported in the original NDA submission in which sugammadex may have played a role; however, with a near doubling of the safety database since that time, there is no additional evidence to suggest that sugammadex may increase patient mortality

7.3.2 Nonfatal Serious Adverse Events

In their analysis of serious adverse events (SAEs), the Applicant used their pooled Phase 1-3 trials and considered treatment-emergent events that occurred within 7 days of study drug administration. They also compared the events as tabulated in the safety database for the original NDA submission (2007) and compared those to the cumulative safety database for the resubmission (2012). Table 12 below, copied from the resubmission, displays their results. Based on these data the Applicant concluded that:

Overall the incidences were considered to be comparable between the two treatment groups. Between the doses of sugammadex and the two datasets (2007 and 2012), there were no clinically relevant differences in SAE incidence rate in the various SOC's.

Based on this analysis of the SAE data, this reviewer concurs with the Applicant's observation; however, it is important to note that SAE data from the active-controlled, i.e., neostigmine-controlled, studies are not included in this analysis neither are data from studies in which no anesthetic or NMBA were administered. Therefore, this reviewer created Table 13, which includes all SAEs reported for intravenous injections or infusions of sugammadex grouped by SOC and compared to those of subjects treated with either placebo or neostigmine, regardless of whether an anesthetic or an NMBA was administered. The data in the table indicates that, overall and for each individual SOC, there are no substantial differences between sugammadex and either placebo or neostigmine. The table also indicates that, overall and for each individual SOC, there is no dose-dependency for SAEs and sugammadex.

Table 12. Number (%) of exposures for adult subjects who received anesthesia and/or NMBA and placebo or sugammadex in pooled Phase 1-3 Trials with at least one SAE (Table 34, p. 102 in section 5.3.5.3 of the NDA resubmission)

| | 0 mg/kg (Placebo) | | 2 mg/kg | | 4 mg/kg | | 16 mg/kg | | Total | |
|---|-------------------|--------------|--------------|--------------|--------------|---------------|-------------|-------------|---------------|---------------|
| | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 |
| System Organ Class | N=140 | N=544 | N=605 | N=838 | N=580 | N=1798 | N=98 | N=98 | N=1926 | N=3407 |
| At least one SAE | 6 (4.3) | 38 (7.0) | 44 (7.3) | 46 (5.5) | 28 (4.8) | 107 (6.0) | 5 (5.1) | 5 (5.1) | 99 (5.1) | 180 (5.3) |
| Infections and infestations | 1 (0.7) | 5 (0.9) | 3 (0.5) | 4 (0.5) | 6 (1.0) | 18 (1.0) | 0 (0.0) | 0 (0.0) | 11 (0.6) | 24 (0.7) |
| Neoplasms benign, malignant and unspecified | 0 (0.0) | 2 (0.4) | 1 (0.2) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 2 (0.1) |
| Blood and lymphatic system disorders | 0 (0.0) | 1 (0.2) | 1 (0.2) | 1 (0.1) | 1 (0.2) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 3 (0.1) |
| Immune system disorders | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Psychiatric disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.3) | 5 (0.3) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 5 (0.1) |
| Nervous system disorders | 1 (0.7) | 5 (0.9) | 1 (0.2) | 1 (0.1) | 2 (0.3) | 4 (0.2) | 0 (0.0) | 0 (0.0) | 4 (0.2) | 6 (0.2) |
| Eye disorders | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Ear and labyrinth disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 1 (0.0) |
| Cardiac disorders | 1 (0.7) | 4 (0.7) | 5 (0.8) | 5 (0.6) | 2 (0.3) | 7 (0.4) | 0 (0.0) | 0 (0.0) | 8 (0.4) | 13 (0.4) |
| Vascular disorders | 0 (0.0) | 4 (0.7) | 2 (0.3) | 2 (0.2) | 2 (0.3) | 11 (0.6) | 0 (0.0) | 0 (0.0) | 5 (0.3) | 14 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 0 (0.0) | 1 (0.2) | 7 (1.2) | 7 (0.8) | 5 (0.9) | 8 (0.4) | 0 (0.0) | 0 (0.0) | 14 (0.7) | 17 (0.5) |

| | 0 mg/kg (Placebo) | | 2 mg/kg | | 4 mg/kg | | 16 mg/kg | | Total | |
|--|-------------------|--------------|--------------|--------------|--------------|---------------|-------------|-------------|---------------|---------------|
| | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 |
| System Organ Class | N=140 | N=544 | N=605 | N=838 | N=580 | N=1798 | N=98 | N=98 | N=1926 | N=3407 |
| Gastrointestinal disorders | 1 (0.7) | 3 (0.6) | 9 (1.5) | 9 (1.1) | 3 (0.5) | 7 (0.4) | 0 (0.0) | 0 (0.0) | 17 (0.9) | 21 (0.6) |
| Hepatobiliary disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Skin and subcutaneous tissue disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Musculoskeletal and connective tissue disorders | 0 (0.0) | 3 (0.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (0.4) | 0 (0.0) | 0 (0.0) | 2 (0.1) | 10 (0.3) |
| Renal and urinary disorders | 0 (0.0) | 1 (0.2) | 1 (0.2) | 1 (0.1) | 1 (0.2) | 4 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.2) | 6 (0.2) |
| General disorders and administration site conditions | 0 (0.0) | 3 (0.6) | 2 (0.3) | 2 (0.2) | 1 (0.2) | 8 (0.4) | 0 (0.0) | 0 (0.0) | 3 (0.2) | 10 (0.3) |
| Investigations | 2 (1.4) | 2 (0.4) | 13 (2.1) | 13 (1.6) | 4 (0.7) | 6 (0.3) | 4 (4.1) | 4 (4.1) | 25 (1.3) | 27 (0.8) |
| Injury, poisoning and procedural complications | 1 (0.7) | 15 (2.8) | 12 (2.0) | 13 (1.6) | 6 (1.0) | 38 (2.1) | 1 (1.0) | 1 (1.0) | 24 (1.2) | 57 (1.7) |
| Surgical and medical procedures | 0 (0.0) | 0 (0.0) | 1 (0.2) | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (1.0) | 1 (1.0) | 2 (0.1) | 3 (0.1) |

Table 13. Serious adverse event counts for all subjects who received intravenous study drug

| Treatment Group | Placebo n (%) | Sugammadex [mg/kg] n (%) | | | | | | | | | | Neostigmine n (%) |
|--|------------------|-----------------------------|------------|------------|-----------|------------|-----------|------------|-----------|------------|-------------------------|----------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | Total | |
| Number of subjects for treatment group | 336 | 124 | 178 | 613 | 9 | 729 | 28 | 154 | 39 | 127 | 2005 | 804 |
| Blood and lymphatic system disorders | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 2 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (0) | 0 (0) |
| Cardiac disorders | 4 (1) | 3 (2) | 0 (0) | 6 (1) | 0 (0) | 7 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 17 (1) | 2 (0) |
| Cardiovascular disorders, general | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (11) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Ear and labyrinth disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Eye disorders | 1 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Gastrointestinal disorders | 4 (1) | 3 (2) | 3 (2) | 12 (2) | 0 (0) | 10 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 28 (1) | 11 (1) |
| General disorders and administration site conditions | 3 (1) | 0 (0) | 0 (0) | 3 (0) | 0 (0) | 7 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 10 (0) | 8 (1) |
| Hepatobiliary disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) |
| Immune system disorders | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 1 (0) | 0 (0) |
| Infections and infestations | 4 (1) | 1 (1) | 1 (1) | 6 (1) | 0 (0) | 19 (3) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 28 (1) | 7 (1) |

| Treatment Group | Placebo n (%) | Sugammadex [mg/kg] n (%) | | | | | | | | | | Neostig- mine n (%) |
|---|------------------|-----------------------------|----------|-----------|----------|-----------|----------|----------|----------|----------|-------------------|---------------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | Total | |
| Injury, poisoning and procedural complications | 21 (6) | 2 (2) | 0 (0) | 20 (3) | 0 (0) | 38 (5) | 0 (0) | 2 (1) | 0 (0) | 4 (3) | 66 (3) | 16 (2) |
| Investigations | 2 (1) | 0 (0) | 0 (0) | 15 (2) | 0 (0) | 8 (1) | 0 (0) | 1 (1) | 3 (8) | 5 (4) | 32 (2) | 0 (0) |
| Metabolism and nutrition disorders | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Musculoskeletal and connective tissue disorders | 3 (1) | 0 (0) | 2 (1) | 0 (0) | 0 (0) | 9 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 11 (1) | 0 (0) |
| Neoplasms benign, malignant and unspecified | 2 (1) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 2 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (0) | 0 (0) |
| Nervous system disorders | 9 (3) | 0 (0) | 0 (0) | 5 (1) | 0 (0) | 4 (1) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 10 (0) | 0 (0) |
| Psychiatric disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 7 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 7 (0) | 0 (0) |
| Renal and urinary disorders | 1 (0) | 4 (3) | 0 (0) | 1 (0) | 0 (0) | 6 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 11 (1) | 3 (0) |
| Respiratory, thoracic and mediastinal disorders | 2 (1) | 2 (2) | 0 (0) | 10 (2) | 0 (0) | 12 (2) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 25 (1) | 5 (1) |
| Skin and subcutaneous tissue disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 2 (0) | 0 (0) |
| Surgical and medical procedures | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 4 (0) |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (Complete Response)
 (b) (4) (sugammadex sodium)

| Treatment Group | Placebo n (%) | Sugammadex [mg/kg] n (%) | | | | | | | | | | Neostig- mine n (%) |
|--------------------|--------------------|-----------------------------|------------------|--------------------|-------------------|---------------------|------------------|------------------|------------------|--------------------|---------------------|---------------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | Total | |
| Vascular disorders | 4 (1) | 1 (1) | 0 (0) | 3 (0) | 0 (0) | 11 (2) | 0 (0) | 0 (0) | 0 (0) | 2 (2) | 17 (1) | 4 (0) |
| Totals | 63 (19) | 16 (13) | 7 (4) | 85 (14) | 1 (11) | 147 (20) | 2 (7) | 4 (3) | 3 (8) | 14 (11) | 279 (14) | 69 (9) |

In addition to comparing SAEs based on SOC, it is important to consider SAEs based on preferred terms as some events may be classified under different SOCs predicated on the context in which they occurred. For example, hemorrhage was classified under “vascular disorders” as well as “injury, poisoning and procedural complications.” The Applicant looked at SAEs based on preferred terms but within the individual SOCs rather than on their own. This was done for both the pooled placebo-controlled and pooled neostigmine-controlled trials, and they found no differences with sugammadex in either group.

Therefore, a table of the 411 SAEs sorted by preferred terms created. In all, there were 219 preferred term categories; very few for which there were more than a single SAE. There was no apparent dose-dependence of any of the SAEs after sugammadex treatment. It was noted however, that some of the SAEs, which were similar in nature, were categorized under a variety of preferred terms. Specifically, haemorrhage, incisional haemorrhage, muscle haemorrhage, and operative haemorrhage were some of the terms used to describe bleeding that occurred following study drug administration. In addition, there were a number of cardiac arrhythmias that were listed by specific terms, e.g., atrial fibrillation and bradycardia, but not grouped under the same higher level terms. To address the possibility that a safety signal exists in these data, **Table 14** was created by grouping similar terms. A total of 17 preferred terms described bleeding events:

- Abdominal haematoma
- Gastrointestinal haemorrhage
- Haematoma
- Haemorrhage
- Incision site haematoma
- Intraventricular haemorrhage
- Muscle haemorrhage
- Operative haemorrhage
- Post procedural haematoma
- Post procedural haemorrhage
- Procedural haemorrhage
- Pulmonary haemorrhage
- Subcutaneous haematoma
- Upper gastrointestinal haemorrhage
- Urinary bladder haemorrhage
- Wound haemorrhage

The cardiac events included the following 12 preferred terms:

- Acute myocardial infarction (n=1 for sugammadex, placebo, and neostigmine)
- Atrial fibrillation (n=6 for sugammadex)
- Bradycardia (n=1 for placebo)
- Cardiac arrest (n=1 for sugammadex)

- Electrocardiogram QT corrected interval prolonged (n=2 for placebo; n=27 for sugammadex)
- Electrocardiogram QT prolonged (n=1 for sugammadex)
- Electromechanical dissociation (n=1 for sugammadex)
- Myocardial infarction (n=1 for placebo and sugammadex)
- Tachyarrhythmia (n=1 for sugammadex)
- Tachycardia (n=1 for sugammadex)
- Ventricular fibrillation (n=1 for placebo)
- Ventricular tachycardia (n=1 for sugammadex)

The table indicates that SAEs related to bleeding occur no more frequently with sugammadex than for placebo, and that bleeding events are not dose-related for sugammadex treatment.

For SAEs related to cardiac rhythm, the table indicates that overall there were no more events following sugammadex treatment than there were following placebo. It is interesting to note that the higher doses of sugammadex, i.e., 12 and 16 mg/kg, were associated with an increased frequency of these events. The clinical significance of this finding is uncertain due to the limited number of subjects in these treatment groups (166 in total).

The bleeding and cardiac adverse events are of particular note because they comprise two of the three clinical safety issues identified for adults that were included in the Complete Response letter issued at the end of the first review cycle. The third issue was anaphylaxis/hypersensitivity. For this issue, there was one SAE with the preferred term anaphylactic shock, which occurred following the administration of 16 mg/kg of sugammadex and one SAE labeled hypersensitivity that occurred following administration of placebo. Each of these three issues will be visited in greater detail, including reviews of the narratives for the SAEs in section 7.3.5 below.

Most of the other SAEs appeared to be unlikely related to study drug and could be readily explained by the subjects' underlying medical problems, surgical procedure, or medications administered in the perioperative period, e.g., opioids for post-operative pain. The 50 SAEs related to bleeding; the 48 events related to cardiac rhythm; and the two cases of anaphylaxis/hypersensitivity were considered to be most likely to be related to sugammadex administration. In addition to these, there were SAEs of flushing, urticaria, hypotension and bronchospasm that were also considered as possibly related to sugammadex, and may have been part of anaphylactic reactions that were not classified as such. These findings differ from the Applicant's. In the ISS database, only 26 of the 425 SAEs were classified by the Investigators as possibly or probably related to the administration of sugammadex. All but one of these was related to hemorrhage, cardiac rhythm disturbances or allergic type reactions. The other SAE they considered possibly related to sugammadex psychotic behavior that followed a 4 mg/kg dose. That patient, who had a history of a "psychotic episode," was reported to

have 1 hour of “psychotic behavior” immediately postoperatively that resolved spontaneously.

In summary, the analysis of SAEs reported in the clinical trials indicates that, overall, the safety profile for sugammadex is not substantially different than placebo or neostigmine, with the possible exception of cardiac rhythm adverse events. These events included a range of conduction abnormalities most of which occurred within minutes following the administration of sugammadex and that resolved spontaneously. It is important to note that if these events are caused by sugammadex, it is only with the highest proposed dose, i.e., 16 mg/kg, that sugammadex appears to differ substantially from placebo and neostigmine.

Table 14. Serious adverse events related to bleeding and cardiac rhythm abnormalities.

| SAE Types | placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine | |
|------------------------------|---------|--------------------|---|----|---|----|---|---|----|----|-------|-------------|--|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | Total | | |
| All hemorrhage and hematomas | | | | | | | | | | | | | |
| n | 11 | 4 | 1 | 10 | 0 | 16 | 0 | 1 | 0 | 2 | 34 | 5 | |
| % | 3 | 3 | 1 | 2 | 0 | 2 | 0 | 1 | 0 | 2 | 2 | 1 | |
| All cardiac-rhythm | | | | | | | | | | | | | |
| n | 6 | 2 | 0 | 18 | 0 | 11 | 0 | 1 | 3 | 6 | 41 | 1 | |
| % | 2 | 2 | 0 | 3 | 0 | 2 | 0 | 1 | 8 | 5 | 2 | 0 | |

7.3.3 Dropouts and/or Discontinuations

For most of the clinical development program, sugammadex was administered as an intravenous bolus, the way it would be used in clinical practice. Therefore, discontinuations of administration were possible only in the trials where the study drug was infused or in crossover trials where a subject did not proceed to a subsequent period. Trials 19.4.108 and 19.4.109 involved infusions of study drugs over 4-minute periods; trial 19.4.109 was also a crossover study. The Applicant reported that the infusion of sugammadex was not discontinued in any subject in these two trials. Therefore, there were only subject withdrawals from the trials due to an adverse event (AE) rather than discontinuations of treatment per se.

Table 15 below contains the Applicant's summary of study discontinuations for both the original NDA submission and the resubmission. This summary was limited to the pooled Phase 1-3 placebo-controlled studies.

Table 15. Subject disposition for placebo-controlled studies (from Table 18 on p. 71 of section 5.3.5.3 of the resubmission)

| | 0 mg/kg (Placebo) | | 2 mg/kg | | 4 mg/kg | | 16 mg/kg | | Total ^a sugammadex | |
|-----------------------------------|----------------------|-------------|-------------|-------------|-------------|--------------|------------|------------|----------------------------------|--------------|
| | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 | 2007 | 2012 |
| Total number of subjects exposed | 140 | 544 | 605 | 838 | 580 | 1798 | 98 | 98 | 1926 | 3407 |
| Completed study | 137 (98) | 534 (98) | 597 (99) | 830 (99) | 574 (99) | 1764 (98) | 95 (97) | 95 (97) | 1891 (98) | 3343 (98) |
| Discontinued due to adverse event | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 3 (0) | 1 (1) | 1 (1) | 4 (0) | 6 (0) |
| Discontinued due to other reason | 3 (2) | 9 (2) | 8 (1) | 8 (1) | 5 (1) | 31 (2) | 2 (2) | 2 (2) | 31 (2) | 58 (2) |

^a Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20, 32 mg/kg). There were no new subjects since the 2007 submission exposed to doses of sugammadex that are not displayed.

The Applicant indicated that the subject in the placebo group discontinued from the trial due to an AE had an episode of ventricular fibrillation, considered unrelated to the study drug by the Investigator. Three subjects in the

sugammadex 4 mg/kg dose group discontinued trials due to multiple AEs. Two subjects in the < 2 mg/kg group were discontinued from trials due to the AE of “neuromuscular blocking therapy.” This was the only AE which led to discontinuation that occurred in more than one subject within a dose group. One subject in the 16 mg/kg dose group discontinued from the trial due to the AE of unwanted awareness during anesthesia.

Two subjects who discontinued from trials had AEs of unwanted awareness during anesthesia and neuromuscular blocking therapy which were both considered to be related to study drug (1 sugammadex and 1 placebo) by the Investigators

In the Pooled Neostigmine-controlled trials, one subject in the neostigmine group discontinued the trial due to AEs of gastric perforation and “procedural complications.” These AEs were considered to be unrelated to trial medication by the investigator. No subjects in the sugammadex group discontinued from a trial due to an AE in this pooled group.

The individual cases of discontinuations due to an AE are described and discussed below. Note that there were 8 cases of discontinuation following treatment with sugammadex, not 6 as reported in the Applicant’s table above. This was due to how they pooled the data for the table.

Discontinuations Following Sugammadex Treatments

1. In Trial 19.4.101, Subject 013 dropped out of the study due to an episode of Wolff-Parkinson-White (WPW) syndrome that was noted in ECGs taken at 30 and 60 minutes after receiving a 2 mg/kg dose of sugammadex as part of the second treatment period in the study. The subject had received placebo in the first treatment period. The Applicant reported that the subject had ECGs considered within the normal limits at pre-dose, at 2 minutes post-dose, and at 10 minutes post-dose. The subject reportedly had no symptoms at the time the WPW conduction abnormalities were observed and his vital signs were described as normal. A follow-up ECG at 2 hours post-dose was within normal limits. The Applicant states that the subject did not participate in the third period of the study. The Applicant notes that during the first treatment period, i.e., after placebo treatment, the subject’s ECG also had WPW syndrome findings, suggesting that its appearance was not present only during active treatment.

The Applicant’s statement that the ECG abnormality was noted in the first period of the study suggests this is an ongoing but sporadic condition for the subject. However, that does not rule out the possibility the sugammadex might have played a role in its occurrence in the second period. It also raises the question as to why the subject was permitted to

continue after the first period but not the second given this was a healthy volunteer study. The study report indicated that his continuation in the study after period was an error.

2. In Trial 19.4.105, Subject 101019 received a 4 mg/kg dose of sugammadex during treatment period 2. Six days later, the baseline laboratory values for period 3 indicated an increased aspartate aminotransferase that returned to baseline levels 4 weeks later (197 U/L to 23 U/L) along with a similar increase and return to baseline for blood creatine phosphokinase (5490U/L to 157 U/L) levels. The subject was discontinued from the trial. It was noted that the subject was on no concomitant medications at the time of the event.

The narrative described only aspartate aminotransferase and blood creatine phosphokinase increases; however, a review of this subject's other laboratory test results for the same study period indicated that her total bilirubin levels increased and recovered (14 μ mol/L to 7 μ mol/L) and her alanine aminotransferase levels behaved similarly (92 U/L to 14 U/L). Without another likely cause for the sudden increase in the laboratory parameters, they should be considered as probably due to treatment with sugammadex as the subject met the criteria for entry into this healthy volunteer study.

3. In Trial 19.4.106, Subject 008 was scheduled to receive a 32 mg/kg dose of sugammadex; however, about midway through the infusion, i.e., 17 mL of sugammadex or 22 mg/kg, the subject experienced paresthesia in the skin of hands, and face, visual disturbance, dysgeusia (a metallic taste), nausea, tachycardia and stomach discomfort (an upset stomach). The paresthesia and visual disturbance were described as moderate in intensity. The paresthesia consisted of a tingling, then later, a cramping sensation. The subject was also reported to have tachycardia, but whether there were concomitant changes in blood pressure could not be determined due to failure of the blood pressure cuff. The sudden onset and combination of the adverse events prompted the investigator to stop the infusion. Later flushing (flushed skin in arms) and some erythematous rash was observed. The erythematous rash was located on the abdomen and was neither elevated nor itchy. The symptoms of subject 008 were at first interpreted as hyperventilation, but after appearance of the flushing and rash, an allergic reaction was considered. All of the symptoms resolved without treatment. Additional skin tests were performed to further investigate the underlying cause and indicated an allergic reaction to sugammadex.

Based on the constellation of symptoms and their temporal relationship to the administration of sugammadex, the reaction would have been more

appropriately classified as anaphylaxis and probably related to the study drug

4. In Trial 19.4.109, subject 101073 was scheduled to receive a 32 mg/kg dose of sugammadex in period 3. Two minutes after the infusion was begun, the subject experienced a possible allergic reaction consisting of a burning sensation over the whole body, nausea, a sensation of heaviness in the whole body, agitation. The infusion of the study drug was stopped at that point. One day later, a rash was observed on arm where the infusion took place. The subject recovered from all adverse events. The Investigator considered the adverse events as possibly related to sugammadex.

Given the temporal relationship to the study drug and that this was a healthy volunteer, thorough QT study, the adverse events should all be considered as likely due to the study drug.

5. In Trial 19.4.204, subject 204103001 underwent a scheduled splenectomy on (b) (6) and was treated with a 1 mg/kg dose of sugammadex at the end of surgery. Recovery from neuromuscular blockade was incomplete. Approximately 30 minutes later, the Investigator administered neostigmine (2 doses 10 minutes apart) due to safety concerns because the TOF ratio had not recovered to 90% by the time the subject arrived in the post-anesthesia care unit. Adequate recovery was noted approximately 1 hour after the second dose of neostigmine. The adverse event was reported as “neuromuscular block prolonged” and was considered by the Investigator to be the most important of several AEs that leading to the patient’s withdrawal from the trial. (The other AEs leading to trial discontinuation included electrocardiogram QT prolonged, blood albumin decreased (32 g/L to 18 g/L), hematocrit decreased (0.4 to 0.3), protein total decreased (82 g/L to 42 g/L), and urinary beta-N-acetyl-D-glucosaminidase increased.) All of the adverse events were considered to be unlikely related to study drug.

Not reported in the narrative was that creatine kinase also increased from 18 U/L to 94 U/L. While some of the adverse events could be explained by the subject’s underlying medical problems and the surgical procedure, the prolonged neuromuscular blockade and QT intervals cannot be. The prolonged neuromuscular blockade is likely due to an inadequate dose of sugammadex; the QT prolongation might be in part due to neostigmine or other anesthetic agents but should be considered possibly due to the sugammadex in this scenario.

6. In Trial 19.4.204, subject 204103009 underwent bilateral varicocelectomies on the testes. At the end of surgery, for which

rocuronium was used as the neuromuscular blocking agent, a 0.5 mg/kg bolus dose of sugammadex was administered at 1-2 PTCs. The subject's recovery from the neuromuscular blockade was considered slow by the Investigator. Neostigmine was then administered to expedite recovery and the adverse events "neuromuscular block prolonged" was attributed to the study drug and was the cause of the subject's discontinuation from the trial. The event was considered by the Investigator as definitely related to study drug.

Given the dose of sugammadex and the timing of its administration, at the return of 1-2 post-tetanic contractions, it is not surprising that recovery from neuromuscular blockade was prolonged. The Investigator's a classification of the study drug appears to be most appropriate.

7. In Trial 19.4.205, subject 0042 underwent surgery for correction of a deviated nasal septum. She was induced with IV fentanyl, propofol, and rocuronium, and maintained with IV propofol. The subject reported awareness during anesthesia beginning approximately 1 hour after the start of anesthesia and 30 minutes after the administration of a 16 mg/kg dose of sugammadex. Inhalation anesthesia with isoflurane was added to the anesthetic regimen at this time, and the subject recovered completely after 1 minute. Although the subject completed the administration of sugammadex, she was subsequently withdrawn from the trial due to the adverse event. The Investigator considered the event as possibly related to the study drug.

It is not clear how it was determined that the subject was aware intraoperatively. The protocol did not mandate monitoring such as bispectral index monitoring, but this would alert the clinician to the possibility of awareness and allow for corrective action, which would explain the addition of the inhaled anesthetic. Given the timing of the event before administration of study drug, it would be impossible that the drug was responsible for the effect. Whether there was a second change in the subject's status after the study drug was given is not clear from the narrative and the CRF. Therefore, considering the event as possibly related to study drug is not unreasonable.

8. In Trial 19.4.311, subject 112011 was scheduled for surgery to treat bilateral gastroc equinus contracture. As part of the anesthetic procedure the subject received a 4 mg/kg dose of sugammadex. Three days later, the subject developed nausea, abdominal pain, hypotension and cyanosis. IV fluid was given for hypovolemia. The following day, the subject had an exploratory laparotomy during which she was diagnosed with a perforated colon and sepsis. That same day she had an episode of pulseless electrical activity and was resuscitated. The subject was put on

mechanical ventilation in the ICU and antibiotic treatment was started. One week later, she underwent an “abdominal washout” that was performed in the OR. The subject was discharged 4 weeks after sugammadex administration and was reported to have recovered with sequelae: generalized muscle weakness. All of the adverse events were classified as not related to study drug.

Given that the underlying condition, i.e., perforated colon, was unlikely related to the study drug, it is reasonable to assert that it did not contribute to the subsequent sepsis, incidence of pulseless electrical activity, and 4 weeks later, the generalized weakness

Discontinuation Following Neostigmine Treatments

1. In Trial 19.4.302, subject 110014 underwent a laparoscopic adjustable gastric band placement. As part of the anesthetic procedure the subject received a 70 mcg/kg dose of neostigmine at the end of her surgery. Two days later, the subject was discharged in good condition only to return to the emergency room two days after complaining of nausea, vomiting, abdominal tightness, weakness and dyspnea. Five days after administration of the study drug, a CT scan showed pneumoperitoneum and an ileus. The following day, the subject underwent laparoscopy at which time two holes in the posterior gastric wall and an abdominal abscess were discovered. During the procedure, the gastric band was removed, the abscess was drained, the holes were repaired, and a gastrostomy tube was inserted and a chest tube placed to drain a left pleural effusion. At that time, the subject was seriously ill with sepsis, renal insufficiency, heart failure and pulmonary atelectasis. She was kept intubated in the surgical ICU. The subject was ultimately discharged 24 days after her original procedure. Six months later, she was reported to be recovering. The subject discontinued due the adverse events all of which were considered by the Investigator as unrelated to the study drug.

Based on the nature of the subject’s surgical procedure and the adverse events that ensued, they can all be ascribed to the surgery rather than the study drug as was appropriately done by the Investigator.

Discontinuation Following Placebo Treatments

1. In Trial P07038, subject 31832 was a 65 year old with pre-existing conditions that included atrial fibrillation bradycardia-tachycardia syndrome, coxarthrosis, hyperuricemia and hypertension. He underwent total hip arthroplasty and died of ventricular fibrillation 7 days after surgery and the administration of the placebo study drug. This case is described in the Section 7.3.1 above.

Summary and Conclusions

The discontinuations that occurred during the development program were few in number due to the acute use of sugammadex in the controlled setting of the operating room or clinical research facility. Given the limitations associated with eight events that occurred with sugammadex and single events that occurred with neostigmine and placebo treatments, it was not possible to determine whether there were any trends in the findings or differences between the treatment groups. The data do suggest that doses of sugammadex less than 2 mg/kg will not provide clinically relevant benefits for patients and that anaphylaxis from sugammadex can have a substantial impact on a patient's post-operative course.

7.3.4 Significant Adverse Events

Of the 22,961 treatment-emergent adverse events that occurred with intravenously administered study drugs, 803 were rated as "severe" by the Investigators. **Table 16** compares the severe adverse events across the three treatment groups: placebo, sugammadex, and neostigmine, with the sugammadex group further subdivided by dose. The table provides the breakdown of the severe events according to whether they also qualified as serious adverse event and according the system organ classification to which they were assigned by the Applicant.

Of the 425 SAEs in the database, 183 (43%) were classified as severe. The percentages were different across treatments groups: 62%, 43%, and 36% for placebo, sugammadex, and neostigmine, respectively, with sugammadex and neostigmine not substantially different from one another, but substantially less than placebo. For sugammadex, there is no apparent dose dependency for the occurrence of severe adverse events based on the two types of adverse events (AE and SAE) and the total number of severe adverse events per dose group.

For each SOC, there was no apparent difference between sugammadex and the two alternative treatments, and no indication that severe adverse events were sugammadex-dose dependent for any of the SOC.

The individual SOCs were examined for "pockets" of severe AEs for individual sugammadex doses. Doses for which there were less than 30 subjects were not included in the analysis do to the effect that a single subject would have on the outcome. This assessment revealed that the only SOC for which there was a greater than 5% occurrence of severe AEs was "injury, poisoning and procedural complications." For thee 274 severe AEs, the preferred terms were examined for each treatment group for 5 or more occurrences. Incision site complication and post procedural hemorrhage had 5 (1%) events each in the 2 mg/kg sugammadex group and incision site complication also had 7 (1%) events in the

4 mg/kg sugammadex group. Interestingly, the greatest number of occurrences was in the procedural pain group. There were 24 (3%) cases involving neostigmine, 7 (2%) cases involving placebo, and 91 (4%) cases involving sugammadex. Within the sugammadex doses

- 4 (2%) cases occurred with 1 mg/kg treatment;
- 38 (6%) cases occurred with 2 mg/kg treatment;
- 1 (11%) case occurred with 3 mg/kg treatment;
- 46 (6%) cases occurred with 4 mg/kg treatment; and
- 2 (2%) cases occurred with the 16 mg/kg dose

Review of the verbatim terms listed each as “postoperative pain,” occasionally specifying the surgical site as the source. Given the similarity for incidence rates between treatment groups, it does not appear that sugammadex has a direct impact on postoperative pain; the lack of a dose effect for this AE also supports that conclusion.

Summary and Conclusions

Analysis of the severe adverse events occurring for the three treatment groups and various dose groups of sugammadex did not indicate that sugammadex was associated with greater risk for such events compared to placebo or neostigmine or that the risk for such events was greater with increased doses of sugammadex. These findings were consistent across SOCs and preferred terms for the events occurring most frequently.

Table 16. Summary of severe adverse events N(%) by type of event and system organ class

| Treatment | Pla- cebo | Sugammadex (mg/kg) | | | | | | | | | | | Neo- stigmine |
|--|--------------|--------------------|------------|-------------|-----------|-------------|-----------|------------|------------|-----------|------------|-------------|------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 20 | 32 | Total | |
| N | 336 | 124 | 178 | 613 | 9 | 729 | 28 | 154 | 127 | 6 | 112 | 2080 | 856 |
| Type of AE | | | | | | | | | | | | | |
| AE | 43 (13) | 21 (17) | 26 (15) | 125 (20) | 5 (56) | 197 (27) | 6 (21) | 12 (8) | 14 (11) | 1 (17) | 2 (2) | 409 (20) | 120 (14) |
| SAE | 39 (12) | 7 (6) | 5 (3) | 46 (8) | 0 (0) | 55 (8) | 0 (0) | 1 (1) | 5 (4) | 0 (0) | 0 (0) | 119 (6) | 25 (3) |
| Total | 39 (12) | 28 (23) | 31 (17) | 171 (28) | 5 (56) | 252 (35) | 6 (21) | 13 (8) | 19 (15) | 1 (17) | 2 (2) | 119 (6) | 25 (3) |
| System Organ Class | | | | | | | | | | | | | |
| Blood and lymphatic system disorders | 3 (1) | 1 (1) | 0 (0) | 2 (0) | 0 (0) | 4 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 7 (0) | 2 (0) |
| Body as a whole - general disorders | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 1 (11) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (0) | 0 (0) |
| Cardiac disorders | 5 (1) | 5 (4) | 0 (0) | 4 (1) | 0 (0) | 7 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 16 (1) | 3 (0) |
| Cardiovascular disorders, general | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Centr & periph nervous system disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (22) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) |
| Ear and labyrinth disorders | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 1 (0) |
| Eye disorders | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) |
| Gastrointestinal disorders | 6 (2) | 3 (2) | 6 (3) | 26 (4) | 0 (0) | 27 (4) | 0 (0) | 0 (0) | 5 (4) | 0 (0) | 0 (0) | 67 (3) | 25 (3) |
| General disorders and administration site conditions | 6 (2) | 1 (1) | 0 (0) | 9 (1) | 0 (0) | 10 (1) | 3 (11) | 0 (0) | 1 (1) | 1 (17) | 0 (0) | 25 (1) | 10 (1) |
| Hepatobiliary disorders | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 3 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (0) | 0 (0) |
| Immune system disorders | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 | 0 |

| Treatment | Pla- cebo | Sugammadex (mg/kg) | | | | | | | | | | | Neo- stigmine |
|---|--------------|--------------------|-----------|------------|-----------|------------|----------|----------|----------|----------|----------|------------|------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 20 | 32 | Total | |
| | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (1) | (0) | (0) | (0) | (0) |
| Infections and infestations | 4 (1) | 0 (0) | 1 (1) | 5 (1) | 0 (0) | 10 (1) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 17 (1) | 5 (1) |
| Injury, poisoning and procedural complications | 25 (7) | 5 (4) | 13 (7) | 66 (11) | 1 (11) | 85 (12) | 0 (0) | 3 (2) | 4 (3) | 0 (0) | 0 (0) | 177 (9) | 57 (7) |
| Investigations | 4 (1) | 0 (0) | 2 (1) | 8 (1) | 0 (0) | 25 (3) | 0 (0) | 3 (2) | 0 (0) | 0 (0) | 2 (2) | 40 (2) | 3 (0) |
| Liver and biliary system disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Metabolic and nutritional disorders | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (11) | 0 (0) | 1 (4) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 3 (0) | 0 (0) |
| Metabolism and nutrition disorders | 1 (0) | 0 (0) | 0 (0) | 2 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (0) | 0 (0) |
| Musculoskeletal and connective tissue disorders | 4 (1) | 1 (1) | 3 (2) | 4 (1) | 0 (0) | 12 (2) | 1 (4) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 22 (1) | 4 (0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (0) |
| Nervous system disorders | 11 (3) | 2 (2) | 3 (2) | 15 (2) | 0 (0) | 9 (1) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 30 (1) | 13 (2) |
| Platelet, bleeding & clotting disorders | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| Psychiatric disorders | 1 (0) | 1 (1) | 1 (1) | 4 (1) | 0 (0) | 6 (1) | 0 (0) | 0 (0) | 3 (2) | 0 (0) | 0 (0) | 15 (1) | 5 (1) |
| Renal and urinary disorders | 0 (0) | 3 (2) | 2 (1) | 1 (0) | 0 (0) | 17 (2) | 0 (0) | 1 (1) | 1 (1) | 0 (0) | 0 (0) | 25 (1) | 7 (1) |
| Reproductive system and breast disorders | 1 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 3 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 5 (0) | 0 (0) |
| Respiratory, thoracic and mediastinal disorders | 2 (1) | 3 (2) | 0 (0) | 11 (2) | 0 (0) | 18 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 32 (2) | 7 (1) |
| Skin and subcutaneous tissue disorders | 0 (0) | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 2 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 4 (0) | 1 (0) |
| Surgical and medical procedures | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |

Clinical Review
 Arthur Simone, MD, PhD
 NDA 022225 (Complete Response)
 (b) (4) (sugammadex sodium)

| Treatment | Pla- cebo | Sugammadex (mg/kg) | | | | | | | | | | | Neo- stigmine |
|--------------------|--------------|--------------------|----------|----------|----------|-----------|----------|----------|----------|----------|----------|-----------|------------------|
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 16 | 20 | 32 | Total | |
| | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) | (0) |
| Vascular disorders | 3 (1) | 1 (1) | 0 (0) | 7 (1) | 0 (0) | 10 (1) | 0 (0) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 20 (1) | 7 (1) |

7.3.5 Submission Specific Primary Safety Concerns

The review of safety conducted at the time of the original NDA submission resulted in the identification of three issues for which the risks associated with sugammadex had not been adequately evaluated to allow the benefit-risk analysis to be completed, and therefore, resulted in the Division taking a Complete Response action. These issues included:

1. Anaphylaxis/hypersensitivity reactions
2. Insufficient information on the effects of sugammadex on coagulation pathways and perioperative bleeding
3. Cardiac arrhythmias

The first two issues were identified as deficiencies in the Complete Response letter that had to be addressed prior to approval. The issue of cardiac arrhythmias was not considered a deficiency; rather, it was a safety signal that could possibly be addressed by appropriate labeling and postmarketing surveillance if the risk could not be further quantified by a clinical study. The Applicant has addressed all three of these issues in the resubmission, and each is considered in detail in the subsections that follow.

7.3.5.1 Anaphylaxis and Hypersensitivity

Preliminary Note

On July 12, 2013, the Office of Scientific Investigations notified the Division that they had uncovered a problem with the conduct of Trial P06042 during their inspection of Site #2 located in the United Kingdom. The inspection revealed there was potential unblinding of 53 out of 95 randomized subjects. Specifically, sugammadex is different in color from the normal saline placebo. To maintain the study blinding, the syringes were to have been masked and the investigator giving the product was not to have been involved with adverse event evaluation. That did not occur at this site. The investigator both administered the study drugs and performed adverse event evaluations. The investigator was reported to have noticed that the viscosity of the product changed as the dosing increased. This situation persisted for 6-8 weeks of the study before the Applicant was made aware of the problem and took steps to address it. Although a note to file was made, which was discovered by the FDA inspector, the Applicant failed to notify the Agency of the problem and made no mention of it in the clinical study report. There were only 4 centers involved with Trial P06042; the only site in the United States has been closed due to bankruptcy proceedings and the source documents are presently unavailable for inspection. The two remaining sites are located in Germany or the Netherlands.

The unblinding of the subjects' treatments in this study raises concerns for the validity of the findings from that site as the assessment of hypersensitivity and anaphylaxis symptoms is subjective. The failure to report the protocol violation in the clinical study report and to notify the Division when the issue became known to the Applicant raises additional concerns over the validity of the study as a whole. The inability to examine source documents at the U.S. site only worsens the situation.

Due to these findings, the Advisory Committee meeting scheduled for July 18, 2013, was cancelled. At the time this review was completed, the issue had not been resolved and, it is unclear whether the Applicant will be able to salvage this study, which was pivotal to the product being approved in this cycle. Therefore, a recommendation for a second Complete Response action is being made.

Although it is not possible to draw conclusions from the data in Trial P06042 at this time, the study is reviewed below. If all the data from the study were found to be valid, the conclusions drawn would be upheld; otherwise, the comments regarding the study design and protocol-specified methodology are still applicable.

Background

In the original NDA submission, the Applicant reported a number of “hypersensitivity” reactions in subjects treated with sugammadex. According to the Division of Pulmonary and Allergy Drug Products (DPADP) [later the Division of Pulmonary and Allergy Products (DPAP); now the Division of Pulmonary, Allergy and Rheumatology Products (DPARP)], these reactions met the criteria for being labeled anaphylactic. In all, there were five cases that meet the diagnostic criteria for anaphylaxis. In their Annual Report, dated February 27, 2008, which was submitted during the first review cycle for the NDA, the Applicant reported 7 additional subjects as having anaphylactic or hypersensitivity reactions. According to the reviewers at DPADP, the drug reactions of two of these subjects met the criteria for anaphylaxis. As there were 1973 adults and 51 children exposed to sugammadex during the clinical development program, the overall incidence of anaphylaxis was estimated as 0.3% (7/2024).

In their consultation of May 13, 2005, DPADP noted that “Anaphylaxis is a clinical syndrome characterized by acute onset of an illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems. Clinical criteria for the diagnosis of anaphylaxis have recently been proposed. The recently proposed criteria focus on clinical presentation and not on mechanism.”

The criteria they referenced specified that anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

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 or uvula), and at least one of the following:
 - a. Respiratory compromise (e.g., dyspnea, wheezing bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips, tongue, or uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheezing, bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

- b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

The more inclusive criteria, i.e., number 1 above, were used by DPADP for that and subsequent consultations.

To investigate these adverse events, the Applicant conducted a clinical study designed to evaluate skin prick test (SPT) and intradermal skin tests (IDT) of sugammadex in healthy volunteers that were not previously exposed to the product and in individuals previously exposed to sugammadex, both with and without clinical symptoms of hypersensitivity with exposure (Trial 19.4.110). Subjects with a positive SPT or IDT to sugammadex were further evaluated for possible cross reactivity to penicillin. The SPT and IDT results, indicated that one subject of 17 (6%) exposed to sugammadex, was hypersensitive to sugammadex, but this subject had an allergic reaction to sugammadex in a previous study. One control subject, who was previously exposed to sugammadex without clinical allergy symptoms, had a positive IDT to sugammadex. This was considered by the Applicant to possibly be a false positive IDT because the subject had increased and comparable levels of urine methylhistamine at baseline and post treatment. Based on the findings, the Applicant concluded that the results did not indicate cross reactivity between sugammadex and penicillin. DPADP noted in their consultation that the quantitative evaluation of SPT and IDT results by the Applicant did not add any additional information over the descriptive clinical evaluations and that penicillin skin testing would not address the possibility that cross-reactivity of sugammadex to other agents occurs. Furthermore, DPADP noted that of the twelve patients who were previously exposed to sugammadex, two (17%) had positive skin tests, one of whom had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. There were no unexposed subjects who had a positive skin test indicating that sugammadex does not produce a non-specific positive skin test. This information suggested that exposure to sugammadex may induce sensitization and production of sugammadex-specific IgE and for those patients there would be a risk for development of anaphylaxis if re-exposed to sugammadex.

The sugammadex drug development plan did not evaluate the safety of subsequent or repeated exposure to the drug, which raised a safety concern due to the likelihood of its wide used, if approved, and the likelihood it would be used in some patients more than once. As it appears sugammadex induces sensitization and production of sugammadex-specific IgE in a percentage of those exposed, it is likely that some of these sensitized patients would develop anaphylaxis or allergic reaction with subsequent exposure. The magnitude of this risk or the predictive value of skin testing in identifying patients who are at risk of such a reaction with re-exposure could not be determined with the information available in the original NDA submission; therefore, DPADP

recommended that the Applicant develop in vitro tests of sugammadex-specific IgE, IgG, IgM in order to further characterize the mechanism for these reactions. In addition to evaluating the risk for an allergic reaction among subjects with subsequent exposure, both in a general population and in a population of patients who have positive skin tests to sugammadex. They considered it important to better define the risk of anaphylactic and hypersensitivity reactions before the product is approved.

While there was a possibility, as suggested by the Applicant, that the extent of the anaphylactic reactions that will occur with sugammadex will consist only of mild rashes and gastrointestinal symptoms and mild-to-moderate changes in hemodynamic parameters, all of which might be self-limited and not require intervention, there was evidence to indicate that such a conclusion was not appropriate. In fact, the cases anaphylaxis reported from the clinical development program and the laboratory testing showed that sugammadex has allergenic potential and can cause anaphylaxis. The cases identified were serious allergic reactions with multi-organ involvement even though they were not severe in the sense that the subjects did not require active resuscitation. It cannot be assumed that sugammadex-induced anaphylaxis is minor or non-life-threatening. Since the clinical development program did not evaluate the safety of repeated exposures, the potential for more serious injury and even death in sensitized patients was a major risk that had not been formally addressed. There was concern that repeat exposures may result in more severe reactions, as is usually observed in drug hypersensitivity. There was no evidence to indicate that sugammadex would behave differently from other known immunogenic drugs. Therefore, the life-threatening potential from and the relatively high frequency of anaphylaxis for sugammadex along with its expected wide usage, were concerning. Based on the analyses of the data and recommendations of DPADP, the available data were considered insufficient to characterize the risk of anaphylaxis associated with sugammadex and to perform the benefit:risk analysis required to approve the product.

It should be noted that the input of two outside consultants was sought during the review process of the anaphylactic reactions, (b) (4) of the Mayo Clinic and (b) (4) of the Medical College of Georgia, who independently reviewed the suspected cases of anaphylaxis. Both consultants concurred with DPADP that sugammadex appears to cause anaphylaxis and recommended further study of the safety of repeat exposure.

In addition, it should be noted that the initial findings of hypersensitivity and anaphylaxis were presented at the meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) held on March 11, 2008. The meeting took place prior to DPADP having had the opportunity to provide their input and without committee members who had expertise in the area of anaphylaxis, due to the priority review timeline and the need to schedule the Advisory Committee

meeting within that timeline. Overall, the committee members concurred with the Applicant on the following points:

1. The reactions to sugammadex did not appear to be life-threatening, and therefore, did not qualify as “anaphylactic” reactions.
2. The “hypersensitivity” reactions appeared to be rare and mild, often resolving without intervention or requiring only minimal amounts of treatment for rapid and complete resolution.
3. The “hypersensitivity” reactions generally occurred shortly after the administration of sugammadex in a setting in which the patients were carefully monitored by clinical staff who were qualified to recognize and treat reactions, even anaphylactic reactions, should they occur.

For the ALSDAC committee members, the anaphylactic reactions did not pose a major safety concern that should negatively impact the approval of the product.

Based on the lack of expertise among ALSDAC committee members for anaphylactic-related issues, the input from allergy experts in DPADP, and the input from outside experts in anaphylaxis, the Division decided to override the ALSDAC recommendation to approve sugammadex and considered the issue of sugammadex induced anaphylaxis a major risk that had not been adequately characterized in the NDA submission. In concurrence with DPADP recommendations, the Division determined the lack of information to be a deficiency in the development program that had to be addressed to sufficiently characterize the safety profile of sugammadex to permit the benefit:risk analysis needed to determine whether it should be approved.

Initial Regulatory Action and Follow Up

In the Complete Response letter of July 31, 2008, the following deficiency, which precluded approval of the product, was noted:

The sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug. Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure. As widespread use of sugammadex sodium is expected, an individual patient may be exposed to the drug multiple times. This expected pattern of use is of concern because the risk of Type I hypersensitivity, including anaphylaxis, is likely to increase on repeat exposure.

To address the deficiency, the Applicant was required to provide the following information:

Characterization of the safety of sugammadex sodium on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions. Exposure of subjects to repeat doses of sugammadex sodium should occur at time intervals sufficient to permit formation of drug-specific IgE, such as at least a minimum of 5 to 6 weeks. Define the frequency, time course of events related to sugammadex sodium administration, and other characteristics of the adverse reactions. Attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium. The clinical program will inform the safety risk of sugammadex sodium on repeat exposure. Development of a predictive test will be useful in predicting risk and potentially in avoiding exposures to patients at risk for an anaphylactic reaction.

A Post-Action meeting was held with the Applicant on December 1, 2008. The following were the key discussion points related to sugammadex-related anaphylaxis:

1. The Applicant reported that all antibody testing for Trial 19.4.110 had been negative and concluded that the underlying mechanism for the sugammadex-related hypersensitivity reactions were not immunoglobulin-mediated. DPAP did not agree with this assessment as the negative predictive value of these assays is limited. While positive antibody results would be consistent with the skin testing results and provide insight into the pathophysiology, a negative result does not exclude the possibility of an immunoglobulin-mediated reaction. In addition, whether results of IgE/IgG testing were positive or negative, the risk of repeated exposures still needed to be assessed in a clinical setting given the anticipated widespread use of the drug. Delineating the underlying mechanism might be helpful in developing ways to minimize risk but would not replace the need for a formal safety assessment of repeated exposures.
2. The Applicant was encouraged to explore both IgE/IgG-mediated and non-IgE/IgG mediated mechanisms; however, they were reminded that a negative ELISA test result would not be sufficient to eliminate the possibility of antibody-based hypersensitivity reactions.
3. The strength of animal data to support repeat exposure in man was limited given the lack of a good animal model for anaphylaxis. Controlled data in humans was required. The original clinical program did not formally

assess the safety of repeat exposure at time intervals sufficient to permit formation of drug-specific IgE in an adequate number of patients.

4. The Agency would review any protocols to address these issues and provide feedback to assure the trials were adequately designed.

NDA Resubmission

To address the deficiency listed in the Complete Response, the Applicant provided the results of a repeat-dose clinical study, Trial P06042, for which DPARP provided feedback. DPARP considered the proposed study design, duration, interval of exposure, and patient number to be adequate.

P06042 was a randomized, double-blind, placebo-controlled, parallel-group, repeat-dose study that evaluated the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects age 18 to 55 years old. A total of 480 subjects received a single-blind, saline placebo test dose at Week 0; those who experienced a reaction to the placebo dose were excluded from the rest of the study. Of the 480 subjects enrolled, 448 were randomized in a 1:1:1 ratio to receive the following doses intravenously on Day 8 (Week 1), Day 36 (Week 5), and Day 78 (Week 11):

- Sugammadex 4 mg/kg (n=148)
- Sugammadex 16 mg/kg (n=150)
- Saline placebo (n=150)

The protocol also provided for antibody testing, serum tryptase, and other serological markers of contact system activation in subjects who had hypersensitivity reactions as well as in a subset of subjects who had no reactions for comparison. Similarly, skin prick and intradermal testing were performed in subjects with hypersensitivity reactions and in a subset of non-reacting patients for comparison. Patients were domiciled at the study site starting the evening before the scheduled dose and released the morning after the day of each dose. All adverse events and related data (e.g., laboratory measurements, physical exam results) were adjudicated by an independent committee that remained blinded to study treatment. Subjects who reported “severe and/or serious signs and symptoms” of hypersensitivity at any time in the study were discontinued.

Based on predefined hypersensitivity signs and symptoms, the Applicant identified 68 incidents of suspected hypersensitivity in 49 subjects. These cases were presented to an Adjudication Committee comprised of independent allergist/immunologists and anesthesiologists for review. The committee classified 8 subjects as having had a hypersensitivity reaction. Of these 8 subjects, the committee characterized the symptoms of one subject as meeting two definitions of anaphylaxis: NIAID/FAAN criterion #1 and the Rüggeberg criteria (refer to the attached DPARP consult for more detailed information). The committee also classified 2 other subjects as having met level 2 certainty: the

Rüggeberg criteria alone. DPARP reviewed the 68 suspected cases and used the NIAID/FAAN criterion #1 for identifying anaphylaxis cases; they identified 3 cases of anaphylaxis (all in the 16 mg/kg dose group) from among the 68, which they noted represented an incidence rate of 1% (3/298). These 3 cases were among the 8 above that met both definitions for anaphylaxis. For the other 5 subjects, 4 cases occurred with the 16 mg/kg dose and 1 case occurred with the 4 mg/kg dose.

DPARP's review of the 68 potential hypersensitivity cases also noted the following:

1. Out of the 49 subjects, 4 were randomized to the placebo arm, 10 were randomized to sugammadex 4 mg/kg, and 35 were randomized to sugammadex 16 mg/kg for a total of 45 subjects exposed to sugammadex.
2. Of those subjects who received sugammadex, a majority of the subjects who experienced hypersensitivity symptoms were in the sugammadex 16mg/kg dose group (35/45, 78%) and reacted in ≤ 5 minutes (40/45, 89%) on the first dose (30/45, 67%).
3. Most of these subjects did not require medical intervention (43/45, 96%) and ultimately completed the study (36/45, 80%).

DPARP also reported that skin testing in this study, both SPT and IDT, were essentially negative. The only positive intradermal reaction occurred at a low dilution and many other tests were read as indeterminate. They indicated that, while this would be inconclusive on its own, the additional finding of non-elevated tryptase levels suggests direct or IgE-mediated mast cell degranulation does not appear to be the cause of the hypersensitivity reactions. They also noted that intact and IgE-stripped basophils did not show evidence of histamine release upon drug exposure, suggesting a lack of direct and IgE-mediated basophil mediator release. Drug specific IgE and IgG levels were negative, suggesting that the reactions are not immunoglobulin-mediated. Lastly, they noted that there were no differences between subjects with and without hypersensitivity in cytokine release, complement activation, or kallikrein levels. Based on the totality of the findings, DPARP agreed with the Applicant that sensitization does not occur upon repeat exposures and that the risk of hypersensitivity reactions does not increase with repeat exposure. They also noted the following safety related points based on their review of Trial P06042:

1. For hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, flushing, urticaria, and cough.
2. Flushing, hypotension, nausea, pruritus, sneezing, tachycardia, urticaria, and vomiting, showed a dose-response for sugammadex occurring more frequently with high doses than with lower doses or placebo.

3. Hypersensitivity reactions were more frequently noted in the 16 mg/kg dose group, occurring within minutes of dosing, and with the first dose of sugammadex.

Postmarketing Findings

Since the first approval of sugammadex in the European Union on July 25, 2008, the Applicant reports the distribution of over (b) (4) vials for use in adult and pediatric patients. They also report that they have continuously monitored the product's safety since its initial launch. The postmarketing data that has accumulated through June 15, 2012, was provided with the NDA resubmission.

Anaphylaxis reports were identified by the Applicant by querying the narrow Anaphylaxis Standard MedDRA Query (SMQ), along with narrow terms from the "Anaphylactic/ anaphylactoid shock" sub-SMQ in the Shock SMQ. Serious hypersensitivity reports were identified by querying the broad Anaphylaxis SMQ, along with the preferred term "hypersensitivity." A total of 144 reports were identified in this manner: 87 reports of anaphylaxis and 57 reports of serious hypersensitivity.

DPARP has reviewed the 144 post-marketing reports. They note that there is a consistent constellation of symptoms described including: rash, bronchospasm, urticaria, edema, and hypotension. It was also noted that a majority of these cases required medical intervention with epinephrine, corticosteroids, antihistamines, or a combination of the three. While the Applicant has sought adjudication of these reports by an external committee and has quantified the number of cases of anaphylaxis, DPARP did not attempt to quantify the frequency of anaphylaxis from this database, as they felt the controlled clinical data to be more reliable. The post-marketing reports do provide a means of further characterizing the types of hypersensitivity reactions that have been observed with use of sugammadex in the controlled clinical studies.

Summary and Conclusions

Due to the OSI investigation findings for Trial P06042, it is not possible at this time to draw definitive conclusions regarding the potential for increased risk of anaphylaxis with repeat exposures to sugammadex. Based on the findings from Trial P06042, the data in the original NDA submission and the postmarketing data available to date, DPARP has concluded that sugammadex causes anaphylaxis and hypersensitivity events. The risk for these reactions appears to increase with higher doses. They indicated that whether this risk is greater than the risk for other drug products commonly used in the perioperative setting is difficult to determine; furthermore, there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-

benefit assessment for sugammadex should depend primarily on the efficacy and safety data specific to sugammadex and its expected use in the clinical setting.

From an anesthesia clinical perspective, the comments and recommendations by our colleagues in DPARP apply for the proposed uses of sugammadex. Specifically, the Applicant cannot be considered to have adequately addressed the issue of anaphylaxis until the questions of the validity of the data and the findings from Trial P06042 have been resolved. If the data cannot be relied upon, the Applicant should be required to repeat the study. The data currently available indicate that sugammadex does cause anaphylaxis and the risk associated with its repeated use in patients needs to be quantified before the benefit:risk analysis can be performed. As suggested by DPARP, the approvability of sugammadex needs to be predicated on its benefits and risks for the proposed indication and not whether it poses a similar level of risk compared to products that have different indications, even if they are commonly used in the perioperative setting.

7.3.5.2 Coagulation and Perioperative Bleeding

Background

In the original NDA submission, the Applicant did not assess coagulation parameters as part of the clinical laboratory investigations. Instead, they conducted two *in-vitro* studies mixing whole blood with sugammadex. These studies indicated that sugammadex causes statistically significant increases in the mean measured values of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the international normalized ratio for PT (INR); although, the mean values were reported to have been within normal limits of the laboratory performing the analyses. The Applicant indicated that the values were increased for concentrations of sugammadex comparable to peak plasma concentrations associated with a 16 mg/kg dose; however, changes for comparable concentrations of the other proposed doses were not evaluated.

In an effort to determine whether there was a clinical impact from these changes, the Applicant conducted a post hoc analysis in which aggregated data from the Phase 2 and 3 trials were evaluated for adverse events related to hemorrhage. Overall, there were such events reported in 6% of sugammadex-treated subjects but only in 3% of placebo-treated subjects. By repeating the analysis and limiting the preferred terms and expanding the sugammadex-treatment group to the Total Sugammadex group, i.e., adding subjects from studies not involving surgical procedures, the difference between treatment groups dropped to 0.5%.

It was noted that the Applicant, in discussing the potential mechanism of sugammadex interference with the coagulation parameters, stated that the mechanism is unknown and that “it is unknown what the clinical relevance of this is.”

Due to the safety concerns related to postoperative bleeding and the need for some patients to be anticoagulated perioperatively and for other patients to be anticoagulated during certain surgical procedures and then have the anticoagulation reversed at the end of the procedure, e.g., coronary artery bypass grafting using a cardiopulmonary bypass machine, it was considered imperative that the mechanism by which sugammadex affects coagulation and the extent to which it affects bleeding in patients be elucidated prior to the product being approved for marketing. An understanding of any drug-drug interaction that might occur between sugammadex and commonly used anticoagulants was also considered critical for the safe use of the product in the surgical population.

Initial Regulatory Action and Follow Up

In the Complete Response letter of July 31, 2008, the following deficiency, which precluded approval of the product, was noted:

The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program. The in vitro assessment indicated that sugammadex increased activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT) and the International Normalized Ratio (INR). In a comparison of hemorrhagic adverse events between placebo- and sugammadex-treated subjects, which were not included in protocol-specified safety assessments, fewer events were observed in the placebo-treated groups. A difference in these events persisted when the comparison was further refined. The mechanism and the clinical significance of the effects of sugammadex on coagulation are not known.

To address the deficiency, the Applicant was required to provide the following information:

Studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting.

During the Post-Action meeting that was held on December 1, 2008, the following issues were discussed:

1. The Applicant stated that they had conducted a study (Trial 19.4.115) to assess coagulation parameters and observed mild transient increases for aPTT/PT. The PK-PD analysis revealed no statistically significant relationship between sugammadex plasma concentrations and aPTT. A statistically significant relationship was found for PT(INR). At the mean maximum sugammadex plasma concentration after a 4 mg/kg or 16 mg/kg sugammadex dose, the predicted PT(INR) increase was 6% and 22%, respectively.
2. The Applicant stated that sugammadex was interacting with Factor 10a, but not in a clinically relevant manner that would translate into a bleeding risk.
3. The Applicant reported that they observed additive effects with Vitamin K.
4. The Division stated that to have its concerns fully addressed, data regarding the mechanism of action, the dose response, the pharmacodynamic effect and possible interactions between sugammadex

and other drugs affecting coagulation (e.g., heparin, warfarin, aspirin, and clopidogrel bisulfate) would need to be submitted.

5. The Division indicated that mechanistic data from vitro studies, studies in appropriate nonclinical models of bleeding, and data on coagulation parameters in a healthy volunteer trial may provide a substantial understanding of the effects of sugammadex on coagulation and may help limit the data needed from a clinical study to complete the benefit:risk analysis. However, the effects of sugammadex when it binds with non-NMBA moieties and the impact that has on postadministration bleeding would not likely be addressed by these studies. There was a concern that the effects of sugammadex on coagulation may present differently when used as intended in the clinical setting compared to carefully controlled studies that do not expose subjects to all the medications typically used in the perioperative period. Therefore, clinical trials assessing bleeding were needed.
6. The Agency would review any protocols to address these issues and provide feedback to assure the trials were adequately designed.

NDA Resubmission

The Applicant conducted two drug-drug interaction studies, one that evaluated a potential interaction between sugammadex and aspirin (Trial P07025) and one that evaluated a potential interaction between sugammadex and enoxaparin or unfractionated heparin (Trial P07044). These trials were designed with input from the Division of Hematology Products (DHP)

Trial P07025 was a Phase 1, randomized, double-blind, placebo-controlled, 4-period cross-over, drug-drug interaction study that evaluated the effect of sugammadex and aspirin on platelet aggregation and coagulation parameters in healthy male volunteers. The primary objective of the trial was to investigate the potential for an interaction between sugammadex (4 mg/kg) and aspirin on platelet aggregation (PA) using collagen-induced whole blood aggregometry following multiple daily doses of 75 mg of aspirin. The Applicant concluded from the study that:

1. There was no clinically significant interaction between sugammadex and aspirin on platelet aggregation.
2. There was no clinically significant interaction between sugammadex and aspirin on aPTT and PT.
3. There was no clinically significant interaction between sugammadex and aspirin on the cutaneous bleeding time.

DHP had the following comments and conclusions regarding this study:

1. There was no evidence of a clinically meaningful additive antiaggregant effect of sugammadex when administered with aspirin.

2. There was no evidence of an additive effect of sugammadex with aspirin compared to aspirin alone on the prolongation of aPTT and PT.

Study P07044 was a Phase 1, randomized, double-blind, placebo-controlled, 4 period, two-part cross-over study to that evaluated the potential interaction between 4 mg/kg and 16 mg/kg dose of sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity in healthy volunteers. The primary objective of the trial was to investigate the potential effect of 4 mg/kg and 16 mg/kg sugammadex on the anti-Xa activity of enoxaparin and on the aPTT activity of unfractionated heparin (UFH).

Pharmacokinetic data indicated there was no effect of either enoxaparin or UFH on the C_{max} or AUC_{0-6 hr} of sugammadex. The PK/PD data showed that there was a sugammadex dose-related increase in both the aPTT and the PT whether sugammadex was given with placebo, enoxaparin or UFH. The Applicant concluded that there was no clinically significant effect of sugammadex on the anti-Xa activity induced by enoxaparin, or on the prolongation of the aPTT induced by UFH.

DHP reviewed the study report and had the following comments and conclusions:

1. The metrics used by the Applicant were those most commonly used to measure the anticoagulant adequacy of enoxaparin and UFH.
2. There was no clinically relevant effect of 4 mg/kg and 16 mg/kg doses of sugammadex on the anti-Xa activity of enoxaparin.
3. The administration of sugammadex induced a dose-dependent prolongation of both the PT and the aPTT as had been previously noted. All prolongations reverted to baseline within 1 hour.

Based on the data from these two studies, DHP concluded that there was a noticeable, but small, dose-related, short term effect of sugammadex on the anticoagulant activity of both enoxaparin and UFH. Based on the data from the sponsor's companion clinical study (P07038, discussed below), these changes induced by sugammadex were not clinically significant because they did not lead to an increase in the frequency of bleeding in patients who had undergone major orthopedic surgery of the lower extremity. Additionally, there was probably no clinically meaningful drug-drug interaction on platelet aggregation, the aPTT or the PT when sugammadex is given together with aspirin as compared to the effects of aspirin alone on these parameters.

To evaluate the frequency of bleeding in patients undergoing surgery with the use of rocuronium or vecuronium that was reversed with sugammadex, the Applicant conducted Trial P07038, which was a randomized, controlled, parallel-

group, double-blind trial comparing sugammadex to “usual care” (i.e., neostigmine or placebo/spontaneous recovery) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin. The protocol for this study was reviewed by DHP and, after revisions, was determined to be appropriately designed to address the issue. Its key features included the following:

1. The study would enroll subjects who were to have major orthopedic surgery on the hip or knee, thereby providing a reasonably homogeneous population whose frequency of bleeding was quite well known and that was enriched for possible hemorrhagic events because of the use of drugs given for thromboprophylaxis.
2. Subjects must have received anticoagulant/antiplatelet therapy prior to surgery to better capture of any drug-drug interactions that increase bleeding. The short-lived effects of sugammadex on aPTT and PT might not be evaluable if thromboprophylaxis were administered after surgery.
3. Enrollees would receive thromboprophylaxis using one of several approved regimens because of the high frequency (40-60%) of venous thromboembolic events that occurs without the use of anticoagulants.
4. Enrollment of this population would include many elderly subjects with mild to moderate renal dysfunction (Creatinine clearance \geq 30 ml/min and \leq 60 ml/min). Since previous studies had shown that this degree of renal dysfunction was not associated with an increase in peak concentrations of SU (but only a somewhat longer $\frac{1}{2}$ life) and that the effect of SU on the increase in aPTT and PT was dissipated over approximately 30 minutes, it would be important to assess bleeding in such patients. The protocol was designed to assess the frequency of bleeding over the 24 hour period following administration of SU so that any effects of renal dysfunction on bleeding after SU use could be determined.
5. The primary endpoint was the incidence of adjudicated bleeding events within 24 hours of the administration of study drug.

The major findings from the study included the following, for which the Applicant and DHP were in agreement:

1. The adjudicated incidence of bleeding was 2.9% of subjects randomized to the sugammadex arm versus 4.1% in the usual care arm. These events included both major bleeding (2.0% vs 3.4% in the sugammadex and usual care arms, respectively) as defined in the protocol and unexpected non-major bleeding (0.9% versus 0.7% in the sugammadex and usual care arms, respectively) as determined by the Adjudication Committee. For the majority of events, the relationship between the trial drug and bleeding was determined to be “possible”.
2. The frequency of the bleeding endpoint in this trial was lower than anticipated based on a review of the experience in patients undergoing

orthopedic surgery of the lower extremity (5%), particularly for subjects assigned to the sugammadex arm. This led to an extension of the study with an increase in the number of subjects enrolled, i.e., from the planned 800 subjects to when either the number of adjudicated, suspected unanticipated adverse events of bleeding reached 33 or a total of 1200 subjects had been enrolled. These findings suggested that although sugammadex is associated with a brief period of elevation in the aPTT and PT, these laboratory findings do not predict an increase in the frequency of bleeding.

3. Despite the use of drugs designed to impair the coagulation response (particularly heparin or one of its congeners) in all of these patients, there did not appear to be a synergistic effect on post-operative bleeding.
4. A secondary endpoint for the trial extended the time of observation for the bleeding from the first 24 hours after surgery to 14 days after surgery. There was some increase in major and unexpected non-major bleeding during the extension, but most of those events were considered to be unlikely related to trial drug administration.
5. Patients with a reduced creatinine clearance appeared to have a greater frequency of bleeding than those with a normal creatinine clearance, but there was no difference in the relative risk of bleeding whether patients were treated with sugammadex or placebo in each subgroup.
6. At 10 minutes after trial drug administration, there was a small, but statistically significant, increase in the aPTT in subjects in the sugammadex arm compared to baseline [4.7% (CI, 3.4%, 5.9%)] and in subjects in the sugammadex arm compared to the usual care arm [5.5% (CI, 3.7%, 7.3%)]. Similar comparative increases were noted in the PT measurements [4.5% (CI, 3.3%, 5.8%) and 3.0% (CI, 1.3%, 4.7%)], respectively. At 60 minutes after trial drug administration, the laboratory findings had dissipated.
7. All bleeding endpoints occurred at a lesser frequency in the sugammadex treated subjects than in the usual care subjects, but these differences were not statistically significant.
8. There were no significant differences between sugammadex and usual care treatments for incidence of postoperative anemia or venous thromboembolic events.
9. There was a small, but noticeable, increase in aPTT at 3 minutes after trial drug administration in subjects who received SU but not in those in the usual care arm. Most of the increase had dissipated by 30 minutes and was completely ablated at 60 minutes.

DHP did not find issues with any of the results presented for this study or disagree with any of the conclusions reached by the Applicant. They concurred that there is no evidence that the administration of sugammadex to patients undergoing major orthopedic surgery of the lower limb and receiving thromboprophylaxis with heparin have a greater frequency of hemorrhage than

patients receiving usual care (with neostigmine or placebo), even though patients treated with sugammadex have some prolongation of the aPTT and the PT that lasts for less than 60 minutes after administration. From the perspective of DHP, the trial was performed in accord with the agreed upon protocol.

Postmarketing Findings

Hemorrhage events that were reported to the Applicant from the initial approval of sugammadex in July 2008 through June 15, 2012, totaled five. All of the events were serious adverse events including two deaths. These events were also reviewed by DHP.

Four of the cases reported an actual bleeding event

1. Two cases of bleeding at the operative site:
 - a. One report for bleeding of the parotid gland, which required additional surgery at 8 hours after administration of sugammadex. The reporter attributed the cause of the bleed to “sutural insufficiency” and not to sugammadex.
 - b. One report of bleeding of the tonsil, which occurred several hours after the administration of sugammadex, required additional surgery, but was not attributed to the product as the bleeding “occurred in the surgical field.”
2. One case involved a patient who developed disseminated intravascular coagulation after the onset of anaphylaxis. He was found to have bleeding at multiple surgical sites following total gastrectomy. This patient died 3 days after his initial surgery from a combination of multiorgan failure and cardiac arrest.
3. One case involved a patient who experienced bradycardia leading to cardiac arrest within a minute of receiving sugammadex. The patient was treated with an intra-aortic balloon pump and went on to have an intra-abdominal hemorrhage due to laceration of the aorta. The patient died 19 days following her surgery.
4. One case had little detailed information but described a patient who underwent an orthopedic surgery involving the femur and late that day was reported to have hypotension, bradycardia, increased vascular permeability, and hemorrhagic shock.

DHP concurred with the Applicant that these reports do not suggest a bleeding problem that is related to the use of sugammadex. From an anesthesia perspective, these reports did not suggest that sugammadex causes bleeding; they were consistent with events that might be expected to occur in a small number of patients following surgery. While the risk of bleeding from sugammadex appears to be small, the cardiovascular changes following sugammadex administration that ultimately to the patients’ bleeding events are

noteworthy, particularly as they appear to be related to possible anaphylactic reactions.

Summary and Conclusions

DHP indicated that on the basis of the data generated in Study P07038, there is no evidence that there is an increase in bleeding after the administration of sugammadex compared to neostigmine/placebo to patients who have undergone major orthopedic surgery of the lower limb and have received thromboprophylaxis with heparin or low molecular weight heparin. Furthermore, while sugammadex may transiently increase aPTT and PT(INR), the effect does not impact the risk for bleeding. The use of sugammadex in conjunction with aspirin has no effect on platelet aggregation, aPTT and PT, and cutaneous bleeding time. There is no clinically relevant effect of 4 mg/kg and 16 mg/kg doses of sugammadex on the anti-Xa activity of enoxaparin.

From an anesthesia perspective, the studies conducted have demonstrated that sugammadex has a transient affect on aPTT, PT and INR that may need to be taken into account for laboratory assessments made within an hour of sugammadex administration, but that does not affect postoperative bleeding or the risk of thromboembolic events. Sugammadex was shown to not have a clinically meaningful affect on the anticoagulant properties of aspirin, enoxaparin, heparin and low molecular weight heparin. The risk of postoperative bleeding following administration of sugammadex is no greater than that following neostigmine or spontaneous recovery from either rocuronium or vecuronium. These studies have addressed the deficiency listed in the Complete Response letter.

7.3.5.3 Cardiac Arrhythmias

Background

In the original NDA submission, the Applicant included the clinical study reports for two thorough QT studies: Trial 19.4.109 and Trial 19.4.105.

Trial 19.4.109 was a single-center, randomized, double-blind, placebo-controlled, 6-period crossover trial that evaluated the occurrence of QTc prolongation in healthy volunteers for:

- Single intravenous doses, 4 mg/kg or 32 mg/kg, of sugammadex alone
- A combination of a 32 mg/kg intravenous dose of sugammadex with rocuronium (1.2 mg/kg) or vecuronium (0.1 mg/kg) administered simultaneously with the sugammadex, but via separate catheter lumens, over 4 minutes
- An intravenous dose of 400 mg moxifloxacin administered over 60 minutes was used to establish assay sensitivity.

The Applicant reported that for all treatment groups (sugammadex alone and sugammadex in combination with rocuronium or vecuronium), the largest upper limit of the 95% confidence interval (CI) for the time-matched change from baseline in the individually corrected QT intervals (QTcI) compared to placebo for all time points, at both sugammadex doses, was less than 10 milliseconds, the margin of regulatory concern. For moxifloxacin, the positive control, the estimate of the maximum time-matched change from baseline in QTcI compared to placebo was 20.8 milliseconds (90% CI: 18.5 to 23.1 milliseconds, which supported assay sensitivity for the trial. They concluded that this thorough QT/QTc trial with 4 mg/kg and 32 mg/kg doses of sugammadex alone and 32 mg/kg sugammadex in combination with rocuronium or vecuronium was negative according to the criteria of ICH-E14 and that sugammadex alone or in combination with rocuronium or vecuronium was not associated with QTc prolongation of clinical concern.

Trial 19.4.105 was a single-center, placebo-controlled, 5-period crossover trial designed to determine the effect of single intravenous (IV) doses of 4 and 32 mg/kg sugammadex on QTc interval prolongation in healthy volunteers. An intravenous dose of 400 mg moxifloxacin was used to demonstrate assay sensitivity. The trial was open-label for moxifloxacin and double-blind for sugammadex and placebo. The primary parameter was the individually corrected QTc interval (QTcI).

The Applicant reported that the time-matched mean QTcI difference between the sugammadex and the placebo groups was close to zero for each time point. In addition, the upper limits of the one-sided 95% CIs for the largest time-matched mean QTcI differences from placebo were below the 10-millisecond margin of

regulatory concern. They noted that the maximum mean QTcI difference from placebo was 1.8 milliseconds (upper limit 95% CI: 4.3 milliseconds) and 2.8 milliseconds (upper limit 95% CI: 5.3 milliseconds) after 4 mg/kg and 32 mg/kg sugammadex, respectively. For moxifloxacin, the estimate for the maximum time-matched mean QTcI difference to placebo was 18.6 milliseconds (90% CI: 15.4 to 21.8 milliseconds) thereby establishing assay sensitivity. They concluded that, according to the criteria of the ICH E14 guidance, 4 mg/kg and 32 mg/kg doses of sugammadex are not associated with QTc prolongation of clinical concern.

The two studies were reviewed by the Agency's Interdisciplinary Review Team for QT Studies. They concluded that the Study 19.4.109 was conducted in a satisfactory manner, and although there was a concentration-dependent increase in the QTcI, the increase for the suprathreshold dose (32 mg/kg) did not result in a clinically significant increase. The results for Study 19.4.105 were comparable, and the Interdisciplinary Review Team opted to not repeat their analysis, since the Applicant assessed the same doses as in the other study.

The Applicant also analyzed the morphological features of ECGs collected across studies. They reported that no differences from placebo were noted for heart rate, the PR interval, as well as the QRS complex, T wave, and U wave morphologies.

In the review of the original NDA submission, a tabulation of the adverse event database for cardiac arrhythmias and acute myocardial infarction resulted in the findings shown in Table 17. The data indicated that, overall, there was not a substantial difference between sugammadex and neostigmine treatments for cardiac arrhythmias; although there appeared to be a possible difference between sugammadex and placebo. Furthermore, there generally appeared to be no sugammadex-dose dependency for arrhythmias overall. On inspection of the individual arrhythmias, it was noted that bradycardia, QTc interval prolongation, and tachycardia were reported more frequently than the other arrhythmias and that these adverse events occurred in more sugammadex dose groups than did the others. Table 18 provides the percentages of subjects exposed at each dose group who had these three more common arrhythmias. The data in the table indicate that, for bradycardia and tachycardia, the frequencies are similar to those of neostigmine and not sugammadex-dose dependent. For QTc prolongation, the findings appear to be similar; although the 8% occurrence with the less-than-maximum labeled sugammadex dose of 12 mg/kg raised the concern that there may be a safety signal here despite the findings from the two thorough QT studies. It should be noted that none of the prolonged QTc intervals was associated with an incidence of Torsade de Pointes.

Table 17. Summary of cardiac arrhythmia and acute myocardial infarction adverse events from the original NDA safety database

| | Pla- cebo | Sugammadex (mg/kg) | | | | | | | | | Neo- stig- mine |
|--|--------------|-----------------------|----------|-----------|-----------|----------|-----------|-----------|-----------|----------|-----------------------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | |
| N | 336 | 124 | 178 | 613 | 729 | 28 | 154 | 39 | 127 | 164 | 209 |
| Adverse Event | | | | | | | | | | | |
| Acute myocardial infarction | 1 | | | | | | | | | | |
| Atrial fibrillation | 2 | 1 | | 7 | | | | | | | 1 |
| AV block - 1° | 1 | | | | | | | | | | |
| AVblock - 2° | | | | | | | | | | 1 | |
| Bradycardia | 3 | 1 | 1 | 9 | 6 | 1 | 6 | 1 | 8 | | 6 |
| T wave abnormality | 1 | | | | | | | | | | 1 |
| QTc interval prolonged | 2 | | 1 | 13 | 5 | | 2 | 3 | 4 | | 2 |
| Supraventricular and ventricular extrasystoles | 1 | | | 1 | | | | | | 1 | 3 |
| Tachycardia | 4 | | 5 | 24 | 26 | 1 | 2 | 0 | 6 | 1 | 13 |
| Ventricular tachycardia | | | | 1 | | | | | | 1 | |
| Wolff Parkinson White | | | | 1 | | | | | | | |
| Total | 15 | 2 | 7 | 56 | 37 | 2 | 10 | 4 | 18 | 4 | 26 |
| % of N | 4 | 2 | 4 | 9 | 5 | 7 | 6 | 10 | 14 | 2 | 12 |

Table 18. Bradycardia, QTc prolongation, and tachycardia AEs from the original NDA safety database

| | Plac- ebo | Sugammadex (mg/kg) | | | | | | | | | | Neostig- mine (mcg/kg) | |
|---------------------------------------|--------------|-----------------------|-----|-----|-----|----|-----|----|-----|-----|-----|------------------------------|--|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 | |
| N | 336 | 124 | 178 | 613 | 729 | 28 | 154 | 39 | 127 | 164 | 135 | 74 | |
| Adverse Event | | | | | | | | | | | | | |
| Bradycardia | 3 | 1 | 1 | 9 | 6 | 1 | 6 | 1 | 8 | | 6 | | |
| % of N | 1 | 1 | 1 | 1 | 1 | 4 | 4 | 3 | 6 | | 4 | | |
| QTc interval prolonged | 2 | | 1 | 13 | 5 | | 2 | 3 | 4 | | | 2 | |
| % of N | 1 | | 1 | 2 | 1 | | 1 | 8 | 3 | | | 3 | |
| Tachycardia | 4 | | 5 | 24 | 26 | 1 | 2 | | 6 | 1 | 11 | 2 | |
| % of N | 1 | | 3 | 4 | 4 | 4 | 1 | | 5 | 1 | 8 | 3 | |
| Total (all arrhythmias and acute MIs) | 15 | 2 | 7 | 56 | 37 | 2 | 10 | 4 | 18 | 4 | 22 | 4 | |
| % of N | 4 | 2 | 4 | 9 | 5 | 7 | 6 | 10 | 14 | 2 | 16 | 5 | |

A similar analysis was conducted with only the serious adverse events (SAEs). As indicated in Table 19, QTc prolongation was the only SAE to occur in multiple sugammadex dose groups and at a frequency that suggests a possible safety signal when compared to the neostigmine and placebo treatments.

Table 19. Summary of cardiac arrhythmia and acute myocardial infarction SAE data from the original NDA safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | Neostigmine (mcg/kg) | |
|-----------------------------|------------|--------------------|-----------|----------|----------|----------|----------|----------------------|----|
| | | 0.5 | 2 | 4 | 8 | 12 | 16 | 50 | 70 |
| N | 336 | 124 | 613 | 729 | 154 | 39 | 127 | 135 | 74 |
| Adverse Event | | | | | | | | | |
| Acute myocardial infarction | 1 | | | | | | | | |
| Atrial fibrillation | | 1 | 3 | | | | | | |
| QTc interval prolonged | 2 | | 13 | 4 | 1 | 3 | 4 | | |
| % of N | 1 | | 2 | 1 | 1 | 8 | 3 | | |
| Ventricular tachycardia | | | 1 | | | | | | |
| Total | 3 | 1 | 17 | 4 | 1 | 3 | 4 | | |
| % of N | 1 | 1 | 3 | 1 | 1 | 8 | 3 | | |

These data were presented to the Anesthetic and Life Support Drugs Advisory Committee in 2008. Although some of the committee members expressed concern over the serious nature of some of the arrhythmias, the concern was assuaged by the following:

1. The arrhythmias generally occurred within minutes of the administration of sugammadex at a time while patients are intensively monitored for cardiac problems and treatments are readily available if needed.
2. Most of the events resolved either spontaneously or with minimal intervention.
3. The numbers of adverse events were in the same range of those for neostigmine, and the data for neostigmine may have been affected by the coadministration of glycopyrrolate.
4. While the effect size for sugammadex was almost double that of the placebo group, it might have been possible that the confidence intervals overlapped.

Ultimately, the committee recommended that sugammadex be approved; however, they considered postmarketing surveillance for cardiovascular events to be an important aspect of the product's approval.

Initial Regulatory Action and Follow-Up

Based on the safety analyses conducted during the review of the NDA, there was no clear evidence that sugammadex, on its own, caused the cardiac arrhythmias observed in the clinical studies. Whether the product in some way contributed to the risk for these events was uncertain. Although the thorough QTc studies appeared to exonerate sugammadex from the QTc prolongation, those studies did not assess the risk in the presence of an anesthetic or at the end of a surgical procedure. Whether sugammadex, in combination with the stress, blood loss, and hemodynamic changes associated with surgical procedures or with the numerous anesthetic agents used during the procedure, may increase the risk for arrhythmias was not known.

In addition to the issues above, sugammadex was a new molecular entity and little was known about the arrhythmogenic potential of cyclodextrins when used in the perioperative setting. Based on these considerations, it was recommended in the complete response letter that the Applicant conduct:

A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

Due to the size of the safety database in the original NDA submission, the benign outcomes for most of the arrhythmias, and the ability of clinicians to detect and treat the arrhythmias should they occur in the clinical setting for which sugammadex is intended, it was determined that the risk for these adverse events had been sufficiently evaluated such that the study described above was not essential for the product's approval. Rather, the study would help determine whether sugammadex poses a risk for arrhythmias, and if so, it would better define that risk.

Following the issuance of the Complete Response letter, the Applicant submitted the results of a meta-analysis of the QTcF data from the placebo-controlled studies that included ECG assessments. In that analysis, a total of 374 patients treated with sugammadex and 77 patients treated with placebo were evaluated. ECG data were available for these subjects at 2 and 30 minutes following the administration of study drug. The results, as reported by the Applicant, revealed that both at 2 and 30 minutes after treatment there was no relevant average QTcF prolongation comparing sugammadex to placebo (-1.1 and -0.9 ms respectively). Furthermore, they noted that when investigating QTcF outliers using criteria as suggested by ICH E14, observed data provided no indication that patients treated with sugammadex had a significantly increased frequency of

prolonged QTcF values as compared to placebo treated patients; when summarizing patients with a value satisfying any outlier criterion (i.e., a QTcF value > 450 ms and/or a change from baseline > 30 ms), the frequency of patients was 41% for sugammadex versus 38% on placebo.

Based on all the information available to that point and internal discussions with the Division of Cardiovascular and Renal Products, the Division of Anesthesia, Analgesia, and Addiction Products concurred with the Applicant that sugammadex is not likely to pose an increased risk for QT prolongation or arrhythmias in the surgical setting, and therefore, it was not necessary to conduct a study of the frequency and severity of cardiac arrhythmias and QTc prolongation as previously requested. It was noted that if sugammadex were to be approved, the cardiac adverse events observed in the clinical trials would be included in the label and monitoring for these events in the postmarketing period would need to be continued.

Despite the Division's position regarding the need for another cardiac study, the Applicant conducted Trial P06315 to evaluate the effect of a therapeutic dose, 4.0 mg/kg, of sugammadex in combination with maintenance anesthesia using propofol or sevoflurane, on QTc prolongation. The trial was a double-blind, randomized, multi-site, placebo-controlled, parallel-group, 2-factorial study with factors for single-blind anesthetic maintenance (propofol versus sevoflurane) and double-blind reversal agent (sugammadex versus placebo), in healthy subjects. Study drug was administered after anesthesia had been maintained for 20 minutes. An additional arm of subjects treated with neostigmine (50 mcg/kg) and glycopyrrolate 10 mcg/kg) was also evaluated using a single-center, open-label design.

The Applicant reported that sugammadex 4 mg/kg was not associated with relevant QT/QTc prolongation as compared to placebo when combined with maintenance anesthesia with propofol or sevoflurane. For all prespecified timepoints, up to 30 minutes after study drug administration, the estimated differences between sugammadex and placebo in change of QTcF from baseline and corresponding upper one-sided 95% confidence limits were below the margin of 10 msec for each type of maintenance anesthetic separately as well as combined over both anesthetic arms. In addition, the Applicant noted that mean QTcF increases exceeding the level of regulatory relevance were observed during maintenance anesthesia, i.e., prior to study drug administration, with both propofol and sevoflurane. The mean QTcF prolongations compared to pre-anesthesia baseline were most pronounced for sevoflurane (mean QTcF prolongations exceeding 30 msec), while during maintenance anesthesia with propofol, mean QTcF prolongations exceeding 10 msec were observed. Furthermore, during maintenance anesthesia with propofol, incidental QTcF values between 450 and 480 ms were reported, but no QTcF values exceeding 480 msec. During maintenance anesthesia with sevoflurane, the incidence of

QTcF values between 450 and 480 msec was higher than during maintenance with propofol, and QTcF values between 480-500 msec or exceeding 500 msec were observed.

The Interdisciplinary Review Team for QT Studies reviewed the study findings and concurred that no significant QTc prolongation effect of sugammadex was detected, and the largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/sugammadex were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

The NDA Resubmission

Since the time of the initial regulatory action, sugammadex has been approved and marketed in a number of countries. Its use in the intended clinical setting has resulted in a number of cardiac arrhythmias being reported as adverse events to the IND. In addition, the Applicant has conducted another 20 clinical trials during the same time period, and in the process, has doubled the safety database. As part of the resubmission of the NDA, the Applicant was instructed to analyze both the clinical trial data and the postmarketing data evaluating the occurrence of all arrhythmias. Each analysis will be considered below.

Clinical Trial Safety Database

To compare the incidence of arrhythmias across treatment groups, the Applicant performed Broad and Narrow Standardized MedDRA Query (SMQ) analyses for "Cardiac Arrhythmias" in both the pooled placebo-controlled trials and the pooled neostigmine-controlled trials. The analyses were performed only for adverse events captured during the "treatment period," defined as starting with the administration of the study drug and ending 7 days later. The findings from the two analyses are combined in Table 20. For both sets of pooled data, the Applicant calculated the 95% confidence intervals according to the method of Miettinen and Numinen. They reported no significant differences between sugammadex and its comparators for any of the SMQs in either the broad or narrow searches.

Table 20. Number (%) of subject exposures with AEs within Cardiac Arrhythmias related SMQs during the treatment period (combined data from Tables 69 and 70 on pp. 197-198 and 200-201 in Section 5.3.5.3 of the resubmission)

| Standardized MedDRA Query | SMQ search | Pooled Placebo-Controlled Trials | | Pooled Neostigmine-Controlled Trials | |
|---|------------|----------------------------------|---------------|--------------------------------------|-------------------|
| | | Sugammadex N=1078 | Placebo N=544 | Sugammadex N=797 | Neostigmine N=804 |
| Cardiac arrhythmias | Narrow | 12 (1.1) | 9 (1.7) | 4 (0.5) | 7 (0.9) |
| | Broad | 39 (3.6) | 21 (3.9) | 26 (3.3) | 39 (4.9) |
| - Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) | Narrow | 12 (1.1) | 9 (1.7) | 4 (0.5) | 7 (0.9) |
| | Broad | 13 (1.2) | 10 (1.8) | 6 (0.8) | 7 (0.9) |
| - Bradyarrhythmias (incl conduction defects and disorders of sinus node function) | Narrow | 10 (0.9) | 4 (0.7) | 0 (0.0) | 0 (0.0) |
| - Conduction defects | Narrow | 10 (0.9) | 4 (0.7) | 0 (0.0) | 0 (0.0) |
| - Disorders of sinus node function | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| - Bradyarrhythmia terms, nonspecific | Narrow | 0 (0.0) | 1 (0.2) | 1 (0.1) | 0 (0.0) |
| - Cardiac arrhythmia terms, nonspecific | Narrow | 1 (0.1) | 0 (0.0) | 1 (0.1) | 1 (0.1) |
| - Tachyarrhythmias (both supraventricular and ventricular tachyarrhythmias) | Narrow | 2 (0.2) | 6 (1.1) | 4 (0.5) | 7 (0.9) |
| | Broad | 3 (0.3) | 7 (1.3) | 6 (0.8) | 7 (0.9) |
| - Supraventricular tachyarrhythmias | Narrow | 1 (0.1) | 2 (0.4) | 4 (0.5) | 6 (0.7) |

| Standardized MedDRA Query | SMQ search | Pooled Placebo-Controlled Trials | | Pooled Neostigmine-Controlled Trials | |
|---|------------|----------------------------------|------------------|--------------------------------------|----------------------|
| | | Sugammadex N=1078 | Placebo N=544 | Sugammadex N=797 | Neostigmine N=804 |
| | Broad | 1 (0.1) | 3 (0.6) | 6 (0.8) | 6 (0.7) |
| - Ventricular tachyarrhythmias | Narrow | 1 (0.1) | 4 (0.7) | 0 (0.0) | 2 (0.2) |
| | Broad | 2 (0.2) | 4 (0.7) | 0 (0.0) | 2 (0.2) |
| - Tachyarrhythmia terms, nonspecific | Narrow | 2 (0.2) | 0 (0.0) | 2 (0.3) | 0 (0.0) |
| - Arrhythmia related investigations, signs and symptoms | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Broad | 27 (2.5) | 11 (2.0) | 21 (2.6) | 35 (4.4) |
| - Congenital and neonatal arrhythmias | Narrow | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| | Broad | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Shock-associated circulatory or cardiac conditions (excluding torsade de pointes) | Narrow | 2 (0.2) | 3 (0.6) | 2 (0.3) | 3 (0.4) |
| | Broad | 4 (0.4) | 4 (0.7) | 3 (0.4) | 5 (0.6) |
| Torsade de pointes, shock-associated conditions | Narrow | 16 (1.5) | 6 (1.1) | 2 (0.3) | 2 (0.2) |
| | Broad | 18 (1.7) | 7 (1.3) | 3 (0.4) | 4 (0.5) |

The next step taken by the Applicant was an evaluation of the individual components of the broad SMQ for arrhythmia. The results are shown in Table 21. The Applicant noted that a similar rate of “bradycardia” following sugammadex treatment (0.5%) compared to placebo treatment (0.6%) and that the incidences of bradycardia in the neostigmine-controlled trials was 1.6% in the neostigmine group and 0.1% in the sugammadex group.

They also noted a higher rate of “tachycardia” was observed for sugammadex than placebo (0.9% and 0.6%, respectively) but stated that the “remaining AEs of the “arrhythmia related investigations” collection term (i.e. syncope, palpitations, loss of consciousness, electrocardiogram abnormal) occurred at rates expected in the adult surgical population.” A source to support this statement was not provided.

Table 21. Arrhythmia-related Investigations (signs and symptoms) (Broad SMQ) in pooled Phase 1-3 placebo-controlled studies (Table 67 on p. 193 of Section 5.3.5.3 of the resubmission)

| Standardized MedDRA Query Search Preferred Term | Placebo | | Sugammadex | |
|---|------------|------------|-------------|------------|
| | N | % | N | % |
| Number of Treated Subjects | 544 | 100 | 3407 | 100 |
| Total | 11 | 2.0 | 78 | 2.3 |
| Bradycardia | 3 | 0.6 | 16 | 0.5 |
| Cardiac arrest | 0 | 0.0 | 1 | 0.0 |
| Electrocardiogram abnormal | 0 | 0.0 | 2 | 0.1 |
| Heart rate decreased | 1 | 0.2 | 3 | 0.1 |
| Heart rate increased | 0 | 0.0 | 4 | 0.1 |
| Loss of consciousness | 0 | 0.0 | 1 | 0.0 |
| Palpitations | 1 | 0.2 | 8 | 0.2 |
| Syncope | 3 | 0.6 | 13 | 0.4 |
| Tachycardia | 3 | 0.6 | 32 | 0.9 |

The Applicant did not conduct a similar analysis for the pooled Phase 1-3 neostigmine-controlled trials.

Bradycardia and Tachycardia

The Applicant performed additional analyses looking at bradycardia and tachycardia, the two most common cardiac adverse events reported in the clinical studies.

To this end, the Applicant evaluated the pooled Phase 1-3 trials for the percentage of exposures in subjects with treatment-emergent markedly abnormal pulse rate values, i.e., a heart rate outside the range of 50-120 bpm that was also a change from baseline ≥ 15 bpm. Their findings are summarized in Table 22; they reported the number of incidents as small and the incidences of markedly abnormal values were similar for sugammadex subjects and placebo subjects.

Table 22. Markedly Abnormal pulse rates at any In-Treatment post-baseline timepoint in pooled Phase 1-3 placebo-controlled studies (Table 113 on p. 300 of Section 5.3.5.3 of the NDA resubmission)

| Parameter | Total ^A Sugammadex (N=1078) | Placebo (N=544) |
|---|--|-----------------|
| Pulse Rate markedly decreased (n [%] of subjects) | 17 (2) | 6 (1) |
| Minimum Pulse Rate value at any timepoint | 37.0 bpm | 35.0 bpm |
| Pulse Rate markedly increased (n [%] of subjects) | 12 (1) | 7 (1) |
| Maximum Pulse Rate value at any timepoint | 134.0 bpm | 136.0 bpm |

The Applicant also reported that no time point trends were observed for the percent of exposures in subjects with markedly abnormal values. However, a dose trend for markedly decreased pulse rate was present as was a dose trend for the bradycardia AEs exhibited in Table 23.

Table 23. Number (%) of exposures associated with drug-related adverse events for pulse rate abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 112 on p. 299 of Section 5.3.5.3 in the NDA resubmission)

| MedDRA Preferred Term | Placebo (N=544) | Sugammadex | | | |
|-----------------------|--------------------|--------------------|---------------------|--------------------|--------------------------------|
| | | 2 mg/kg (n=838) | 4 mg/kg (n=1798) | 16 mg/kg (n=98) | Total ^A (N=3407) |
| At least one AE | 8 (1.5) | 12 (1.4) | 29 (1.6) | 6 (6.1) | 58 (1.7) |
| Tachycardia | 3 (0.6) | 9 (1.1) | 18 (1.0) | 3 (3.1) | 32 (0.9) |
| Bradycardia | 4 (0.7) | 2 (0.2) | 7 (0.4) | 2 (2.0) | 17 (0.5) |
| Heart rate increased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 1 (1.0) | 4 (0.1) |
| Heart rate decreased | 1 (0.2) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 3 (0.1) |
| Heart rate irregular | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 2 (0.1) |

In the pooled placebo-controlled trials, the Applicant states that the overall percentage of subjects with treatment-emergent markedly abnormal pulse rate values was small, and the AEs related to pulse rate abnormalities were similar in incidence between the sugammadex group and the placebo group, as indicated in Table 24.

Table 24. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled placebo-controlled trials in order of decreasing incidence in the total sugammadex group (Table 114 on p. 300 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex | Placebo |
|-----------------------|-------------------------------|---------|
| | (N=1078) | (N=544) |
| At least one AE | 22 (2.0) | 8 (1.5) |
| Bradycardia | 12 (1.1) | 4 (0.7) |
| Tachycardia | 5 (0.5) | 3 (0.6) |
| Heart rate decreased | 2 (0.2) | 1 (0.2) |
| Heart rate increased | 2 (0.2) | 0 (0.0) |
| Heart rate irregular | 1 (0.1) | 0 (0.0) |

^A Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

In a shift analyses of heart rate changes, from vital sign data, the Applicant looked at the proportion of patients in all pooled Phase 1-3 studies who were not bradycardic (>50 beats/minute) at baseline but became bradycardic (<50 beats/minute) after study drug administration. For all doses of sugammadex, there were a greater proportion of patients who experienced a decrease in heart rate below 50 beats/minutes compared with those in the placebo group as seen in Table 25.

In a similar fashion, the Applicant determined the proportion of patients in each group in the pooled Phase 1-3 trials database who were not bradycardic at baseline (heart rate >50 bpm) but had a marked reduction (>20 bpm) after study drug administration. They considered the proportion of patients with a marked reduction to be very small in all groups and not different between groups at 2 minutes, though there was a slight increase in the sugammadex group when instances were pooled across all timepoints. The results are summarized in Table 26.

Lastly, the Applicant looked to see if there was a difference in the occurrence of clinically significant bradycardia, as indicated by the administration of atropine within an hour of study drug administration, based on NMBA, i.e., rocuronium or

vecuronium. The findings are summarized in Table 27. Rocuronium had the greater incidence of atropine treatment. There did not appear to be any dose dependence for the use of atropine with either NMBA.

Table 25. Number (%) of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline for exposures in pooled Phase 1-3 studies by time point (Table 77 on p. 208 of Section 5.3.5.3 of the NDA resubmission)

| Time after study drug administration | Sugammadex | | | | | | | | | | | | | | |
|--------------------------------------|------------|----|-----|---------|----|-----|----------|-----|-----|----------|----|------|------------------|-----|-----|
| | Placebo | | | 2 mg/kg | | | 4 mg/kg | | | 16 mg/kg | | | Total sugammadex | | |
| | (N=544) | | | (N=838) | | | (N=1798) | | | (N=98) | | | (N=3407) | | |
| | N | n | % | N | n | % | N | n | % | N | n | % | N | n | % |
| 2 min | 464 | 5 | 1.1 | 811 | 30 | 3.7 | 1680 | 68 | 4.0 | 89 | 5 | 5.6 | 3042 | 122 | 4.0 |
| 5 min | 422 | 7 | 1.7 | 699 | 34 | 4.9 | 1592 | 60 | 3.8 | 56 | 4 | 7.1 | 2768 | 108 | 3.9 |
| 10 min | 476 | 8 | 1.7 | 806 | 30 | 3.7 | 1662 | 51 | 3.1 | 93 | 6 | 6.5 | 3202 | 107 | 3.3 |
| Any timepoint | 467 | 15 | 3.2 | 818 | 52 | 6.4 | 1696 | 112 | 6.6 | 94 | 10 | 10.6 | 3249 | 202 | 6.2 |

N=Number of subject exposures in treatment group or with heart rate measure

n=number of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline.

Table 26. Number (%) of subject exposures for subjects with a decrease ≥ 20 bpm resulting in a heart rate ≤ 50 bpm for exposures pooled Phase 1-3 trials by time point (Table 78 on p. 210 of Section 5.3.5.3 of the NDA resubmission)

| Time after study drug administration | Sugammadex | | | | | | | | | | | | | | |
|--------------------------------------|------------|---|-----|---------|---|-----|----------|---|-----|----------|---|-----|------------------|----|-----|
| | Placebo | | | 2 mg/kg | | | 4 mg/kg | | | 16 mg/kg | | | Total sugammadex | | |
| | (N=544) | | | (N=838) | | | (N=1798) | | | (N=98) | | | (N=3407) | | |
| | N | n | % | N | n | % | N | n | % | N | n | % | N | n | % |
| 2 min | 464 | 1 | 0.2 | 811 | 1 | 0.1 | 1680 | 3 | 0.2 | 89 | 1 | 1.1 | 3042 | 6 | 0.2 |
| 5 min | 422 | 0 | 0.0 | 699 | 2 | 0.3 | 1595 | 5 | 0.3 | 56 | 1 | 1.8 | 2768 | 8 | 0.3 |
| 10 min | 466 | 0 | 0.0 | 806 | 5 | 0.6 | 1662 | 4 | 0.2 | 93 | 1 | 1.1 | 3202 | 10 | 0.3 |
| Any timepoint | 467 | 1 | 0.2 | 818 | 7 | 0.9 | 1696 | 8 | 0.5 | 94 | 3 | 3.2 | 3249 | 19 | 0.6 |

N=Number of subject exposures in treatment group or with heart rate measure

n=number of subject exposures with heart rate ≥ 50 bpm at baseline and heart rate < 50 bpm after baseline.

Table 27. Number of exposures for adult subjects who received NMBA and placebo or sugammadex in pooled Phase 2-3 studies who were administered atropine within one hour after study drug, by NMBA (Table 79 on p. 212 of Section 5.3.5.3 of the NDA resubmission)

| NMBA | Placebo | | | Sugammadex | | | | | | | | | Total sugammadex | | |
|------------|---------|---|-----|------------|---|-----|----------|---|-----|--------|-----|-----|------------------|----|-----|
| | (N=467) | | | (N=812) | | | (N=1709) | | | (N=93) | | | (N=3108) | | |
| | N | n | % | N | n | % | N | n | % | N | n | % | N | n | % |
| Rocuronium | 321 | 3 | 0.9 | 713 | 9 | 1.3 | 1269 | 8 | 0.6 | 93 | 1 | 1.1 | 2437 | 19 | 0.8 |
| Vecuronium | 146 | 0 | 0.0 | 96 | 0 | 0.0 | 436 | 1 | 0.2 | --- | --- | --- | 652 | 1 | 0.2 |

N=Number of subject exposures per treatment group
 n=number of subject exposures administered atropine

Using the pooled neostigmine-controlled trials, the Applicant conducted similar analyses and reported that the overall percentage of subjects with treatment-emergent markedly abnormal pulse rate values was small regardless of timepoint Table 28. They also noted that the incidence of markedly abnormal pulse rate increases was low and similar between the two treatment groups; however, there were more incidences of markedly decreased pulse rate present in the neostigmine group, 7% versus 1% for the total sugammadex group

Table 28. Markedly abnormal values at any in-treatment timepoint and minimum and maximum pulse rate values in pooled Phase 3 neostigmine-controlled studies (Table 115 on p. 301 of Section 5.3.5.3 of the NDA resubmission)

| Parameter | Total ^A Sugammadex (N=797) | Neostigmine (N=804) |
|---|---|------------------------|
| Pulse Rate markedly decreased (n [%] of subjects) | 9 (1) | 55 (7) |
| Minimum Pulse Rate value at any timepoint | 38.0 bpm | 32.0 bpm |
| Pulse Rate markedly increased (n [%] of subjects) | 7 (1) | 14 (2) |
| Maximum Pulse Rate value at any timepoint | 135.0 bpm | 140.0 bpm |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

In the pooled neostigmine-controlled trials, heart-rate adverse events occurred with greater frequency following treatment with neostigmine than with sugammadex as indicated in Table 29.

Table 29. Number (%) of exposures associated with adverse events for pulse rate abnormalities in pooled neostigmine-controlled trials in order of decreasing incidence in the total sugammadex group (Table 116 on p. 302 in Section 5.3.5.3 in the NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex | Neostigmine |
|-----------------------|----------------------------------|-------------|
| | (N=797) | (N=804) |
| At least one AE | 16 (2.0) | 32 (4.0) |
| Tachycardia | 13 (1.6) | 15 (1.9) |
| Bradycardia | 2 (0.3) | 13 (1.6) |
| Heart rate irregular | 1 (0.1) | 0 (0.0) |
| Heart rate increased | 0 (0.0) | 4 (0.5) |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

The Applicant did not perform shift analyses using the vital signs data for the pooled-neostigmine trials as they had for the pooled Phase 1-3 trials.

In summary, the Applicant concluded the following based on their analyses of the clinical trial data available at the time of the NDA resubmission:

- Sugammadex is not associated with QT/QTc prolongation beyond the level of regulatory concern when 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.
- Sugammadex does not demonstrate any clinically relevant QT/QTc prolongation, or an increase in the incidence of categorical or change-from-baseline outliers when compared to placebo in a meta-analysis of QTc data across the clinical development program
- Sugammadex is not associated with an increase in the incidence of AEs of QTc prolongation compared to placebo, when the QT interval is appropriately corrected for HR using the Fridericia formula, in an analysis of reported AEs of the integrated clinical development database.
- 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.
- For bradycardia in particular, there appears to be a small mean overall effect on heart rate when sugammadex is administered for the reversal of some NMBAs. This effect seems to be dependent on the choice of background NMBA and more consistently observable with rocuronium than in the setting of vecuronium. Furthermore, this effect seems to translate in rare bradycardic events that are easily detected. The clinical trial database did not suggest a risk for clinically important bradycardia.

For the purposes of this review, the same approach that was used for analyzing the cardiac arrhythmias in the original NDA submission was repeated here.

The safety database that was analyzed for this portion of the review consisted of all subjects who received treatment in the clinical studies in which sugammadex, placebo, or neostigmine were administered intravenously. The serious adverse events from this database that were related to cardiac arrhythmias or acute myocardial infarction are summarized in Table 30. Since the original NDA submission, 12 new SAEs have been added to this list bringing the total to 42 with an overall frequency for SAEs of 1%. The only SAE that occurred with a frequency greater than 1% in any sugammadex dose group was QTc prolongation. With a doubling of the size of the safety database compared to the original NDA submission, only three additional incidents of QT prolongation have

been reported as SAEs: two more in the 4 mg/kg dose group and one more in the 16 mg/kg dose group. (See Table 19 for the summary of SAEs from the original NDA submission.) Overall, this represents a decrease in frequency from 1.4% to 0.7% for SAEs of QTc prolongation with sugammadex treatment, which is not substantially different than that observed with placebo treatment, i.e., 0.2%. It should be noted that there were no reports of Torsades de Pointes associated with any of the QTc prolongations or in the entire safety database.

Atrial fibrillation was the only other arrhythmia to occur more than once in any dose group and more than twice with sugammadex treatment. Two new incidents were reported with the resubmission, but the overall incidence remains less than 0.2%.

Also of note is that there were no SAEs of bradycardia; two SAEs for tachycardia; and a single incident of cardiac arrest, all of which occurred since the original NDA submission.

Table 30. Summary of serious adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | Neostigmine |
|--------------------------------|---------|--------------------|-----|------|-----|----|-----|-------|-------------|
| | | 0.5 | 2 | 4 | 8 | 12 | 16 | Total | 50 mcg/kg |
| N | 1318 | 137 | 856 | 2198 | 156 | 39 | 348 | 3734 | 814 |
| Preferred Term | | | | | | | | | |
| Acute myocardial infarction | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 2 | 1 |
| Atrial fibrillation | 0 | 1 | 4 | 1 | 0 | 0 | 0 | 6 | 0 |
| Bradycardia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| QTc interval prolonged | 2 | 0 | 13 | 6 | 1 | 3 | 5 | 28 | 0 |
| % | 0 | 0 | 2 | 0 | 1 | 8 | 1 | 1 | 0 |
| Electromechanical dissociation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Tachycardia | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 2 | 0 |
| Ventricular fibrillation | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular tachycardia | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| Total | 6 | 2 | 18 | 11 | 1 | 3 | 6 | 42 | 1 |
| % | 0 | 1 | 2 | 1 | 1 | 8 | 2 | 1 | 0 |

All adverse events related to cardiac arrhythmias and acute myocardial infarction are summarized for the NDA resubmission in Table 31. Compared to the events

reported in the original NDA submission (see Table 17), 68 new AEs have been reported resulting in an overall decline in the incidence from 6% to 5%.

The AE table indicates that the more commonly occurring adverse events are, as it was with the original NDA submission, bradycardia, QTc prolongation, and tachycardia. With the resubmission, there were 29 new AEs of bradycardia; a single new AE of QTc prolongation and 28 new AEs for tachycardia. The overall incidence of each of these AEs has decreased since the original NDA submission such that they do not differ substantially from neostigmine or placebo treatments. For each of these AEs, there is no indication of dose dependence with sugammadex treatment.

The other AE of note in the table is atrial fibrillation. There are 5 new AEs for this arrhythmia for a total of 13 events. The overall frequency has decreased from 0.4% to 0.3%, which is between the frequencies observed for placebo (0.2%) and neostigmine (0.5%). As with the other AEs, there is no indication that the occurrence of atrial fibrillation is dose dependent with sugammadex treatment.

An additional analysis was performed to assess whether changes in heart rate, and therefore the potential for bradycardia or tachycardia, were time dependent following treatment with sugammadex versus placebo or neostigmine. The Applicant was asked to provide the heart rate data collected as part of vital signs assessments for both the pooled placebo-controlled and pooled neostigmine-controlled trials. Those data that were collected within half an hour of study drug administration were then analyzed and used to populate Table 32 and Table 33 below. The data in neither of the tables suggests a time dependent change in heart rate associated with sugammadex or neostigmine. However, there appeared to be a steady increase in heart rate for the 30 minutes following placebo treatment. Given clinical setting during which the study drugs were administered, i.e., the end of surgery with the effects of the anesthetic agents wearing off while the patient is still intubated, it would be generally expected for the patients to experience increases in their heart rates barring some pharmacological intervention. The responses to placebo, therefore, are not unexpected. Similar responses were observed with neostigmine despite its cholinergic effect, which may have been counterbalanced with the co-administration of an anticholinergic agent such as atropine. The mixed responses observed with sugammadex are, therefore, somewhat perplexing. While the mean values of the heart rate changes are not clinically significant, the possibility that some patients may experience clinically relevant increases in heart rate while others experience clinically relevant decreases for a particular dose would explain the occurrence of AEs for both bradycardia and tachycardia reported within individual sugammadex dose groups.

Table 31. Summary of adverse events related to cardiac arrhythmia and acute myocardial infarction in the resubmission safety database

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
|--|-----------|--------------------|----------|-----------|-----------|----------|-----------|-----------|-----------|----------|------------|----------------------|-----------|
| | | 0.5 | 1 | 2 | 4 | 6 | 8 | 12 | 16 | 32 | Total | 50 | 70 |
| N | 1318 | 137 | 220 | 856 | 2198 | 29 | 156 | 39 | 348 | 164 | 4147 | 814 | 42 |
| Adverse Event | | | | | | | | | | | | | |
| Acute myocardial infarction | 2 | | | | 1 | | | | | | 1 | 2 | |
| Atrial fibrillation | 2 | 1 | | 7 | 5 | | | | | | 13 | 4 | |
| Atrial flutter | | | | | 2 | | | | | | 2 | | |
| Atrioventricular block (1°) | 1 | | | | | | | | | | 0 | | |
| Atrioventricular block (2°) | 1 | | | | | | | | | 1 | 1 | | |
| Bradycardia | 9 | 1 | 1 | 14 | 30 | 1 | 6 | 1 | 8 | | 62 | 65 | |
| % | 1 | 1 | 0 | 2 | 1 | 3 | 4 | 3 | 2 | 0 | 1 | 8 | 0 |
| Cardiac arrest | | | | | | | | | | | 0 | 1 | |
| T wave abnormality | 1 | | | | | | | | | | 0 | 1 | |
| PR interval prolonged | | | | | | | | | | | 0 | | |
| QTc interval prolonged | 3 | | 1 | 13 | 6 | | 2 | 3 | 4 | | 29 | | 2 |
| % | 0 | 0 | 0 | 2 | 0 | 0 | 1 | 8 | 1 | 0 | 1 | 0 | 5 |
| Supraventricular and Ventricular extrasystoles | 1 | | | 1 | 2 | | | | | 1 | 3 | 4 | |
| Tachycardia | 7 | | 5 | 26 | 47 | 1 | 2 | | 11 | 1 | 93 | 21 | 2 |
| % | 1 | 0 | 2 | 3 | 2 | 3 | 1 | 0 | 3 | 1 | 2 | 3 | 5 |
| Ventricular fibrillation | 1 | | | | | | | | | | | | |
| Ventricular tachycardia | | | | 1 | | | | | | 1 | | 1 | |
| WPW | | | | 1 | | | | | | | | | |
| Total | 28 | 2 | 7 | 63 | 93 | 2 | 10 | 4 | 23 | 4 | 208 | 99 | 4 |
| % of N | 2 | 1 | 3 | 7 | 4 | 7 | 6 | 10 | 7 | 2 | 5 | 12 | 10 |

Table 32. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Placebo (N=544) | Sugammadex | | | |
|--|-----------------|-----------------|-----------------|-----------------|----------------|
| | | 2 mg/kg (N=156) | 4 mg/kg (N=592) | 16 mg/kg (N=38) | Total (N=1078) |
| 2 | 2.2% (1.1) | 0.0% (-0.5) | -0.1% (-0.3) | -1.0% (-1.9) | 0.4% (-0.1) |
| 5 | 4.9% (2.7) | -3.8% (-2.8) | 5.1% (2.8) | * | 3.3% (1.6) |
| 10 | 9.7% (5.4) | -1.1% (-1.3) | 10.4% (5.8) | -1.1% (-1.7) | 5.7% (2.9) |
| 30 | 11.7% (6.5) | 4.2% (2.1) | 16.4% (9.4) | -2.1% (-2.4) | 10.4% (5.6) |

Table 33. Mean % changes (absolute changes in bpm) in heart rate from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Neostigmine (N=804) | Sugammadex | | |
|--|---------------------|-----------------|-----------------|---------------|
| | | 2 mg/kg (N=305) | 4 mg/kg (N=491) | Total (N=797) |
| 2 | 5.0% (5.0) | -0.6% (-0.7) | 1.6% (1.6) | 0.3% (0.2) |
| 5 | 7.2% (7.0) | 0.8% (0.7) | 7.1% (6.7) | 4.7% (4.4) |
| 10 | 2.7% (2.3) | 4.8% (4.7) | 4.8% (4.8) | 4.8% (4.7) |
| 30 | 16.7% (16.6) | 12.0% (12.0) | 20.4% (19.8) | 17.2% (16.8) |

Comments and Conclusions

Based on the additional QT study conducted by the Applicant and the analyses of the safety database from the clinical trials, which has doubled in size since the original NDA submission, the following conclusions were made:

1. Appropriately designed and conducted thorough QT studies have demonstrated that sugammadex, at doses intended for clinical use, does not prolong the QTc interval when administered:
 - a. Alone, i.e., not in the presence of anesthetic agents or neuromuscular blocking agents (NMBAs)
 - b. In combination with rocuronium or vecuronium but not in the presence of anesthetic agents

- c. In the presence of anesthetic agents but not in combination with an NMBA
2. The risk of QTc prolongation with sugammadex does not exceed the risk with placebo or neostigmine to a clinically relevant extent.
 3. QTc prolongation that was observed in the clinical trials was not associated with any episodes of Torsades de Pointes.
 4. The risk of cardiac arrhythmias and acute myocardial infarction were not increased to a clinically significant degree by treatment with sugammadex compared to treatment with placebo or neostigmine.
 5. Episodes of tachycardia and bradycardia that qualified as adverse events occurred following administration of sugammadex but not at frequencies that substantially differed from neostigmine or that exceeded that from placebo by a clinically relevant amount.

Based on the information provided in the NDA submission, the Applicant has sufficiently characterized the risk of cardiac arrhythmias and QTc prolongation to allow an informed benefit:risk assessment and appropriate labeling of the product without the need for further clinical studies.

Postmarketing Findings

Since the first approval of sugammadex in the European Union on July 25, 2008, the Applicant reports the distribution of over (b) (4) vials for use in adult and pediatric patients. They have continuously monitored the product's safety since its initial launch and have provided the postmarketing data that has accumulated through June 15, 2012 with the NDA resubmission.

In the Clinical Overview section of their resubmission (Section 2.5), the Applicant noted the following on pages 147-148:

The most frequently reported arrhythmia-related events (55 of 69 events) were increases in ventricular rate (30 of 69 events reported as tachycardia, heart rate increases, sinus tachycardia) or decreases in ventricular rate (25 of 69 events reported as bradycardia, heart rate decreases, sinus bradycardia). Upon review of the individual event reports,

- The majority of ventricular/supraventricular tachyarrhythmias were reported in the context of anaphylaxis (ie, 25 events out of the 30 events reported as tachycardia, etc) and are thought to be related to that event.
- A total of 6 of 25 events of bradyarrhythmias occurred during anaphylaxis. A total of 8 of 25 cases were confounded by use of propofol (listing 'bradycardia' as an expected AE in the prescribing information).

Ten reports (with 11 events) of cardiac or cardio-pulmonary arrest were identified. In total, 6 of the 10 cases were non-fatal, and 4 cases were fatal.

For 55 of the 64 reports, a medical outcome was provided, and 51 of the 55 patients recovered. The 4 fatal cases were caused by cardiac or cardio-pulmonary arrest. These fatal cases were all patients with serious co-morbid medical conditions, and most patients had multiple concurrent medications at the time of the cardiac arrest.

The findings for the 69 events are summarized in Table 34 that was included in the ISS. These events comprised 18% of the postmarketing database.

Table 34. Postmarketing arrhythmia-related adverse events (Table 80 on p. 217 in Section 5.3.5.3 of the NDA resubmission)

| Preferred Term | Number of Events (Serious) | Life Threatening | Non-Life Threatening |
|--------------------------------|----------------------------|------------------|----------------------|
| Tachycardia | 18 (15) | 14 | 4 |
| Bradycardia | 18 (10) | 8 | 10 |
| Cardiac arrest | 9 (9) | 7 | 2 |
| Heart rate increased | 8 (4) | 6 | 2 |
| Heart rate decreased | 5 (3) | 0 | 5 |
| Sinus bradycardia | 2 (2) | 0 | 2 |
| Sinus tachycardia | 2 (2) | 0 | 2 |
| Supraventricular tachycardia | 2 (2) | 0 | 2 |
| Arrhythmia | 1 (1) | 0 | 1 |
| Atrioventricular block | 1 (1) | 1 | 0 |
| Cardio-respiratory arrest | 2 (2) | 1 | 1 |
| Supraventricular extrasystoles | 1 (1) | 0 | 1 |
| Total Events | 69 (52) | 37 | 32 |

The Applicant provided an analysis of the individual reports, which are summarized below using the Applicant’s description of the events. Just as tachycardia and bradycardia were the two most common AEs reported for sugammadex in the clinical trials, they were the most common cardiac events reported postmarketing. The Applicant divided the summary into these two categories in addition to cardiac arrest and other arrhythmia events.

Tachycardia

A total of 30 tachycardia-related events were reported in the postmarketing database; 23 were classified as “serious.” The following points were noted by the Applicant:

- The outcome was reported for 29 of the 30 events:
 - 28 were described as recovered/recovering; 1 was listed as persisted.
 - The report of persistent tachycardia (report 2012SP014073) described eventual recovery of tachycardia in the setting of adjudicated anaphylaxis following sugammadex administration.
- 26 of the 30 tachycardia-related events were reported in the context of “serious hypersensitivity”

- 24 occurred in the context of cases of adjudicated anaphylaxis, including the tachycardia event reported concurrently with bradycardia (report 2011SP50935).
- 2 other cases involved a serious non-adjudicated anaphylaxis or hypersensitivity-related event
 - report 2010SP048707 concerned a patient who developed increased heart rate in association with hypotension, decreased oxygen saturation, and acute renal failure requiring massive fluid replacement and adrenaline,
 - report 2011SP022849 concerned 'heart rate increased' in a 4 months-old child with pyrexia and erythema, who received 2mg/kg sugammadex following surgery for correction of a harelip. Treatment included steroid and other non-specified corrective actions that led to recovery.
- 4 cases with tachycardia-related events not associated with serious hypersensitivity or anaphylaxis
 - Two reports described tachycardia or supraventricular tachycardia in the setting of bronchospasm.
 - 2011SP026872 described atelectasis with mucous plug and oxygen desaturation in an elderly male with a history of smoking and hypertension
 - 2011SP044223 concerned a 77 year old male who presented with severe bronchospasm and supraventricular tachycardia following anesthesia with propofol, fentanyl, sevoflurane, rocuronium, and sugammadex for reversal of NMB. Treatment consisted of salbutamol, atrovent, ranitidine and methylprednisolone with recovery.
 - 2009-195127-NL concerned a patient who developed tachycardia (heart rate from 70 to 120 BPM) associated with non-serious generalized rash, 6 minutes after administration of sugammadex via the same intravenous line as anesthetics that resolved spontaneously without treatment.
 - 2010SP042405 described supraventricular tachycardia (not further specified) following administration of sugammadex that resolved spontaneously within 10 minutes.

Bradycardia

The database contains 25 reports of bradycardia related events in patients treated with sugammadex. The following points were noted by the Applicant:

- The outcome was reported for 19 of the 25 events
 - 17 recovered
 - 1 patient was recovering
 - 1 patient had a fatal outcome.
- One additional case (2009SP039392) reported as “cardiac arrest” included a description of a slowed heart rate in the report narrative, but bradycardia/heart rate decreased was not specifically coded as an AE. This case was also included here in the review.
- Therefore, this review includes 26 bradycardia-related cases.
- 10 reports, 3 serious, provided insufficient information for a complete analysis such as timing of bradycardia/heart rate decreased in relation to sugammadex administration, pulse rate, age, and/or concomitant medications. (2010SP065217, 2010SP065667, 2011SP023822, 2011SP023823, 2011SP023824, 2011SP023826, 2011SP031473, 2011SP049664, 2012SP011426, 2012SP018400)
 - 2 of the 10 cases (2011SP031473, 2011SP049664), both serious, were patients in whom bradycardia or heart rate decreased was reported in association with non-adjudicated anaphylactic reaction/anaphylactic shock.
 - 5 of the 10 provided an outcome: all were recovered or recovering.
 - 4 of the 10 (2 of “heart rate decreased” and 2 of “bradycardia”) were obtained from the literature
 - Treatment of bradycardia was provided in one report (2010SP065667): The patient was given a bolus dose of glycopyrrolate.
 - One patient recovered without treatment for bradycardia (heart rate = 42 bpm) that lasted a few seconds (2011SP023823) (nonserious)
 - One patient (2012SP018400) (serious) concerned a 74 year old female who experienced both atrioventricular block and bradycardia 15 minutes after administration of sugammadex. The physician indicated the patient had been given multiple drugs at the time of the AEs with significant increase measured in the blood level of one of the drugs not specified).
- 3 reports (2010SP060108, 2011SP041926, and 2011SP050935), all serious, described bradycardia concurrent with adjudicated anaphylaxis. Treatment information, provided in all 3 cases, included methylprednisolone, adrenalin, dopamine and/or atropine.
 - One case (2011SP050935), described both tachycardia and bradycardia in addition to anaphylaxis. It involved a 49 year old male with hypertension who experienced hypotension (blood pressure = 70/35 mmHg), loss of consciousness, tachycardia (heart rate = 125 bpm), and erythema, 10 minutes after administration of sugammadex.

This was followed by bradycardia (heart rate = 40 bpm) and hypotension (blood pressure = 60/38 mmHg) that resolved with administration of atropine and dopamine.

- 13 cases (10 serious and 3 non-serious) described the time to onset of bradycardia as shortly after the administration of sugammadex. 10 cases received rocuronium; in the other 3 cases, the NMBA used was not reported.
 - Three of the 13 cases reported cardiac arrest.
 - One of the 3 cases (2009SP039392) described a slowed heart rate in the report narrative; however, bradycardia was not specifically coded
 - the other 2 cases (2010SP048709 and 2011SP018197) each reported 'bradycardia' and 'cardiac arrest'.
 - In these 3 cases indicates that bradycardia preceded the event of cardiac arrest.
 - In 2 of the 13 cases, the bradycardia recovered spontaneously
 - 1 of the 13 cases recovered with cardiac massage
 - 11 of the 13 cases had responded to anticholinergic agents, primarily atropine.
 - In 6 cases, where it was specified, the time to onset of bradycardia ranged from a few seconds to 2 minutes, and recovery in general was reported to be within minutes following treatment.
 - These 13 cases are described in more detail as follows:
 - 2009-200236-NL ("medically significant") concerned a 75 year old female on concomitant beta blockers for an unknown indication who was administered rocuronium during surgery for a ventral hernia. A few seconds following administration of sugammadex 4 mg/kg, the patient presented with bradycardia (a decrease from 45-50 bpm to 23 bpm). Atropine 2 mg was administered with recovery. It was reported the physician was not certain if bradycardia was related to sugammadex.
 - 2009-200336-NL (non-serious) concerned a male patient, < 50 years of age with no reported medical history or concomitant medications who underwent an otorhinolaryngological surgical procedure. Information regarding anesthetic agents used was not provided. It was reported that almost immediately following administration of sugammadex (dose not reported), the patient presented with bradycardia described as a heart rate dropping from 70-80 bpm to 40 bpm and lasting 15-30 seconds before it resolved spontaneously.
 - 2009SP039392 (life threatening) concerned a female smoker with obesity, paraplegia, COPD, and an unspecified psychiatric disorder on concomitant risperidone who was

- administered thiopental, sufentanil citrate, rocuronium, and cefazolin prior to Caesarean section. After 40 minutes, no response of the post tetanic count was noted and sugammadex 16 mg/kg was administered. Reversal of NMB was obtained after 25 seconds, and following another 30 seconds, the patient experienced bradycardia (from 70 to 50 bpm), then cardiac arrest (described as “flat record”). The patient recovered following treatment with atropine 1 mg.
- 2009SP042432 (medically significant) concerned a 30 year old female with no reported relevant medical history who underwent an uneventful colonoscopy with propofol, sufentanil citrate, and rocuronium. Two minutes following administration of sugammadex, the patient experienced bradycardia (heart rate was not provided) and systolic blood pressure of 30-35 mmHg. The patient recovered 1 minute following atropine administration. Electrocardiogram was reported as normal.
 - 2010SP012437 (medically significant) concerned a 13 year old male with no medical history of respiratory issues who underwent surgery for torsion of testicle with rocuronium without complications. One minute following administration of sugammadex 2 mg/kg, the patient experienced sinus bradycardia (heart rate not provided) that resolved immediately following administration of atropine.
 - 2010SP013630 (non-serious) concerned a male patient who experienced bradycardia “when he received BRIDION” that was treated with atropine. Essential information was not provided including the patient’s age, medical history, concomitant medications, anesthesia agents administered, type of surgery, dose of sugammadex, heart rate, and time to recovery of bradycardia following atropine administration. No additional information, specifically NMBA used, is available.
 - 2010SP042846 (medically significant) concerned a 70 year old female with a history of asthma, obesity and several other unspecified comorbidities who due to asthma, underwent rapid sequence induction with rocuronium for an unspecified surgery in the prone position. Prior to reversal of NMB, the patient’s heart rate was reported to be 65-70 bpm. After administration of sugammadex, the patient experienced sinus bradycardia described as heart rate of 35 bpm. The patient was treated with atropine with recovery. ECG was reported as normal.
 - 2010SP048709 (life threatening) concerned a 61 year old female with no reported medical history who underwent

surgery for inguinal hernia. Anesthesia administered included propofol, sevoflurane, fentanyl, and rocuronium. One minute following administration of sugammadex, bradycardia developed resulting in cardiac arrest (not further specified) that was treated with cardiac massage with immediate recovery. Additional clinical details such as heart rate and blood pressure were not provided.

- 2011SP001409 (life threatening) concerned a 56 year old female treated for depression (unspecified), and described as generally healthy who underwent arthroscopic shoulder surgery in the seated position. Anesthesia agents included midazolam, propofol, fentanyl, isoflurane, and rocuronium. Thirty seconds following slow administration of sugammadex, the patient experienced bradycardia (heart rate = 40 bpm, rapidly dropping to 19 bpm) that recovered immediately following administration of atropine 1 mg.
- 2011SP011565 (prolonged hospitalization) concerned a 65 year old male with a history of paroxysmal atrial fibrillation, chronic obstructive pulmonary disease (COPD), and dysphonia on concomitant warfarin, tiotropium bromide, and budesonide/formoterol fumarate dehydrate who underwent laryngeal microsurgery with propofol, alfentanil, sevoflurane, and rocuronium. The patient presented with bradycardia (28 bpm) upon receiving sugammadex. The patient was treated with atropine and recovered.
- 2011SP017389 (life threatening) concerned a 39 year old male on concomitant ritonavir and other unspecified antiretroviral agents for an unknown indication who experienced severe bradycardia (heart rate not provided) within minutes following the administration of sugammadex that was treated with atropine with recovery. The NMBA used was not provided.
- 2011SP018197 describes a 58 year old female who underwent total abdominal hysterectomy/bilateral salpingo-oophorectomy, omentectomy, and lymph node dissection for ovarian cancer. Anesthetics administered were midazolam, propofol, fentanyl, and rocuronium. Postoperatively, she developed bradycardia, cardiac arrest, and anaphylactic shock (nonadjudicated), one minute after administration of sugammadex 200 mg. She was treated successfully with cardiac massage, adrenaline, and atropine. Following recovery from bradycardia and cardiac arrest, abdominal CT showed no intra-abdominal hemorrhage and transesophageal echocardiography (TEE) confirmed stable myocardial wall motion despite arteriospasm revealed by

angiogram. Intra-aortic balloon pumping was initiated and heparin 2000 units was administered with immediate prolongation of activated partial thromboplastin time (aPTT) of >200 seconds. Approximately 8 hours later, CT indicated significant intra-abdominal hemorrhage. The patient died 19 days after surgery. Autopsy revealed intra-abdominal hemorrhage from a lacerated aorta. It was reported that the aortic laceration was likely a result of vibration from intra-aortic balloon pumping in an aorta weakened by prior lymph node dissection. It is unlikely that bleeding was related to sugammadex, as it appears to be related to procedures used to maintain blood pressure in a surgically weakened aorta.

- 2012SP012074 (life threatening) concerned a 49 year old female treated for hypothyroidism, hypertension and epilepsy with levothyroxine, atenolol, and mysoline who underwent transanal resection with propofol, fentanyl, and rocuronium. One minute following administration of sugammadex and while still intubated, the patient experienced bradycardia that transitioned into asystole. The patient experienced the arrhythmia for 30 seconds. The patient was treated with atropine 0.5 mg and supraventricular pacing 0.01 mg with recovery (time to recovery following treatment not specified).

Cardiac Arrest

In the postmarketing database, there were 10 reports (11 events, all serious) of cardiac arrest that were reported in patients treated with sugammadex. The Applicant stated that for 8 of the cases, there were no other arrhythmias reported as having preceded the event. However, they noted that one of the 8 cases (2009SP039392) did report bradycardia in the narrative; although, bradycardia was not specifically coded, and 2 additional cases (2010SP048709 and 2011SP018197) each reported “bradycardia” and “cardiac arrest.” Information provided for these 3 cases indicated that bradycardia preceded the event of cardiac arrest; therefore, the Applicant reported on them in the *Bradycardia* section above. The remaining 7 cases contained 8 events (one case reported both cardiac arrest and cardio-respiratory arrest). The ages of the patients, where reported, ranged from 60-90 years. Four of the patients recovered and 3 had a fatal outcome. The Applicant summarized the reports as follows:

- 2009-200337-NL (cardiac arrest-medically significant), with limited information, described a patient who experienced an “event similar to cardiac arrest” almost immediately after administration of sugammadex, described as 0 pulse lasting 1-2 seconds that recovered spontaneously.

- 2010SP063043 (cardiac arrest-life threatening) concerned a 72 year old patient who underwent hepatectomy for cholangiocellular carcinoma. At the conclusion of the procedure, the patient received sugammadex for NMB reversal. Immediately after extubation, blood pressure decrease developed, followed by pulseless electrical activity lasting 3 minutes. The patient also developed erythema. Cardiac massage was performed and the patient was reintubated. The patient stabilized after administration of phenylephrine, noradrenaline, polaramine, and methylprednisolone and recovered on the same day. From generalized redness, anaphylaxis was suspected. The physician noted that the patient was not using beta blockers, ACE inhibitors, asthma medication, anticonvulsants, or antidepressants. The patient received povidone-iodine during the procedure. No other drugs were used shortly before or after sugammadex administration.
- 2011SP018052 (cardio-respiratory arrest-life threatening) concerned a 60 year old male with a history of cerebellar infarction, Meniere's disease, and sleep apnea on concomitant carvedilol, betahistine mesylate, azelnidipine, candesartan cilexetil, and trichlormethiazide who experienced pulselessness, 15 minutes after administration of sugammadex 200 mg that recovered with cardiac massage, noradrenaline and atropine. Sick sinus syndrome was later suspected.
- 2012SP002848 (cardiac arrest, cardio-respiratory arrest-medically significant) described an 83 year old male with a medical history of "bad general condition and altered blood pressure" who presented with asystole and cardio-respiratory arrest right after administration of sugammadex. It was reported that due to the patient's "bad general condition", beta blockers had to be administered during intervention. The patient recovered the same day. The reporter considered that due to the patient's poor general health, asystole and cardiorespiratory arrest were unlikely related to sugammadex. No further information was provided.
- 2010SP035329 (cardiac arrest) concerned a 90 year old with dialysisdependent renal failure and peritonitis with sepsis who died from cardiac arrest, 5 days after administration of sugammadex 200 mg. The reporting physician indicated the patient was elderly and ill and that myocardial ischemia was the possible cause of death, and further indicated the patient's death was not related to sugammadex.
- 2011SP003528 (cardiac arrest) describes a 68 year-old man with a history of prostate cancer who underwent total gastrectomy. After receiving BRIDION, the patient developed decreased blood pressure and unmeasurable pulse. Anaphylactoid shock was diagnosed and the patient underwent treatment with norepinephrine, epinephrine and cardiac massage. Transesophageal echocardiography was performed, revealing a dissection of the descending aorta. The patient

- developed disseminated intravascular coagulation (DIC) and intra-abdominal hemorrhage, and returned to the operating room for control of intra-abdominal bleeding. The source of the hemorrhage was multiple surgical sites within the abdomen. Two days after the initial surgery, the patient developed mesenteric ischemia and underwent subtotal colectomy. Multiorgan failure was diagnosed. Despite treatment, the patient died 3 days post initial surgery.
- 2012SP017236 (cardiac arrest) concerned a 76 year old female with stomach cancer, gastrectomy and chemotherapy on concomitant sodium bicarbonate and digoxin (indication not reported) who underwent thoracotomy for removal of blood clots from a chest tube insertion. In addition to rocuronium, the patient received noradrenalin and amiodarone on admission to the operating room (indication not reported). Two minutes after administration of sugammadex 200 mg, the patient experienced cardiac arrest due to massive pulmonary edema and subsequently died. Additional details such as the patient's clinical condition prior to surgery and the indication for the chest tube were not provided.

Other Arrhythmia Events (Arrhythmia, Supraventricular Extrasystoles)

The Applicant summarized two additional cases that did not fit with the categories above:

- 2011SP033442 was non-serious and reported "arrhythmia." Insufficient information was provided in all aspects of the report including time to onset of arrhythmia following sugammadex administration, specific description of the arrhythmia, treatment and outcome.
- 2011SP014274 was serious and reported "supraventricular extrasystoles." The case concerned a female with lupus erythematosus and nephritis treated with chronic corticosteroid therapy, and deep vein thrombosis treated with anticoagulant therapy. She experienced supraventricular extrasystoles, described as occurring right after administration of sugammadex and lasting for 1 hour. The patient was monitored by electrocardiogram and recovered after 30-45 minutes without treatment.

Applicant's Analyses and Conclusions of the Postmarketing Data

The Applicant reviewed the literature for studies and reports of cardiac arrhythmias in the perioperative period. Based on their estimate of the use of the sugammadex which was predicated on sales data and their estimate for underreporting of adverse events during postmarketing use, they concluded that the adverse events describe above are rare when compared with reports of perioperative arrhythmia in the literature. Specifically, based on 3,276,086 vials

sold worldwide as of 15-Jun-2012, an estimate that only 90% of the product had been administered as of the cutoff date, and an estimate that due to underreporting of spontaneous events in the postmarketing environment only 10% of the cases were reported, they estimated the incidence of arrhythmias and cardiac arrest to be 21.7 per 100,000 operations [95% CI: 20.0; 23.4]. They considered this estimated arrhythmia incidence of 0.022% to be very low compared to the background incidence of arrhythmias in the range of 14-22%, as reported in the epidemiologic literature.

The Applicant noted that an analysis of cardiac arrhythmias occurring after administration of sugammadex would be confounded by other medications given in an operating room setting. They noted that with the exception of 4 fatalities in patients with serious comorbidities, all patients with an outcome reported recovered from these events.

Tachyarrhythmias were the most commonly reported of the arrhythmias with 97% (29/30) described as serious and 67% (20/30) considered life-threatening. Twenty-four events (80%) occurred in the setting of adjudicated anaphylaxis, and were likely related to that event. They noted that tachycardia is labeled in the context of anaphylaxis, and is the setting in which a majority of these reports occurred; most of the remaining reports contained confounding factors.

Bradyarrhythmias were the second most commonly reported arrhythmia events; however, 10 of the 26 reports contained insufficient information for evaluation. Three (12%) of the events occurred in the setting of anaphylaxis. The remaining 13 reports described a hemodynamically stable patient who received sugammadex, developed bradycardia shortly thereafter, and went on to resolve: 11 with the administration of atropine, one spontaneously, and one with cardiac massage. Most of these patients (10/13) received rocuronium. One patient died 19 days after surgery; the remainder recovered. The Applicant stated that although these 13 cases represented a small number of reports in the context of the number of patients treated with sugammadex since market introduction, these reports of onset of bradycardia immediately following administration of sugammadex followed by recovery with treatment may represent a pattern suggesting that very rare events of bradycardia may occur after use of sugammadex.

There were a total of 7 reports of cardiac arrest in the absence of an identifiable arrhythmia, 3 of which were fatal. The fatal cases occurred in patients with serious co-morbid medical conditions and most patients had multiple concurrent medications at the time of the cardiac arrest.

The remaining reports of arrhythmia were isolated reports, with 2 reports received since market introduction.

The Applicant noted that for all these patients, being in an operating room setting, they were uniquely placed to receive timely and appropriate treatment from trained personnel. They concluded that, there is not sufficient evidence in the above reports to attribute causality of cardiac arrhythmias to sugammadex, but state that they will continue to monitor reports of cardiac arrhythmias.

Comments and Conclusions

It is difficult, if not impossible, to determine the frequency with which adverse events occur in the postmarketing setting. The Applicant's efforts at doing so are laudable, but the utility of their findings for determining the risks of arrhythmias and cardiac arrest with sugammadex is limited at best. It needs to be noted that the incidence of adverse events for tachycardia and bradycardia in the clinical development program was 1.6% and 0.3%, respectively, which is orders of magnitude greater than the Applicant's estimate of 0.022% based on postmarketing information.

Regardless of the actual incidence for tachycardia and bradycardia, their association with anaphylactic reactions striking: 80% and 12%, respectively. The association of cardiac arrest with some of the episodes of bradycardia is also noteworthy. Indeed, on November 16, 2012, the Applicant added the adverse event "bradycardia" to its Company Core Data Sheet in the sections corresponding to Adverse Events and Warnings and Precautions. The wording in the Warnings section is:

Marked bradycardia:

In rare instances, marked bradycardia has been observed within minutes after the administration of sugammadex for reversal of neuromuscular blockade. Bradycardia may occasionally lead to cardiac arrest. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Treatment with anti-cholinergic agents such as atropine should be administered if clinically significant bradycardia is observed.

With the physiological changes that occur with anesthesia and surgery and the multiple drugs administered in the perioperative period, it may not be possible to establish causality for the arrhythmias and cardiac arrests reported above; however, their temporal relationship to the administration of sugammadex at a time when other drugs are being discontinued, raises the level of suspicion that sugammadex may have contributed to their occurrence. Perhaps more important is the setting in which they are occurring. At the time sugammadex is administered and for the 30 minutes thereafter, the patient is being continuously monitored in the operating room or post-anesthesia care unit by clinicians and

nurses trained to detect and treat arrhythmias and cardiac arrest and who have the equipment and medications to do so expeditiously.

To assure clinicians are aware of the risks of bradycardia and tachycardia, and their association with anaphylactic reactions and cardiac arrest, the product's label should include the warning stated above (the currently proposed label lacks that warning) as well as a statement describing the associated with anaphylaxis.

The postmarketing adverse reactions related to cardiac arrhythmias otherwise reflect the findings from the clinical trials.

Summary and Conclusions

The Applicant has demonstrated, through appropriate clinical trials, that sugammadex does not cause QTc prolongation whether it is administered alone, with rocuronium or vecuronium, or in the presence of the most commonly used general anesthetic agents, propofol and sevoflurane. The clinical experience in other trials and postmarketing reflect these findings. In those instances where prolonged QTc intervals were observed, the patients did not experience arrhythmic episodes, most notably, Torsades de Pointes.

With the doubling of the safety database, the Applicant has shown that the risk of arrhythmias following treatment with sugammadex is small and not substantially greater than that of placebo or substantially different than that of neostigmine. Given the setting in which sugammadex is administered, arrhythmias are likely to be detected within seconds to minutes of their initiation and treated appropriately within seconds to minutes of being detected; thereby reducing the likelihood of an unfavorable outcome should they occur.

The postmarketing experience for sugammadex indicates that tachycardia and bradycardia are the most likely arrhythmias to occur following sugammadex administration. It is not possible to predict if either is likely to occur and thereby treat patients prophylactically. However, the association of both these arrhythmias with anaphylaxis, especially tachycardia, and the association of cardiac arrest with bradycardia is a safety issue clinicians should be aware of and ready to treat when they elect to use sugammadex.

In summary, the Applicant has demonstrated that sugammadex does not pose a risk for QTc prolongation or a clinically significant increase in risk for cardiac arrhythmias following surgery and general anesthesia. Clinicians need to monitor patients carefully for the relatively small risks of bradycardia and tachycardia and the risks of anaphylaxis and cardiac arrest with which they have been associated. Overall, the risk of cardiac arrhythmias has been better characterized than it was in the original NDA submission and can be more

meaningfully incorporated into the product's label. Although this was not a deficiency identified in the Complete Response letter, it was a recommendation, and the Applicant has fulfilled it.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant reported a total of 22,961 adverse events (AEs) categorized under 1,146 preferred terms for their entire clinical development program. To identify common AEs for the purposes of evaluating the safety of sugammadex for its intended use and product labeling, the following steps were taken to refine the AE database:

1. AEs occurring prior to treatment with study drug were removed from the database. This included eliminating 128 AEs that were reported in Schering-Plough sponsored studies and which occurred prior to administration of study drug and recurred after its administration with a level of severity no worse than observed pretreatment. Thus, a total of 6,674 AEs were eliminated.
2. Those AEs that were not associated with the intravenous administration of study drug were removed. This included AEs from intradermal and skin prick testing conducted as part of studies to assess immunogenicity, a total of 13 AEs.
3. AEs associated with moxifloxacin and succinylcholine were removed because these products were not relevant as comparators for the intended clinical use of sugammadex. This resulted in 489 AEs being removed.
4. Preferred terms for which there were fewer than 25 AEs reported for all sugammadex dose groups combined were removed. There were a total of 4,914 subject exposures for sugammadex in the safety database. The preferred terms for which there were 25 or more AEs within the sugammadex treatment group were therefore associated with an incidence of $\geq 0.5\%$. This would allow for combining preferred term AEs that are similar, e.g., bradycardia and heart rate decreased, before applying a 1% incidence cutoff, and limit the possibility for splitting of terms to affect the safety analysis. This step reduced the number of preferred terms to 75 and the number of sugammadex-related AEs to 7,683.

The result of these steps is Table 35 below.

Table 35. Adverse event counts for AEs occurring with a frequency of greater than 0.5% in sugammadex-treated subjects

| System Organ Class | Preferred Term | Placebo (N=1759) | | Sugammadex (N=4914) | | Neostigmine (N=804) | |
|--|----------------------------------|------------------|---|---------------------|----|---------------------|----|
| | | n | % | n | % | n | % |
| Blood and lymphatic system disorders | Anaemia | 49 | 3 | 125 | 3 | 38 | 5 |
| Body as a whole - general disorders | Therapeutic response decreased | 1 | 0 | 28 | 1 | 0 | 0 |
| Cardiac disorders | Tachycardia | 4 | 0 | 37 | 1 | 11 | 1 |
| Ear and labyrinth disorders | Vertigo | 9 | 1 | 41 | 1 | 22 | 3 |
| Gastrointestinal disorders | Abdominal distension | 2 | 0 | 29 | 1 | 7 | 1 |
| | Abdominal pain | 13 | 1 | 90 | 2 | 22 | 3 |
| | Abdominal pain upper | 6 | 0 | 25 | 1 | 14 | 2 |
| | Constipation | 73 | 4 | 264 | 5 | 113 | 14 |
| | Diarrhoea | 30 | 2 | 97 | 2 | 20 | 2 |
| | Dry mouth | 1 | 0 | 34 | 1 | 20 | 2 |
| | Dyspepsia | 5 | 0 | 26 | 1 | 9 | 1 |
| | Flatulence | 11 | 1 | 71 | 1 | 12 | 1 |
| | Nausea | 112 | 6 | 854 | 17 | 236 | 29 |
| | Vomiting | 59 | 3 | 384 | 8 | 104 | 13 |
| General disorders and administration site conditions | Chills | 15 | 1 | 91 | 2 | 12 | 1 |
| | Fatigue | 8 | 0 | 29 | 1 | 4 | 0 |
| | Oedema peripheral | 25 | 1 | 91 | 2 | 32 | 4 |
| | Pain | 17 | 1 | 199 | 4 | 131 | 16 |
| | Pyrexia | 18 | 1 | 209 | 4 | 45 | 6 |
| Infections and infestations | Naso-pharyngitis | 33 | 2 | 48 | 1 | 6 | 1 |
| | Urinary tract infection | 13 | 1 | 37 | 1 | 20 | 2 |
| Injury, poisoning and procedural complications | Anaemia postoperative | 52 | 3 | 76 | 2 | 19 | 2 |
| | Anaesthetic complication | 1 | 0 | 62 | 1 | 1 | 0 |
| | Incision site complication | 0 | 0 | 87 | 2 | 16 | 2 |
| | Incision site pain | 6 | 0 | 116 | 2 | 64 | 8 |
| | Post procedural complication | 22 | 1 | 58 | 1 | 12 | 1 |
| | Post procedural haemorrhage | 7 | 0 | 35 | 1 | 12 | 1 |
| | Post procedural nausea | 6 | 0 | 53 | 1 | 14 | 2 |
| | Post procedural pain | 0 | 0 | 33 | 1 | 0 | 0 |
| | Postoperative wound complication | 3 | 0 | 42 | 1 | 1 | 0 |
| | Procedural complication | 6 | 0 | 77 | 2 | 34 | 4 |
| | Procedural hypertension | 23 | 1 | 103 | 2 | 23 | 3 |
| | Procedural hypotension | 8 | 0 | 115 | 2 | 24 | 3 |

| | | | | | | | |
|---|---|-----|----|------|----|-----|----|
| | Procedural nausea | 27 | 2 | 53 | 1 | 24 | 3 |
| | Procedural pain | 199 | 11 | 1398 | 28 | 426 | 53 |
| | Procedural vomiting | 12 | 1 | 35 | 1 | 14 | 2 |
| | Seroma | 1 | 0 | 25 | 1 | 22 | 3 |
| | Wound complication | 14 | 1 | 42 | 1 | 17 | 2 |
| | Wound haemorrhage | 8 | 0 | 31 | 1 | 18 | 2 |
| | Wound secretion | 19 | 1 | 27 | 1 | 5 | 1 |
| Investigations | Blood creatine phosphokinase increased | 1 | 0 | 32 | 1 | 3 | 0 |
| | Electrocardiogram QT corrected interval prolonged | 2 | 0 | 25 | 1 | 0 | 0 |
| | Haemoglobin decreased | 2 | 0 | 31 | 1 | 13 | 2 |
| | Oxygen saturation decreased | 0 | 0 | 25 | 1 | 4 | 0 |
| Metabolism and nutrition disorders | Hypocalcaemia | 4 | 0 | 30 | 1 | 4 | 0 |
| | Hypokalaemia | 28 | 2 | 69 | 1 | 28 | 3 |
| Musculoskeletal and connective tissue disorders | Arthralgia | 64 | 4 | 108 | 2 | 7 | 1 |
| | Back pain | 25 | 1 | 117 | 2 | 19 | 2 |
| | Musculoskeletal pain | 6 | 0 | 33 | 1 | 11 | 1 |
| | Myalgia | 8 | 0 | 31 | 1 | 8 | 1 |
| | Pain in extremity | 16 | 1 | 61 | 1 | 15 | 2 |
| Nervous system disorders | Dizziness | 21 | 1 | 172 | 4 | 62 | 8 |
| | Dysgeusia | 7 | 0 | 193 | 4 | 5 | 1 |
| Nervous system disorders | Headache | 98 | 6 | 287 | 6 | 58 | 7 |
| | Hypoaesthesia | 9 | 1 | 54 | 1 | 6 | 1 |
| | Paraesthesia | 9 | 1 | 47 | 1 | 7 | 1 |
| | Somnolence | 8 | 0 | 25 | 1 | 4 | 0 |
| Psychiatric disorders | Anxiety | 1 | 0 | 43 | 1 | 15 | 2 |
| | Insomnia | 24 | 1 | 145 | 3 | 57 | 7 |
| | Sleep disorder | 57 | 3 | 118 | 2 | 43 | 5 |
| Renal and urinary disorders | Bladder spasm | 1 | 0 | 29 | 1 | 5 | 1 |
| | Oliguria | 9 | 1 | 29 | 1 | 17 | 2 |
| | Urinary retention | 12 | 1 | 41 | 1 | 6 | 1 |
| Respiratory, thoracic and mediastinal disorders | Cough | 17 | 1 | 57 | 1 | 24 | 3 |
| | Dyspnoea | 9 | 1 | 45 | 1 | 11 | 1 |
| | Oropharyngeal pain | 31 | 2 | 36 | 1 | 10 | 1 |
| | Pharyngolaryngeal pain | 11 | 1 | 115 | 2 | 20 | 2 |
| Skin and subcutaneous tissue disorders | Erythema | 7 | 0 | 50 | 1 | 39 | 5 |
| | Hyperhidrosis | 3 | 0 | 25 | 1 | 7 | 1 |
| | Pruritus | 9 | 1 | 89 | 2 | 27 | 3 |
| | Rash | 11 | 1 | 40 | 1 | 14 | 2 |
| Vascular disorders | Haematoma | 26 | 1 | 72 | 1 | 34 | 4 |
| | Hypertension | 16 | 1 | 74 | 2 | 11 | 1 |
| | Hypotension | 10 | 1 | 58 | 1 | 36 | 4 |

Combining similar preferred terms, e.g., vertigo and dizziness or post procedural pain and procedural pain, and then eliminating the preferred terms with total frequencies less than 1% for sugammadex and preferred terms for which the frequencies of placebo treatments were the same as or greater than sugammadex resulted in Table 36 below.

Table 36. Adverse event counts for AEs occurring with a greater frequency for sugammadex than placebo and with a frequency > 1% for sugammadex

| System Organ Class | Preferred Term | Placebo (N=1759) | | Sugammadex (N=4914) | | Neostigmine (N=804) | |
|--|----------------------------|------------------|----|---------------------|----|---------------------|----|
| | | n | % | n | % | n | % |
| Cardiac disorders | Hypertension | 39 | 2 | 177 | 4 | 34 | 4 |
| | Hypotension | 18 | 1 | 173 | 4 | 60 | 7 |
| | Constipation | 73 | 4 | 264 | 5 | 113 | 14 |
| | Nausea | 145 | 8 | 960 | 20 | 274 | 34 |
| | Vomiting | 71 | 4 | 419 | 9 | 118 | 15 |
| General disorders and administration site conditions | Chills | 15 | 1 | 91 | 2 | 12 | 1 |
| | Edema peripheral | 25 | 1 | 91 | 2 | 32 | 4 |
| | Pyrexia | 18 | 1 | 209 | 4 | 45 | 6 |
| | Anesthetic complication | 1 | 0 | 62 | 1 | 1 | 0 |
| | Incision site complication | 0 | 0 | 87 | 2 | 16 | 2 |
| | Pain | 402 | 23 | 2362 | 48 | 747 | 93 |
| | Procedural complication | 6 | 0 | 77 | 2 | 34 | 4 |
| Nervous system disorders | Dizziness | 30 | 2 | 213 | 4 | 84 | 10 |
| | Dysgeusia | 7 | 0 | 193 | 4 | 5 | 1 |
| | Insomnia | 24 | 1 | 145 | 3 | 57 | 7 |
| Skin and subcutaneous tissue disorders | Erythema | 7 | 0 | 50 | 1 | 39 | 5 |
| | Pruritus | 9 | 1 | 89 | 2 | 27 | 3 |

Most of the differences between placebo- and sugammadex-treatments in the frequencies of the AEs were less than a few percentage points. Those which occurred with sugammadex at rates greater than 3 percentage points over placebo included:

- Nausea
- Vomiting
- Pain (including: arthralgia, back pain, musculoskeletal pain, myalgia, pain in extremity, oropharyngeal pain, pharyngolaryngeal pain, procedural pain, post procedural pain, abdominal pain, and incision site pain)
- Dysgeusia

Table 37 indicates that of the four AEs above, only dysgeusia appears to be sugammadex-dose dependent.

Table 37. Incidence of adverse events for nausea, vomiting, pain and dysgeusia by study drug and dose of sugammadex

| | Placebo | Sugammadex (mg/kg) | | | | | | | | | | | | Neo-stigmine |
|---------------|---------|--------------------|-----|----|------|----|-----|----|-----|----|-----|----|----|--------------|
| | | <2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 64 | 96 | |
| N | 1759 | 340 | 844 | 12 | 2493 | 28 | 156 | 39 | 649 | 6 | 323 | 12 | 12 | 804 |
| Adverse Event | | | | | | | | | | | | | | |
| Nausea | 33 | 3 | 30 | 0 | 70 | 0 | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 38 |
| % | 2 | 1 | 4 | 0 | 3 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 5 |
| Vomiting | 71 | 55 | 86 | 1 | 240 | 1 | 12 | 3 | 20 | 0 | 1 | 0 | 0 | 118 |
| % | 4 | 16 | 10 | 8 | 10 | 4 | 8 | 8 | 3 | 0 | 0 | 0 | 0 | 15 |
| Pain | 402 | 197 | 583 | 5 | 1428 | 2 | 46 | 8 | 82 | 1 | 6 | 1 | 3 | 747 |
| % | 23 | 58 | 69 | 42 | 57 | 7 | 29 | 21 | 13 | 17 | 2 | 8 | 25 | 93 |
| Dysgeusia | 7 | 0 | 1 | 0 | 29 | 0 | 2 | 0 | 79 | 0 | 73 | 1 | 8 | 5 |
| % | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 12 | 0 | 23 | 8 | 67 | 1 |

Compared to neostigmine treatment, no AEs occurred with a frequency of greater than 1 percentage point for sugammadex treatment with the exception of dysgeusia. For nausea, vomiting and pain, the AEs having a greater frequency with sugammadex treatment compared to placebo treatment, the frequency of these AEs was more than 5 percentage points higher in the neostigmine-treatment group than in the sugammadex-treatment group.

The Applicant took a different approach to analyzing the common adverse events. They looked at the pooled Phase 1-3 studies for placebo-controlled and neostigmine-controlled trials and the pooled Phase 1 studies separately and did not evaluate all of the pooled (intravenous treatment) data as was done above. The findings from each of their analyses are summarized in Table 38, Table 39, and Table 40 below. The data in Table 38 and Table 39 indicate that there were no major differences between sugammadex and either placebo or neostigmine for the pooled Phase 1-3 studies. The data in Table 40 for the Pooled Phase 1 studies (in which no neuromuscular blocking agent or anesthetic were administered) are more consistent with those in Table 36 in that nausea and dysgeusia occur substantially more often with sugammadex than with placebo – the only two specific AEs to do so, and the two which comprise approximately half the total AEs reported for those SOC. It is interesting to note that both of these AEs appear to be sugammadex-dose dependent.

Table 38. Number (%) of adverse events in pooled placebo-controlled trials for AEs with incidence for sugammadex of at least 1% and at least twice of that for placebo (Table 28 on p. 89 of Section 5.3.5.3 of the NDA resubmission)

| System Organ Class | Preferred Term | Sugammadex (N=1078) | Placebo (N=544) | Difference (95% CI) ^A non-weighted |
|--|--------------------------------------|---------------------|-----------------|--|
| Injury, poisoning and procedural complications | Procedural hypotension | 36 (3.3) | 8 (1.5) | 1.9 (0.2, 3.3) |
| | Anaesthetic | 35 (3.2) | 1 (0.2) | 3.1 (2.0, 4.3) |
| | Airway complication of anaesthesia | 14 (1.3) | 0 | 1.3 (0.6, 2.2) |
| General disorders and administration site conditions | Therapeutic response decreased | 16 (1.5) | 1 (0.2) | 1.3 (0.4, 2.2) |
| Investigations | Beta 2 microglobulin urine increased | 13 (1.2) | 2 (0.4) | 0.8 (-0.2, 1.7) |
| | Albumin urine present | 11 (1.0) | 1 (0.2) | 0.8 (-0.1, 1.7) |

^A 95% confidence interval according to Miettinen and Nurminen method.

Table 39. Number (%) of subject exposures associated with adverse events in pooled neostigmine-controlled trials (incidence $\geq 2\%$ in one or more treatment groups) (Table 30 on p. 94 of Section 5.3.5.3 in the NDA resubmission)

| MedDRA 15.0 System Organ Class | Preferred Term | Total ^A | Sugammadex Neostigmine |
|--|----------------|--------------------|------------------------|
| | | (N=797) | (N=804) |
| Reproductive system and breast disorders | Total | 13 (1.6) | 18 (2.2) |

N=Number of subject exposures per treatment group

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

Table 40. Number (%) of subject exposures associated with adverse events in pooled Phase 1 trials in descending incidence by total sugammadex (incidence $\geq 2\%$ in one or more treatment groups) (Table 32 on p. 96 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA 15.0 System Organ Class | Preferred Term | Placebo (N=1215) | Sugammadex | | | |
|--|------------------|---------------------|------------------|--------------------|---------------------|--------------------------------|
| | | | 2 mg/kg (n=6) | 4 mg/kg (n=695) | 16 mg/kg (n=551) | Total ^A (N=1507) |
| | | | At least one AE | Total | 249 (20.5) | 1 (16.7) |
| Nervous system disorders | Total | 76 (6.3) | 0 (0.0) | 70 (10.1) | 114 (20.7) | 251 (16.7) |
| | Dysgeusia | 4 (0.3) | 0 (0.0) | 21 (3.0) | 78 (14.2) | 149 (9.9) |
| | Headache | 55 (4.5) | 0 (0.0) | 36 (5.2) | 28 (5.1) | 76 (5.0) |
| Gastrointestinal disorders | Total | 39 (3.2) | 0 (0.0) | 43 (6.2) | 67 (12.2) | 151 (10.0) |
| | Nausea | 9 (0.7) | 0 (0.0) | 18 (2.6) | 50 (9.1) | 85 (5.6) |
| General disorders and administration site conditions | Total | 52 (4.3) | 0 (0.0) | 37 (5.3) | 23 (4.2) | 88 (5.8) |
| Infections and infestations | Total | 50 (4.1) | 0 (0.0) | 31 (4.5) | 24 (4.4) | 62 (4.1) |
| | Naso-pharyngitis | 26 (2.1) | 0 (0.0) | 13 (1.9) | 16 (2.9) | 33 (2.2) |
| Respiratory, thoracic and mediastinal disorders | Total | 33 (2.7) | 0 (0.0) | 18 (2.6) | 17 (3.1) | 51 (3.4) |
| Skin and subcutaneous tissue disorders | Total | 12 (1.0) | 0 (0.0) | 10 (1.4) | 15 (2.7) | 34 (2.3) |

N=Number of subject exposures per treatment group.

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

Based on their analyses, the Applicant has proposed the following wording for the sugammadex label regarding adverse reactions that occurred during the clinical trials:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect (b) (4) subjects exposed to [TRADENAME] and 544 to placebo in (b) (4)

Recurrence of Neuromuscular Blockade

In clinical studies with subjects treated with rocuronium or vecuronium, where sugammadex was administered using a dose labeled for the depth of neuromuscular blockade, an incidence of (b) (4) was observed for recurrence of neuromuscular blockade as based on neuromuscular monitoring or clinical evidence [see *Warnings and Precautions (5.7)*].

(b) (4)
Hypersensitivity reactions, including anaphylaxis, have occurred in (b) (4)

Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, and swelling of tongue (b) (4). Severe hypersensitivity reactions can be fatal.

(b) (4)
A randomized, double-blind study examined the incidence of drug hypersensitivity reactions in healthy volunteers given up to 3 doses of placebo (b) (4), sugammadex 4 mg/kg (b) (4) or sugammadex 16 mg/kg (b) (4). Reports of suspected hypersensitivity were adjudicated by a blinded committee. The incidence of adjudicated hypersensitivity was (b) (4) in the placebo, sugammadex 4 mg/kg and sugammadex 16 mg/kg groups, respectively. (b) (4)

(b) (4)

(b) (4)

Bronchospasm

In one clinical trial in patients with a history of pulmonary complications [see *Use in Specific Populations (8.9)*], bronchospasm was reported as a possibly related adverse event

(b) (4)

The Applicant's proposed table for common adverse events does not appear to be adequate; although it accurately reflects the data that met the criteria for the pooled Phase 1-3 placebo-controlled studies. Table 36 provides a more comprehensive list of AEs likely to be observed in clinical practice, in particular, the occurrence of dysgeusia. The additional information regarding anesthetic complications, recurrence of neuromuscular blockade, and bronchospasm are appropriate to include in this section of the labeling. However, the information regarding anaphylaxis and hypersensitivity are more appropriately placed in the Warnings and Precautions section of the labeling along with the warning about bradycardia that may lead to cardiac arrest (described in Section 7.3.5.3 above).

Summary and Conclusions

The adverse events that were commonly observed with sugammadex in the clinical trials did not occur with much greater frequency than with placebo treatment except for nausea, vomiting, pain and dysgeusia. Only dysgeusia and chills occurred more frequently with sugammadex treatment than with neostigmine treatment, and only dysgeusia appeared to be sugammadex-dose dependent.

Overall, the safety of sugammadex as it relates to common adverse events has not changed substantially from what was reported in the original NDA submission despite a doubling of the size of the safety database. In the original submission, procedural pain, nausea, and vomiting occurred with a frequency greater than 10% in the placebo controlled pooled Phase 1-3 studies. Anesthetic complications occurred next most frequently (8%). Dysgeusia was observed following 13% of exposures (versus 2% for placebo) in the pooled Phase 1 studies. With the increase in the size of the database, the incidence of some of the common AEs has changed but not to a clinically relevant degree. Importantly, no new safety issues were identified with the data analyses performed by the Applicant or for this review.

7.4.2 Laboratory Findings

The Applicant summarized the hematology and biochemistry data using the following time points and values of interest:

- Baseline (i.e., last measurement before administration of the trial medication)
- Post-baseline (20 min, 60 min, +4-6 hr, 8 hr and 24 hr)
- Minimum and maximum values
- Endpoint values
- Final visit (i.e., post-anesthetic visit for surgical subjects).

For urinalysis data, the Applicant used a similar approach, which was identical to the hematology and biochemistry data with the exception of post-baseline summaries that begin at 4 hours for urinalysis data but at 20 minutes for the other laboratory investigations. The time points and values of interest for the urinalysis data were the following:

- Baseline (i.e., last measurement before administration of the trial medication)
- Post-baseline (+4-6 hr, 8 hr and 24 hr)
- Minimum and maximum values
- Endpoint values
- Final visit (i.e., post-anesthetic visit for surgical subjects)

The Applicant used descriptive statistics, shift analyses and markedly abnormal laboratory values to compare the laboratory assessments data for sugammadex-, placebo-, and neostigmine-treated subjects. Their approach for each of these analyses is summarized below.

Descriptive Statistics

Descriptive statistics used by the Applicant included mean (SD), median, minimum, and maximum observed values, and absolute and percent mean (SD), median, minimum, and maximum changes from baseline.

Shift Analysis

Based on predefined normal ranges and safety ranges, the results of the clinical laboratory tests were classified into one of the following categories:

- Category A: value \leq lower safety range
- Category B: value $>$ lower safety range and value \leq lower normal range
- Category C: value $>$ lower normal range and value $<$ upper normal range
- Category D: value \geq upper normal range and value $<$ upper safety range
- Category E: value \geq upper safety range

Shift tables were constructed to determine the categorical shifts from baseline to post-baseline. Each shift was designated by a code. For example, code "AD" denoted a shift of a value from Category A (below or equal to the lower safety range) at baseline to Category D (above or equal to the upper normal range but below the upper safety range) at post-baseline assessment. The percentage of subjects with categorical shifts was presented by treatment group. Shifts of particular interest were called notable shifts. Notable shifts in downward direction defined as those downward shifts resulting in a value belonging to Category A or B (i.e., EA, DA, CA, BA, EB, DB, or CB). Notable shifts in upward direction were defined as those upward shifts resulting in a value belonging to Category D or E (i.e., AD, BD, CD, AE, BE, CE, or DE). The notable shift categories are illustrated in Table 41 below.

Table 41. Notable shift categories (Table 89 on p. 258 in Section 5.3.5.3 of the NDA resubmission)

| Baseline Category | Post-baseline Category | | | | |
|-------------------|------------------------|----------|----|--------|--------|
| | A | B | C | D | E |
| A | -- | -- | -- | Upward | Upward |
| B | Downward | -- | -- | Upward | Upward |
| C | Downward | Downward | -- | Upward | Upward |
| D | Downward | Downward | -- | -- | Upward |
| E | Downward | Downward | -- | -- | -- |

Markedly Abnormal Values

The number and percent of exposures for subjects with markedly abnormal post-baseline values, identified as having values outside of the safety ranges, were summarized by treatment group.

In addition to the above, those laboratory values that were out-of-range and considered by the Investigator to be clinically significant were to be recorded as AEs.

Hematology

Descriptive Analysis

The Applicant reported that in the pooled Phase 1-3 trials, baseline values for all hematology analytes were similar across the dose groups, and there were no dose trends for mean and median changes from baseline. For specific analytes related to coagulation, i.e., activated partial thromboplastin time, prothrombin time, and INR, absolute change from baseline was similar between the

sugammadex dose groups and placebo. Overall, total white blood cell and absolute neutrophil count increased slightly, while absolute eosinophils, hemoglobin, and lymphocyte count decreased slightly. The analytes had similar changes from baseline between the sugammadex dose groups and placebo. For the timepoints 20 minutes, 60 minutes, and 3 hours the neutrophil count increase was greater in the sugammadex treatment groups than placebo treatment groups.

The Applicant also noted that the results for the pooled Phase 1-3 neostigmine-controlled trials and the pooled placebo-controlled trials did not differ from those of the overall pooled Phase 1-3 trial statistics.

A review of the data confirmed the Applicant's reported findings.

Shift Analysis

The Applicant reported that no dose trends were detected in their shift analysis. Overall, there were more notable downward shifts than notable upward shifts in hemoglobin, hematocrit, lymphocyte, and red blood cell count. There were more notable upward shifts in aPTT, total white blood cell count, absolute neutrophil count, and prothrombin time.

A review of the data confirmed the Applicant's report of the findings. The shifts in aPTT and PT are discussed in further detail in section 7.3.5.2 above.

Treatment Emergent Markedly Abnormal Values

The Applicant reported that in the Pooled Phase 1-3 trials, there were no dose trends and the percent of number of exposures of subjects with markedly abnormal post-baseline hematology values was similar between sugammadex and placebo dose groups. The only hematology-related AEs that occurred in more than 1.0% of the total sugammadex group were anemia (3.6%) and anemia postoperative (2.1%). There was no dose trend and the values for these two AEs were higher in the placebo group than the values for the total sugammadex group.

Table 42 below was created by the Applicant and summarizes the AEs related to hematology laboratory parameters for the pooled Phase 1-3 trials. Their summary for the neostigmine-controlled trials are found in Table 43 below.

Table 42. Number (%) of exposures associated with adverse events in pooled Phase 1-3 Trials in order of decreasing incidence in the total sugammadex group (Table 90 on pp. 260-261 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | | Placebo N=544 | Sugammadex | | | |
|------------------------------------|--|------------------|---------------------|----------------------|---------------------|------------------------------|
| | | | 2 mg/kg n=838 | 4 mg/kg n=1798 | 16 mg/kg n=98 | Total ^A N=3407 |
| At least one AE | | 109(20.0) | 44 (5.3) | 209(11.6) | 5 (5.1) | 271 (8.0) |
| Red blood cells | Anemia | 50 (9.2) | 21 (2.5) | 93 (5.2) | 3 (3.1) | 122 (3.6) |
| | Anemia postoperative | 51 (9.4) | 7 (0.8) | 66 (3.7) | 0 (0.0) | 73 (2.1) |
| | Hemoglobin decreased | 2 (0.4) | 8 (1.0) | 19 (1.1) | 0 (0.0) | 30 (0.9) |
| | Hematocrit decreased | 0 (0.0) | 4 (0.5) | 12 (0.7) | 0 (0.0) | 18 (0.5) |
| | International normalised ratio increased | 1 (0.2) | 0 (0.0) | 5 (0.3) | 0 (0.0) | 5 (0.1) |
| | Hemorrhagic anemia | 1 (0.2) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 4 (0.1) |
| | Red blood cell count decreased | 0 (0.0) | 1 (0.1) | 2 (0.1) | 1 (1.0) | 4 (0.1) |
| | Iron deficiency anemia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Prothrombin level increased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Prothrombin time prolonged | 1 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Red blood cell count increased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| White blood cells and differential | Neutrophil count increased | 1 (0.2) | 1 (0.1) | 12 (0.7) | 0 (0.0) | 13 (0.4) |
| | White blood cell count increased | 2 (0.4) | 1 (0.1) | 7 (0.4) | 0 (0.0) | 10 (0.3) |
| | Leukocytosis | 0 (0.0) | 1 (0.1) | 4 (0.2) | 0 (0.0) | 7 (0.2) |
| | Lymphocyte count decreased | 1 (0.2) | 1 (0.1) | 5 (0.3) | 0 (0.0) | 6 (0.2) |
| | Monocyte count increased | 0 (0.0) | 1 (0.1) | 3 (0.2) | 0 (0.0) | 4 (0.1) |
| | Basophil count increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Neutrophilia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 1 (0.0) |
| Platelets | Thrombocytopenia | 2 (0.4) | 2 (0.2) | 9 (0.5) | 0 (0.0) | 11 (0.3) |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

Comments and Conclusions

Aside from changes in aPTT, PT and the INR that occur within minutes after sugammadex administration and resolve within an hour, there were no clinically significant changes in hematological laboratory assessments that occurred substantially more frequently with sugammadex than with placebo or neostigmine. There were no sugammadex-dose dependent changes in the laboratory assessments, and compared to placebo and neostigmine, there were no differences in adverse events related to those assessments.

Biochemistry

Descriptive Statistics

The Applicant reported that the baseline values for all biochemistry analytes were similar across the dose groups, and there were no dose trends or clinically significant differences in mean and median changes from baseline. Although the total sugammadex group was similar to placebo, they noted that a dose related trend for decrease in lactate dehydrogenase (LDH) may be present.

A review of the data confirmed the Applicant's findings. The LDH findings were noted in the original NDA submission, the changes do not appear to be clinically relevant.

Shift Analysis

The Applicant stated that no dose trends were detected in the shift analysis. Overall, there were more notable downward than upward shifts in albumin, alkaline phosphatase, bilirubin, calcium, fasting triglycerides, total cholesterol, haptoglobin, haptoglobin type 2-1, lactate dehydrogenase, magnesium, potassium, total protein, sodium, and urea nitrogen. There were also more notable upward than downward shifts in alanine aminotransferase, aspartate aminotransferase, chloride, creatine phosphokinase, fasting glucose, triglycerides, and creatinine. They indicated that these shifts were not considered clinically relevant.

A review of the data confirmed the Applicant's findings. The trends observed in the original NDA database, appear to persist in the updated database, i.e., in both treatment groups, all upward shifts in total cholesterol and triglycerides were observed only in subjects who received rocuronium as the NMBA. In addition, subjects of both groups who received rocuronium (compared to those who received vecuronium) had more upward shifts in CK and more downward shifts in

sodium. Conversely, subjects of both treatment groups who received vecuronium (compared to those who received rocuronium) had more downward shifts in albumin, haptoglobin, magnesium, and total protein, and more upward shifts in fasting glucose. The changes observed do not appear to be clinically relevant.

Treatment Emergent Markedly Abnormal Values

The Applicant reported that, in the Pooled Phase 1-3 trials, there were no dose-dependent trends for the percent of exposures of subjects with markedly abnormal post-baseline biochemistry values that met their pre-specified criteria. The percent of exposures of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was similar between the sugammadex-treated groups and the placebo-treated group except for fasting glucose, which increased in the sugammadex group. Of note were significant markedly low biochemistry values for haptoglobin. Most AEs related to abnormalities of biochemistry clinical laboratory tests were reported to have occurred in 1% or less of the total sugammadex group, and no dose-dependent trends were observed. The only biochemistry-related AE that occurred in more than 1% of the total sugammadex group was hypokalemia (2.0%).

The Applicant noted that, in the pooled placebo-controlled trials, the percent of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria did not substantially differ between the two treatment groups except for elevated fasting glucose which was 6% higher in the sugammadex-treatment group than the placebo-treatment group. They also noted that both treatment groups had markedly low values measured for haptoglobin. The incidence of AEs related to abnormalities of biochemistry clinical laboratory tests was low overall (<1%), and the differences in incidence between the sugammadex group and the placebo group were not clinically relevant according to the Applicant.

In the Pooled Neostigmine-controlled trials, the Applicant noted that the percent of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was generally similar between the two treatment groups. The incidence of AEs related to abnormalities of biochemistry clinical laboratory tests was reported as low overall, and there were no clinically significant treatment group differences.

Table 44 and Table 45 below were created by the Applicant and summarize the AEs related to biochemical laboratory parameters for the placebo-controlled trials and the neostigmine-controlled trials, respectively.

Table 44. Number (%) of exposures associated with adverse events in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (Table 97 on pp. 268-269 in Section 5.3.5.3 of the NDA resubmission)

| Preferred Term | | Placebo | Sugammadex | | | |
|-----------------|---------------------------------------|----------|------------|-----------|----------|--------------------|
| | | | 2 mg/kg | 4 mg/kg | 16 mg/kg | Total ^A |
| | | N=544 | n=838 | n=1798 | n=98 | N=3407 |
| At least one AE | | 41 (7.5) | 67 (8.0) | 146 (8.1) | 4 (4.1) | 241 (7.1) |
| Liver | Aspartate aminotransferase increased | 1 (0.2) | 8 (1.0) | 7 (0.4) | 0 (0.0) | 17 (0.5) |
| | Alanine aminotransferase increased | 1 (0.2) | 8 (1.0) | 3 (0.2) | 0 (0.0) | 12 (0.4) |
| | Gamma-glutamyltransferase increased | 0 (0.0) | 6 (0.7) | 4 (0.2) | 0 (0.0) | 12 (0.4) |
| | Hepatic enzyme increased | 0 (0.0) | 0 (0.0) | 4 (0.2) | 0 (0.0) | 4 (0.1) |
| | Blood bilirubin increased | 1 (0.2) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| | Hyperbilirubinaemia | 0 (0.0) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.1) |
| | Blood lactate dehydrogenase increased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| | Liver function test abnormal | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| | Transaminases increased | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Kidney | Protein total decreased | 0 (0.0) | 3 (0.4) | 4 (0.2) | 0 (0.0) | 8 (0.2) |
| | Blood creatinine increased | 1 (0.2) | 0 (0.0) | 5 (0.3) | 1 (1.0) | 7 (0.2) |
| | Blood albumin decreased | 0 (0.0) | 1 (0.1) | 2 (0.1) | 0 (0.0) | 4 (0.1) |
| | Azotaemia | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| | Hypoalbuminaemia | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) |
| | Blood creatine increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Blood urea increased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Creatinine renal clearance decreased | 1 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Hypoproteinaemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 1 (0.0) |
| Blood glucose | Hyperglycaemia | 3 (0.6) | 7 (0.8) | 12 (0.7) | 0 (0.0) | 24 (0.7) |
| | Hypoglycaemia | 1 (0.2) | 1 (0.1) | 5 (0.3) | 0 (0.0) | 6 (0.2) |
| | Blood glucose increased | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 4 (0.1) |

| Preferred Term | Placebo | Sugammadex | | | | |
|--|--|------------|----------|----------|--------------------|----------|
| | | 2 mg/kg | 4 mg/kg | 16 mg/kg | Total ^A | |
| | N=544 | n=838 | n=1798 | n=98 | N=3407 | |
| Diabetes mellitus | 0 (0.0) | 1 (0.1) | 1 (0.1) | 0 (0.0) | 2 (0.1) | |
| Blood glucose abnormal | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) | |
| Type 2 diabetes mellitus | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) | |
| Calcium, Phosphorus, Magnesium, Potassium and Electrolytes | Hypokalaemia | 27 (5.0) | 17 (2.0) | 49 (2.7) | 1 (1.0) | 68 (2.0) |
| | Hypocalcaemia | 4 (0.7) | 14 (1.7) | 12 (0.7) | 0 (0.0) | 29 (0.9) |
| | Blood potassium decreased | 1 (0.2) | 2 (0.2) | 11 (0.6) | 0 (0.0) | 13 (0.4) |
| | Hypomagnesaemia | 0 (0.0) | 7 (0.8) | 4 (0.2) | 0 (0.0) | 12 (0.4) |
| | Hyperkalaemia | 0 (0.0) | 5 (0.6) | 6 (0.3) | 0 (0.0) | 11 (0.3) |
| | Blood magnesium decreased | 0 (0.0) | 4 (0.5) | 4 (0.2) | 0 (0.0) | 8 (0.2) |
| | Hyponatraemia | 0 (0.0) | 3 (0.4) | 3 (0.2) | 0 (0.0) | 6 (0.2) |
| | Blood calcium decreased | 0 (0.0) | 2 (0.2) | 3 (0.2) | 0 (0.0) | 5 (0.1) |
| | Hypophosphataemia | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 4 (0.1) |
| | Blood phosphorus decreased | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| | Calcium deficiency | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Other biochemistry | Blood creatine phosphokinase increased | 1 (0.2) | 9 (1.1) | 13 (0.7) | 2 (2.0) | 30 (0.9) |
| | C-reactive protein increased | 3 (0.6) | 0 (0.0) | 12 (0.7) | 0 (0.0) | 12 (0.4) |
| | Haptoglobin decreased | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 5 (0.1) |
| | Antithrombin III decreased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Blood alkaline phosphatase increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Blood cholesterol increased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Blood sodium decreased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Hypercholesterolaemia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Iron deficiency | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Metabolic acidosis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Troponin increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Blood triglycerides increased | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |

^A Total column includes exposures of subjects administered doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

Table 45. Incidence of Markedly High Biochemistry Values at any In-treatment Post-baseline Timepoint and Corresponding Maximum Observed Values in Adult Subjects in Pooled Neostigmine-controlled Trials (Table 101 on p. 275 in Section 5.3.5.3 of the NDA resubmission)

| Biochemistry Analyte (units) | Total ^a Sugammadex (N=797) | | | Neostigmine (N=804) | | |
|---|---------------------------------------|--------|---------|---------------------|-------|---------|
| | N | n (%) | Maximum | N | n (%) | Maximum |
| Alanine aminotransferase (ALAT, SGPT) (U/L) | 176 | 5 (3) | 191 | 164 | 3 (2) | 138 |
| Aspartate aminotransferase (ASAT, SGOT) (U/L) | 176 | 6 (3) | 294 | 164 | 7 (4) | 181 |
| Bilirubin total (umol/L) | 176 | 3 (2) | 70.1 | 164 | 5 (3) | 56.4 |
| Cholesterol total (mmol/L) | 175 | 7 (4) | 7.25 | 163 | 4 (2) | 7.51 |
| Creatine (phospho)kinase (CK) (U/L) | 175 | 14 (8) | 1424 | 163 | 7 (4) | 1576 |
| Creatinine (umol/L) | 176 | 1 (1) | 197.1 | 164 | 0 (0) | 129.1 |
| Gamma glutamyl transferase (GGT) (U/L) | 175 | 5 (3) | 241 | 163 | 9 (6) | 580 |
| Haptoglobin (g/L) | 175 | 0 (0) | 4.46 | 163 | 1 (1) | 4.80 |
| Lactate dehydrogenase (LDH) (U/L) | 175 | 0 (0) | 565 | 163 | 0 (0) | 713 |
| Potassium (K) (mmol/L) | 176 | 3 (2) | 7.3 | 164 | 1 (1) | 7.3 |
| Urea nitrogen (BUN) (mmol/L) | 176 | 0 (0) | 9.00 | 164 | 1 (1) | 10.71 |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

A review of the data confirmed the Applicant's reported findings. The increased blood creatinine level AEs appear to have been the only AEs to change in a dose-dependent fashion with sugammadex; however, the overall changes in AE frequency did not differ substantially from that of the placebo-treatment group. AEs for blood creatine phosphokinase increased occurred more frequently with sugammadex than placebo, but the overall difference was small and there was no indication of dose dependence. Compared to neostigmine, there appeared to be no clinically relevant differences in the number of markedly high values or the maxima for sugammadex treated subjects.

Summary and Conclusions

The findings for biochemistry laboratory parameters have not changed substantially since the original NDA was submitted. While some notable changes were observed, none appeared to be clinically relevant, and overall, the changes observed with sugammadex were neither greater than those for placebo nor different from those of neostigmine to an extent that was clinically relevant.

Urinalysis

Urinalysis data collected by the Applicant in the pooled Phase 1-3 integrated database included the results of sediment analysis for the analytes casts, crystals, RBC count, hyaline cylinders, WBC count, round epithelial cells, squamous epithelial cells, and yeast, in addition to urine specific gravity, pH, beta-2-microglobulin, urine creatinine, microalbumin, urine protein, and N-acetylglucosaminidase (NAG). The same approach used for analyzing the hematology and biochemistry laboratory data were applied to the urinalysis data.

Descriptive Statistics

The Applicant noted that the pooled Phase 1-3 trials dose groups were well-matched for mean and median baseline values and that no dose trends or trends by timepoint were observed for mean or median changes from baseline. The sugammadex dose group descriptive statistics were similar to the pooled placebo-controlled and the pooled neostigmine-controlled group descriptive statistics.

A review of the data tables confirmed the Applicant's findings, which do not appear to have changed substantially from those in the original NDA submission.

Shift Analysis

The pooled Phase 1-3 group was reported to have shown more notable downward than upward shifts in erythrocyte count, leukocyte count, and N-acetylglucosaminidase, and more notable upward than downward shifts in beta-2-microglobulin and microalbumin (creatinine dependent). Differences between the amount of notable upward and downward shifts were considered small and they reported that no dose trends were detected in the shift analysis. Shift analyses findings in the pooled placebo-controlled group were reported to be similar to those of the shift analyses by sugammadex dose. The pooled neostigmine-controlled groups were reported to have shown very small if any differences between notable upward and downward shifts.

A review of the data tables confirmed the Applicant's reported findings.

Treatment Emergent Markedly Abnormal Values

The Applicant reported that the treatment groups in the pooled Phase 1-3 trials showed no dose trends for the percent of exposures in subjects with markedly abnormal post-baseline urinalysis values that met their pre-specified criteria. In the sugammadex group, there were markedly abnormal increased post-baseline values for beta-2-microglobulin, microalbumin (creatinine-dependent), microalbumin (non-creatinine-dependent) and N-acetylglucosaminidase. In

addition, there were markedly abnormal decreased post-baseline values for urine creatinine.

For the pooled placebo-controlled group, the Applicant reported that the incidences of markedly high urine values for Beta-2-microglobulin were higher in the sugammadex treatment group, while for microalbumin and NAG, incidences were higher in the placebo treatment groups. In the pooled neostigmine-controlled group, the percent of subjects with markedly abnormal post-baseline values at the final visit that met the Applicant's pre-specified criteria was reported to be generally similar between the two treatment groups with the exception of N-acetylglucosaminidase that was 5% higher in the sugammadex-treatment group than in the neostigmine-treatment group.

Most of AEs related to abnormalities of the urinalysis occurred in 2% or less of the Total sugammadex group, according to the Applicant, and no dose-dependent trends were observed for sugammadex treatment. The incidences of AEs were similar between sugammadex, neostigmine and placebo treatment groups. Table 46 summarizes the AE findings.

Table 46. Number (%) of exposures associated with adverse events for urinalysis abnormalities in pooled Phase 1-3 trials in order of decreasing incidence in the total sugammadex group (Table 104 on pp. 280-281 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA 15.0 PT | | Placebo | Sugammadex (mg/kg) | | | |
|--|---|----------|--------------------|----------|---------|--------------------|
| | | | 2 | 4 | 16 | Total ^A |
| | | N=544 | n=838 | n=1798 | n=98 | N=3407 |
| At least one AE | | 15 (2.8) | 43 (5.1) | 47 (2.6) | 2 (2.0) | 126 (3.7) |
| Urine red blood cells | Hematuria | 3 (0.6) | 6 (0.7) | 12 (0.7) | 0 (0.0) | 19 (0.6) |
| | Blood urine present | 1 (0.2) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 7 (0.2) |
| | Red blood cells urine | 0 (0.0) | 0 (0.0) | 7 (0.4) | 0 (0.0) | 7 (0.2) |
| | Post procedural hematuria | 0 (0.0) | 2 (0.2) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| | Red blood cells urine positive | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Urine white blood cells and differential | White blood cells urine | 0 (0.0) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.1) |
| | White blood cells urine positive | 1 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Urine NAG | Beta-N-acetyl-D-glucosaminidase increased | 1 (0.2) | 10 (1.2) | 5 (0.3) | 0 (0.0) | 23 (0.7) |

| | | | | | | |
|----------------------------|---|---------|---------|---------|---------|----------|
| | Beta-N-acetyl-D-glucosaminidase decreased | 0 (0.0) | 0 (0.0) | 3 (0.2) | 0 (0.0) | 3 (0.1) |
| Urine protein and albumin | Albumin urine present | 1 (0.2) | 8 (1.0) | 9 (0.5) | 0 (0.0) | 24 (0.7) |
| | Beta 2 microglobulin urine increased | 2 (0.4) | 9 (1.1) | 6 (0.3) | 0 (0.0) | 24 (0.7) |
| | Beta 2 microglobulin increased | 2 (0.4) | 6 (0.7) | 1 (0.1) | 0 (0.0) | 12 (0.4) |
| | Microalbuminuria | 0 (0.0) | 1 (0.1) | 1 (0.1) | 1 (1.0) | 3 (0.1) |
| | Albuminuria | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Proteinuria | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Urine glucose | Glycosuria | 0 (0.0) | 3 (0.4) | 2 (0.1) | 0 (0.0) | 6 (0.2) |
| | Ketonuria | 0 (0.0) | 3 (0.4) | 1 (0.1) | 0 (0.0) | 6 (0.2) |
| Other urine biochemistry | Bilirubin urine | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Creatinine urine decreased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| | Urine bilirubin increased | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| | Urobilinogen urine | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Urine microscopic analysis | Urinary casts present | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| | Urinary sediment present | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Other urinalysis | Urine output decreased | 4 (0.7) | 4 (0.5) | 8 (0.4) | 1 (1.0) | 16 (0.5) |
| | Crystal urine present | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| | Urine analysis abnormal | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |

N = number of subject exposures per treatment group

n=Number of subject exposures per dose group

^A Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

The Applicant's reported findings were confirmed by review of the data tables.

Summary and Conclusions

Overall, the changes that occurred in laboratory assessments of urine after treatment with sugammadex did not appear to differ in a clinically meaningful way from placebo or neostigmine or by dose of sugammadex. The findings in the updated safety database do not differ markedly from those of the original NDA submission.

Summary and Conclusions

The Applicant has provided an adequate assessment of the effects of sugammadex on hematological, biochemical and urological laboratory parameters. The assessment contained in the original NDA submission was considered adequate with the exception of coagulation parameters, which were not evaluated at all in the subjects participating in any of the clinical studies. For those parameters that were evaluated, none were considered to have been altered to a clinically significant extent by the administration of sugammadex based on comparisons to placebo and neostigmine treatments. The same is true for the updated safety database, with the exception of changes noted, i.e., increases in the values, for aPTT, PT and INR, which occurred following sugammadex administration and persisted for less than one hour. The changes in the coagulation parameters (described more fully in Section 7.3.5.2 of this review) were not associated with an increased risk of bleeding, and sugammadex was shown not to affect the action of anticoagulants commonly administered in the perioperative period.

7.4.3 Vital Signs

The Applicant used descriptive statistics, including the mean, Standard Deviation (SD), median, minimum, and maximum observed values, and absolute and percent mean (SD), median, minimum, and maximum changes from baseline to characterize the effects on vital signs that were observed with the various treatment groups. The number and percent of subjects with markedly abnormal values, according to the pre-defined safety ranges, were also summarized by treatment group. The subjects with markedly abnormal values are identified as were adverse events (AEs) that were considered related to vital signs abnormalities.

In all trials, blood pressure and pulse rate were to be measured in the supine position after a 5-minute rest. In addition, out-of-range vital signs values that were considered by the Investigator to be clinically significant were to be recorded as AEs.

Pooled Phase 1-3 trials

In the Phase 1-3 trials where a neuromuscular blocking agent (NMBA) was administered, vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and central body temperature. Blood pressure and pulse rate data were summarized by the Applicant according to the following time intervals:

- Baseline (i.e., last measurement before the administration of study drug)
- Post-baseline (2, 5, 10, 30, 60, and 120 min and 3 hours)
- Minimum and maximum values (from start of study drug to 6 hours later)
- Final visit (last measurement after study drug till 6 hours later).
- Post-anesthetic visit (from 6 hours after study drug until 48 hours after study drug, or Day 2)
- Follow-up visit (from Day 4 onwards)

In the pooled Phase 1-3 trials, the Applicant summarized respiratory rate data only at baseline (i.e., screening) and the final visit. Central body temperature (CBT) was measured continuously throughout the anesthetic period; “yes” or “no” responses to the question “Was the CBT maintained at $\geq 35^{\circ}\text{C}$ during the entire NMT monitoring?” are summarized.

Phase 1 trials

In the pooled Phase 1 dataset of non-anesthetized healthy volunteers who did not receive an NMBA, vital signs included blood pressure, pulse rate, respiratory rate, temperature, and body weight. Blood pressure and pulse rate data were summarized according to the following time intervals:

- Baseline (i.e., before the administration of the trial medication)
- At 2 min, 10 min, 15 min, 30 min, 35 min, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-baseline

Body temperature, body weight, and respiratory rate data were summarized for the pooled Phase 1 population only at baseline and follow-up. Similarly, body weight, height, and body temperature data were summarized for screening and follow-up.

The Applicant excluded data from Trial 19.4.105 in the pooled Phase 1 dataset for the analysis of blood pressure and pulse rate. In this trial, the protocol did not require any post-baseline vital signs measurements were required by protocol, and follow-up vital signs were taken at least 7 days after dosing.

Vital sign data from trial 19.4.107 were also excluded from the pooled analysis by the Applicant because SBP, DBP, and pulse rate data were collected only for the following time intervals:

- Screening, baseline (i.e., prior to drug administration),
- At 2 min, 35 min, and 60 min post-baseline, and
- At follow-up.

The Applicant used the values in Table 47 for determining changes in blood pressure and heart rate that were classified as “markedly abnormal.” To qualify, a parameter had to meet both conditions, i.e., it had to be outside the safety range and be a change from baseline that met or exceeded the “criteria value.”

Table 47. Absolute value cutoffs and changes for blood pressure and heart rate that were used to determine “markedly abnormal values” (from Table 138 on p. 4317 in Appendix A of Section 5.3.5.3 in the NDA resubmission)

| Parameter | Safety Range | | Criteria Value | |
|---------------------------------|--------------|------|----------------|----------|
| | Low | High | Decrease | Increase |
| Systolic blood pressure (mmHg) | 90 | 160 | 20 | 20 |
| Diastolic blood pressure (mmHg) | 45 | 95 | 15 | 15 |
| Heart rate (bpm) | 50 | 120 | 15 | 15 |

Systolic Blood Pressure

In the placebo-controlled trials, the Applicant reported that SBP increased after trial drug administration. Mean and median absolute increases from baseline in the placebo group were similar in magnitude across the timepoints, while the mean and median absolute increases from baseline in the sugammadex-treatment group were more variable and were 0.5 to 7 mmHg higher compared to placebo. The largest difference between the two groups was observed at 30 min post-baseline (median increase 7 mmHg for sugammadex; 0 mmHg for placebo). The Applicant noted that at the 2 min and 10 min timepoints, results for subjects who were paralyzed with vecuronium were dissimilar to those of the overall group and the rocuronium subset. At both of these timepoints, mean percent change

from baseline was numerically larger in the vecuronium/placebo group than in the vecuronium/sugammadex group, as follows:

- 2 min: 0.7% sugammadex/vecuronium, 5.6% placebo/vecuronium
- 10 min: -0.3% Org sugammadex/vecuronium, 2.0% placebo/vecuronium

These data are summarized in Table 52 near the end of this section of the review.

The Applicant also noted that it is difficult to assess the significance of the larger mean SBP increases from baseline at 30 min in the sugammadex group compared to the placebo group due to the varied timing of the administration of sugammadex across the protocols. When higher doses of sugammadex were administered at 3 minutes following rocuronium, it was given very early in the course of the surgical procedure, and at 30 min following administration of the study drug, it is possible that the surgery was not completed, that the subject remained anesthetized, and that SBP values therefore remained well below pre-anesthetic levels. Conversely, when lower sugammadex doses were administered toward the end of surgery for “routine reversal,” the 30 min SBP values were likely higher because they were returning to pre-anesthetic levels in the awakening subjects.

The Applicant also stated that the difference from placebo can also be partially explained by the fact that sugammadex-treated subjects, having received an agent that actively reverses the effects of neuromuscular blockade, were weaned from anesthesia earlier than placebo subjects. In placebo subjects, the effects of neuromuscular blockade took longer to wane, and thus, these subjects were kept under anesthesia longer than the sugammadex-treated subjects.

The AEs related to systolic blood pressure were summarized by the Applicant in

Table 48 below. The Applicant noted that in the pooled placebo-controlled Phase 1-3 trials, there were more markedly abnormal decreases in SBP that met the pre-specified criteria in than markedly abnormal increases. They also observed that there was a dose-related trend for decreased SBP and for the AE “procedural hypotension” in the sugammadex-treated subjects, with incidences generally higher in the 16 mg/kg dose group.

Table 48. Number (%) of exposures associated with blood pressure related adverse events in pooled Phase 1-3 placebo-controlled studies (Table 105 on p. 208 in section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | Placebo | Sugammadex | | | |
|----------------------------|-----------|------------|------------|-----------|--------------------|
| | | 2 mg/kg | 4 mg/kg | 16 mg/kg | Total ^A |
| | (N=544) | (n=838) | (n=1798) | (n=98) | (N=3407) |
| At least one AE | 59 (10.8) | 75 (8.9) | 182 (10.1) | 20 (20.4) | 331 (9.7) |
| Procedural hypotension | 8 (1.5) | 20 (2.4) | 63 (3.5) | 10 (10.2) | 110 (3.2) |
| Procedural hypertension | 22 (4.0) | 33 (3.9) | 46 (2.6) | 7 (7.1) | 97 (2.8) |
| Hypertension | 14 (2.6) | 13 (1.6) | 39 (2.2) | 1 (1.0) | 65 (1.9) |
| Hypotension | 11 (2.0) | 11 (1.3) | 33 (1.8) | 3 (3.1) | 56 (1.6) |
| Blood pressure decreased | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 6 (0.2) |
| Blood pressure increased | 2 (0.4) | 0 (0.0) | 2 (0.1) | 1 (1.0) | 6 (0.2) |
| Orthostatic hypotension | 0 (0.0) | 1 (0.1) | 2 (0.1) | 0 (0.0) | 3 (0.1) |
| Blood pressure diastolic | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| Hypertensive crisis | 2 (0.4) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 2 (0.1) |
| Blood pressure fluctuation | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Blood pressure systolic | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Intracranial hypotension | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Ocular hypertension | 1 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Pulmonary hypertension | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |
| Systolic hypertension | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.0) |

^A The total sugammadex column includes subjects exposed to any of the doses of sugammadex evaluated in these trials.

The incidence of AEs related to abnormalities of SBP was described by the Applicant as low overall, and the differences in incidence between the sugammadex group and the placebo group were not considered by them to be clinically relevant, although procedural hypotension was higher in the sugammadex-treatment group. Table 49 summarizes these findings.

Table 49. Summary of markedly abnormal, post-baseline, systolic blood pressure values in pooled placebo-controlled trials (Table 106 on p. 291 in Section 5.3.5.3 of the NDA resubmission)

| Parameter | Total ^A Sugammadex (N=1078) | Placebo (N=544) |
|---|--|-----------------|
| SBP markedly decreased (n [%] of exposures) | 53 (5) | 20 (4) |
| Minimum SBP value at any timepoint | 50.0 mmHg | 65.0 mmHg |
| SBP markedly increased (n [%] of exposures) | 129 (12) | 73 (13) |
| Maximum SBP value at any timepoint | 240.0 mmHg | 237.0 mmHg |

^A Total column includes subjects exposed to all doses of sugammadex.

For the pooled neostigmine-controlled trials, the Applicant stated that the descriptive statistics for SBP in the sugammadex treatment group were similar to the neostigmine treatment group.

The incidence of AEs related to abnormalities of SBP was low overall, and the differences in incidence between the sugammadex group and the neostigmine group were not considered clinically relevant by the Applicant. These are summarized in Table 50 below.

Table 50. Number (%) of exposures associated with blood pressure related adverse events in pooled Phase 1-3 neostigmine-controlled studies (Table 109 on p. 294 in section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex (N=797) | Neostigmine (N=804) |
|------------------------------------|---------------------------------------|---------------------|
| At least one AE | 67 (8.4) | 83 (10.3) |
| Hypertension | 23 (2.9) | 11 (1.4) |
| Hypotension | 16 (2.0) | 33 (4.1) |
| Procedural hypertension | 14 (1.8) | 17 (2.1) |
| Procedural hypotension | 14 (1.8) | 23 (2.9) |
| Blood pressure diastolic increased | 1 (0.1) | 0 (0.0) |
| Blood pressure fluctuation | 1 (0.1) | 0 (0.0) |
| Blood pressure systolic increased | 1 (0.1) | 1 (0.1) |

^A The total sugammadex column includes subjects exposed to any of the doses of sugammadex (2, 3, and 4 mg/kg) evaluated in these trials.

The Applicant noted that in the pooled neostigmine-controlled trials, the percent of subjects with markedly abnormal post-baseline SBP values was small and comparable between the sugammadex and neostigmine groups, as indicated in Table 51 below.

Table 51. Summary of markedly abnormal, post-baseline, systolic blood pressure values in pooled neostigmine-controlled trials (Table 108 on p. 293 in Section 5.3.5.3 of the NDA resubmission)

| Parameter | Sugammadex (N=797) | Neostigmine (N=804) |
|--|--------------------|---------------------|
| SBP markedly decreased (n [%] of subjects) | 35 (4) | 36 (4) |
| Minimum SBP value at any timepoint | 65.0 mmHg | 67.0 mmHg |
| SBP markedly increased (n [%] of subjects) | 100 (13) | 127 (16) |
| Maximum SBP value at any timepoint | 237.0 mmHg | 210.0 mmHg |

Based on the analyses they performed, the Applicant concluded that there were no clinically important effects of sugammadex on SBP. In sugammadex-treated subjects who received an NMBA, and a 2 mg/kg or 4 mg/kg dose of sugammadex, there was a tendency for increased SBP at 30 min post-dose. However, at the higher dose of 16 mg/kg, there was a tendency for decreased SBP. The Applicant thought these differences were likely to be artifacts and related to the timing of administration of the study drugs rather than an effect of sugammadex alone.

Comments and Conclusions

The overall differences between sugammadex and placebo as well as between sugammadex and neostigmine were relatively small and not likely clinically relevant as indicated by the Applicant. It was interesting to note that “Procedural Hypotension” and “Procedural Hypertension” both appeared as possibly dose-dependent for sugammadex and both occurred substantially more often following a 16 mg/kg dose of sugammadex than for placebo and lower doses of sugammadex as indicated in Table 48 above. The significance of this finding is not clear, particularly as it involved both hypo- and hypertension.

In addition to the analyses performed for the NDA resubmission, it was considered important to look for both a time- and dose-dependency of any changes in blood pressure and heart rate. To this end, the Applicant was instructed to create tables showing the percent and absolute changes from baseline for both of these vital signs as they were measured during the first minutes following study drug administration. Table 52 and Table 53 below summarize these findings for systolic blood pressure.

Table 52. Mean % changes (absolute changes in mmHg) in systolic blood pressure from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Placebo (N=544) | Sugammadex | | | |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|
| | | 2 mg/kg (N=156) | 4 mg/kg (N=592) | 16 mg/kg (N=38) | Total (N=1078) |
| 2 | 0.0% (-0.6) | 2.5% (1.7) | 2.7% (1.8) | 6.3% (5.2) | 4.1% (3.1) |
| 5 | 9.0% (7.6) | -1.7% (-2.0) | 9.9% (8.6) | * | 7.0% (5.8) |
| 10 | 0.3% (-0.5) | 1.6% (0.7) | 3.6% (2.7) | 3.4% (1.5) | 3.0% (1.8) |
| 30 | 20.3% (17.8) | 11.8% (11.1) | 26.3% (23.4) | 6.3% (4.5) | 17.9% (15.8) |

* No assessments were made at this time point.

Table 53. Mean % changes (absolute changes in mmHg) in systolic blood pressure from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Neostigmine (N=804) | Sugammadex | | |
|--|---------------------|-----------------|-----------------|-----------------|
| | | 2 mg/kg (N=305) | 4 mg/kg (N=491) | Total (N=797) |
| 2 | 5.0% (5.0) | -0.6% (-0.7) | 1.6% (1.6) | 0.3% (0.2) |
| 5 | 7.2% (7.0) | 0.8% (0.7) | 7.1% (6.7) | 4.7% (4.4) |
| 10 | 2.7% (2.3) | 4.8% (4.7) | 4.8% (4.8) | 4.8% (4.7) |
| 30 | 16.7% (16.6) | 12.0% (12.0) | 20.4% (19.8) | 17.2% (16.8) |

These tables suggest there may be a dose-dependent increase in SBP that occurs around 5 minutes following sugammadex administration and resolves by 10 minutes after administration. The increase is less than 10 mmHg for the 2 and 4 mg/kg doses of sugammadex and not known for the 16 mg/kg dose. These changes are not substantially different than those observed for either placebo or neostigmine and are not likely to be clinically relevant.

Both tables indicate substantial increases in the mean SBP and percent changes from baseline at 30 minutes following drug administration for all of the treatment groups. These changes were observed with all treatment groups and all doses of sugammadex (without an apparent dose dependency). It is likely that these

increases reflect the clinical situation at that time, i.e., the patients are being, or have been, weaned from the anesthetic agents in preparation for extubation and transfer to the recovery area. During this period, marked increases in blood pressure and heart rate are not uncommon due to the intense stimulus related to the presence of an endotracheal tube and surgical site pain associated with movement and the possible need for analgesics.

These analyses indicate that the doses of sugammadex proposed for marketing do not alter SBP in a clinically meaningful way either at the end of surgery or during the early stages of anesthetic recovery.

Diastolic Blood Pressure

The analyses conducted by the Applicant for diastolic blood pressure were the same as those they performed for systolic blood pressure.

In the Pooled Placebo-controlled trials, the Applicant reported that the overall percentage of subjects with treatment-emergent markedly abnormal DBP values was small and similar between the two treatment groups regardless of timepoint as indicated in Table 54 below. They also reported that the incidence of AEs related to abnormalities of DBP was low overall, and the differences in incidence between the sugammadex group and the placebo group were not clinically relevant (the data for these findings were summarized and incorporated into Table 48 above).

Table 48

Table 54. Summary of markedly abnormal, post-baseline, diastolic blood pressure values in pooled placebo-controlled trials (Table 110 on p. 296 in Section 5.3.5.3 of the NDA resubmission)

| Parameter | Sugammadex (N=1078) | Placebo (N=544) |
|--|---------------------|-----------------|
| DBP markedly decreased (n [%] of subjects) | 40 (4) | 15 (3) |
| Minimum DBP value at any timepoint | 20.0 mmHg | 24.0 mmHg |
| DBP markedly increased (n [%] of subjects) | 93 (9) | 51 (9) |
| Maximum DBP value at any timepoint | 122.0 mmHg | 125.0 mmHg |

In the Pooled Neostigmine-controlled trials, the Applicant reported that the overall percentage of subjects with treatment-emergent markedly abnormal DBP values was small and similar between the two treatment groups regardless of timepoint. These data are summarized in Table 55 below. The incidence of AEs related to abnormalities of DBP was low overall, and the differences in incidence between the sugammadex group and the neostigmine group were not clinically relevant. The data for these findings were summarized and incorporated into Table 50 above.

Table 55. Summary of markedly abnormal, post-baseline, diastolic blood pressure values in pooled neostigmine-controlled trials (Table 111 on p. 297 in Section 5.3.5.3 of the NDA resubmission)

| Parameter | Sugammadex (N=797) | Neostigmine (N=804) |
|--|--------------------|---------------------|
| DBP markedly decreased (n [%] of subjects) | 25 (3) | 24 (3) |
| Minimum DBP value at any timepoint | 24.0 mmHg | 20.0 mmHg |
| DBP markedly increased (n [%] of subjects) | 66 (8) | 64 (8) |
| Maximum DBP value at any timepoint | 151.0 mmHg | 131.0 mmHg |

The Applicant concluded that sugammadex does not affect DBP in a clinically relevant way.

Comments and Conclusions

As was the case for SBP, the overall differences between sugammadex and placebo as well as between sugammadex and neostigmine for DBP were relatively small and not likely clinically relevant as indicated by the Applicant. The approach used to assess any time- or dose-dependent effects of

sugammadex on SBP was also applied to DBP. Table 56 and Table 57 below summarize the mean percent and mean absolute value changes from baseline for DBP during the first 30 minutes following study drug administration and for the doses of sugammadex proposed for marketing.

Table 56. Mean % changes (absolute changes in mmHg) in diastolic blood pressure from baseline in the pooled placebo-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Placebo (N=544) | Sugammadex | | | |
|--|-----------------|-----------------|-----------------|-----------------|----------------|
| | | 2 mg/kg (N=156) | 4 mg/kg (N=592) | 16 mg/kg (N=38) | Total (N=1078) |
| 2 | 0.6% (-0.2) | 6.8% (2.9) | 1.7% (0.2) | 9.3% (4.1) | 5.6% (2.2) |
| 5 | 11.6% (5.1) | -0.9% (-1.3) | 10.7% (4.8) | * | 7.8% (3.3) |
| 10 | 1.6% (0.1) | 4.1% (1.3) | 3.1% (0.8) | 6.2% (1.6) | 3.9% (1.1) |
| 30 | 20.5% (9.2) | 13.3% (6.5) | 24.2% (11.2) | 5.9% (1.9) | 17.4% (7.9) |

* No assessments were made at this time point.

Table 57. Mean % changes (absolute changes in mmHg) in diastolic blood pressure from baseline in the pooled neostigmine-controlled trials (provided by Applicant on 8/9/13)

| Time After Study Drug Administration (minutes) | Neostigmine (N=804) | Sugammadex | | |
|--|---------------------|-----------------|-----------------|-----------------|
| | | 2 mg/kg (N=305) | 4 mg/kg (N=491) | Total (N=797) |
| 2 | 5.6% (3.2) | -1.1% (-0.9) | 1.1% (0.4) | -0.2% (-0.4) |
| 5 | 6.8% (3.3) | 1.0% (0.3) | 5.9% (2.7) | 4.0% (1.8) |
| 10 | 0.6% (-0.3) | 5.9% (2.9) | 3.2% (1.2) | 4.9% (2.3) |
| 30 | 13.0% (6.6) | 12.7% (6.8) | 18.6% (9.2) | 16.3% (8.3) |

Both of the tables indicate that there is an increase in DBP at 5 minutes following sugammadex administration, as was observed for SBP. The changes are small, less than 5 mmHg, for the 2 and 4 mg/kg doses and not known for the 16 mg/kg dose. These changes are not substantially different than those observed for either placebo or neostigmine and are not likely to be clinically relevant.

As was observed for SBP, both tables indicate substantial increases in the mean DBP and percent changes from baseline at 30 minutes following drug

administration for all three treatments. These changes likely reflect the clinical setting and not an effect of the treatments.

These analyses indicate that the doses of sugammadex proposed for marketing do not alter DBP in a clinically meaningful way either at the end of surgery or during the early stages of anesthetic recovery.

Heart Rate

Safety related to bradycardia and tachycardia is addressed in Section 7.3.5.3 above with other cardiac issues.

Respiratory Rate

The Applicant reported that for the pooled Phase 1-3 trials, in the Total sugammadex group, mean baseline respiratory rate was 14 breaths per minute (bpm), and median baseline respiratory rate was 13 bpm. Mean and median baseline values across the dose groups ranged from 13 bpm to 17 bpm (mean) and from 12 bpm to 16 bpm (median). Mean and median changes from baseline to the final visit were small, and no dose trend was apparent for change from baseline.

In the pooled Phase 1-3 trials, no dose trends were apparent for the AEs related to abnormalities of respiratory rate, which are summarized in Table 58 below.

Table 58. Number (%) of Exposures Associated with Adverse Events for Respiratory Rate Abnormalities in Pooled Phase 1-3 Trials by PT in Order of Decreasing Incidence in the Total Sugammadex Group (Table 117 on p. 303 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | (Placebo) (N=544) | Sugammadex | | | |
|----------------------------|----------------------|--------------------|---------------------|--------------------|--------------------------------|
| | | 2 mg/kg (n=838) | 4 mg/kg (n=1798) | 16 mg/kg (n=98) | Total ^A (N=3407) |
| At least one AE | 0 (0.0) | 3 (0.4) | 4 (0.2) | 0 (0.0) | 18 (0.5) |
| Respiratory rate decreased | 0 (0.0) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 6 (0.2) |
| Bradypnoea | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 4 (0.1) |
| Hyperventilation | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| Hypoventilation | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 3 (0.1) |
| Respiratory rate increased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Tachypnoea | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |

^A Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

In the pooled neostigmine-controlled trials, the Applicant noted that the incidences of AEs related to respiratory rate abnormalities were similar between the neostigmine-treated group and sugammadex-treated groups and occurred at most in 0.2% of subjects as shown in Table 59 below.

Table 59. Number (%) of exposures associated with adverse events in pooled neostigmine-controlled trials by pt in order of decreasing incidence in the total sugammadex group (from Table 119 on p. 305 in Section 5.3.5.3 of the NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex (N=797) | Neostigmine (N=804) |
|----------------------------|--|------------------------|
| At least one AE | 1 (0.1) | 2 (0.2) |
| Respiratory rate decreased | 1 (0.1) | 0 (0.0) |
| Hypoventilation | 0 (0.0) | 2 (0.2) |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

Comments and Conclusions

Sugammadex had no apparent clinically relevant effect on respiratory rate and was no different in this regard than placebo or neostigmine. It is interesting to note that hypoventilation was so rarely reported for any of the treatments. Given the respiratory depressant effects of many of the anesthetic agents and narcotics used postoperatively for analgesia and the slower recovery from neuromuscular blockade with placebo and neostigmine, it would not have been unexpected to observe more reports of hypoventilation, if only in those two treatment groups. To some extent this may be explained by the timing of the assessments. At 2 and 5 minutes following study drug administration, many of the subjects were likely to still be intubated; by 30 minutes after the study drug, most of the anesthetic agents and the neuromuscular blocking agent would not have a major impact on ventilation; thereby leaving the 10 minute assessment as the one in which subjects might be most vulnerable.

Body Temperature

The Applicant reported that there were no apparent dose trends for the AEs related to abnormalities of core body temperature (CBT) in the pooled clinical trials. The AEs are summarized in Table 60 below. Incidences of pyrexia were higher in the sugammadex exposures than in placebo exposures. “Chills” was the only other AE with at incidence of at least 1%.

Table 60. Number (%) of exposures associated with adverse events in pooled phase 1-3 trials in order of decreasing incidence in the total sugammadex group (table 120 on p.306 in section 5.3.5.3 of the NDA resubmission).

| MedDRA Preferred Term | Placebo | Sugammadex | | | |
|-----------------------------|----------|------------|-----------|----------|--------------------|
| | | 2 mg/kg | 4 mg/kg | 16 mg/kg | Total ^A |
| | N=544 | n=838 | n=1798 | n=98 | N=3407 |
| At least one AE | 32 (5.9) | 101 (12.1) | 150 (8.3) | 8 (8.2) | 319 (9.4) |
| Pyrexia | 17 (3.1) | 68 (8.1) | 98 (5.5) | 5 (5.1) | 206 (6.0) |
| Chills | 13 (2.4) | 26 (3.1) | 39 (2.2) | 4 (4.1) | 86 (2.5) |
| Body temperature increased | 0 (0.0) | 4 (0.5) | 8 (0.4) | 0 (0.0) | 13 (0.4) |
| Feeling cold | 1 (0.2) | 3 (0.4) | 10 (0.6) | 0 (0.0) | 13 (0.4) |
| Postoperative fever | 1 (0.2) | 6 (0.7) | 2 (0.1) | 0 (0.0) | 13 (0.4) |
| Feeling hot | 0 (0.0) | 2 (0.2) | 1 (0.1) | 0 (0.0) | 6 (0.2) |
| Feeling of body temperature | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Hypothermia | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 2 (0.1) |
| Body temperature | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Body temperature decreased | 0 (0.0) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Hyperthermia | 1 (0.2) | 0 (0.0) | 1 (0.1) | 0 (0.0) | 1 (0.0) |
| Temperature intolerance | 0 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) | 1 (0.0) |

^A Total column includes subjects exposed to all doses of sugammadex (<2, 2, 3, 4, 6, 8, 12, 16, 20 and 32 mg/kg).

The Applicant noted that incidences of pyrexia and chills were similar between the placebo-treated group and the sugammadex-treated groups in the pooled placebo-controlled trials, i.e., 17 (3.1%) versus 44 (4.1%) and 13 (2.4%) versus 25 (2.3%), respectively.

Similarly, the Applicant noted that the incidences of AEs were not substantially different between the neostigmine treated group and sugammadex treated groups as indicated in Table 61 below.

Table 61. Number (%) of exposures associated with adverse events for body temperature abnormalities in pooled neostigmine-controlled trials by preferred term in order of decreasing incidence in the total sugammadex group (Table 122 on p. 308 of Section 5.3.5.3 in the NDA resubmission)

| MedDRA Preferred Term | Total ^A Sugammadex N=797 | Neostigmine N=804 |
|-----------------------|--|----------------------|
|-----------------------|--|----------------------|

| | | |
|----------------------------|----------|----------|
| At least one AE | 71 (8.9) | 59 (7.3) |
| Pyrexia | 56 (7.0) | 45 (5.6) |
| Chills | 14 (1.8) | 12 (1.5) |
| Body temperature increased | 3 (0.4) | 2 (0.2) |
| Feeling cold | 2 (0.3) | 1 (0.1) |

^A Total column includes subjects exposed to all doses of sugammadex (2, 3 and 4 mg/kg).

Comments and Conclusions

It is not clear why there was an increased incidence of pyrexia with sugammadex treatment for the pooled Phase 1-3 trials. That the difference is not observed when the data are split into the pooled placebo-controlled and neostigmine-controlled trials suggests it was an artifact of data pooling and not a sugammadex-related AE. The possible impact this finding may have on the product's safety is also mitigated by the lack of dose dependency for pyrexia in the pooled trial dataset. Otherwise, sugammadex had no apparent effect on core body temperature compared to placebo and neostigmine.

Overall Summary and Conclusions

Despite a near doubling of the safety database, the updated vital signs data analyses do not indicate any substantial changes in the overall safety of sugammadex compared to that observed with the data contained in the original NDA submission. The various analyses of the vital signs data related to blood pressure, respiratory rate and core body temperature do not indicate that sugammadex, at the doses proposed for clinical use, poses a clinically relevant risk that would affect any of these parameters.

7.4.4 Electrocardiograms (ECGs)

All issues related to ECG data are addressed in Section 7.3.5.3 above.

7.4.5 Special Safety Studies/Clinical Trials

The special safety studies conducted to address the deficiencies noted in the Complete Response letter are reviewed in Section 7.3.5 above.

7.4.6 Immunogenicity

Although sugammadex is not a therapeutic protein, the occurrence of anaphylactic reactions in several of the clinical trials led to the product being investigated for potential immunogenic properties. The findings of those investigations are summarized in Section 7.3.5.1 of this review, which also includes a summary of the input provided by the Division of Pulmonary, Allergy, and Rheumatology Products regarding this issue.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency is described in greater detail in the adverse events and serious adverse events sections above. Dysgeusia and possibly anaphylaxis are sugammadex-dose dependent.

7.5.2 Time Dependency for Adverse Events

Most adverse events occurred within 12 hours of sugammadex administration in the pooled placebo-controlled studies with 42% of AEs occurring between 1 and 12 hours following administration of sugammadex, which was similar to the 48% for placebo treatment reported in the same timeframe. After 24 hours, the incidence of AEs was 37% with sugammadex but 52% for placebo treatments. The findings were similar in the pooled neostigmine-controlled studies.

7.5.3 Drug-Demographic Interactions

The Applicant performed an evaluation of AE incidence rates for sugammadex and its comparators by the sub-populations of age, race, gender, and ethnicity for the pooled datasets by treatment group. The intrinsic factor groups were defined as:

- Age (<65 year vs. ≥65 year)
- Gender (male vs. female)
- Race (Caucasian vs. non-Caucasian)
- Ethnicity (Hispanic or Latino vs. non-Hispanic or Latino)

The Applicant's findings are reported below.

Age

The majority of reported AE incidences were not clinically significantly different between the sugammadex and placebo groups or between the age groups. There is an increase in incidence of most AEs with increasing age. This difference occurred in both the sugammadex and the placebo treatment groups. For example, procedural pain was the most frequently reported AE, and it was reported more frequently for subject exposures ≥65 years of age in the sugammadex group (45%) and the placebo group (38%) than for subject

exposures <65 years of age at 30% and 26% in the sugammadex and placebo groups, respectively.

Gender

More incidences of AEs occurred in females than males, however they were evenly distributed between the sugammadex and placebo treatment groups. Overall there were no clinically relevant differences in AEs reported between genders.

Race

There were too few subject exposures in the non-Caucasian placebo group (n=31) to make meaningful comparisons with this group. No clinically meaningful differences between sugammadex and placebo were observed with respect to Caucasian exposures. Compared to neostigmine, for most AEs, incidences were higher for Caucasian subjects than for non-Caucasian subjects, but these were reported evenly between treatment groups.

Ethnicity

Only comparisons of non-Hispanic ethnicity between treatment groups could be made due to the small sample sizes in the Hispanic/Latino groups. Between the sugammadex and placebo treatment groups, there were similar incidences of AEs for the non-Hispanic/Latino exposures.

A review of the data tables used by the Applicant to generate the findings above determined them to be accurate. In summary, older, Caucasian, and female demographics were associated with higher incidence rates for adverse events compared to their counterparts; however, within any demographic subgroup there was no substantial difference in the incidence rates of AEs by treatment.

7.5.4 Drug-Disease Interactions

The effects of sugammadex were studied on individuals with renal impairment (mild to severe), hepatic impairment, cardiac conditions and pulmonary conditions. None of the studies indicated an exacerbation or worsening of the subject's underlying condition, and there was no indication from the data that a dose adjustment of sugammadex was necessary for patients with any of these conditions.

7.5.5 Drug-Drug Interactions

Drug-drug interactions relate to its pharmacodynamics: the complex formation with other molecules. Therefore, there are three types of drug-drug interactions that can occur, alone or in combination:

1. Uptake by sugammadex of a co-administered non-NMBA drug resulting in reduced free concentration of this co-administered drug
2. Preferential binding of sugammadex to a non-NMBA molecule resulting in diminished sugammadex-NMBA complex formation and a reduced NMB reversal effect of sugammadex
3. Displacement of bio-inactivated NMBA from the sugammadex-NMBA complex by another molecule, leading to potential recurrence of NMBA activity and risk of recurrent NMB

The Applicant has conducted four drug-drug interaction trials since the original submission to investigate these possible interactions. The findings are summarized below:

1. Toremifene has a relatively high binding affinity for sugammadex; it may also have a relatively high plasma concentration such that some displacement of vecuronium or rocuronium from sugammadex might occur.
2. The interaction between 4 mg/kg of sugammadex and a progestogen was predicted to lead to a decrease in progestogen exposure (34% of AUC) similar to the decrease seen when a daily dose of an oral contraceptive is taken 12 hours too late, which might lead to a reduction in effectiveness, i.e., the equivalent to one missed daily dose of oral contraceptives containing a progestogen. Non-oral contraceptives are also affected, and the Applicant recommends use of a non-hormonal contraceptive for 7 days following sugammadex administration.
3. There was no clinically relevant displacement of NMBA observed after administration of high doses of flucloxacillin (not approved in the U.S.).

In addition to the above, no clinically relevant interactions were reported during the clinical trials.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity studies were not required of this product due to the acute indication and the relatively short half-life. Although sugammadex is absorbed by bone, the amount absorbed in adults is small, and the duration of its presence in bone is short enough that preclinical and clinical assessments of carcinogenicity were not indicated.

7.6.2 Human Reproduction and Pregnancy Data

There are no human reproduction or pregnancy data available for sugammadex.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessments of the effects of sugammadex on growth were made as a pediatric indication is not sought at present.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

An overdose of sugammadex would be considered a dose greater than that required to reverse the level of neuromuscular blockade present at the time of administration. Alternatively, a dose greater than the to-be-labeled maximum dose (16 mg/kg) could be considered as an overdose. In a human tolerance trial, sugammadex was reported to be well tolerated at doses up to 96 mg/kg. The only adverse events that appeared to be dose related were dysgeusia and possibly anaphylaxis. Overall, the risk from overdose is small, and the most serious reaction, anaphylaxis, is one for which the patient can be monitored and readily treated, if necessary.

Sugammadex is administered in a controlled setting by medical professions to patients who are unconscious. In addition, sugammadex does not readily cross the blood-brain barrier, is not structurally similar to known drugs of abuse, and undergoes relatively rapid systemic clearance. In the clinical trials, there was no evidence of behavioral changes or alterations in mood or mentation. All of these factors would indicate that it has low abuse potential.

Sugammadex is used acutely, and its pharmacodynamic activity is not associated with physical or psychological dependence. Therefore, it is not expected to be associated with either withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

There were multiple requests for information that were issued to the Applicant during this review cycle. The information provided in response was incorporated into this review in the appropriate sections. There was no safety update provided at the 120-day point of this review cycle.

There were no new safety issues identified with the NDA resubmission and no outstanding safety issues that the Applicant failed to address.

8 Postmarket Experience

The post marketing safety reports submitted by the Applicant are discussed in Section 7 above. It should be noted that the Applicant submitted only serious unlabeled event reports to the IND and in this submission. A request for all postmarketing reports resulted in 654 reports being submitted. The Applicant indicated that it was not possible to provide the reports in a searchable data format.

A review of the reports indicated that the largest percentage related to anaphylactic reactions with cardiovascular changes occurring second most frequently; although the difference was substantial for the two. Given the limitations of postmarketing reports in terms of the data submitted, the rates at which they are under reported, and the lack of accurate numbers of exposures, a qualitative assessment was the best that could be made. In that regard, the postmarketing reports were consistent with adverse events reported in the clinical trails, with the exception that bradycardia, sometimes severe and leading to cardiac arrest was reported in the postmarketing safety database but not in the clinical trial database. Otherwise, there was no indication of a new safety signal in the review of these events.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

Labeling recommendations were made in the sections above. Specific edits will be made with other disciplines prior to the start of labeling negotiations with the Applicant.

9.3 Advisory Committee Meeting

The advisory committee meeting scheduled for this cycle was cancelled do to concerns over the validity of study P06042, which is pivotal for characterizing the risk profile of sugammadex and for which the advisory committee's expert input was considered essential prior to a regulatory action being taken.

9.4 Reviews of Individual Clinical Studies

The key clinical studies for this submission are discussed in Sections 6 and 7 above.

9.5 Post Marketing Safety Reports Received Since the Original NDA Submission

Postmarketing reports are discussed in Section 8 above.

9.6 Consultations

9.6.1 Consultations Related to Anaphylaxis and Hypersensitivity

The consultations are arranged chronologically beginning with those from the original NDA submission.

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: 5/13/05

To: Arthur Simone, M.D., Ph.D., Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Charles E. Lee, M.D., Medical Team Leader
Division of Pulmonary and Allergy Products, HFD-570

Through: Badrul A. Chowdhury, M.D., Ph.D., Director
Division of Pulmonary and Allergy Products, HFD-570

Subject: Medical Officer consultation regarding anaphylaxis adverse events
occurring with sugammadex sodium

General Information

NDA/IND#: NDA 22-225, N-000,
IND 68,029, N-088, 2/27/08

Sponsor: Organon USA, Inc.

Drug Product: Bridion (sugammadex sodium)

Request From: Allison Meyer, Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products

Date of Request: 2/27/08

Date Received: 4/8/08

Materials: Consultation request

Reviewed: IND submission
FDA background and slides, Anesthetics and Life Support Drugs
Advisory Committee Meeting, 3/11/08

1. EXECUTIVE SUMMARY

Adverse events suggestive of anaphylaxis and drug hypersensitivity occurred during the clinical development program for sugammadex sodium. The sponsor recently submitted information that identified 7 subjects who had such adverse events. Two of these subjects met recently proposed diagnostic criteria for anaphylaxis. There were 1973 adults and 51 children exposed during the clinical development program for sugammadex, representing an incidence of anaphylaxis of 0.1%.

The sponsor conducted a skin test study with previously exposed and unexposed control patients to characterize these reactions. Of the twelve patients who were previously exposed to sugammadex, two had positive skin tests (8.3%), one who had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. There were no unexposed subjects who had a positive skin test; sugammadex does not produce a non-specific positive skin test. This information suggests that exposure to sugammadex may induce sensitization and production of sugammadex-specific IgE in a percentage of those exposed. Such patients would be at risk for development of anaphylaxis if re-exposed to sugammadex.

The sugammadex drug development plan did not evaluate the safety of subsequent or repeated exposure to the drug. This is of particular concern, since wide use is anticipated and one can expect that some patients will be exposed more than once. As noted above, it appears that the product induces sensitization and production of sugammadex-specific IgE in a percentage of those exposed. It is likely that some of these sensitized patients would develop anaphylaxis or allergic reaction with subsequent exposure. The magnitude of this risk or the predictive value of skin testing in identifying patients who are at risk of such a reaction with re-exposure cannot be determined with the available information.

It is expected that the product will be used in an operating room setting, which may mitigate some risk from anaphylaxis if the event is recognized and treated appropriately. Labeling the product that it should be used only for anesthesia emergencies may increase the risk/benefit balance for the drug, but may not be practical. Labeling the product that it should only be used once may be an appropriate approach to addressing the risk from repeat exposure until studies may be conducted to evaluate this risk.

We recommend that DARRP ask the sponsor to develop in vitro tests of sugammadex-specific IgE, IgG, IgM in order to further characterize the mechanism for these reactions. In addition, there would be benefit in asking the sponsor to evaluate the risk for reaction among subjects with subsequent exposure, both in a general population and in a population of patients who have positive skin tests to sugammadex. It would be essential to define this risk of reaction before it is widely used and patients are exposed on multiple occasions.

2. BACKGROUND

Sugammadex sodium is a modified gamma-cyclodextrin proposed for the indication of reversal of neuromuscular blockade. It forms a high affinity inclusion complex with the neuromuscular blocker rocuronium, thereby preventing its binding at the neuromuscular junction and allowing renal excretion of the complex. Sugammadex is a NME, the NDA is a priority review, and the drug considered an important advance in anesthesia drugs. It is likely to be very widely used once approved. The product is not approved in any country. The Anesthetics and Life Support Drugs Advisory Committee met on March 11, 2008 and unanimously recommended approval of sugammadex for marketing.

Adverse events suggestive of anaphylaxis and drug hypersensitivity occurred during the clinical development program for sugammadex sodium. The sponsor recently submitted information that identified 7 subjects who had such adverse events. There were 1973 adults and 51 children exposed during the clinical development program for sugammadex [IND 68,029, N-088, 2/27/08, pages 34-35]. The adverse events are summarized below:

- 12 (8)/ 19.4.106 – paresthesia, visual disturbance, nausea, rash, palpitations, tachycardia, stomach discomfort, flushing, onset within one minute, increased serum tryptase, positive intradermal skin test, (IDT)
- 17 (1)/19.4.105 – nasal congestion, globus sensation, need to sneeze, onset not noted
- 18 (28)/ 19.4.105 – palpitations, tachycardia, ventricular extrasystoles, bigeminy, flushing, increased respiratory rate, onset within 30 minutes
- 19 (73)/ 19.4.109 – metallic taste, burning and warm sensation of body, nausea, abdominal cramps, rash on arm on side of infusion, onset within 2 minutes
- 20 (30)/ 19.4.105 – paresthesias, feeling warm in arms and legs, globus sensation, difficulty breathing, tachycardia, flush, abnormal auscultation (does not note what was ausculted), rash on forearms, onset within 2 minutes
- 21 (24)/19.4.105 – bitter taste, papules on neck, onset not noted
- (7)/19.4.105 – rash on upper part of body, onset after one day

Reviewer comments:

Anaphylaxis is a clinical syndrome characterized by acute onset of an illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems. Clinical criteria for the diagnosis of anaphylaxis have recently been proposed.^{1, 2} The recently proposed criteria focus on clinical presentation and not on mechanism. These clinical criteria will be used for this consultation.

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

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)*

2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*
 - a. *Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)*
 - b. *Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)*
 - c. *Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)*
 - d. *Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)*
3. *Reduced BP after exposure to known allergen for that patient (minutes to several hours):*
 - a. *Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. *Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline*

Based on the above criteria, there are two cases that meet the diagnostic criteria for anaphylaxis: Subjects 12 (8)/ 19.4.106 and 20 (30)/ 19.4.105. There were 1973 adults and 51 children exposed during the clinical development program for sugammadex, therefore representing an incidence of anaphylaxis of 0.1% (2/2024).

Because of the concerns raised by these adverse events, the sponsor conducted a clinical study designed to evaluate skin prick test and intradermal skin tests of sugammadex in healthy volunteers that were not previously exposed to the product and in individuals previously exposed to sugammadex, both with and without clinical symptoms of hypersensitivity with exposure.

This consultation briefly reviews the skin test clinical study and addresses questions presented by DAARP.

3. CLINICAL TRIAL, PROTOCOL 19.4.110

3.1. Title

Active and placebo controlled study with an open-label part to evaluate the skin prick and intradermal tests with sugammadex in a control group and a single-blind part to investigate the alleged hypersensitive reactions of selected volunteers [page 12]

3.2. Study outline

This study was conducted as a single center, placebo-controlled study to investigate the hypersensitivity against sugammadex, via skin prick test (SPT) and intradermal tests (IDT). The study consisted of two phases, an open label control phase (Phase A) and a single-blind testing phase (Phase B). Three groups of subjects were enrolled [page 12]:

- Subjects who were not previously exposed to sugammadex (Phase A)
- Subjects who were previously exposed to sugammadex without clinical symptoms of hypersensitivity to sugammadex (control subjects of Phase B)

- Subjects who were previously exposed to sugammadex with clinical symptoms indicative of hypersensitivity to sugammadex (Phase B)

In Phase A, there were 11 subjects who received SPTs and 9 subjects that received IDTs. In Phase B, there were 12 subjects who received SPTs and 11 subjects that received IDTs. Phase A was unblinded. The investigator was blinded to the prior history of reaction to sugammadex in Phase B [page 48].

3.3. Inclusion criteria

Inclusion criteria follow below [page 41]:

- Subject is male or female and at least 18 and not older than 65 years of age at the day of the first testing
- Subject is able and willing to sign the informed consent form prior to screening

3.4. Exclusion criteria

Exclusion criteria follow below [pages 41-42]:

- Known drug allergy for subjects in Phase A and control subjects in Phase B
- Previous exposure to sugammadex for subjects included in Phase A
- Medication or drug use of any kind within two weeks of the first test (including OTC and excluding vitamins and trace elements), except for paracetamol and oral contraceptives, if applicable
- Use of injectable steroids during the last 6 weeks, oral steroids during the last month, antihistamines, psychotropic drugs or beta-adrenergic blocking agents during the last 5 days, local steroids during the last 7 days or topical corticosteroids applied to the forearm during the last 2 weeks
- Moderate or highly pigmented skin, sun tan or eczematous skin, to an extent that would make the determination of wheals and flares impossible
- Clinically relevant finding in the medical history, vital signs assessment, physical examination or clinical laboratory which may influence the study results
- Positive pregnancy tests
- Female subjects of childbearing potential not using any method of birth control or using only hormonal contraception as birth control
- Positive test results on hepatitis B surface antigen or hepatitis C antibody
- Positive test results on HIV 1/2 serology
- Positive drug or alcohol screen results
- Current participation in other clinical studies or having participated in a clinical study from 30 days prior to first dosing

3.5. Study treatments and skin test procedures

SPTs (percutaneous prick of drop applied to volar surface of arms) [pages 43-45]:

- Saline negative control and histamine 10 mg/mL positive control
- Sugammadex titrated SPTs with the following dilutions and concentrations:

| | |
|----------|------------|
| 1:10,000 | 0.01 mg/mL |
| 1:1000 | 0.1 mg/mL |
| 1:100 | 1.0 mg/mL |

| | |
|------|----------|
| 1:10 | 10 mg/mL |
| 1:1 | 50 mg/mL |

The mean diameter of the wheals after application of histamine positive control had to be at least 4 mm. Furthermore, the mean wheal diameter of the negative control had to be smaller than 3 mm and less than 50% of the mean wheal diameter after histamine application. The SPT with sugammadex was considered to be positive when a flare was present and the mean diameter of the wheals was at least 75% of the mean diameter of the wheals after histamine application [pages 50-52].

IDTs (0.03 mL intradermally to volar surface of arms) [page 45]:

- Saline negative control and histamine 0.01 mg/mL positive control
- Sugammadex titrated IDTs with the following dilutions and concentrations:

| | |
|-----------|-------------|
| 1:100,000 | 0.001 mg/mL |
| 1:10,000 | 0.01 mg/mL |
| 1:1000 | 0.1 mg/mL |
| 1:100 | 1.0 mg/mL |
| 1:10 | 10 mg/mL |
| 1:1 | 50 mg/mL |

The mean diameter of the wheals after application of histamine had to be at least 8 mm. Furthermore, the mean wheal diameter of the negative control had to be smaller than 5 mm and less than 50% of the mean wheal diameter after histamine application. The IDT with sugammadex was considered to be positive when a flare was present and the mean diameter of the wheals was at least 75% of the mean diameter of the wheals after histamine application [pages 51-52].

The sponsor presented descriptive statistics for ratios of mean wheal diameters due to highest concentration of sugammadex over the mean wheal diameter of histamine. In addition, the sponsor performed a quantitative analysis of sugammadex hypersensitivity status of the previously exposed hypersensitive subjects considering each subject's highest sugammadex concentration for the SPT and for the IDT. Hypersensitivity was assumed if the reaction of the mean wheal diameter after sugammadex treatment over the mean wheal diameter of histamine exceeded the upper limits for SPT and IDT with sugammadex for the calculated 95% tolerance interval [page 64].

Penicillin skin testing was to be performed in any subject that had a positive SPT or IDT to sugammadex to evaluate possible cross reactivity [page 57].

Serum tryptase and urine methylhistamine samples were drawn prior to skin testing in Phase 2. Serum tryptase could be repeated 30 minutes after the last IDT and urine methylhistamine could be repeated 1 hour after the last IDT at the investigator's discretion [page 56].

3.6. Results

3.6.1. Phase A

There were 11 previously unexposed control subjects enrolled and tested in Phase A. Of the 11, none had a positive SPT result to sugammadex.

IDTs were performed in 9 of 11 previously unexposed control subjects. Two subjects discontinued and did not have IDTs. One discontinued because of adverse events (headache and vomiting) and another had a negative control on IDT that exceeded the maximum of 5 mm. None of the 9 previously unexposed control subjects had a positive IDT to sugammadex [pages 73, 79].

3.6.2. Phase B

There were 12 previously exposed subjects enrolled in and tested in Phase B. There were 6 control subjects who were previously exposed to sugammadex and had no history of hypersensitivity symptoms and 6 subjects who were previously exposed to sugammadex who had symptoms suggestive of hypersensitivity [pages 73, 79]. None of the 12 subjects had a positive SPT.

During the IDT after the application of the negative control NaCl Subject 19, alleged hypersensitive subject, presented a mean wheal diameter, which exceeded the pre-defined limit of 5 mm for the negative control and discontinued the study. Therefore, intradermal tests with sugammadex were performed for five of six alleged hypersensitive subjects and for all six control subjects [page 80].

Two subjects, one control subject and one alleged hypersensitive subject, had positive IDTs to sugammadex. Subject 22, of the control subgroup, had positive IDTs to sugammadex at concentrations of 0.001 mg/mL and 0.01 mg/mL. This subject was previously tested to sugammadex in a previous study and had a positive skin test at that time, as well. Subject 12, of the alleged hypersensitive subgroup, had a positive IDT to sugammadex at the concentration of 1 mg/mL [page 80].

Both Subjects 22 and 12 had tryptase and urine methylhistamine levels were performed after testing. Both subjects had negative serum tryptase levels. Subject 22, of the control subgroup, had increased urine methylhistamine levels at baseline and post-skin testing. Subject 12, of the alleged hypersensitivity subgroup, had negative methylhistamine levels at baseline and post-skin testing.

Reviewer comment:

The sponsor theorized that this Subject 22 may have had a false positive skin test, based on the elevated urine methylhistamine levels and the potential that increased levels of histamine may predispose to false positive results. It would be more appropriate to conclude that this is a true positive skin test in a patient that was sensitized with prior exposure to sugammadex, particularly in light of the low concentrations of sugammadex that produced the positive skin test.

The sponsor conducted a quantitative evaluation of SPT and IDT results from Phase B [pages 81-85]. The subjects identified as being sensitive to sugammadex with the quantitative evaluation were the same as those identified with the descriptive evaluation discussed above, Subjects 22 and 12.

Reviewer comment:

The quantitative evaluation of SPT and IDT results do not add any additional information over the descriptive clinical evaluation.

Both Subjects 22 and 12 had penicillin skin testing to assess potential cross-reactivity with sugammadex. Penicillin skin testing was negative for both subjects [page 87].

Reviewer comment:

It is not possible to comment on the penicillin skin testing results since descriptions of the skin testing materials and procedure are not provided. Penicillin skin testing would not address the possibility that cross-reactivity of sugammadex to other agents occurs.

3.7. Sponsor conclusions

The sponsor concluded that, based on the SPT and IDT results, Subject 22 was hypersensitive to sugammadex. This subject had previously tested positive to sugammadex in a previous study. One control subject, who was previously exposed to sugammadex without previous clinical allergy symptoms, had a positive IDT to sugammadex. The sponsor concluded that this may indicate a false positive IDT because the subject had increased and comparable levels of urine methylhistamine at baseline and post treatment. The sponsor also concluded that the results do not indicate cross reactivity between sugammadex and penicillin.

4. DISCUSSION

Adverse events suggestive of anaphylaxis and drug hypersensitivity occurred during the clinical development program for sugammadex sodium. The sponsor recently submitted information that identified 7 subjects who had such adverse events. Two of these subjects met recently proposed diagnostic criteria for anaphylaxis. There were 1973 adults and 51 children exposed during the clinical development program for sugammadex, representing an incidence of anaphylaxis of 0.1%.

The sponsor conducted skin testing to evaluate the potential mechanism for these reactions. Skin testing, if properly performed, represents an in vivo test for specific IgE. The predictive value of skin testing in identifying patients who will develop anaphylaxis with subsequent exposure varies, depending on the drug and the clinical history of the patient.^{3, 4}

The sponsor's skin testing procedures, both SPT and IDT, were appropriate. Appropriate controls and a titrated skin test procedure that used a wide range of concentrations of drug were employed. Appropriate subjects were enrolled for the study, including normal unexposed subjects, exposed subjects with no history of reaction, and exposed with a history suggestive of anaphylaxis. The sponsor's criteria for a positive skin test were

appropriate and their descriptive clinical evaluation of skin test results was appropriate. The sponsor's quantitative evaluation of skin test results does not provide any additional useful information, other than to validate the results of the descriptive evaluation.

Of the twelve patients who were previously exposed to sugammadex, two had positive skin tests (8.3%), one who had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. There were no unexposed subjects who had a positive skin test; sugammadex does not produce a non-specific positive skin test. This information suggests that exposure to sugammadex may induce sensitization and production of sugammadex-specific IgE in a percentage of those exposed. Such patients would be at risk for development of anaphylaxis if re-exposed to sugammadex.

The sugammadex drug development plan did not evaluate the safety of subsequent or repeated exposure to the drug. This is of particular concern, since wide use is anticipated and one can expect that some patients will be exposed more than once. As noted above, it appears that the product induces sensitization and production of sugammadex-specific IgE in a percentage of those exposed. It is likely that some of these sensitized patients would develop anaphylaxis or allergic reaction with subsequent exposure. The magnitude of this risk or the predictive value of skin testing in identifying patients who are at risk of such a reaction with re-exposure cannot be determined with the available information.

The patient with a positive skin test and a previous history of anaphylaxis developed anaphylaxis with the first exposure to the drug. The mechanism for reaction with first exposure is unclear and may come from nonspecific histamine release from drug, complement activation from the drug or drug-rocuronium complexes, or due to prior sensitization from a cross-reactive agent. It should be noted that drugs may cause anaphylaxis due to both IgE-mediated and non-IgE mediated etiologies. An example is vancomycin, which may produce both IgE-mediated and non-specific mast cell degranulation and anaphylaxis. The reaction with first exposure does not minimize the concerns raised by the positive skin tests in patients who have previously exposed.

It is expected that the product will be used in an operating room setting, which may mitigate some risk from anaphylaxis if the event is recognized and treated appropriately. Labeling the product that it should be used only for anesthesia emergencies may increase the risk/benefit balance for the drug, but may not be practical. Labeling the product that it should only be used once may be an appropriate approach to the addressing the risk from repeat exposure until studies may be conducted to evaluate this risk.

We recommend that DARRP ask the sponsor to develop in vitro tests of sugammadex-specific IgE, IgG, IgM in order to further characterize the mechanism for these reactions. In addition, there would be benefit in asking the sponsor to evaluate the risk for reaction among subjects with subsequent exposure, both in a general population and in a population of patients who have positive skin tests to sugammadex. It would be essential to define this risk of reaction before it is widely used and patients are exposed on multiple occasions.

5. REFERENCES

- 1 Sampson HA, et. al. *J Allergy Clin Immunol.* 115(3):584-591, 2005.
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- 3 Adkinson NF. Drug allergy. In: Adkinson NF, Bochner BS, Yunginger JW, Holgate ST, Busse WW, Simons FER, editors. *Middleton's Allergy: principles and practice.* 6th ed. Philadelphia: Mosby; 2003. pp. 1679-1694.
- 4 Demoly D, Piette V, Bousquet J. In vivo methods for study of allergy. In: Adkinson NF, Bochner BS, Yunginger JW, Holgate ST, Busse WW, Simons FER, editors. *Middleton's Allergy: principles and practice.* 6th ed. Philadelphia: Mosby; 2003. pp. 1679-1694.

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DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: June 16, 2008
To: Arthur Simone, M.D., Ph.D., Medical Officer
Division of Anesthesia, Analgesia, and Rheumatology Products
(DAARP)
From: Susan Limb, MD, Medical Reviewer Through:
Sally Seymour, MD, Medical Team Leader Through:
Badrul Chowdhury, MD, PhD, Division Director
Subject: Anaphylaxis adverse events occurring with sugammadex sodium

General Information

NDA/IND#: NDA 22-225; IND 68-029
Sponsor: Organon USA, Inc.
Drug Product: (b)(4)® (sugammadex sodium)
Request From: Allison Meyer, Project Manager (DAARP) Date
of Request: June 10, 2008
Date Received: June 10, 2008
Materials: Case report forms, expert opinion summary (April 17, 2008
Reviewed: submission), Skin test and basophil assay update (May 15, 2008
submission)

I. Executive Summary

This is a medical officer review in response to a consultation request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding sugammadex sodium and potential anaphylactic adverse events that have been reported in the clinical development program. A previous consultation was completed by DPAP on May 13, 2008, on the same subject; this review assesses 5 additional suspected cases of anaphylaxis, results of basophil assay testing, and an expert panel review collated by the Applicant that were not covered in the previous consultation.

Upon review of 12 total suspected cases of anaphylaxis from the clinical trial database as well as supporting allergy testing, we conclude that sugammadex is allergenic with the potential to cause anaphylaxis. The estimated anaphylaxis frequency of 1.4% may be a significant underestimate of the true frequency, since the clinical development program did not assess the safety of repeat exposures. Therefore, DPAP recommends formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population, prior to widespread use. Further elucidation of the underlying immunologic mechanism may facilitate patient screening to minimize the risk of anaphylaxis.

A review of the background and submitted materials is provided below.

II. Background

Sugammadex sodium is a modified gamma-cyclodextrin proposed for the indication of reversal of neuromuscular blockade. Currently, no other drugs are approved for this indication, and if approved, sugammadex would be considered a major advance in anesthetic care. Elective reversal of neuromuscular blockade would significantly shorten anesthesia times, expedite peri-operative care and potentially reduce some of the side effects of extended anesthesia. As a result, sugammadex is expected to be widely used if approved without any restrictions, possibly on the order of tens of thousands of doses per day. In addition, any individual patient may expect to receive multiple doses over the course of a lifetime for different surgical procedures. Sugammadex is a NME and the NDA is currently under priority review in DAARP. The Anesthetics and Life Support Drugs Advisory Committee met on March 11, 2008 and unanimously recommended approval of sugammadex. However, a detailed review of the drug hypersensitivity data was not available for discussion at the time of this meeting.

Adverse events suggestive of anaphylaxis and drug hypersensitivity occurred during the clinical development program for sugammadex. Of 1973 adults and 51 children exposed to the drug during the development program, 7 subjects with AEs suspicious for a drug hypersensitivity reaction were identified by the Applicant. Prompted by these cases, the Applicant conducted a clinical study (Study 19.4.110) to evaluate skin prick testing (SPT) and intradermal skin testing (IDT) in healthy volunteers with no prior sugammadex exposure and in patients with prior exposure with and without symptoms of hypersensitivity reactions. The study design and results of the study were previously reviewed by DPAP at the request for medical officer consultation by DAARP (see Dr. Charles Lee's medical officer consultation dated May 13, 2008 for further details). Based on the results of Study 19.4.110 and the case narratives from the clinical safety database, DPAP concluded that at least 2 of the 7 identified cases met diagnostic criteria for anaphylaxis. Results from Study 19.4.110 indicated that sugammadex induced sensitization, as none of the naïve volunteers tested positive, whereas 2 of 12 patients previously exposed tested positive. Furthermore, 1 of the 2 test-positive patients had had prior symptoms suggestive of anaphylaxis, consistent with development of sugammadex-specific IgE. DPAP noted that the sugammadex drug development program was not designed to assess the safety of repeated exposure, which would be of particular concern given the allergenic potential of the drug. Of note, results of Study 19.4.110 and a detailed review of the drug hypersensitivity data were not available for discussion at the time of the Advisory Committee meeting.

The Applicant organized an independent panel of experts to review the results of Study 19.4.110, the 7 suspect cases from the safety database, as well as 5 additional cases more recently identified. One of these latter cases, Case 115101008, was a subject in Study 19.4.115, an ongoing Phase 1 study of sugammadex for a separate indication of hemostasis, which was not included in NDA 22-225. In a report dated April 17, 2008, the expert panel arrived at the following main conclusions:

1. *The consultants were in consensus that the reactions were not life threatening and strongly preferred the term “hypersensitivity” over “anaphylaxis”.*
2. *All four consultants agreed on the classification of 11 of the 12 possible cases of drug hypersensitivity related to sugammadex administration.*
3. *They also agreed that the most likely mechanism would be shown to be nonimmunologic, non-IgE mediated histamine release from tissue mast cells or basophils.*
4. *The most relevant initial test of mechanism, each recommended, was an in vitro examination of histamine release from cultured human basophils.*

In the current request for consultation, DAARP has requested that DPAP review the expert panel’s summary as well as follow-up SPT and basophil assay results to see if the additional information would alter the recommendations made in the original May 13, 2008 consult.

III. Case review

The Applicant has identified 12 potential cases of anaphylaxis from the clinical development program. Of these cases, at least 3 cases in healthy volunteers meet diagnostic criteria for anaphylaxis recently proposed by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network (Sampson HA et al. *J Allergy Clin Immunol* 2006;117:391-7):

Case 106101008 (Subject 12 in Study 19.4.110) involved a healthy volunteer in the thorough QT Study 19.4.106 who developed paresthesias, tachycardia, blurred vision, nausea, palpitations, and stomach discomfort within 1 to 2 minutes after initiation of the first infusion (8.4 mg/kg). The infusion was stopped due to these symptoms. Eight minutes after the start of the infusion, the patient developed flushing of the arms and approximately 30 minutes later a rash on the abdomen. The subject’s blood pressure and heart rate were 122/66 mmHg and 53 bpm at baseline prior to study drug administration; 30 minutes after the drug was administered, the blood pressure and heart rate were 107/66 mmHg and 75 bpm, respectively. Serum tryptase levels from this event were elevated, consistent with an anaphylactic event; at 1, 3, and 6 hours after infusion, serum tryptase was 19.3, 19.9, and 9.44 mcg/L, respectively (laboratory reference range <15 mcg/L). Follow-up SPT performed as part of the skin-test study 19.4.110 was negative; however, IDT was positive on two separate occasions.

Case 105101030 (Subject 20 in Study 19.4.110) involved a healthy volunteer in the thorough QT Study 19.4.105 who was exposed to escalating doses of sugammadex. The subject experienced pruritus after the first dose of 4 mg/kg, then subsequently had a more pronounced reaction immediately after receiving the 32 mg/kg dose 13 days later. Symptoms included flushing, globus sensation, difficulties breathing, tachycardia up to 130 bpm, rash on the forearms, and paresthesias and sensation of warmth in the arms and legs. Follow-up SPT and IDT were negative for this patient.

Case 105101028 (Subject 18 in Study 19.4.11) involved a healthy volunteer in the thorough QT study 19.4.105 who developed palpitations, tachycardia, and flushing on the chest within 1 to 3 min after first exposure to sugammadex (32 mg/kg). Approximately 30 minutes after drug administration, ventricular bigeminy and tachypnea were reported. Heart rate recordings showed an increase from baseline of 73 bpm to 137 bpm, as well as a decrease in room-air oxygen saturation from 100% to 96%. The event was described by the investigator as “tachycardia intermittent (tachyarrhythmia) due to allergic reaction.” Follow-up SPT and IDT were negative.

Three other cases among healthy subjects are worth noting (Cases 109101073, 105101001, and Case 115101008). Although not meeting full criteria for anaphylaxis, these cases are notable for the immediate occurrence of symptoms suggestive of mediator-release and drug hypersensitivity following sugammadex administration in otherwise healthy volunteers.

Case 109101073 (Subject 19 in Study 19.4.110) developed nausea, burning sensation, a sensation of heaviness, agitation, and abdominal cramps within 2 to 6 min after infusion of a second dose of 32 mg/kg sugammadex. These symptoms were later followed by sleepiness approximately 15 minutes later and then an infusion site rash 21 hours later that persisted for 1 day. The CRF describes the episode as a “possible allergic reaction.” The patient received Ringer’s lactate solution, which may have prevented or masked any clinically significant changes in blood pressure. Skin testing was uninformative in this case as the patient had a positive IDT to the negative control solution.

Case 115101008 reported a bitter taste with a sensation of increased salivary flow immediately upon receipt of his first dose of sugammadex. He then developed pruritus and a macular eruption with a central urticarial lesion on the left shoulder 10 minutes later, followed by a tingling sensation in the fingers, cold hands, and tingling in the palate 15 to 30 minutes after receipt of the drug. This patient received IV clemastine 30 minutes after sugammadex infusion, which may have mitigated more pronounced clinical symptoms of anaphylaxis. The case narrative notes that the investigator administered clemastine “in order to prevent evolution to more serious symptoms of hypersensitivity.” The urticarial lesion on the shoulder resolved approximately 15 minutes after clemastine injection. The patient tested negative on follow-up SPT and IDT, but was noted to have an increase in urinary methylhistamine following IDT (95 \pm 162 μ M/M creatinine). The patient’s past medical history is notable for a history of fungal skin infections over a 3-year period, as the chemical structure of sugammadex is similar to antifungal agents and there is a theoretical potential for cross-reactivity.

Case 105101001 (Subject 17 in Study 19.4.110) was a healthy volunteer who developed a need to sneeze, nasal congestion, and globus sensation within 1 to 2 minutes after a second exposure to sugammadex. SPT and IDT were negative.

Two additional healthy volunteer cases involving rash with pruritus (Case 105101024) and isolated rash (Case 105101007) were also identified, but the rashes appeared several hours after drug infusion, making the association with sugammadex less clear. However, these are healthy subjects with no other apparent cause for rash or pruritus, and these limited dermatological manifestations may be markers for sugammadex sensitization. Upon subsequent exposure, such patients could be at risk for multi-system allergic reactions, including anaphylaxis.

The remaining 4 cases involve patients who received sugammadex in the setting of various surgical procedures. At least 2 of these 4 cases (Cases 302103105 and 311107013) meet diagnostic criteria for anaphylaxis, although these cases are confounded by polypharmacy, comorbid conditions, and expected effects of surgery (e.g. abdominal pain following abdominal surgery). SPT and IDT were not performed in these patients, and serum tryptase and urinary histamine/methylhistamine were not collected.

IV. Frequency of anaphylaxis

Based on this case review, there are at least 3 clear cases of anaphylaxis in healthy volunteers with another 2 possible surgical cases identified from the sugammadex clinical database. The safety database for NDA 22-225 consists of 2024 unique adult and pediatric patients who have been exposed to sugammadex; 209 of the 2024 were healthy volunteers enrolled in Phase 1 studies. In our calculation of the anaphylaxis rate, we have excluded the Phase 2 and 3 data due to the number of confounding factors that make adjudication of these surgical cases difficult. We then calculate a frequency of anaphylaxis of 1.4% (3/209) in a healthy volunteer population. This frequency is quite high and is likely an underestimate, since the clinical development program did not assess the safety of repeated exposures. For reference, the frequency of allergen immunotherapy-induced anaphylaxis is estimated at 0.5% of all injections and at 0.01 to 0.05% of all courses of penicillin. In general, the current incidence of anaphylaxis during general anesthesia has been reported to range from 1 in 4000 to 1 in 250,000 (Blessings-Moore et al. The Joint Task Force on Practice Parameters. *J Allergy Clin Immunol* 2005 Mar;115(3 Suppl 2):S483-523). Even if we recalculate the rate using the entire safety database for NDA 22-225, the rate is still high, falling between 0.1 to 0.3% depending on whether the 2 equivocal surgical cases are included in the numerator (3/2024 or 5/2024). Furthermore, we suspect that the real rate of anaphylaxis may be substantially higher in patients with prior exposures to sugammadex, as would be expected in other examples of drug hypersensitivity.

V. Mechanistic studies

In vitro basophil histamine-release assays are primarily used as a research tool to measure the secretory response of basophils activated by IgE cross-linking in the presence of a specific allergen. While these assays can be useful for helping to distinguish between IgE- and non-IgE-mediated mechanisms, these cell-based assays are technically challenging and not widely available, generally requiring processing of whole blood within 24 hours. There are no standardized, validated reagents for these types of assays. In addition, up to 25% of patients tested are “non-responders,” failing to release histamine in this test despite other evidence of allergic sensitization. As a result, the

basophil histamine release assay is of limited clinical utility for diagnosing allergy in individual patients.

Ex vivo mast cell-mediator release assays, such as the skin microdialysis assay submitted by the Applicant, are another investigational tool for evaluating the release of histamine and other mast cell mediators in the presence of various substances, including drugs. While these assays can provide insight into the underlying pathophysiology, these types of tests are in the preliminary stages of development and are far from being used for clinical diagnosis.

In general, it would be helpful to elucidate the mechanism responsible for the hypersensitivity reactions, as this information may allow for patient screening and improved risk assessment. The results of the basophil histamine assays submitted by the Applicant were not suggestive of an IgE-mediated mechanism, and the mast cell skin assay did not show evidence of histamine release from mast cells in skin directly exposed to sugammadex. While these results are of interest, the underlying mechanism cannot be determined or ruled out on the basis of these results alone, given the assay limitations outlined above.

Whether IgE-mediated or not, the underlying mechanism does not alter the clinical diagnosis of anaphylaxis and the risk for serious injury or even death. Results from the skin testing study, Study 19.4.110, show that sugammadex sensitizes patients and IDTs were selectively positive only in patients with prior exposure. Combined with the clinical cases, this information indicates that that sugammadex sensitization can lead to clinically relevant drug hypersensitivity reactions, including anaphylaxis.

VI. Discussion

The cases and laboratory testing show that sugammadex has allergenic potential and can cause anaphylaxis. The cases identified were serious allergic reactions with multi-organ involvement. Although the cases were not severe in the sense that the patients did not require active resuscitation, we cannot assume that sugammadex-induced anaphylaxis is minor or non-life-threatening. The most striking case of anaphylaxis with an elevated serum tryptase, Case 106101008, may have resulted in more severe injury had the infusion not been stopped. Furthermore, since the clinical development program did not evaluate the safety of repeated exposures, the potential for more serious injury and even death in sensitized patients remains a major risk that has not been formally addressed. As Case 105101030 illustrates, repeat exposures may result in more severe reactions, as is usually observed in drug hypersensitivity. We do not have any evidence to indicate that sugammadex would behave differently from other known immunogenic drugs.

The life-threatening potential, combined with a relatively high frequency of anaphylaxis and expected wide usage, are concerning. Therefore, the main recommendations outlined in DPAP's May 13, 2008, consult remain unchanged. DPAP recommends formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population, prior to widespread use of sugammadex. Further elucidation of the underlying immunologic mechanism, e.g. development of an

assay for sugammadex-specific IgE, may facilitate patient screening to improve the risk:benefit ratio of elective sugammadex use.

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DIVISION OF PULMONARY AND ALLERGY PRODUCTS
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Date: November 25, 2008
To: Allison Meyer, Project Manager (DAARP)
From: Susan Limb, MD, Medical Reviewer Through:
Sally Seymour, MD, Medical Team Leader
Through: Badrul Chowdhury, MD, PhD, Division Director
Subject: Sugammadex end-of-review meeting

General Information

NDA/IND: NDA 22-225, IND 68029
Sponsor: Organon USA, Inc.
Drug Product: Sugammadex sodium ((b) (4) ®)
Protocol: N/A
Request From: Allison Meyer, Project Manager (DAARP) Date
of Request: 11/13/2008
Date Received: 11/13/2008
Materials: End-of-review meeting package; IgE/IgG assay validation studies
Reviewed:

Executive Summary

This is a medical officer review in response to two consultation requests from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding sugammadex sodium and hypersensitivity reactions. Sugammadex sodium is a modified gamma-cyclodextrin proposed for the indication of reversal of neuromuscular blockade. In the original development program, both anaphylaxis and other hypersensitivity reactions were observed. Two previous consultations were completed by DPAP on May 13, 2008 and on June 16, 2008. The DPAP consultations concluded that sugammadex is allergenic with the potential to cause anaphylaxis. At that time, DPAP recommended formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population, prior to widespread use. In addition, DPAP and DAARP sought the input of two outside consultants, (b) (4) of the Mayo Clinic and (b) (4) of the Medical College of Georgia, who independently reviewed the suspected cases of anaphylaxis. The consultants concurred that sugammadex appears to cause anaphylaxis and recommended further study of the safety of repeat exposure.

A Not Approvable letter was issued by DAARP on July 31, 2008, citing inadequate safety assessment of anaphylaxis risk and repeat exposure, as well as the effect of sugammadex on coagulation. In response, the Applicant has submitted results of IgG/IgE validation studies and testing as well as questions in anticipation of an End-of-

Review meeting, seeking clarification of the issues raised in the Not Approvable letter. DAARP has requested DPAP's input regarding the following: 1) IgE/IgG test results; and 2) the hypersensitivity issues for discussion at the End-of-Review meeting (Questions 2-5).

The Applicant reports that all antibody testing has been negative, concluding that the underlying mechanism for the sugammadex-related hypersensitivity reactions are not immunoglobulin-mediated. DPAP does not agree with this assessment. The negative predictive value of these assays is limited. While positive antibody results would be consistent with the skin testing results and provide insight into the pathophysiology, a negative result does not exclude the possibility of an immunoglobulin-mediated reaction. Furthermore, whether results of IgE/IgG testing are positive or negative, the risk of repeated exposures still needs to be assessed in a clinical setting given the likely widespread use of the drug. Delineating the underlying mechanism may be helpful in developing ways to minimize risk but does not replace the need for a formal safety assessment of repeated exposures. In addition, DPAP suggests that DAARP obtain input from the Division of Therapeutic Proteins on the validation data submitted to support the IgE/IgG assays.

An overview of the IgE/IgG testing and the Applicant's questions (in *italics*) and DPAP's proposed responses (in **bold**) are provided below.

IgE/IgG assays

The Applicant has developed IgE/IgG assays for anti-sugammadex antibodies and has submitted the results of validation studies and IgE/IgG test results from a subset of patients. The sera for testing was obtained from Study 19.4.110, a study previously conducted to evaluate skin prick testing (SPT) and intradermal skin testing (IDT) in healthy volunteers with no prior sugammadex exposure and in patients with prior exposure with and without symptoms of hypersensitivity reactions. The study design and results of Study 19.4.110 were previously reviewed by DPAP at the request for medical officer consultation by DAARP (see Dr. Charles Lee's medical officer consultation dated May 13, 2008 for further details). Based on the results of Study 19.4.110 and the case narratives from the clinical safety database, DPAP concluded that at least 2 of the 7 identified cases met diagnostic criteria for anaphylaxis. Results from Study 19.4.110 indicated that sugammadex induced sensitization, as none of the naïve volunteers tested positive, whereas 2 of 12 patients previously exposed tested positive. Furthermore, 1 of the 2 test-positive patients had had prior symptoms suggestive of anaphylaxis, consistent with development of sugammadex-specific IgE. Serum from one other patient (Subject 101008 in Study 19.4.115), another patient with a suspected hypersensitivity reaction was also tested for IgE and IgG antibodies. The patient's reaction occurred 10 minutes after the first dose of sugammadex received as part of a hemostasis study. The reaction included itching, urticaria, tingling sensations of the fingers and palate, vertigo, and headache, following by urinary frequency and taste perversion the next day. The urticaria resolved 15 minutes after clemastine injection. This case is reviewed in more detail in the previous DPAP consultation dated June 16, 2008.

Eleven of the 12 patients in Study 19.4.110 had sera for testing. All patients tested negative for anti-sugammadex antibodies according to the Applicant. For Patient 101008 in Study 19.4.115, two samples were tested and shown to be inconclusive and negative, respectively. The first sample was taken 20 minutes post-dose, and the Applicant states that circulating sugammadex may have interfered with assay results. The second sample was taken 8 days after dosing.

The Applicant concludes from these results that the mechanism of the hypersensitivity reactions is not immunoglobulin-mediated. DPAP does not agree with this assessment and believes that the negative predictive value of these assays is limited. While positive antibody results would be consistent with the mechanism suggested by the skin test study and the observed cases, a negative result does not exclude the possibility of an immunoglobulin-mediated reaction. Furthermore, whether results of IgE/IgG testing are positive or negative, the risk of repeated exposures still needs to be assessed in a clinical setting for reasons previously outlined. DPAP suggests that DAARP obtain input from the Division of Therapeutic Proteins on the validation data submitted to support the IgE/IgG assays.

Questions

2. *The action letter states “Sugammadex sodium caused anaphylaxis in approximately 1% of healthy subjects exposed to a single dose of the drug. Some patients exposed to sugammadex sodium in the setting of anesthesia also had reactions suggestive of a Type I hypersensitivity reaction on first exposure.” Please identify these subjects/patients.*

Division response: Two of the 209 healthy subjects (1%) in the clinical safety database were identified as cases of anaphylaxis: Cases 106101008 and 105101030. The following cases did not meet full criteria of anaphylaxis but had symptoms suggestive of Type I hypersensitivity reactions: 105101028, 109101073, 115101008, and 105101001.

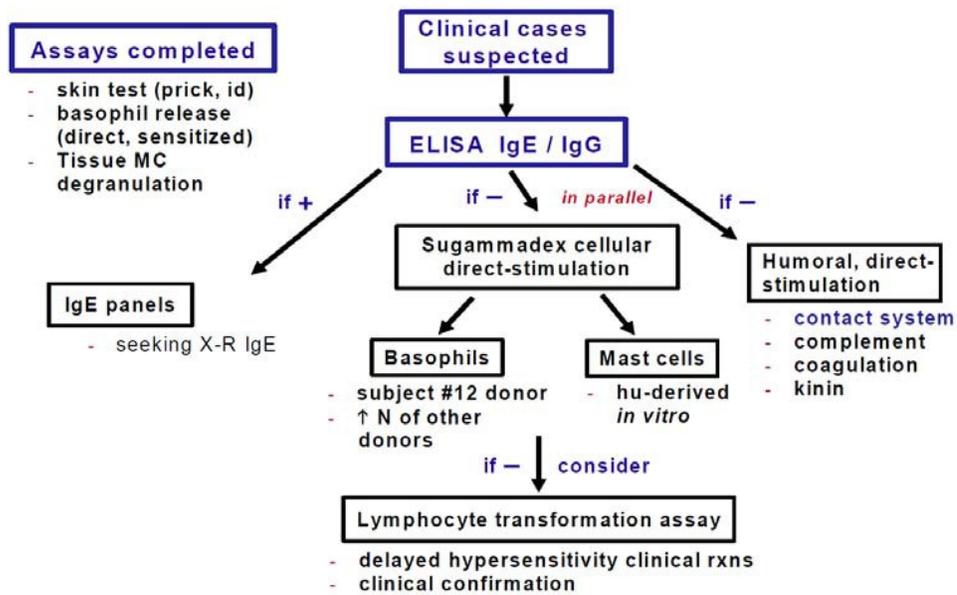
3. *The Sponsor has sera from 7 of the previously identified cases of possible hypersensitivity, and we are in the process of analyzing these samples in a well controlled, validated ELISA format.*

a. *We believe that if these analyses are negative, they would confirm the negative results of the in vitro basophil release, the in situ skin mast cell microdialysis and the skin prick test observations in vivo, thereby significantly reducing the likelihood that an IgE/IgG-mediated mechanism is operative, and excluding this mechanism from further consideration. Does the Agency concur?*

b. *In a continuing effort to elucidate a mechanism we propose additional studies to be conducted in parallel, i.e. direct (non-IgE/non-IgG) mediated release from basophils, mast cells and non-cellular, humoral mechanisms as outlined in Figure 1 below. Does the Agency concur with this experimental approach?*

Figure 1: Decision Tree

to identify mechanism of action for sugammadex clinical hypersensitivity reactions



Division response: We encourage you to explore both IgE/IgG-mediated and non-IgE/IgG mediated mechanisms, as proposed in Figure 1. However, we do not agree that negative ELISA testing eliminates the possibility of antibody-based hypersensitivity reactions.

4. The Agency has requested repeat exposure data in man for sugammadex specifically addressing the nature and frequency of anaphylaxis and other hypersensitivity reactions. Currently, we have significant nonclinical repeated exposure data in 28 monkeys (2-10 intravenous exposures, mean interval 13 weeks, vast majority of intervals > 5-6 weeks), 46 dogs (daily intravenous exposure for 3 to 4 weeks) and 292 rat (daily intravenous or subcutaneous dosing for 4 weeks) and multiple exposure in 201 healthy volunteers from 6 clinical trials with mean (min-max) time interval between first and last exposure of 15 (3-22) days.

We believe these data are sufficient to assess whether there is an increased risk of hypersensitivity upon repeated exposure. Can the Agency provide further explanation of why they have requested a multiple exposure trial? What additional information would this trial provide? What is the hypothesis to be tested in such a study and what would be the endpoint(s)?

Division response: The strength of animal data to support repeat exposure in man is limited given the lack of a good animal model for anaphylaxis. Controlled data in humans is required. The original clinical program did not formally assess the safety of repeat exposure at time intervals sufficient to permit formation of drug-specific IgE in an adequate number of patients. A formal study is recommended to assess the rates of sensitization and hypersensitivity reactions that may be anticipated with

widespread use, when individual patients may receive multiple doses of sugammadex over a lifetime. Further study of the clinical features of these reactions may help elucidate the underlying mechanism as well as facilitate the development of predictive screening tests.

5. When conducting immunization protocols, it is standard practice to administer a prime dose of immunogen and consecutive boosting dosages at weekly intervals to evoke a B-cell mediated specific Ig response. According to abundant data in the literature, specific Ig serum-titers reach peak values within 2-3 weeks following a boost dose administration. Can the Agency please provide their rationale for requesting a 5-6 weeks dosing interval for a multiple dose trial with sugammadex?

Division response: The applicability of a typical immunization protocol is questionable, as the kinetics of drug-specific IgE production in drug allergy are not fully understood. Immunization protocols are typically focused on non-IgE antibody responses and based on more immunogenic molecules. There is not much literature characterizing the time course of specific IgE formation in human drug allergy. An interval of 5-6 weeks is likely to be an adequate time period to permit development of a specific IgE response, as previously noted by the Applicant's own consultant, Dr. William Busse, during the June 20, 2008 teleconference. Shorter time intervals with more intense dosing regimens may also suffice. The design of the multiple dose trial is at the Applicant's discretion; submit whatever data is needed to support the time interval and study design selected.

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Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP) Memorandum

Date: August 14, 2013
From: Erika Torjusen, MD, MHS, Medical Officer
(DPARP) Through: Banu Karimi-Shah, MD, Medical
Team Leader (DPARP) Through: Lydia Gilbert-
McClain, Deputy Division Director (DPARP)
To: Division of Anesthesia, Analgesia, and Addiction
Products (DAAAP) Subject: Sugammadex Complete Response

Summary

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was consulted on January 7, 2013 to review the safety concern of anaphylaxis with sugammadex sodium for injection. A full review of the complete response, including a history of previous DPARP consultations, is attached to this memorandum. The results of the review were to be presented at an advisory committee meeting on July 18, 2013. However, just prior to the advisory committee meeting, concerning inspection findings came to light. The inspection of site #2 (of four sites) in the United Kingdom, revealed the unblinding of 53 of 95 subjects, due to lack of adherence to the blinding procedures outlined in the protocol. Due to the differences in viscosity between active drug and saline placebo, the investigator could potentially be aware of the product being administered. As a result, the protocol specified that the investigator giving the product was not be involved in adverse event evaluation. For these 53 patients, the same investigator administered the drug product and assessed adverse event outcomes. This major protocol deviation was reported to the Applicant in a note to file at the time, but was not reported as a deviation in the clinical study report to the FDA. This note to file was discovered by our inspector. Due to questions regarding data integrity, the advisory committee meeting was cancelled.

The unblinding of patients in a safety study such as the repeat dose study (P06042), in which assessment of hypersensitivity and anaphylaxis symptoms is subjective, is of great concern, and calls into question the integrity of the data collected, especially in light of the Applicant's apparent awareness of the protocol deviation, and failure to report it to the FDA. At this time, it is unclear if this is a larger problem at other sites, or isolated to this single site. Whether the Applicant will be able to salvage this study (based on inspections of the other sites) or will need to conduct a new study remains an open question. The original consult is attached for reference; however, the validity of the calculations and the interpretations provided are subject to change pending further information. DPARP understands that DAAAP plans to take a Complete Response action on this application, and to request inspection of

the three remaining study sites. Currently, no conclusions can be drawn from the submitted data, and thus the deficiency of evaluating the safety of repeat doses of sugammadex remains. The deficiency language regarding the lack of repeat-dose safety data can likely remain similar to the original Not Approvable letter. DPARP will provide comments/input as necessary for the Complete Response Letter.

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
(DPARP) CONSULTATION

Date: June 19, 2013
To: Christopher Breder, Cross Disciplinary Team Leader, DAAAP
From: Erika Torjusen, MD, MHS, Medical Reviewer, DPARP
Through: Banu Karimi-Shah, MD, Medical Team Leader, DPARP
Through: Badrul Chowdhury, MD, PhD, Division Director, DPARP
Subject: Sugammadex sodium for injection (Org 25969, SCH 900616, MK-8616)

General Information

NDA#: 22-225
Sponsor: Merck, Sharp & Dohme Corp., (on behalf of Organon USA, Inc., a subsidiary of Merck)
Drug Product: Sugammadex sodium for injection (Org 25969, SCH 900616, MK-8616)
Request From: Diana Walker, Regulatory Project Manager, DAAAP
Date of Request: January 7, 2013
Date Received: January 7, 2013
Materials: NDA 22-225 Resubmission, DPARP Medical Officer Consultations dated
Reviewed: May 2008, Jun. 2008, Nov. 2008, April 2009, Sept. 2009, Dec. 2010

I. Introduction

This Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) medical officer review evaluates the safety concern of anaphylaxis with sugammadex sodium for injection, which is being proposed for marketing in the US as a selective relaxant binding agent indicated for 1) the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium (dose 4 mg/kg), and 2) the immediate reversal of neuromuscular blockade after administration of rocuronium (dose 16 mg/kg). The original new drug application (NDA) was submitted to the Agency on October 31, 2007, by Organon USA, Inc. During the first review cycle, the application was deemed Not Approvable, citing among the clinical deficiencies the evaluation of anaphylaxis, as will be further outlined in the body of this consultative review.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has requested consultation from DPARP on multiple occasions to evaluate the anaphylaxis signal with sugammadex (as listed in the table above). The following review covers the regulatory history of sugammadex by summarizing the prior reviews completed by DPARP, as well as data from a new repeat-dose clinical study presented by the Applicant to address the deficiencies with respect to the evaluation of anaphylaxis, as cited in the Not-Approvable Letter, dated July 31, 2008. The presence of anaphylaxis in both the original controlled development program and this newly submitted repeat-dose clinical trial data will be the primary emphasis of this review.

Sugammadex was approved in the European Union (EU) in July 2008, and has been commercially available since September 2008. From product launch through June 15, 2012, approximately 3,276,086 doses of sugammadex are estimated to have been distributed worldwide. Therefore, a brief summary of post-marketing reports will also be presented, as a means of further characterizing the anaphylaxis signal noted throughout the controlled studies in the clinical development program. Prior to proceeding with a detailed review of the sugammadex new drug application, it is important to orient the advisory committee members as to DPARP's approach to the assessment of anaphylaxis.

II. Definition of Anaphylaxis

Although anaphylaxis has widely been regarded as a severe, potentially fatal, systemic allergic reaction that occurs after contact with an allergy-causing substance, there has been no universal agreement on the clinical definition of anaphylaxis or the criteria for diagnosis. Because the lack of specific diagnostic criteria hampered research, created confusion among health care providers, and led to inconsistent diagnosis and treatment of patients, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened meetings in 2004 and 2005 to address this need. The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the US Food and Drug Administration; the European Academy of Allergy and Clinical Immunology; and the Australasian Society of Clinical Immunology and Allergy. The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems.¹ It is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening.

The three recommended NIAID/FAAN diagnostic criteria are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

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)
2. Two or more of the following that occur rapidly after exposure to a ***likely*** allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

- c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to ***known*** allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to identify cases consistent with anaphylaxis. For the evaluation of new molecular entities, DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling Criterion #1 above, in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. In addition, any cases reported by investigators or other healthcare professionals as “anaphylaxis” or “anaphylactoid” are accepted as cases of anaphylaxis, even if the case report does not detail more specific signs and symptoms.

III. Background and Regulatory History

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex was designed such that its negatively charged core would specifically attract the positively charged ammonium groups of rocuronium and vecuronium, sequestering these neuromuscular blocking agents (NMBA), rendering them unavailable to bind to nicotinic receptors at the neuromuscular junction, resulting in reversal of the neuromuscular blockade.

The original sugammadex new drug application (NDA) was submitted on October 31, 2007, by Organon USA, Inc. As a new molecular entity and a potentially important addition to the armamentarium of the anesthesia community, the application was granted priority review and was presented at a meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) on March 11, 2008. The initial safety database was comprised of 209 healthy volunteers and 2,024 patients who received single doses of sugammadex ranging from 0.1 mg/kg to 96 mg/kg mg. No repeat-dose data dedicated to the evaluation of hypersensitivity were available in the original submission. The ALSDAC unanimously recommended approval of sugammadex; however, a detailed review of the drug hypersensitivity data was not available for discussion at the time of the March 11, 2008, meeting. The preliminary nature of the available data analysis limited our ability to engage the panel members in a more detailed discussion of the spectrum of anaphylaxis and the resultant clinical implications of this safety signal.

After the advisory committee meeting, a consult (May 13, 2008) was requested from the Division of Pulmonary and Allergy Products [now the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)]; in this review the Division will subsequently be referred to as DPARP], to evaluate adverse events suggestive of anaphylaxis and drug hypersensitivity which occurred during the clinical development program for sugammadex. At that point, of 1973 adults and 51 children exposed to the drug during the initial development program, 7 subjects with adverse events suspicious for drug hypersensitivity reaction were identified by the Applicant.

Out of 7 potential cases identified by the Applicant, 2 subjects in the database met the diagnostic NIAID/FAAN criteria for anaphylaxis, indicating a frequency of anaphylaxis of approximately 0.1%.

Prompted by these cases, the Applicant conducted a clinical study (Study 19.4.110) to evaluate skin prick testing (SPT) and intradermal skin testing (IDT) in 23 healthy volunteers with no prior sugammadex exposure and in 12 patients with prior exposure, with and without symptoms of hypersensitivity reactions. Of the 12 patients who were previously exposed to sugammadex, 2 had positive skin tests – one who had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. No unexposed subjects had a positive skin test, suggesting that sugammadex does not produce a non-specific irritant reaction. The results of the skin test study suggested that exposure to sugammadex may induce sensitization. While the underlying mechanism remained uncertain, the possibility of the production of sugammadex-specific IgE and an increased risk of reaction upon re-exposure could not be ruled out and this raised concern, particularly in the absence of any clinical repeat-dose experience.

The Applicant organized an independent panel of experts to review the results of the SPT study, the 7 suspected cases from the safety database, as well as 5 additional cases that had been identified subsequently. The consultants were in consensus that the reactions were not life-threatening and strongly preferred the term “hypersensitivity” over “anaphylaxis.” All four consultants agreed on the classification of 11 of the 12 possible cases of drug hypersensitivity related to sugammadex administration. They also agreed that the most likely mechanism would be shown to be non-immunologic, non-IgE mediated histamine release from tissue mast cells or basophils. Each consultant recommended an in vitro examination of histamine release from cultured human basophils, as the most relevant initial test of mechanism.

DAAAP requested a second consult of DPARP on June 10, 2008, in order to assess the 5 additional suspected cases of anaphylaxis, results of basophil histamine release testing, and the aforementioned expert panel review collated by the Applicant. In a consult response dated June 16, 2008, DPARP addressed each of these issues:

A) Anaphylaxis Case Review

DPARP reviewed the 12 potential cases of anaphylaxis identified by the Applicant. Of these cases, DPARP concluded that at least 3 cases in healthy volunteers met diagnostic criteria for anaphylaxis:

- **Case 106101008** involved a healthy volunteer in the thorough QT Study 19.4.106 who developed paresthesias, tachycardia, blurred vision, nausea, palpitations, and stomach discomfort within 1 to 2 minutes after initiation of the first infusion (8.4 mg/kg). The infusion was stopped due to these symptoms. Eight minutes after the start of the infusion, the patient developed flushing of the arms and approximately 30 minutes later a rash on the abdomen. The subject’s blood pressure and heart rate were 122/66 mmHg and 53 bpm at baseline prior to study drug administration; 30 minutes after the drug was administered, the blood pressure and heart rate were 107/66 mmHg and 75 bpm, respectively. Serum tryptase levels from this event were elevated, consistent with an anaphylactic event; at 1, 3, and 6 hours after infusion, serum tryptase was 19.3, 19.9, and 9.44 mcg/L, respectively (laboratory

reference range <15 mcg/L). Follow-up SPT performed as part of the skin test study 19.4.110 was negative; however, IDT was positive on two separate occasions.

- **Case 105101030** involved a healthy volunteer in the thorough QT Study 19.4.105 who was exposed to escalating doses of sugammadex. The subject experienced pruritus after the first dose of 4 mg/kg, then subsequently had a more pronounced reaction immediately after receiving the 32 mg/kg dose 13 days later. Symptoms included flushing, globus sensation, difficulty breathing, tachycardia up to 130 bpm, rash on the forearms, and paresthesias and sensation of warmth in the arms and legs. Follow-up SPT and IDT were negative for this patient.
- **Case 105101028** involved a healthy volunteer in the thorough QT study 19.4.105 who developed palpitations, tachycardia, and flushing on the chest within 1 to 3 min after first exposure to sugammadex (32 mg/kg). Approximately 30 minutes after drug administration, ventricular bigeminy and tachypnea were reported. Heart rate recordings showed an increase from baseline of 73 bpm to 137 bpm, as well as a decrease in room-air oxygen saturation from 100% to 96%. The event was described by the investigator as “tachycardia intermittent (tachyarrhythmia) due to allergic reaction.” Follow-up SPT and IDT were negative.

Three other cases among healthy subjects were also notable. Although not meeting full criteria for anaphylaxis, these cases were notable for the immediate occurrence of symptoms suggestive of mediator-release and drug hypersensitivity following sugammadex administration in otherwise healthy volunteers. Two additional healthy subjects experienced rash with pruritus and isolated rash, but the rashes appeared several hours after infusion, making the association with sugammadex less clear. However, DPARP remained concerned that these were healthy subjects with no other apparent cause for rash or pruritus, and that these limited dermatological manifestations may be markers of sugammadex sensitization, which could render such patients at risk for multi-system allergic reactions, including anaphylaxis on re-exposure. The remaining 4 cases involved patients who received sugammadex in the setting of various surgical procedures. At least 2 of these 4 cases met diagnostic criteria for anaphylaxis, although the evaluation of these cases was confounded by polypharmacy, co-morbid conditions, and expected effect of surgery.

B) Frequency of Anaphylaxis

Based on this case review, DPARP concluded that there were at least 3 cases of anaphylaxis in healthy volunteers with another 2 possible cases in surgical patients identified from the sugammadex clinical database. At the time of the original NDA submission, the safety database consisted of 2024 unique adult and pediatric patients who had been exposed to sugammadex; 209 of the 2024 were healthy volunteers enrolled in Phase 1 studies. In the calculation of the anaphylaxis frequency, DPARP excluded phase 2 and 3 data due to the number of confounding factors that made adjudication of these cases difficult. As a result, we calculated a frequency of anaphylaxis of 1.4% (3/209) in a healthy volunteer population. DPARP assessed this to be a relatively high frequency of anaphylaxis, and expressed concern that this might be an underestimate since the clinical development program did not evaluate the safety of repeated exposures. Considering the entire database of n=2024, the frequency of anaphylaxis was

calculated to be between 0.1 to 0.3% depending on whether the two surgical cases were included in the numerator (e.g., 3/2024 or 5/2024).

C) Mechanistic studies

DPARP was also asked to review additional mechanistic information submitted by the Applicant. In general, DPARP felt that it would be helpful to elucidate the mechanism responsible for the hypersensitivity reactions, as this information may allow for patient screening and improved risk assessment. The results of the basophil histamine-release assays submitted by the Applicant were not suggestive of an IgE-mediated mechanism, and the mast cell skin assay did not show evidence of histamine release from mast cells in skin directly exposed to sugammadex. While these results are of interest, DPARP concluded that the underlying mechanism could not be determined or ruled out on the basis of these results alone, due to the following limitations:

In vitro basophil histamine-release assays are primarily used as a research tool to measure the secretory response of basophils activated by IgE cross-linking in the presence of a specific allergen. While these assays can be useful for helping to distinguish between IgE- and non-IgE-mediated mechanisms, these cell-based assays are technically challenging and not widely available, generally requiring processing of whole blood within 24 hours. There are no standardized, validated reagents for these types of assays. In addition, up to 25% of patients tested are “non-responders,” failing to release histamine in this test despite other evidence of allergic sensitization. The Applicant submitted an *ex vivo* mast cell-mediator release assay (skin microdialysis), another investigational tool for evaluating the release of histamine and other mast cell mediators in the presence of various substances, including drugs. DPARP deemed the basophil histamine release assay and the skin microdialysis assay to be of limited clinical utility for diagnosing allergy in individual patients. DPARP considered that while these assays may provide insight into the underlying pathophysiology, they remain investigational.

As a result, DPARP concluded that sugammadex has allergenic potential and can cause anaphylaxis. The cases identified were serious allergic reactions with multi-organ involvement. Although the cases were not severe in the sense that the patients did not require active resuscitation, it could not be assumed that sugammadex-induced anaphylaxis would be minor or non-life-threatening. Results from the skin testing study, Study 19.4.110, showed that sugammadex sensitizes patients and IDTs were selectively positive only in patients with prior exposure. From a mechanistic standpoint, whether IgE-mediated or not, the underlying mechanism did not alter the clinical diagnosis of anaphylaxis and the risk for serious injury or even death. DPARP concluded that combined with the clinical cases, this information indicated that that sugammadex sensitization can lead to clinically relevant drug hypersensitivity reactions, including anaphylaxis. The life-threatening potential inherent to anaphylaxis, combined with a relatively high frequency and expected wide usage, were of concern. Furthermore, since the clinical development program did not evaluate the safety of repeated exposures, the potential for more serious injury and even death in patients on re-exposure remained a major risk that had not been formally addressed.

Based on the two consultative reviews (May 13, 2008 and June 16, 2008) and review of the cases by external academic experts, which were largely in agreement with those of the Division, the

Not Approvable Letter (July 31, 2008) outlined the information necessary to resolve these deficiencies: 1) characterize the safety of sugammadex on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions, 2) define the frequency/time course of events related to sugammadex administration, and other characteristics of the adverse reactions, and 3) attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium.

IV. NDA Resubmission (Complete Response)

As a part of the resubmission, the Applicant has provided the results of a repeat-dose clinical study, as outlined in the Not Approvable Letter. In subsequent consultations (April 2009, September 2009, and December 2010), DPARP was asked to review and provide feedback on the clinical study designed by the Applicant to evaluate the risk of hypersensitivity reactions with repeat exposure to sugammadex. DPARP considered the proposed study design, duration, interval of exposure, and patient number to be adequate. An overview of the study design and results are provided below. A more detailed review of the protocol can be found in Appendix 1.

A) Repeat Dose-Clinical Study (P06042)

1) Study Overview

P06042 was a randomized, double-blind, placebo-controlled, parallel-group, repeat-dose study to evaluate the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects age 18 to 55. A total of 480 subjects received a single-blind, saline placebo test dose at Week 0, and patients who experienced a reaction to the placebo dose were screened out. Of the 480 subjects enrolled, 448 were randomized in a 1:1:1 ratio to receive the following doses intravenously on Day 8 (Week 1), Day 36 (Week 5), and Day 78 (Week 11):

- Sugammadex 4 mg/kg (n=148)
- Sugammadex 16 mg/kg (n=150)
- Saline placebo (n=150)

Additionally, antibody testing, serum tryptase, and other serological markers of contact system activation were assessed in patients with hypersensitivity reactions and in a subset of non-reacting patients for comparison. Similarly, skin prick and intradermal testing were performed in patients with hypersensitivity reactions and in a subset of non-reacting patients for comparison.

Patients were domiciled at the study site starting the evening before the scheduled dose and released the morning after the day of each dose. All adverse events and related data (e.g. laboratory measurements, physical exam results, etc.) were adjudicated by an independent committee that remained blinded to study treatment. Patients who reported hypersensitivity symptoms to placebo at Week 0 were discontinued. Patients who reported “severe and/or serious signs and symptoms” of hypersensitivity at any time in the study were also be discontinued

2) Patient Disposition

Patient disposition for study P06042 is summarized in Table 1.

| Table 1: Patient Disposition - Study P06042 | | | |
|--|----------------------------|---|--|
| | Placebo (N=150) | Sugammadex 4 mg/kg (N=148) | Sugammadex 16 mg/kg (N=150) |
| | n (%) | | |
| Patients who completed the study | 135 (90.0) | 135 (91.2) | 127 (84.7) |
| Patients who withdrew early | 15 (10.0) | 13 (8.8) | 23 (15.3) |
| Reasons for withdrawal | | | |
| <i>Adverse Events</i> | 2 (1.3) | 4 (2.7) | 10 (6.7) |
| <i>Lost to Follow Up</i> | 2 (1.3) | 1 (0.7) | 2 (1.3) |
| <i>Consent Withdrawn</i> | 2 (1.3) | 3 (2.0) | 5 (3.3) |
| <i>Non-Compliance</i> | 9 (6.0) | 5 (3.4) | 6 (4.0) |
| Hypersensitivity-Related† | 1 (0.7) | 2 (1.4) | 7 (4.7) |
| <i>Adverse Events</i> | 1 (0.7) | 1 (0.7) | 4 (2.7) |
| <i>Consent Withdrawn</i> | 0 | 0 | 2 (1.3) |
| <i>Non-Compliance</i> | 0 | 1 (0.7) | 1 (0.7) |

† Subjects with suspected hypersensitivity reactions after one randomized dose
Source: Table 5, p. 79, Clinical Study Report P06042 Module 5.3.5.4 (10.1) and Section 16.2.7.5, p. 576-578, Clinical Study Report P06042, Module 5.3.5.4 (16.2.7.5).

As seen in Table 1, adverse events were the second most common reason for discontinuation, accounting for 16 subject discontinuations, with a majority of these discontinuations being from the sugammadex 16 mg/kg group. Overall, 10 subjects in the study discontinued treatment after experiencing suspected hypersensitivity symptoms: 7 were from the sugammadex 16 mg/kg group, 2 were from sugammadex 4 mg/kg, and 1 was from the placebo group. Reported reasons for discontinuation varied and included adverse events (n=6), consent withdrawn (n=2), and non-compliance with protocol (n=2). The 2 subjects in the 4 mg/kg sugammadex group who discontinued the study due to a suspected hypersensitivity reaction experienced nausea and/or flushing. In the 16 mg/kg sugammadex group, the subjects who discontinued experienced the following symptoms:

- Subject 270: anaphylactic shock, hypotension, urticaria
- Subject 218: urticaria
- Subject 030: urticaria
- Subject 269: nausea
- Subject 237: erythema, flushing, nausea, urticaria
- Subject 025: flushing, urticaria, rhonchi

3) Overview of Results

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2), the Applicant identified 68 cases of suspected hypersensitivity in 49 subjects. These were sent by the Applicant to an Adjudication Committee comprised of independent allergist/immunologists and anesthesiologists for review. The committee classified 8 subjects as having had a hypersensitivity reaction. Of these 8 subjects, the committee characterized the

symptoms of one subject as meeting the definition of anaphylaxis as defined by NIAID/FAAN criterion #1 and the criteria of Rüggeberg et al². The committee also classified 2 other subjects as having met level 2 certainty of the Rüggeberg definition.

DPARP has reviewed the 68 suspected cases resulting from the Applicant's search. Those listings, which included adverse events that were consistent with anaphylaxis, were then crosschecked with case narratives. A final determination of anaphylaxis for these cases was made using NIAID/FAAN criterion #1, the most conservative method for identifying anaphylaxis cases (as outline in Section II above). Using this method, DPARP identified 3 cases of anaphylaxis among the 68 potential hypersensitivity cases in 49 subjects. These three cases are reviewed briefly below.

a) Anaphylaxis Case Review

- **Subject 270:** A 55-year old white female subject developed severe nausea, moderate vomiting, and mild muscle spasms on her back immediately following administration of the initial dose of sugammadex 16 mg/kg. The subject then developed severe hypotension (67/42), moderate tachycardia, mild numbness of the lips, severe generalized urticaria without itching, severe flushing, decreased oxygen saturation, decreased pulmonary function (peak expiratory flow from median baseline value of 315 L/min to a value of 150 L/min), moderate headache, severe chills, a moderate dry mouth, and two episodes of vomiting. The subject was treated with epinephrine SC and Benadryl IV. Subsequently, all symptoms resolved within 30 minutes without sequelae.
- **Subject 025:** A 24-year old white male subject developed flushing, sneezing, nasal congestion, and increased lacrimation immediately following the initial dose of sugammadex 16 mg/kg. The subject then developed urticaria on the face and upper body, and rhonchi were heard on auscultation of the lungs. All symptoms resolved approximately 1 hour following the administration of sugammadex. No medication was given to treat these symptoms.
- **Subject 030:** A 52-year old white male subject developed mild dysgeusia and cough immediately following the initial dose of 16 mg/kg sugammadex. The subject then developed mild urticaria on the back and chest. All symptoms resolved within 1.5 hours without sequelae. No medication was given to treat these symptoms.

Based on this case review, DPARP identified 3 cases of anaphylaxis in healthy subjects in this repeat dose clinical trial. Study P06042 consisted of 298 unique healthy volunteer subjects who received sugammadex. As a result, we calculated a frequency of anaphylaxis of 1.0% (3/298) in a healthy volunteer population. It is of note that all three cases of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

b) Review of Other Hypersensitivity Cases

Of the 8 cases of hypersensitivity identified by the Applicant, the 3 subjects which met the diagnostic criteria for anaphylaxis have been described in detail above. Among the 5 additional subjects adjudicated as having a hypersensitivity reaction, 4 subjects were in the sugammadex 16 mg/kg group, and 1 subject in the 4 mg/kg group. With the exception of 1 subject in the 16

mg/kg group who experienced urticaria with the 2nd dose, all hypersensitivity reactions occurred with the first dose. One subject in the 16 mg/kg experienced urticaria on all three administrations of sugammadex, while one subject in the 4 mg/kg group experienced pruritic rash on the first two administrations, and no reaction with the third administration.

DPARP reviewed the 68 potential hypersensitivity cases in 49 subjects in order to further characterize the types of reactions observed. Out of these 49 subjects, 4 were randomized to the placebo arm, 10 were randomized to sugammadex 4mg/kg, and 35 were randomized to sugammadex 16mg/kg for a total of 45 subjects exposed to sugammadex. Of those subjects who received sugammadex, a majority of the subjects who experienced hypersensitivity symptoms were in the sugammadex 16mg/kg dose group (35/45, 77.8%) and reacted in ≤ 5 minutes (40/45, 88.9%) on the first dose (30/45, 66.7%). Most of these subjects did not require medical intervention (43/45, 95.6%) and ultimately completed the study (36/45, 80.0%).

See Table 2 for a summary of the hypersensitivity-related adverse events occurring in $\geq 2\%$ of subjects in any treatment group in study P06042.

| Table 2. Summary of Hypersensitivity Adverse Events[†] Occurring in $\geq 2\%$ of Subjects in Any Treatment Group – Study P06042 | | | |
|---|----------------------------|---|--|
| | Placebo (N=150) | Sugammadex 4 mg/kg (N = 148) | Sugammadex 16 mg/kg (N = 150) |
| Number of subjects with hypersensitivity adverse event | n = 4 (2.7) | n = 10 (6.8) | n = 35 (23.3) |
| Preferred Term | n (%) | | |
| Abdominal Pain | 1 (0.7) | 0 | 3 (2.0) |
| Cough | 2 (1.3) | 1 (0.7) | 5 (3.3) |
| Flushing [†] | 1 (0.7) | 2 (1.4) | 8 (5.3) |
| Hypotension | 0 | 0 | 3 (2.0) |
| Nausea | 2 (1.3) | 8 (5.4) | 24 (16.0) |
| Pruritus | 0 | 2 (1.4) | 3 (2.0) |
| Rhinitis [†] | 3 (2.0) | 1 (0.7) | 2 (1.3) |
| Sneezing | 0 | 0 | 3 (2.0) |
| Tachycardia | 0 | 2 (1.4) | 4 (2.7) |
| Urticaria | 0 | 0 | 7 (4.7) |
| Vomiting | 2 (1.3) | 3 (2.0) | 4 (2.7) |

[†] Predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2), with the exception of flushing and rhinitis; pre-defined terms were specifically erythema and rhinorrhea, respectively.
Source: Table 19, p. 126, Clinical Study Report P0642, Module 5.3.5.4.

As can be seen in the table above, the most common hypersensitivity adverse events reported in study P06042 were nausea, flushing, urticaria, and cough. Several hypersensitivity symptoms, including flushing, hypotension, nausea, pruritus, sneezing, tachycardia, urticaria, and vomiting, showed a dose-response, more frequently occurring in the high dose group when compared to the low dose group and placebo.

4) Mechanistic Study Review

The sponsor conducted additional mechanistic research to evaluate the potential underlying mechanisms of action for any observed hypersensitivity and/or anaphylaxis reactions. Specifically, the mechanistic research aimed to investigate a possible IgE/IgG-mediated hypersensitivity reaction (i.e., anti-sugammadex IgE and IgG assay, skin testing, tryptase, basophil histamine-release testing) and other potential underlying mechanisms (contact/complement system activation and parameters of neutrophil or cytokine activation).

In study P06042, skin testing, both by skin prick and intradermal, were essentially negative. The only positive intradermal reaction occurred at a low dilution (1:10) and many other tests were read as indeterminate. While on its own this would be inconclusive, in light of non-elevated tryptase levels, direct or IgE-mediated mast cell degranulation does not appear to be the cause of the hypersensitivity reactions. Additionally, intact and IgE-stripped basophils did not show evidence of histamine release upon drug exposure suggesting a lack of direct and IgE-mediated basophil mediator release. Drug specific IgE and IgG levels were negative, suggesting that the reactions are not immunoglobulin-mediated. Finally, there were no differences between subjects with and without hypersensitivity in cytokine release, complement activation, or kallikrein levels.

While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.

B) Post-Marketing Reports of Hypersensitivity

Sugammadex is approved in more than 70 countries and marketed in more than 40 countries worldwide, with a total of 3,276,086 vials sold as of June 15, 2012.

The Market Authorization Holder pharmacovigilance database Global Pharmacovigilance Corporate Adverse Events Reporting and Evaluation System was searched by the Applicant on July 3, 2012, for postmarketing reports of anaphylaxis and serious hypersensitivity received from healthcare providers, cumulatively from market introduction through June 15, 2012, in patients administered sugammadex. Anaphylaxis reports were identified by querying the narrow Anaphylaxis Standard MedDRA Query (SMQ), along with narrow terms from the "Anaphylactic/ anaphylactoid shock" sub-SMQ in the Shock SMQ. Serious hypersensitivity reports were identified by querying the broad Anaphylaxis SMQ, along with the preferred term "hypersensitivity". A total of 144 reports were identified in this query: 87 reports of anaphylaxis and 57 reports of serious hypersensitivity.

DPARP has reviewed the 144 post-marketing reports. There is a consistent constellation of symptoms described consisting of: rash, bronchospasm, urticaria, edema, and hypotension and a majority of these cases required medical intervention with epinephrine, corticosteroids, and/or antihistamines. There were 5 deaths among the post-marketing reports that seem to be unrelated to drug hypersensitivity and more likely due to underlying co-morbidities or post-surgical complications. While the Applicant has sought adjudication of these reports by an external

committee and has quantified the number of cases of anaphylaxis, DPARP did not attempt to quantify the frequency of anaphylaxis from this database, as we felt the controlled clinical data to be more reliable. Therefore, DPARP has considered these post-marketing reports as a means of further characterizing the types of hypersensitivity reactions that have been observed with use of sugammadex in the controlled clinical studies.

V. Summary and Discussion

Sugammadex sodium is a modified gamma-cyclodextrin being proposed for the indications of 1) the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium (dose 4 mg/kg), and 2) the immediate reversal of neuromuscular blockade after administration of rocuronium (dose 16 mg/kg).

In the original development program, both anaphylaxis and other hypersensitivity reactions were observed. DPARP concluded at that time that sugammadex is potentially allergenic and may cause anaphylaxis, with an estimated anaphylaxis frequency of 1.4% in a population of healthy subjects. When considering the entire database, the frequency of anaphylaxis was estimated to have been between 0.1% and 0.3%. DPARP was concerned that this frequency of anaphylaxis may be a significant underestimate of the true frequency, since the original clinical development program did not assess the safety of repeat exposures. Therefore, DPARP outlined that the Applicant should: 1) characterize the safety of sugammadex on repeat exposure, specifically the nature and frequency of anaphylaxis and other hypersensitivity reactions, 2) define the frequency/time course of events related to sugammadex administration, and other characteristics of the adverse reactions, and 3) attempt to define the immunological basis or other pathophysiology of these adverse events by appropriate tests, including but not limited to the skin test and laboratory tests to evaluate for the production of IgE against sugammadex sodium.

As a part of the resubmission, the Applicant has provided the results of a repeat-dose clinical study. P06042 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the incidence of hypersensitivity after repeated single dose administrations of sugammadex in healthy subjects ages 18 to 55. A total of 480 subjects received a single-blind, saline placebo test dose at Week 0, followed by 3 doses of randomized, double-blind study drug at Weeks 1, 5, and 11. Patients (n=448) were randomized to 1 of 3 treatment groups: 4 mg/kg sugammadex, 16 mg/kg sugammadex, or placebo at sequential interval of 4 and 6 weeks.

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2), the Applicant identified 68 cases of suspected hypersensitivity in 49 subjects, and 3 cases of anaphylaxis. Using NIAID/FAAN criterion #1, DPARP identified 3 cases of anaphylaxis. Study P06042 consisted of 298 unique healthy volunteer subjects who received sugammadex. As a result, the frequency of anaphylaxis was 1.0% (3/298) in this study. It is of note that all three cases of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

Among the hypersensitivity cases that did not meet diagnostic criteria for anaphylaxis, the most common symptoms were nausea, flushing, urticaria, and cough. Several hypersensitivity symptoms, including flushing, hypotension, nausea, pruritus, sneezing, tachycardia, urticaria, and vomiting, showed a dose-response, more frequently occurring in the high dose group when compared to the low dose group and placebo. Hypersensitivity reactions were more frequently

noted in the 16 mg/kg dose group, occurring within minutes of dosing, and with the first dose of sugammadex.

Review of post-marketing reports, in the context of the data from controlled clinical trials, reveals the presence of a consistent constellation of symptoms consisting of rash, bronchospasm, urticaria, edema, and hypotension with the majority of cases being treated with epinephrine, corticosteroids, and/or antihistamines.

Mechanistic data submitted do not elucidate a clear causal mechanism leading to anaphylaxis and hypersensitivity. While these in vitro data do not necessarily rule out an immunologic basis for the reactions, the totality of the available mechanistic and clinical data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.

DPARP concludes that sugammadex causes anaphylaxis and hypersensitivity events. This risk appears to increase with higher doses and does not appear to increase with repeated exposure. Whether this risk is greater than the risk for other drug products commonly used in the peri-operative setting is difficult to determine. The incidence of anaphylaxis during general anesthesia reported in the literature covers a wide range, with estimates from 1:3500 to 1:25,000.^{3,4} Given changes in medical and surgical practices over time, such as the decreased use of latex and utilization of new measures to prevent medical errors, obtaining an accurate estimate of the frequency of peri-operative anaphylaxis in the context of current standards of care is challenging. For this reason, there is no predetermined level of acceptable or unacceptable risk for anaphylaxis for new drug products. Ultimately, the risk-benefit assessment for sugammadex depends primarily on the efficacy and safety data specific to sugammadex and its expected use in a real-world setting.

VI. References

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol.* 2006; 117:391-7
2. Rüggeberg JU et al. Anaphylaxis: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; 25 5675-84
3. Blessing-Moore et al. The Joint Task Force on Practice Parameters. *J Allergy Clin Immunol* 2005. Mar;115(3 Suppl 2):S483-523).
4. Sampson et.al. Symposium on the Definition and Management of Anaphylaxis: Summary report. *J Allergy Clin Immunol*, March 2005; p:584-591

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electronically and this page is the manifestation of the
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signature.**

/s/

ERIKA N TORJUSEN
08/14/2013

BANU A KARIMI SHAH
08/14/2013

LYDIA I GILBERT MCCLAIN
08/14/2013
Acting Division Director

9.6.2 Consultations Related to Coagulation and Bleeding

The consultations are arranged chronologically beginning with those from the original NDA submission.

MEMOR
ANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

DIVISION OF HEMATOLOGY
PRODUCTS

Date: April
12, 2013

From: George G.
Shashaty, M.D.
Medical Reviewer, Division of Hematology Products (DHP)

Subject: Consultation Request received February
11, 2013
Sugammadex
NDA 22225

To: Arthur
Simone, M.D.
Division of Anesthesia, Analgesia and Addiction Products
(DAAAP)

Through: Kathy Robie Suh,
M.D., Ph.D.
Clinical Team Leader, Division of Hematology Products

A
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Ann
Farrell,
M.D.
Director
Division of Hematology Products

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This is the second review cycle for Sugammadex (SU). SU is being developed as a reversing agent for rocuronium- and vecuronium-induced muscle paralysis which is used to permit surgery. Among the concerns stated by FDA after the review of the initial NDA submission (see review dated June 27, 2008, Art Simone, M.D., Ph.D., page 96) was the following:

“3. *Effect of* (b) (4) *on*
coagulation time

The Applicant failed to perform clinical evaluations of the commonly used parameters

for assessing a patient's coagulation times. These include aPTT, PT and the INR. In *in vitro* studies, it was noted that (b) (4) prolongs all of these parameters. The clinical implications for this effect is not known, but could have significant safety implications for patients undergoing surgical procedures with increased risk of blood loss or where postoperative anticoagulation is required. Investigations need to be undertaken to determine the effects of (b) (4) on coagulation times and the mechanism by which it affects them. Knowing the mechanism is important as it could impact how patients are treated for post-operative bleeding or anticoagulation. It is recommended that these investigations be completed prior to consideration of approving (b) (4).

As a result, the Complete Response letter (dated July 31, 2008) sent to the sponsor stated that the following assessment would be required in a re-submission:

“ 2. Studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting”.

Subsequently, the sponsor provided additional *in vitro* data and proposals for clinical studies to address this safety concern. The information and proposals were consulted to DHP for review (see reviews by George Shashaty in DARRTS dated June 7, 2010, December 16, 2010 and October 18, 2011 and by Min Lu dated November 17, 2009). The current submission includes a complete study report (CSR) for a study (Protocol P07038: A randomized, controlled, parallel-group, double-blind trial of sugammadex or usual care (neostigmine) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin). I am in the process of reviewing the CSR of that trial in a separate consult review for this NDA.

The sponsor's resubmission also includes the CSRs for two additional trials, which DHP has been requested to review. These trials are drug-drug interaction studies, one that evaluates a potential interaction between sugammadex and aspirin and one that evaluates a potential interaction between sugammadex and enoxaparin or unfractionated heparin. DHP comments for these studies are provided in this review.

Purpose of the Consult

DAAAP requests the expertise of the Division of Hematology Products to address the following:

“In concert with the Clinical Pharmacology team (Dr. Srikanth Nallani (x6-1580) and Dr. Yun Xu), please evaluate the significance of any changes in the coagulation metrics

and their relationship to the product's pharmacokinetics as reported in Module 5.3.3.5 of the submission. It is titled: Development and application of a mathematical model for the prediction of sugammadex effects on coagulation endpoints APTT and PT(INR).

Please also evaluate the clinical significance, if any, of the findings from the two studies below once the Clinical Pharmacology team has weighed in on the validity of the findings from a PK perspective:

- clinical trial P07044 in healthy subjects to assess for a sugammadex-anticoagulant interaction (\\cdsesub1\evsprod\NDA022225\0046\m5\53-clin-stud-rep\532-rep-stud-pk-human-biostat\5322-rep-hep-metab- interact-stud\p07044\p07044.pdf)
- clinical trial P07025 in healthy subjects to assess for a sugammadex-aspirin interaction (\\cdsesub1\evsprod\NDA022225\0046\m5\53-clin-stud-rep\532-rep-stud-pk-human-biostat\5322-rep-hep-metab- interact-stud\p07025\p07025.pdf)”

Review of the Submission

Study P07044

Study P07044 is a phase 1 trial entitled “A Randomized, Double-Blind, Placebo-Controlled, 4 Period, Two Part Cross-Over Study to Evaluate the Potential Interaction Effect between 4 mg/kg and 16 mg/kg Sugammadex and Enoxaparin or Unfractionated Heparin on Anticoagulant Activity in Young Healthy Volunteers”. The study was performed at a single institution in the Netherlands in accord with Good Clinical Practice by Koos Burggraaf, M.D., Ph.D. from October to December, 2011.

The primary objective of the trial was to investigate the potential effect of 4 mg/kg and 16 mg/kg SU on the anti-Xa activity of enoxaparin and on the aPTT activity of unfractionated heparin (UFH).

The hypothesis was that the administration of a single subcutaneous 40 mg dose of enoxaparin in combination with 4 mg/kg or 16 mg/kg of SU would not increase the anti-Xa activity area-under-the-curve (AUEC)_{3-30 min} to a ratio of > 1.5 as compared to enoxaparin alone (Part 1), or that the administration of a single subcutaneous 5000 IU dose of heparin in combination with 4 mg/kg or 16 mg/kg of SU did not increase the aPTT area-under-the-curve (AUEC)_{3-30 min} to a ratio of > 1.5 as compared to heparin alone (Part 2).

Secondary objectives in Part 1 for subjects treated with enoxaparin were: anti-Xa AUEC_{3-30 min} of 4 mg/kg SU in combination with enoxaparin vs SU alone; anti-Xa AUEC_{3-30 min} of 4 mg/kg SU vs placebo; aPTT AUEC_{3-30 min} of 4 mg/kg SU after enoxaparin vs placebo after enoxaparin; aPTT AUEC_{3-30 min} of 16 mg/kg SU after enoxaparin vs placebo after enoxaparin; aPTT AUEC_{3-30 min} of 4 mg/kg SU in combination with enoxaparin vs 4 mg/kg SU alone; and, aPTT AUEC_{3-30 min} of 4 mg/kg

SU vs placebo. Secondary objectives in Part 2 for subjects treated with UFH were identical to those for subjects treated with enoxaparin, but reversed for anti-Xa and aPTT.

Exploratory objectives included the effects of the above combinations on the PT, the thrombin generation time (TGT), the generation of Xa and the exploration of the relationships between SU plasma concentrations in the presence or absence of the two anticoagulants.

The schedule of treatments is shown in the following figure.

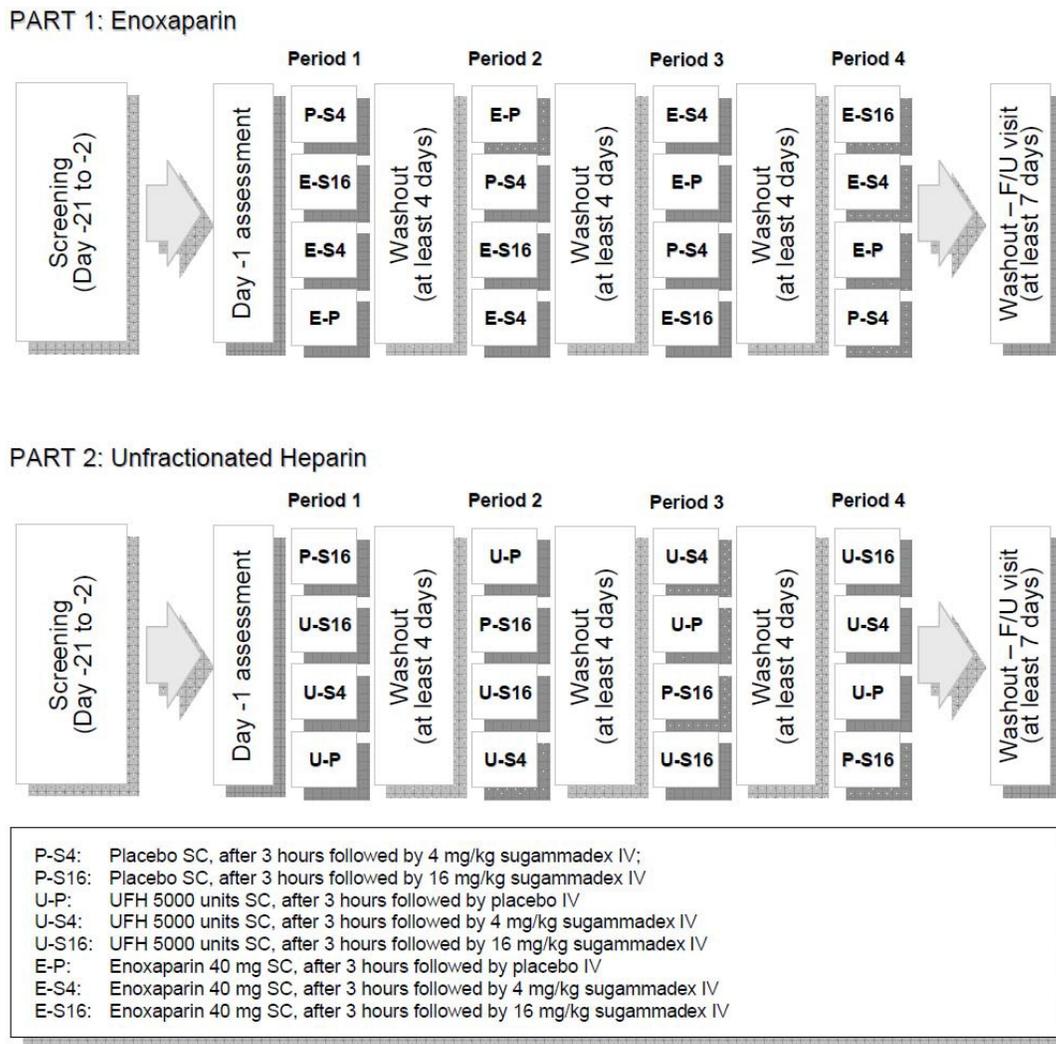


Figure 1: Study Design Diagram

Sponsor submission, page 37

Treatment during the study was as follows:

- Subjects were randomly assigned to a random sequence of 4 periods.

- Period 1-4. Subjects were initially treated with enoxaparin (40 mg), UFH (5000 IU) or placebo, all given subcutaneously.
- Period 1-4. SU or placebo was administered intravenously as a bolus injection within 10 seconds. The dose of SU was 4 mg/kg or 16 mg/kg and the dose of placebo was of similar volume. SU or placebo was given 3 hours after the subcutaneous administration of enoxaparin, UFH or placebo
- There was a washout period of 4 days between periods.

The patient population consisted of healthy volunteers between the ages of 18-45 years. The inclusion and exclusion criteria were numerous but acceptable. For Part 1 of the study, the initial sample size was 12 subjects (3 in each randomized sequence). For Part 2 of the study, the initial sample size was 40 subjects (up to 14 subjects in each randomized sequence).

The schedule of observations/testing is shown in the following table.

Table 1 Study Flow Chart

| Visit | Screen | Period 1 ^A | | | Period 2 ^A | | | Period 3 ^A | | | Period 4 ^A | | | FU ^A |
|--|----------------|-----------------------|----|----------------|-----------------------|----|----------------|-----------------------|----|----------------|-----------------------|----------------|---|-----------------|
| | | -21 to -2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | |
| Explain Study and Obtain Informed Consent(s) | X | | | | | | | | | | | | | |
| Review inclusion/exclusion Criteria | X | X | X | | | | | | | | | | | |
| Demographic Profile | X | | | | | | | | | | | | | |
| Physical Exam | X | X | | | X | | | X | | | | X | | X |
| Medical History | X | X | | | | | | | | | | | | |
| Body Height (cm) and BMI (kg/m ²) | X | | | | | | | | | | | | | |
| Weight (kg) | X | X ^B | | | | | | | | | | | | |
| Elbow Breadth Measurement | X | | | | | | | | | | | | | |
| HIV/HBsAg/HCV | X | | | | | | | | | | | | | |
| Drug/Alcohol Screen | X | X | | | | | | | | | | | | |
| Routine Clinical Laboratory Tests ^C | X ^F | X ^F | | | | | | | | | | | | X |
| Sampling for hypersensitivity research ^D | | | X | X | | X | X | | X | X | | X | X | X |
| Screening Number Assignment | X | | | | | | | | | | | | | |
| Randomization Number Assignment | | | X | | | | | | | | | | | |
| ECG (12-Lead) Safety ^E | X | | | | | | | | | | | | | X |
| Vital Signs (BP, Pulse Rate, Body Temp.) ^E | X | X | | | X ^E | | | X ^E | | | | X ^E | | X ^E |
| Record AEs and Concomitant Meds | X-----X | | | | | | | | | | | | | |
| Anticoagulant/placebo administration | | | | X | | | X | | | X | | | | X |
| Sugammadex Administration | | | | X | | | X | | | X | | | | X |
| Anti-Xa, APTT, PT(INR) | X ^F | X ^F | | | | | | | | | | | | |
| PD blood sampling (anti-Xa, APTT, PT(INR), TGT, factor Xa generation test) | | | | X ^G | | | X ^G | | | X ^G | | | | X ^G |

| Visit | Screen | Period 1 ^A | | | Period 2 ^A | | | Period 3 ^A | | | Period 4 ^A | | | FU ^A |
|--|-----------|-----------------------|----------------|------------------|-----------------------|---|------------------|-----------------------|---|------------------|-----------------------|---|------------------|-----------------------------|
| Day Relative to First Dose ^A | -21 to -2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | 2 | -1 | 1 | 2 | |
| Samples for <i>ex vivo</i> spiking study | | X ^H | | | | | X ^H | | | | | | | X ^H _I |
| Pharmacokinetic Sugammadex Blood Samples | | | X ^J | | | | X ^J | | | X ^J | | | | X ^J |
| Pharmacogenetic Samples ^K | | | X ^L | | | | | | | | | | | |
| Subject Confinement | | X | X | (X) ^M | X | X | (X) ^M | X | X | (X) ^M | X | X | (X) ^M | |
| Outpatient Visits | X | | | | | | | | | | | | | X |

A) Between periods, at least 4 days of washout period is required (i.e. dosing of sugammadex/placebo (T = 0 hr) in the subsequent period should occur at least approximately 96 hrs after the dosing of sugammadex/placebo (T = 0 hr) in the previous period). F/U visit should be planned at least 7 days after the last administration of study medication. F/U visit assessment is also required for discontinued subjects.

B) Weight used for calculation of amount of sugammadex administration.

C) Complete Blood Count (CBC) and differential, chemistry panel, and urinalysis collected at least 4 hrs without food. If needed, unscheduled lab tests can be performed.

D) Blood samples for optional hypersensitivity research will be collected as follows: 1. anti-sugammadex antibodies: predose, and in case of the occurrence of suspected hypersensitivity symptoms additional samples will be taken at 24 hrs post dosing and at FU; 2. tryptase: predose. In case of the occurrence of suspected hypersensitivity symptoms additional samples will be taken at 1, 3, and 24 hrs post dosing and at FU.

E) Additional ECGs and/or BP and pulse rate measurements can be performed if required based on the opinion of the investigator. Note that body temperature is only measured at screening and on Day -1 of Period 1.

F) APTT, PT(INR) and anti-Xa activity will be tested to check eligibility of subjects. APTT and PT(INR) will be included in the Routine Clinical Laboratory Test at Screening and on Day -1 of Period 1. Anti-Xa activity assessment will be conducted separately.

G) Blood sampling for anti-Xa activity and APTT will be performed at pre-dose anticoagulant, - 3:00, -2:30, -2:00, - 1:00, -0:30, -0:10 hrs:min (i.e. pre-dose sugammadex/placebo). Sampling for anti-Xa activity, APTT, PT(INR), TGT, factor Xa generation test will be performed at -0:05 (i.e. pre-dose sugammadex/placebo) and 0:03, 0:10, 0:20, 0:30, 1:00, 3:00 and 6:00 hrs:min post sugammadex/placebo. Blood sampling volume may be reduced in case P07025 results don't support further sampling for TGT and/or Factor Xa generation. See Section 7.6 of the protocol Section 16.1.1.1, Study Procedure (Blood Samples for Determination of Pharmacodynamic Responses).

H) Day -1 of Period 1: Collected in all subjects (including backup subjects) in both Part 1 and 2 prior to randomization. Only samples obtained from subjects, who eventually randomized on Day 1 of Period 1, may be used for spiking experiments.

Day 1 of Period 2: Collected in maximally 12 subjects of Part 1 and the first 20 subjects of Part 2 who reach dosing on Day 1 of Period 2.

I) Samples will only be taken for maximally 12 subjects in Part 1.

J) Sugammadex concentrations will be determined at -0:05 (pre-dose) and 0:03, 0:10, 0:20, 0:30, 1:00, 3:00 and 6:00 hrs:min post dose.

K) Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained pre-dose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained.

L) Blood samples for Pharmacogenetic evaluation will be collected predose (0 hr). DNA sample for pharmacogenetic testing should be drawn only once per subject.

M) Subjects will remain confined to the study site until the completion of study procedures on Day 1 of each period. In case further monitoring of subject is required (e.g. safety, 24 -hour sampling in case of suspected hypersensitivity symptoms), duration of confinement may be extended beyond Day 1 (e.g.. confinement from Day 2 onwards being optional).

Sponsor submission, page 40-41

The clinical supplies are shown in the following table.

Table 2 Identity of Clinical Supplies

| Clinical Material | Dose | Potency | Dosage Form | Batch Number | Lot Number | Expiration Date |
|------------------------------|----------|-----------------------|-------------------------------|--------------|------------|-----------------|
| Sugammadex | 4 mg/kg | 100 mg/mL solution | Single intravenous injection | 529679001 | CD023 | JUN-2012 |
| Sugammadex | 16 mg/kg | 100 mg/mL solution | Single intravenous injection | 529679001 | CD023 | JUN-2012 |
| Placebo (NaCl, 0.9%) | NA | NA | Single intravenous injection | - | 11253014 | MAY-2014 |
| Enoxaparin | 40 mg | 60 mg/0.6 mL solution | Single subcutaneous injection | - | OC145B | AUG-2013 |
| Unfractionated Heparin (UFH) | 5000 IU | 5000 I.E./mL solution | Single subcutaneous injection | - | DF2451 | JAN-2014 |

Sponsor submission, page 48

Blood samples for anti-Xa and aPTT were obtained before the administration of anticoagulant/placebo and at 2.5, 2.0, 1.0, 0.5 and 0.16 hours before SU/placebo administration, and at 0.12 before, and for anti-Xa activity, aPTT, PT, TGT and Xa generation test at 0.05, 0.16, 0.33, 0.5, 1.0, 3.0 and 6 hours after administration of SU/placebo. PK samples were obtained at the same times.

Anti-Xa assays were performed using a commercially available amidolytic chromogenic assay for the determination of heparin(s). The principle of the test was to determine in human plasma the capacity to neutralize added bovine Xa activity. The residual Xa activity is inversely proportional to the heparin concentration. The assays were performed by (b) (4). The aPTT tests were performed using an automated clotting analyzer ((b) (4)) using a reagent that contained rabbit brain phospholipids and a micro silica activator, and the PTs were performed using the same analyzer and Simplastin HTF (Biomerieux), again with all tests performed by (b) (4). Chromogenic substrate assays for thrombin generation and factor Xa generation were performed using commercially available reagents and automated equipment. PK variables (AUClast, Cmax, tmax) and relationship to PD variables were assessed. SU in plasma was determined using a validated liquid chromatography assay with mass spectroscopic detection under the responsibility of the Department of Bioanalytics-Oss, MSD, The Netherlands.

Safety was assessed by history, physical examination, vital signs, laboratory assessments and ECGs. The development of anti-SU antibodies was assessed as indicated in the schedule of observations.

An initial sample size of 12 subjects was planned for Part 1 of the study. This sample size would provide 83% power to reject the primary hypotheses at a one sided significance level of 5%, assuming a true geometric means ratio in anti-Xa AUEC₃₋₃₀ of

1.2 for both SU 4 mg/kg and 16 mg/kg combined with enoxaparin as compared to enoxaparin alone and a within subject CV of 17%. A prespecified interim analysis yielded a CV of < 0.13.

An initial sample size of 40 subjects was planned for Part 2 of the study. This sample size would provide 79% power to reject the primary hypotheses at a one sided significance level of 5%, assuming a true geometric means ratio in aPTT₃₋₃₀ of 1.2 and 1.3 for SU 4 mg/kg and 16 mg/kg, respectively, combined with UFH as compared to UFH alone and a within subject CV of 25%. A prespecified interim analysis yielded a CV of < 0.09.

No formal protocol amendments were made to the study, and there were no major changes to the planned analyses.

Results of the trial

For Part 1, a total of 13 subjects were assigned to one of the four randomized treatment sequences, and all were treated as randomized. One subject discontinued prematurely after having received the investigational drug in the first period because of discolored feces and urine. He was replaced with another subject assigned to the same treatment sequence. Disposition of subjects is shown in the following table.

Table 6 Subject Disposition (%)- Treatment Phase by treatment sequences, Part 1

| Subject Disposition | Treatment Sequence | | | | | | | | Total | |
|------------------------------|-------------------------|-------|-------------------------|-------|-------------------------|-------|-------------------------|-------|-------|-------|
| | P-S4/E-P/ E-S4/E-S16 | | E-S16/P-S4/ E-P/E-S4 | | E-S4/E-S16/ P-S4/E-P | | E-P/E-S4/ E-S16/P-S4 | | | |
| Randomized | 4 | (100) | 3 | (100) | 3 | (100) | 3 | (100) | 13 | (100) |
| Discontinued Treatment Phase | 1 | (25) | 0 | | 0 | | 0 | | 1 | (8) |
| Adverse Event | 1 | (25) | 0 | | 0 | | 0 | | 1 | (8) |
| Completed Treatment Phase | 3 | (75) | 3 | (100) | 3 | (100) | 3 | (100) | 12 | (92) |

P-S4= Placebo + Sugammadex 4mg/kg, E-P= Enoxaparin 40mg SC + Placebo, E-S4= Enoxaparin 40mg SC + Sugammadex 4mg/kg, E-S16= Enoxaparin 40mg SC + Sugammadex 16mg/kg Source: Section 14.1. 1.2
Sponsor submission, page 67

For Part 2, a total of 43 subjects were assigned to one of the four randomized treatment sequences, and all were treated as randomized. Four subjects discontinued prematurely, all because of adverse events (three with mild administration site reactions and one with hemorrhoids). There were three replacements assigned to the same treatment sequences

as those who discontinued. At completion, there were 39 evaluable subjects. Disposition of subjects is shown in the following table.

Table 7 Subject Disposition (%) - Treatment Phase by treatment sequences, Part 2

| Subject Disposition | Treatment Sequence | | | | | | | | Total | |
|------------------------------|--------------------------|-------|--------------------------|-------|--------------------------|-------|--------------------------|-------|-------|-------|
| | P-S16/U-P/ U-S4/U-S16 | | U-S16/P-S16/ U-P/U-S4 | | U-S4/U-S16/ P-S16/U-P | | U-P/U-S4/ U-S16/P-S16 | | | |
| Randomized | 10 | (100) | 10 | (100) | 11 | (100) | 12 | (100) | 43 | (100) |
| Discontinued Treatment Phase | 0 | | 0 | | 2 | (18) | 2 | (17) | 4 | (9) |
| Adverse Event | 0 | | 0 | | 2 | (18) | 2 | (17) | 4 | (9) |
| Completed Treatment Phase | 10 | (100) | 10 | (100) | 9 | (82) | 10 | (83) | 39 | (91) |

P-S16= Placebo + Sugammadex 16mg/kg, U-P= UFH 5000 units SC + Placebo, U-S4= UFH 5000 units SC + Sugammadex 4mg/kg, U-S16= UFH 5000 units SC + Sugammadex 16mg/kg Source: Section 14.1. 2.2

Sponsor submission, page 68

Treatment compliance was documented by the clinical site, which administered all medications.

The addition of SU of 4 mg/kg or 16 mg/kg to enoxaparin did not induce a difference in anti-Xa activity compared to enoxaparin alone. With a dose of SU of 4 mg/kg following placebo, there was no change in anti-Xa activity. The arithmetic means and 90% CIs percentage change in anti-Xa activity from pre-dose SU/placebo by treatment group is shown in the following figure.

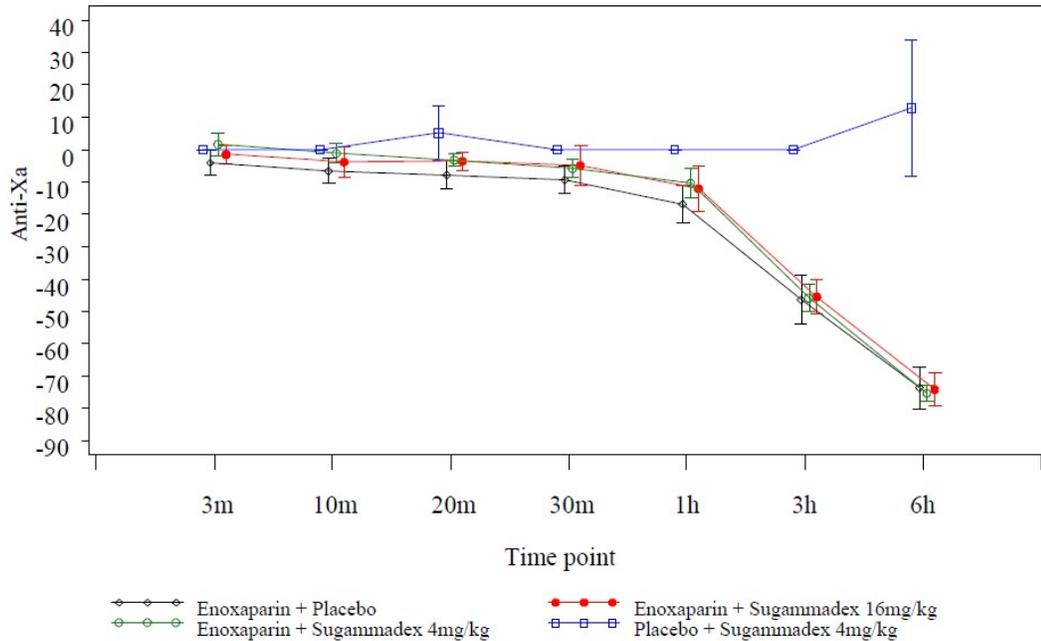


Figure 2: Arithmetic means and corresponding 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for anti-Xa (Part 1).

Sponsor submission, page 73

The mean percentage change in the aPTT from pre-dose SU/placebo/enoxaparin was 5% and 15% at 3 minutes for SU at a dose of 4 mg/kg and 16 mg/kg, respectively, above the increase in aPTT due to enoxaparin alone. The mean aPTT level fell to placebo levels by one hour after SU administration. This is shown in the following figure.

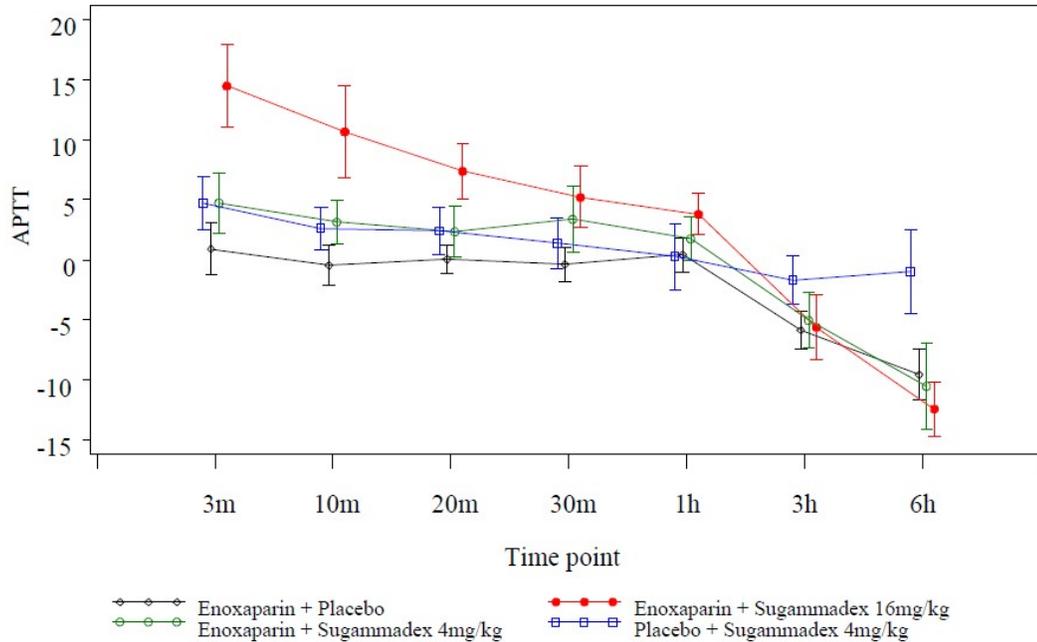


Figure 3: Arithmetic means and corresponding 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for APTT (Part 1).

Sponsor submission, page 74

The $AUEC_{3-30\text{ min}}$ geometric mean ratio for anti-Xa activity (the primary endpoint) of enoxaparin in combination with SU at either 4 mg/kg or 16 mg/kg were both below the prespecified non-inferiority margin of 1.5 for each, and within the 90% CIs (0.98, 1.07 and 0.99, 1.08, respectively), as shown in the following table.

Table 10 Treatment geometric mean ratios and corresponding upper limits of 90% CI's for the $AUEC_{3-30\text{ min}}$ of Anti-Xa (primary analysis)

| Treatment comparison | Geometric mean ratio | Lower limit of the 90% CI | Upper limit of the 90% CI |
|---|----------------------|---------------------------|---------------------------|
| [Enoxaparin + Sugammadex 4mg/kg] vs. [Enoxaparin] | 1.02 | 0.98 | 1.07 |
| [Enoxaparin + Sugammadex 16 mg/kg] vs. [Enoxaparin] | 1.04 | 0.99 | 1.08 |

Source: 14.2.1.1.1

Sponsor submission, page 75

Other secondary and supportive analyses, as well as analyses of secondary endpoints ($AUEC_{3-30\text{ min}}$ geometric mean ratio of anti-Xa of SU at a dose of 4 or 16 mg/kg alone

compared to combination with enoxaparin; anti-Xa AUEC_{3-30 min}; anti-Xa E-max; aPTT AUEC_{3-30 min}) were consistent with the notion of either no additional anti-Xa activity, or at most a small effect on laboratory measures of coagulation induced by SU.

The addition of SU of 4 mg/kg or 16 mg/kg to UFH induced a small difference in AUEC_{3-30 min} in the geometric mean ratio of aPTT compared to the increase induced by enoxaparin alone (ratios of 1.04 and 1.13, respectively). The 90% CIs for these ratios are within the non-inferiority margin of 1.5.

Other secondary and supportive analyses, as well as analyses of secondary endpoints (AUEC_{3-30 min} geometric mean ratio of aPTT of SU at a dose of 4 or 16 mg/kg compared to placebo and compared to combination with enoxaparin; geometric means of aPTT AUEC_{3-30 min} with SU alone at 16 mg/kg, UFH alone or UFH with SU at 4 or 16 mg/kg; aPTT E-max; anti-Xa geometric mean ratio AUEC_{3-30 min}; anti-Xa AUEC_{3-6 hrs}; anti-Xa E-max) were consistent with the notion of either no additional anti-Xa activity, or at most a small effect on laboratory measures of coagulation induced by SU.

The results of these studies are summarized in the following tables.

Part 1

Table 34 Results of primary and secondary analyses, Part 1 (N=13)

| Objective | Endpoint: AUEC _{1-30min} | Treatment comparison | Geometric mean ratio | 2-sided 90% upper CI | Non inferiority margin |
|-----------|--------------------------------------|---|----------------------|----------------------|------------------------|
| Primary | Anti-Xa | [Enoxaparin + Sugammadex 4 mg/kg] vs. [Enoxaparin] | 1.02 | 1.07 | <1.50 |
| | | [Enoxaparin + Sugammadex 16 mg/kg] vs. [Enoxaparin] | 1.04 | 1.08 | <1.50 |
| Secondary | Anti-Xa | [Sugammadex 4 mg/kg] vs. [Placebo] | 1.00 | 1.10 | |
| | | [Enoxaparin + Sugammadex 4 mg/kg] vs. Sugammadex 4mg/kg] | 11.64 | 13.60 | |
| | APTT | [Enoxaparin + Sugammadex 4 mg/kg] vs. [Enoxaparin] | 1.02 | 1.05 | |
| | | [Enoxaparin + Sugammadex 16 mg/kg] vs. [Enoxaparin] | 1.09 | 1.13 | |
| | | [Sugammadex 4 mg/kg] vs. [Placebo] | 1.05 | 1.08 | |
| | | [Enoxaparin + Sugammadex 4 mg/kg] vs. Sugammadex 4 mg/kg] | 1.19 | 1.24 | |

Sponsor submission, page 91

Part 2

Table 35 Results of primary and secondary analyses, Part 2 (N=42)

| Objective | Endpoint: AUEC _{3-30min} ¹ | Treatment comparison | Geometric mean ratio | 2-sided 90% upper CI | Non inferiority margin |
|-----------|---|--|----------------------|----------------------|------------------------|
| Primary | APTT | [UFH + Sugammadex 4mg/kg] vs. [UFH] | 1.04 | 1.06 | <1.5 |
| | | UFH + Sugammadex 16 mg/kg vs. [UFH] | 1.13 | 1.15 | <1.5 |
| Secondary | APTT | [Sugammadex 16 mg/kg] vs. [Placebo] | 1.13 | 1.15 | |
| | | [UFH + Sugammadex 16 mg/kg] vs. [Sugammadex 16 mg] | 1.07 | 1.09 | |
| | Anti-Xa | [UFH + Sugammadex 4mg/kg] vs. [UFH] | 1.00 | 1.03 | |
| | | [UFH + Sugammadex 16 mg/kg] vs. [UFH] | 1.05 | 1.09 | |
| | | [Sugammadex 16 mg/kg] vs. [Placebo] | 0.97 | 1.04 | |
| | | [UFH + Sugammadex 16 mg/kg] vs. Sugammadex 16 mg/kg] | 1.68 | 1.83 | |

Sponsor submission, page 92

Pharmacokinetic studies showed that there was no effect of either enoxaparin or UFH on the C_{max} or AUC_{0-6 hr} of SU. PK/PD studies showed that there was an SU dose-related increase in both the aPTT and the PT whether SU was given with placebo, enoxaparin or UFH. The curves of the relationship were shifted slightly upward when SU was given with either enoxaparin or UFH compared to when SU was given with placebo.

Safety

Exposure to both sugammadex and placebo was generally as specified in the protocol. There were 2 subjects (one placebo and one sugammadex) who received two separate (rather than a single) injections because it was noted that there was left-over volume in the syringes. Three subjects discontinued after the first administration of SU, 4 mg/kg and two subjects discontinued after the first administration of UFH. One subject receiving SU discontinued the study in the enoxaparin arm of the trial due to a discoloration of stool, one subject receiving SU in the UFH arm discontinued due to hemorrhoids, and three subjects receiving UFH discontinued because of administration site reaction. There were no deaths and no serious or severe adverse reactions. All other subjects received all protocol-specified doses.

In general, treatment emergent adverse events were somewhat more frequent when SU was administered with enoxaparin or UFH than when administered either enoxaparin or UFH was administered alone. All treatment emergent adverse events were of mild intensity and involved a variety of organ systems. There were several minor bleeding events (injection site hematoma, epistaxis, hemorrhoidal) that were not considered to be treatment related by the investigator. Approximately 2/3rd of adverse events were considered to be related to SU by the investigator, and about 1/2 of adverse events were considered to be related to enoxaparin/UFH by the investigator. There were no clinically significant perturbations in physical examination, laboratory values or ECGs.

Adverse events reported in Part 1 of the study are shown in the following table.

Table 38 Overall Summary of Adverse Events (All Treated Subjects)

| | Number (%) of Subjects | | | | |
|---|------------------------|----------------------|-------------------------------------|--------------------------------------|-----------------|
| | Sug 4mg/kg (N=13) | Enox 40 mg (N=12) | Sug 4mg/kg+ Enox 40 mg (N=12) | Sug 16mg/kg+ Enox 40 mg (N=12) | Total (N=13) |
| Subjects with AEs ^a | 7 (54%) | 6 (50%) | 8 (67%) | 7 (58%) | 13 (100%) |
| Deaths Subjects with SAEs | 0 | 0 | 0 | 0 | 0 |
| Subjects discontinued due to AEs ^b | 1 (8%) | 0 | 0 | 0 | 1 (8%) |
| Subjects with AEs related to sugammadex ^c | 4(31%) | 2(17%) | 7(58%) | 6 (50%) | 9 (69%) |
| Subjects with AEs related to enoxaparin ^c | 2 (15%) | 4 (33%) | 2 (17%) | 2 (17%) | 7 (54%) |
| Subjects with AEs ^a of reported severe intensity | 0 | 0 | 0 | 0 | 0 |

AE = adverse event; SAE = serious adverse event.

a: Treatment-emergent adverse events, including treatment-related adverse events, SAEs, and AEs of any level of severity, occurring after first randomized dose (All-Subjects Treated Set).

b: Including subjects who discontinued randomized treatment due to an AE that was not treatment-emergent, ie, which started before first dose of randomized treatment or more than 30 days after last dose.

c: Treatment-related adverse events are defined as treatment-emergent adverse events that are “probably” or “possibly” related to study treatment according to the investigator.

Source: Section 14.3.1, Section, 14.3.2 (B-10.0.1, B-1.0.1, B-9.0.1, A-7.0.1, B-2.0.1, B-5.0.1)

Sponsor submission, page 102

Adverse events reported in Part 2 of the study are shown in the following table.

Table 38 Overall Summary of Adverse Events (All Treated Subjects)

| | Number (%) of Subjects | | | | Total (N=13) |
|---|------------------------|----------------------|-------------------------------------|--------------------------------------|-----------------|
| | Sug 4mg/kg (N=13) | Enox 40 mg (N=12) | Sug 4mg/kg+ Enox 40 mg (N=12) | Sug 16mg/kg+ Enox 40 mg (N=12) | |
| Subjects with AEs ^a | 7 (54%) | 6 (50%) | 8 (67%) | 7 (58%) | 13 (100%) |
| Deaths | 0 | 0 | 0 | 0 | 0 |
| Subjects with SAEs | 0 | 0 | 0 | 0 | 0 |
| Subjects discontinued due to AEs ^b | 1 (8%) | 0 | 0 | 0 | 1 (8%) |
| Subjects with AEs related to sugammadex ^c | 4(31%) | 2(17%) | 7(58%) | 6 (50%) | 9 (69%) |
| Subjects with AEs related to enoxaparin ^c | 2 (15%) | 4 (33%) | 2 (17%) | 2 (17%) | 7 (54%) |
| Subjects with AEs ^a of reported severe intensity | 0 | 0 | 0 | 0 | 0 |

AE = adverse event; SAE = serious adverse event.

a: Treatment-emergent adverse events, including treatment-related adverse events, SAEs, and AEs of any level of severity, occurring after first randomized dose (All-Subjects Treated Set).

b: Including subjects who discontinued randomized treatment due to an AE that was not treatment-emergent, ie, which started before first dose of randomized treatment or more than 30 days after last dose.

c: Treatment-related adverse events are defined as treatment-emergent adverse events that are “probably” or “possibly” related to study treatment according to the investigator.

Source: Section 14.3.1, Section, 14.3.2 (B-10.0.1, B-1.0.1, B-9.0.1, A-7.0.1, B-2.0.1, B-5.0.1)

Sponsor submission, page 103

Sponsor Conclusions

Based on the data generated in this trial, the sponsor concluded that there was no clinically significant effect of SU on the anti-Xa activity induced by enoxaparin, or on the prolongation of the aPTT induced by UFH.

Study P07025

Study P07025 is a phase 1 trial entitled “A Randomized, Double-Blind, Placebo-Controlled, 4-Period Cross-Over, Drug-Drug Interaction Study to Evaluate the Effect of Sugammadex and Aspirin on Platelet Aggregation and Coagulation Parameters in Young Healthy Male Volunteers”. The study was performed at a single institution in the Netherlands in accord with Good Clinical Practices by Adam Cohen, M.D., Ph.D. from January to May, 2011.

The primary objective of the trial was to investigate the potential for an interaction between sugammadex (4 mg/kg) and aspirin on platelet aggregation (PA) using collagen-induced whole blood aggregometry in healthy male volunteers. The hypothesis was that the administration of SU following multiple daily doses of 75 mg of aspirin did not increase the inhibition of PA to a degree greater than that achieved with the administration of aspirin alone. To measure PA, the area under the effect curve (AUEC) between 3 to 30 minutes after drug administration was calculated, with a further inhibitory effect demonstrated by an AUEC that was smaller with SU plus aspirin vs. aspirin with placebo. A bound exceeding 0.75 to indicate a non-clinically relevant decrease in PA was based on studies of the interaction between aspirin and clopidogrel.

Secondary objectives were to determine the effects of the combination of sugammadex and aspirin on the activated partial thromboplastin time (aPTT), to compare the effect of the administration of sugammadex alone on the aPTT compared to the administration of placebo, and to assess the potential interaction between sugammadex and aspirin on the cutaneous bleeding time. There were additional exploratory endpoints determined as well.

The schedule of treatments is shown in the following figure.

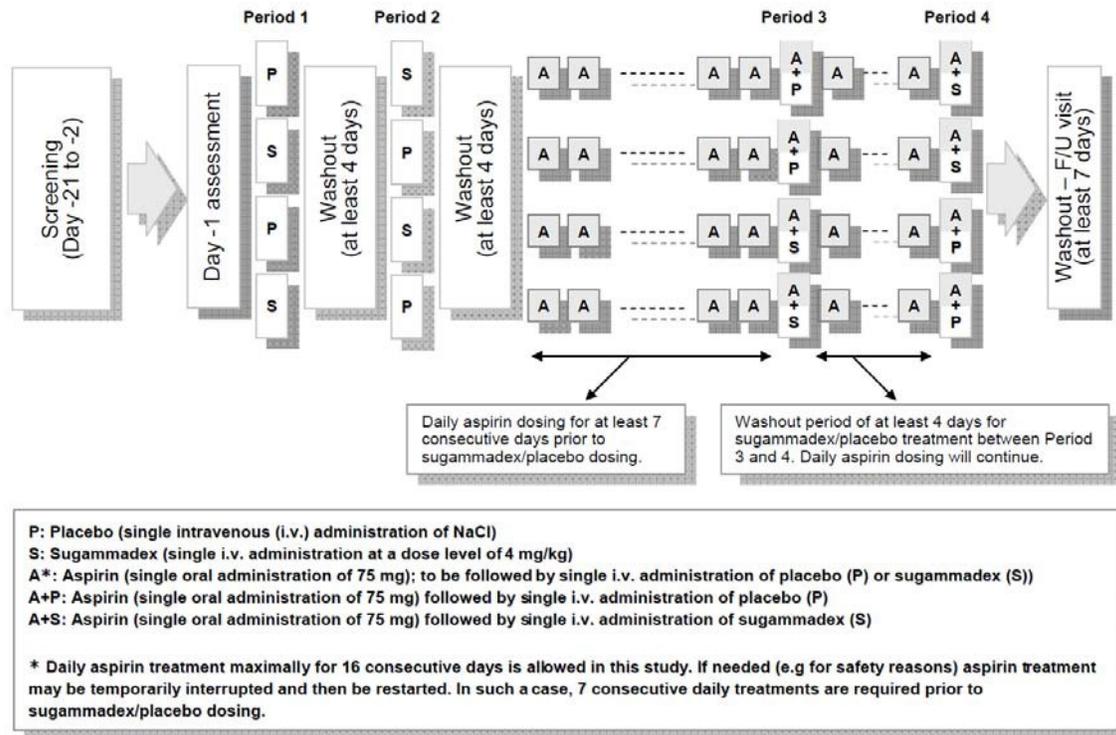


Figure 1 Study Design Diagram
Sponsor submission, page 28

Treatment during the study was as follows:

- Period 1-2. SU or placebo was administered intravenously as a bolus injection within 10 seconds. The dose of SU was 4 mg/kg and the volume of placebo was of equivalent.
- Period 3-4. For at least 7 days prior to treatment with SU or placebo, subjects received 75 mg of oral aspirin daily.

The patient population consisted of healthy volunteers between the ages of 18-45 years. The inclusion and exclusion criteria were numerous but acceptable.

The schedule of observations/testing is shown in the following table.

Table 1 Study Flow Chart

| Relative to dose in the applicable period (days) | Screen | Period 1 | | | Washout period (at least 4 days) | Period 2 | | | Washout period (at least 4 days) | Period 3 | | | Washout (at least 4 days) + aspirin treatment period | Period 4 | | | FU (1) |
|--|-----------|----------|--------|---|-------------------------------------|----------|-------|---|-------------------------------------|----------|-------|---|---|----------|-------|---|--------|
| | -21 to -2 | -1 | 1 | 2 | | -1 | 1 | 2 | | -1 | 1 | 2 | | -1 | 1 | 2 | |
| Explain Study and Obtain Informed Consent(s) | X | | | | | | | | | | | | | | | | |
| Review inclusion/exclusion Criteria | X | X | | | | | | | | | | | | | | | |
| Demographic Profile | X | | | | | | | | | | | | | | | | |
| Physical Exam | X | X | | | | X | | | | X | | | | | | | X |
| Medical History | X | | | | | | | | | | | | | | | | |
| Body Height (cm) | X | | | | | | | | | | | | | | | | |
| Weight (kg) | X | | X (2) | | | | | | | | | | | | | | |
| Body Mass Index (BMI, kg/m ²) | X | | X | | | | | | | | | | | | | | |
| Elbow Breadth Measurement | X | | | | | | | | | | | | | | | | |
| HIV/HBsAg/HCV | X | | | | | | | | | | | | | | | | |
| Drug/Alcohol Screen | X | X | | | | X | | | | X | | | | X | | | |
| Routine Clinical Laboratory Tests (3) | X | X | | | | | | | | | | | | | | | |
| Sampling for hypersensitivity research (4) | | | X | X | | | X | X | | | X | X | | | X | X | X |
| Screening Number Assignment | X | | | | | | | | | | | | | | | | |
| Randomization Number Assignment | | | X | | | | | | | | | | | | | | |
| Record AEs and Concomitant Meds | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG (12-Lead) Safety | X | X | | | | | | | | | | | | | | | X |
| Vital Signs (BP, Pulse Rate, Oral Temp.) (5) | X | X | | | | | | | | | | | | | | | X |
| Aspirin administration (6) | | | | | | | | | X (11) | X | X | X | X (11) | X | X | | |
| Sugammadex/Placebo Administration | | | X | | | | X | | | | X | | | | X | | |
| PD (PA/APTT/PT/ACT/TGT/Factor Xa generation) | X (7) | X (7) | X (8) | | | | X (8) | | | | X (8) | | | | X (8) | | |
| Bleeding time | X | X | X (9) | | | | X (9) | | | | X (9) | | | | X (9) | | |
| Pharmacokinetic Blood Samples | | | X (8) | | | | X (8) | | | | X (8) | | | | X (8) | | |
| TxB ₂ sampling | | | X | | | | X | | | | X | | | | X | | |
| Sample for Pharmacogenetic Analysis | | | X (10) | | | | X | | | | X | | | | X | | |
| Subject Confinement | | X | X | X | | X | X | X | | X | X | X | | X | X | X | |
| Outpatient Visits (11) | X | | | | | | | | | X | | | | X | | | X |
| Subject ID card (12) | | | | X | | | | | | | | | | | | | X |

- (1) F/U visit will be at least 7 days after the administration of the last dose in the last period. F/U visit assessment is also required for discontinued subjects.
- (2) Used for calculation of volume of sugammadex/placebo administration for Period 1-4.
- (3) Complete Blood Count (CBC) and differential, chemistry panel, and urinalysis collected at least 4 hours without food.
- (4) Blood samples for optional hypersensitivity research will be collected as follows: 1. anti-sugammadex antibodies: pre-dose, and in case of the occurrence of suspected hypersensitivity symptoms, additional samples collection at 24 hours after onset of symptoms and at F/U; 2. tryptase: pre-dose and in case of the occurrence of suspected hypersensitivity symptoms, 1, 3, and 24 hours post onset of symptoms 3. additional hypersensitivity research: pre-dose, and in case of the occurrence of suspected hypersensitivity symptoms, additional samples collection at 1, 3, and 24 hours after onset of symptoms.
- (5) Additional ECGs and/or BP and pulse rate measurements can be performed if required based on the opinion of the investigator
- (6) Once daily oral administration of 75 mg aspirin starts right after the washout period following treatment period 2. Daily treatment of at least 7 consecutive days is required to cause sufficient platelet aggregation inhibition prior to sugammadex/placebo treatment. Aspirin is administered daily maximally for 16 consecutive days. If needed (e.g. for safety reasons) aspirin treatment may be temporarily interrupted and then be restarted. In such a case, 7 consecutive daily treatments are required prior to sugammadex/placebo dosing.
- (7) At screening PA (platelet aggregation), APTT and PT/INR will be assessed. On Day -1 of Period 1 only, APTT and PT/INR will be assessed.
- (8) On Day 1, blood samples will be taken at pre-dose (i.e. -5 minutes), 3, 15 and 30 minutes and 1, 3 and 6 hours post-dose.
- (9) Bleeding time will be evaluated at screening and at pre-dose (i.e. -15 minutes) and 5 minutes and 6 hours post sugammadex/placebo dosing.
- (10) Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained pre-dose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained.
- (11) During outpatient periods, on scheduled aspirin treatment days, subjects will visit the site daily for intake of aspirin. Aspirin will be taken at approximately the same time of the day as the administration of sugammadex/placebo in previous periods. Sugammadex or placebo will be administered approximately 30 minutes after aspirin dosing in Periods 3 and 4.
- (12) Subject ID card will be handed over to each subject when they leave the site and be collected at F/U visit.

Sponsor submission, page 29

The clinical supplies are shown in the following table.

Table 2 Identity of Clinical Supplies

| Clinical Material | Dose | Potency | Dosage Form | Batch Number | Lot Number | Expiration Date |
|----------------------|---------|--------------------|------------------------------|--------------|------------|-----------------|
| SCH 900616 | 4 mg/kg | 100 mg/mL solution | Single intravenous injection | PE011 | CD023 | JUN-2012 |
| Placebo (NaCl, 0.9%) | NA | NA | Single intravenous injection | 0522C13 | NA | NOV-2013 |
| Aspirin | 75 mg | 75 mg tablet | Tablet | 0912009 | NA | DEC-2012 |

Sponsor submission, page 37

Platelet aggregation after collagen (1.5µg/ml) stimulation was measured by whole blood aggregometry and expressed in ohms of impedance (Chronolog, model 590). Aggregometry was performed at the Center for Human Drug Research according to standard operating procedures. Pilot studies indicated that aspirin administration causes an approximate reduction of 60% in whole blood platelet aggregation. The AUEC between 3 and 30 minutes was chosen because that is the time of maximal SU activity,

and was the same interval used to measure the effects of SU on the aPTT in a previous study (19.4.115).

The aPTT tests were performed with an automated clotting analyzer ([REDACTED] (b) (4) [REDACTED]) using a reagent that contained rabbit brain phospholipids and a micro silica activator, and the PTs were performed using the same analyzer and Simplastin HTF (Biomerieux) by [REDACTED] (b) (4) [REDACTED]. Activated clotting times were performed using the Hemochron® system as a bedside procedure. Chromogenic substrate assays for thrombin generation and factor Xa generation were performed using commercially available reagents and automated equipment. The bleeding time was determined after a standard incision was made on the volar aspect of the forearm. PK variables (AUClast, Cmax, tmax) and relationship to PD variables were assessed.

Safety was assessed by history, physical examination, vital signs, laboratory assessments and ECGs. The development of anti-SU antibodies was assessed as indicated in the schedule of observations.

An initial sample size of 24 subjects was planned for the study. This sample size would provide 90% power to reject the primary hypothesis at a one sided significance level of 5%, assuming that the true geometric means ratio in AUEC₃₋₃₀ of SU/aspirin combination to aspirin alone is 1 with a within subject CV of 35%.

No formal protocol amendments were made to the study. There were a few minor changes made (sampling time, bioanalytic procedures, elimination of uncertainties) that did not affect the validity of the study.

Results of the trial

A total of 24 subjects were assigned to one of four randomized treatment sequences. Two subjects prematurely discontinued from the study and were replaced in the appropriate treatment sequence. One of the replacement subjects discontinued prematurely. Two of the premature discontinuations were for lack of compliance and one was for a hypersensitivity reaction. In total, therefore, 23 subjects completed the trial.

Subject disposition is shown in the following table.

Table 7: Subject Disposition (%) - Treatment Phase by treatment sequences

| Subject Disposition | Treatment Sequence | | | | | | | | Total | |
|------------------------------|--------------------|-------|-------------|-------|-------------|-------|-------------|-------|-------|-------|
| | P/S/A+P/A+S | | P/S/A+S/A+P | | S/P/A+P/A+S | | S/P/A+S/A+P | | | |
| Randomized | 7 | (100) | 6 | (100) | 6 | (100) | 7 | (100) | 26 | (100) |
| Discontinued Treatment Phase | 2 | (29) | 0 | | 0 | | 1 | (14) | 3 | (12) |
| Adverse Event | 0 | | 0 | | 0 | | 1 | (14) | 1 | (4) |
| Non-Compliance With Protocol | 2 | (29) | 0 | | 0 | | 0 | | 2 | (8) |
| Completed Treatment Phase | 5 | (71) | 6 | (100) | 6 | (100) | 6 | (86) | 23 | (88) |

Subjects that were randomized, but never treated are included in the Discontinued Treatment Phase.

P=Placebo, S=Sugammadex, A=Aspirin

Source: Section 14.1. 2.2

Sponsor submission, page 54

There were several protocol deviations observed as follows:

- Randomization procedure not in sequence for 2 subjects because they were not eventually randomized. Two other subjects then filled the incomplete randomization.
- Deviation from the inclusion/exclusion criteria was observed in 1 subject because his baseline PT (15.3 sec) exceeded the allowable PT for enrollment (15 sec).
- Timing of PK samples was delayed in 2 subjects, and for all subjects, PK/PD pre-dose samples were taken at -16 minutes rather than at -5 minutes for logistical reasons.

The All-Subjects-Randomized group totaled 26 subjects, all of whom received at least one dose of investigational treatment. The All-Subjects-Evaluable group also consisted of the 26 subjects. The demographic characteristics of the study population are shown in the following table.

Table 8 Summary of demographic and baseline characteristics by treatment sequence (All Treated Subjects)

| | Treatment Sequence | | | | Total n=26 |
|------------------------|--------------------|--------------------|--------------------|--------------------|----------------|
| | P/S/A+P/A+S n=7 | P/S/A+S/A+P n=6 | S/P/A+P/A+S n=6 | S/P/A+S/A+P n=7 | |
| Sex (n, %) | | | | | |
| Male | 7 (100) | 6 (100) | 6 (100) | 7 (100) | 26 (100) |
| Race (n, %) | | | | | |
| White | 7 (100) | 5 (83) | 3 (50) | 5 (71) | 20 (77) |
| Non-White | 0 | 1 (17) | 3 (50) | 2 (29) | 6 (23) |
| Multiracial | 0 | 1 (17) | 3 (50) | 2 (29) | 6 (23) |
| Ethnicity (n, %) | | | | | |
| Not Hispanic or Latino | 7 (100) | 6 (100) | 6 (100) | 7 (100) | 26 (100) |
| Age (yrs) | | | | | |
| Mean (SD) | 27.0 (9.3) | 22.3 (2.1) | 29.2 (7.8) | 24.4 (7.6) | 25.7 (7.4) |
| Median | 24.0 | 22.5 | 27.5 | 23.0 | 23.5 |
| Range | 19-46 | 20-25 | 21 - 40 | 19 - 41 | 19-46 |
| Age (n, %) | | | | | |
| 18 - <30 | 6 (86) | 6 (100) | 4 (67) | 6 (86) | 22 (85) |
| 30- <50 | 1 (14) | 0 | 2 (33) | 1 (14) | 4 (15) |
| Weight (kg) | | | | | |
| Mean (SD) | 78.61 (11.16) | 74.87 (9.86) | 79.72 (6.22) | 73.03 (9.51) | 76.50 (9.30) |
| Median | 81.20 | 70.95 | 80.00 | 70.40 | 73.30 |
| Range | 65.3 - 93.9 | 66.2 - 91.5 | 71.8- 86.5 | 61.8-89.5 | 61.8 - 93.9 |
| Height (cm) | | | | | |
| Mean (SD) | 181.00 (7.74) | 184.47 (9.59) | 182.03 (8.09) | 186.13 (7.69) | 183.42 (8.03) |
| Median | 180.00 | 186.80 | 181.70 | 187.30 | 184.55 |
| Range | 173.9 - 193.7 | 166.0 - 191.7 | 174.0- 191.5 | 176.0 - 195.5 | 166.0 - 195.5 |
| BMI | | | | | |
| Mean (SD) | 23.91 (2.99) | 21.87 (2.99) | 24.35 (2.63) | 20.97 (1.96) | 22.75 (2.88) |
| Median | 22.60 | 21.30 | 24.85 | 21.20 | 22.55 |
| Range | 20.6 - 28.2 | 18.6 - 26.1 | 19.6-27.7 | 18.5- 23.3 | 18.5 - 28.2 |
| Elbow Breadth (cm) | | | | | |
| Mean (SD) | 6.81 (0.23) | 6.63 (0.55) | 6.67 (0.34) | 6.93 (0.39) | 6.77 (0.38) |
| Median | 6.80 | 6.75 | 6.70 | 6.90 | 6.80 |
| Range | 6.5 - 7.1 | 5.6 - 7.1 | 6.1 - 7.0 | 6.5-7.6 | 5.6 - 7.6 |

P=Placebo, S=Sugammadex, A=Aspirin, SD=standard deviation, BM=body mass index

Source: Section 14.1.1

Sponsor submission, page 56

The primary endpoint was the $AUEC_{3-30 \text{ min}}$ divided by the actual time span of platelet aggregation. The analyses are based on the mixed model for repeated measures of the log transformed $AUEC_{3-30 \text{ min}}$ with treatment and sequence as factors and log baseline PA as a covariate. Results are shown in the following table and figure.

Table 9 Treatment geometric mean ratios and corresponding lower limits of 90% CI's for the $AUEC_{3-30 \text{ min}}$ of PA

| Treatment comparison | Geometric mean ratio | Lower limit of the 90% CI |
|-------------------------|----------------------|---------------------------|
| Aspirin+Sug. vs Aspirin | 1.01 | 0.91 |
| Sug. vs placebo | 0.99 | 0.96 |
| Sug*Aspirin interaction | 1.02 | 0.91 |

Sponsor submission, page 57

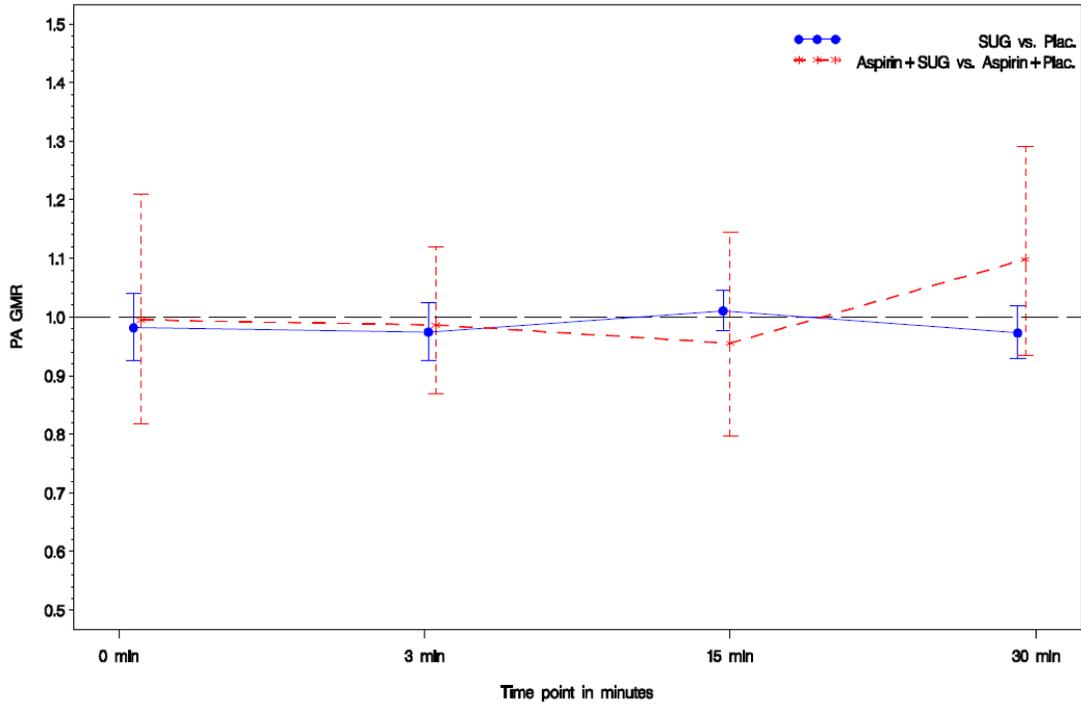


Figure 2 Unadjusted geometric mean ratios of sugammadex alone to placebo alone and aspirin with sugammadex combination to aspirin alone, and corresponding 90% CI's of PA, by time point

Sponsor submission, page 59

A secondary endpoint was the comparison of the effects of SU alone compared to the effects of SU plus aspirin on the aPTT. The following table and figure provide the analysis of the effects of SU or placebo and the effects of aspirin with or without the administration of SU.

Table 11 Treatment geometric mean ratios and corresponding upper limits of 90% CI's for the AUEC_{3-30min} of APTT

| Treatment comparison | Geometric mean ratio | Upper limit of the 90% CI |
|-------------------------|----------------------|---------------------------|
| Sug*Aspirin interaction | 1.01 | 1.04 |
| Sug. vs placebo | 1.06 | 1.07 |
| Aspirin+Sug. Vs Aspirin | 1.07 | 1.10 |

AUEC_{3-30min}: the area under effective curve between 3 and 30 minutes, divided by the time span.

Aspirin+Sug. vs Aspirin : sugammadex after aspirin versus placebo after aspirin

Sug. vs placebo: sugammadex alone versus placebo alone

Sug* Aspirin interaction : joint effect of sugammadex and aspirin as compared to the effect of sugammadex alone time the effect of aspirin alone

Source: Section 14.2.1.2

Sponsor submission, page 60

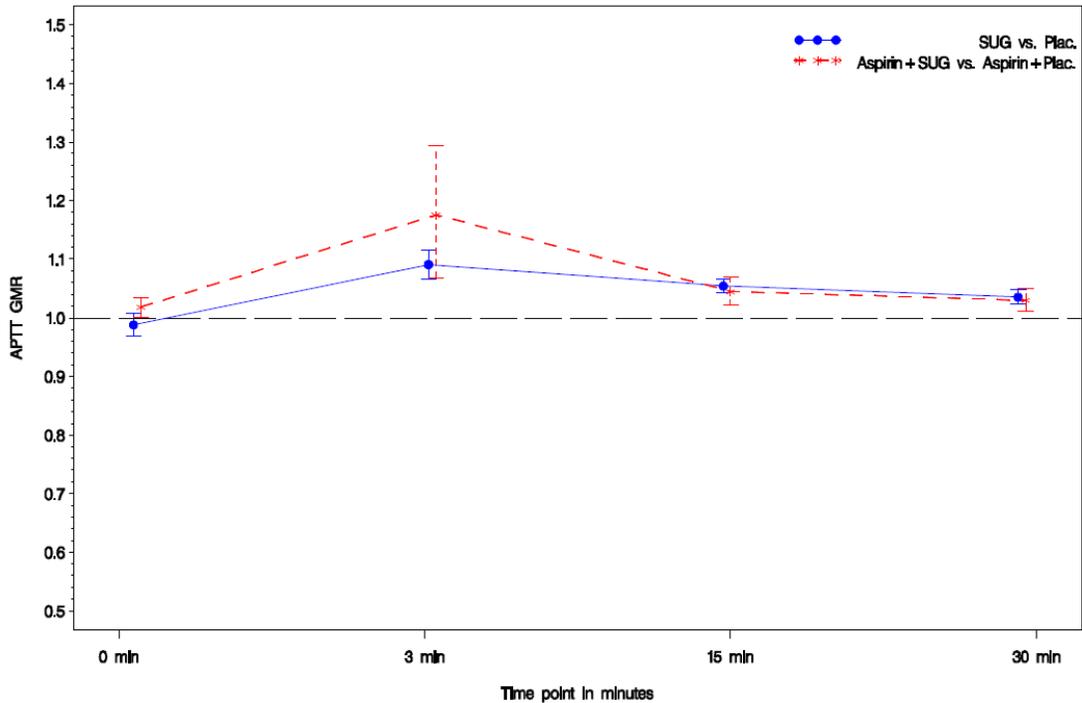


Figure 3 Unadjusted AUEC_{3-30min} geometric mean ratios of sugammadex alone to placebo alone and aspirin with sugammadex combination to aspirin alone, and corresponding 90% CI's of APTT, by time point

Sponsor submission, page 61

Another secondary endpoint was a comparison of the bleeding time at 5 minutes after drug administration between aspirin with or without the administration of SU. The geometric mean ratio for the comparison was 1.20, which was below the upper limit of the 90% CI of 1.45.

Analyses of other prespecified endpoints showed that all of the geometric mean ratios fell between the lower and upper limits of the 90% CIs and are shown in the following table.

Table 15 Treatment geometric mean ratios and corresponding 90% confidence intervals of the AUEC_{3-30min} for the exploratory PD parameters

| Parameter | Treatment comparison | Geometric mean ratio | Lower limit of the 90% CI | Upper limit of the 90% CI |
|---------------------------------|-------------------------|----------------------|---------------------------|---------------------------|
| PT/INR | Aspirin+Sug. vs Aspirin | 1.04 | 1.02 | 1.06 |
| | Sug. vs placebo | 1.05 | 1.04 | 1.06 |
| ACT | Aspirin+Sug. vs Aspirin | 1.00 | 0.97 | 1.04 |
| | Sug. vs placebo | 0.99 | 0.97 | 1.02 |
| TGT peak thrombin concentration | Aspirin+Sug. vs Aspirin | 0.97 | 0.91 | 1.03 |
| | Sug. vs placebo | 1.02 | 0.98 | 1.07 |
| TGT lag time | Aspirin+Sug. vs Aspirin | 1.03 | 0.93 | 1.14 |
| | Sug. vs placebo | 1.11 | 1.06 | 1.17 |
| TGT - time to peak | Aspirin+Sug. vs Aspirin | 1.04 | 0.96 | 1.12 |
| | Sug. vs placebo | 1.04 | 0.99 | 1.09 |
| Factor Xa - peak concentration | Aspirin+Sug. vs Aspirin | 1.00 | 0.97 | 1.02 |
| | Sug. vs placebo | 0.98 | 0.96 | 1.00 |
| Factor Xa - time to peak | Aspirin+Sug. vs Aspirin | 1.00 | 0.98 | 1.01 |
| | Sug. vs placebo | 1.00 | 0.97 | 1.02 |

AUEC_{3-30min}: the area under effective curve between 3 and 30 minutes, divided by the time span.

Aspirin+Sug. vs Aspirin : sugammadex after aspirin versus placebo after aspirin

Sug. vs placebo: sugammadex alone versus placebo alone

Source: Section 14.2. 1.4

Sponsor submission, page 65

The results of the primary and secondary pharmacodynamic endpoints are summarized in the following table.

Table 16 Results of primary and secondary analyses

| Endpoint | Parameter | Treatment comparison | Geometric mean ratio | Two-sided 90% confidence limit | Non inferiority margin |
|-----------|--|---------------------------------------|----------------------|--------------------------------|------------------------|
| Primary | AUEC _{3-30min} of PA ¹ | Aspirin+Sug. vs. Aspirin ² | 1.01 | 0.91 | >0.75 |
| Secondary | AUEC _{3-30min} of APTT ¹ | Aspirin*Sug ³ | 1.01 | 1.04 | <1.5 |
| | | Sug. vs. Placebo ⁴ | 1.06 | 1.07 | <1.5 |
| | BT at 5 minutes | Aspirin+Sug. vs. Aspirin ² | 1.20 | 1.45 | <1.5 |

¹ AUEC_{3-30min}: the area under exposure curve between 3 and 30 minutes, divided by the time span.

² Aspirin+Sug. vs Aspirin: sugammadex after aspirin versus placebo after aspirin.

³ Aspirin*Sug.: joint effect of sugammadex and aspirin as compared to the multiplicative effects of sugammadex alone and aspirin alone.

⁴ Sug. vs placebo: sugammadex alone versus placebo alone.

Sponsor submission, page 71

A pharmacokinetic study showed no difference in the concentration-vs-time profile of SU with or without the administration of aspirin as shown in the following figure.

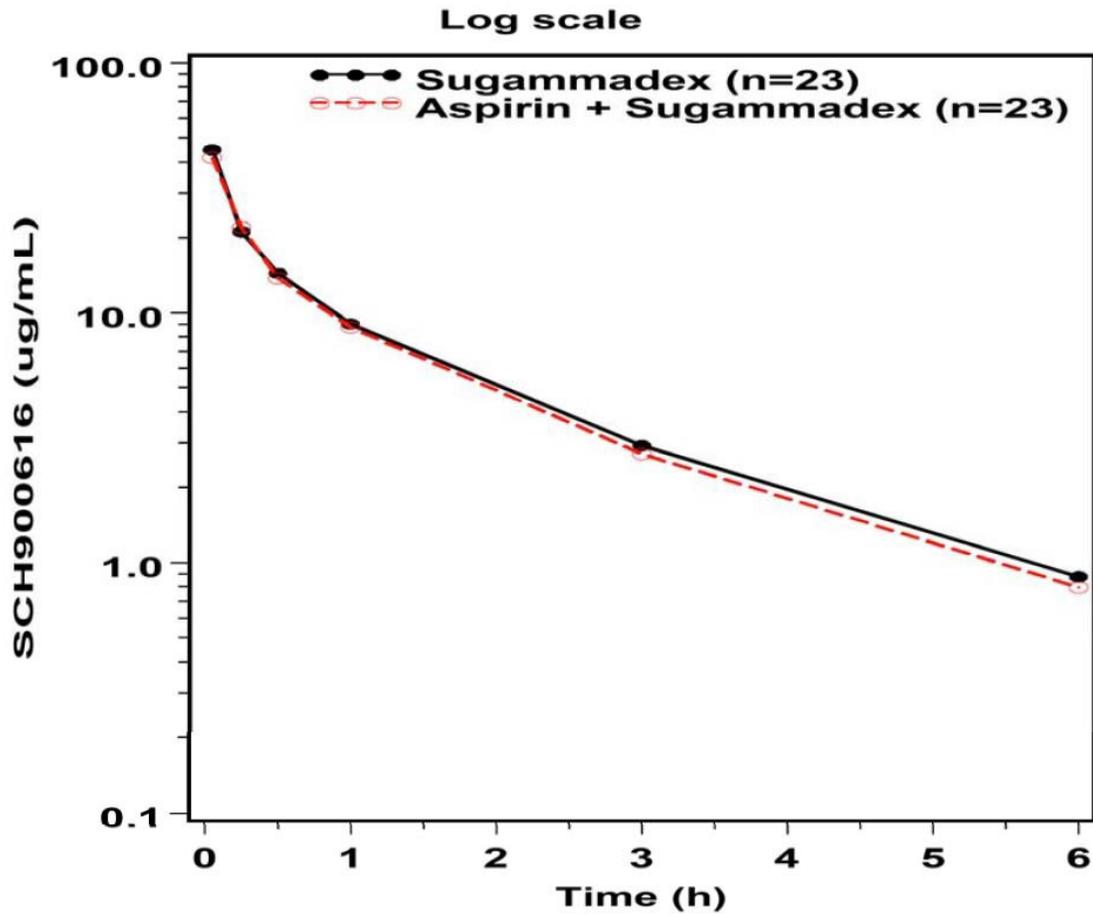


Figure 9 Geometric mean SCH 900616 concentration-versus-time profiles after treatment with SCH 900616 alone (black solid line) or treatment with SCH 900616 on an aspirin medication background (red dashed line) on semi-log scale. Source: Section 14.2.2 (see file name "14.2.2 - 3.2.1").
Sponsor submission, page 72

Safety

In regard to safety assessment, exposure to SU and aspirin adhered to the protocol. Of the three subjects who discontinued from the trial, two received only SU and no aspirin. One of the subjects who discontinued received both SU and aspirin. There were no deaths, serious or severe adverse events. Treatment emergent adverse events are shown in the following table.

Table 18 Overall Summary of Adverse Events (All Treated Subjects)

| | Number (%) of Subjects | | | | |
|---|------------------------|-----------------------|----------------------|------------------------------------|----------|
| | Placebo | Sugammadex 4 mg/kg | Placebo + aspirin | Sugammadex 4 mg/kg + aspirin | Total |
| | (N=25) | (N=25) | (N=23) | (N=25) | (N=26) |
| Subjects with AEs ^a | 8 (32) | 16 (64) | 4 (17) | 13 (57) | 21 (81%) |
| Deaths | 0 | 0 | 0 | 0 | 0 |
| Subjects with SAEs | 0 | 0 | 0 | 0 | 0 |
| Subjects discontinued due to AEs ^b | 0 | 1 (14) | 0 | 0 | 1 |
| Subjects with treatment-related AEs ^c | 4 (16) | 6 (24) | 1 (4) | 6 (26) | 14 (54%) |
| Subjects with AEs ^a of reported severe intensity | 0 | 0 | 0 | 0 | 0 |

AE = adverse event; SAE = serious adverse event.

- a: Treatment-emergent adverse events, including treatment-related adverse events, SAEs, and AEs of any level of severity, occurring after first randomized dose (All-Subjects Treated Set).
- b: Including subjects who discontinued randomized treatment due to an AE that was not treatment-emergent, ie, which started before first dose of randomized treatment or more than 30 days after last dose.
- c: Treatment-related adverse events are defined as treatment-emergent adverse events that are “probably” or “possibly” related to study treatment according to the investigator.

Source: Section 14.3.1, Section, 14.3.2
Sponsor submission, page 75

The most common adverse events were infusion site reactions, nasopharyngitis, headache and somnolence. Two subjects developed dysgeusia and one subject developed a mild hypersensitivity reaction following SU administration. Two subjects developed epistaxis after the administration of SU and aspirin together, and one subject developed a hematoma at the site of vessel puncture after the administration of combined SU and aspirin.

Sponsor conclusions

- There was no clinically significant interaction between SU administered at a dose of 4 mg/kg and aspirin administered at a dose of 75 mg upon collagen-induced platelet aggregation.
- There was no clinically significant interaction between SU administered at a dose of 4 mg/kg and aspirin administered at a dose of 75 mg upon the aPTT and the PT.
- There was no clinically significant interaction between SU administered at a dose of 4 mg/kg and aspirin administered at a dose of 75 mg upon the cutaneous bleeding time.

Reviewer Discussion and Conclusions

In these two studies, the sponsor sought to determine whether or not the administration of SU could have an effect on the anticoagulation induced by enoxaparin or unfractionated heparin or on the platelet inhibitory effect induced by aspirin.

In the first study (P07044), the sponsor sought to determine whether or not sugammadex, at a dose of 4 mg/kg and 16 mg/kg exerted any effect on the anti-Xa activity of enoxaparin or on the aPTT anticoagulant effect of UFH. The metrics used by the sponsor are those most commonly used to measure the anticoagulant adequacy of enoxaparin and UFH. The sponsor selected a geometric mean ratio of the $AUEC_{3-30 \text{ min}}$ of 1.5 (SU/enoxaparin and SU/UFH compared to enoxaparin and UFH, respectively) as the non-inferiority margin below which a clinically meaningful difference could be excluded. Data from the trial indicated that the $AUEC_{3-30 \text{ min}}$ anti-Xa ratios were 1.02 (upper confidence limit, 1.07) and 1.04 (upper confidence limit, 1.08) for SU, 4 mg/kg/enoxaparin and SU, 16 mg/kg/enoxaparin, respectively, compared to enoxaparin alone. The $AUEC_{3-30 \text{ min}}$ aPTT ratios were 1.04 (upper confidence limit, 1.06) and 1.13 (upper confidence limit, 1.15) for SU, 4 mg/kg/UFH and SU, 16 mg/kg/UFH, respectively, compared to enoxaparin alone. Other secondary and exploratory endpoints showed that the administration of SU induced a dose-dependent prolongation of both the PT and the aPTT as had been previously noted. All prolongations reverted to baseline within 1 hour (or earlier).

In the second study (P07025), the sponsor sought to determine whether or not there was a drug-drug interaction between SU and aspirin that might have led to an inhibitory effect on platelet aggregation greater than that induced by aspirin alone. Based on platelet aggregometry in whole blood samples, the chosen metric of $AUEC_{3-30 \text{ min}}$ geometric mean ratio of SU/aspirin vs aspirin alone was 1.01 with a 90% confidence limit of 0.91, which was above the pre-specified non-inferiority margin of 0.75. On the basis of these assumptions, it is agreed that there is no evidence of a clinically meaningful additive anti-aggregant effect of SU when administered with aspirin. Similarly, there was no evidence of an additive effect of SU/aspirin compared to aspirin alone on the secondary endpoints of the prolongation of aPTT and PT.

Based on the data from these two studies, I conclude that there is a noticeable, but small, dose-related, short term effect of SU on the anticoagulant activity of both enoxaparin and UFH. Based on the data from the sponsor's companion clinical study (P07038), which I have reviewed, these changes induced by SU are not clinically significant because they do not lead to an increase in the frequency of bleeding in patients who have undergone major orthopedic surgery of the lower extremity. Additionally, there is probably no clinically meaningful drug-drug interaction on platelet aggregation, the aPTT or the PT when SU is given together with aspirin as compared to the effects of aspirin alone on these parameters.

Recommendations

I have the following recommendations:

- When the label for SU is being formulated, the Clinical Pharmacology section should note the results of these two studies.
- Both of these studies should be reviewed by Clinical Pharmacology, and additional recommendations from them should be considered.
- When Clinical Pharmacology has completed its review of the submission entitled “Development and application of a mathematical model for the prediction of sugammadex effects on coagulation endpoints APTT and PT(INR)”, I shall review it and make additional comments, if appropriate.

----- **This is a representation of an electronic record
that was signed
electronically and this page is the manifestation of the
electronic
signature.**

/s/

GEORGE G SHASHATY
04/12/2013

KATHY M ROBIE SUH
04/12/2013

ANN T FARRELL
04/12/2013

MEMOR
ANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

DIVISION OF HEMATOLOGY
PRODUCTS

Date: May 2, 2013

From: George G. Shashaty, M.D.
Medical Reviewer, Division of Hematology Products

Subject: Consultation Request dated January 7, 2013
NDA 22225
Sugammadex

To: Arthur Simone, M.D.
Division of Neurological Drug Products

Through: Kathy Robie Suh, M.D., Ph.D.
Team Leader, Division of Hematology Products

A
n
d

Edvardas
Kaminskas, M.D.
Deputy Director
Division of Hematology Products

Background

Sugammadex (SU) is being developed as a reversing agent for rocuronium and vecuronium induced muscle paralysis to permit surgery. SU is registered in over 70 countries (including the European Union) for routine and immediate reversal

of neuromuscular blockade. I have previously written three consults to DNP for SU (see reviews for IND 68029 in DARRTS dated June 7, 2010, December 16, 2010 and October 18, 2011), and Min Lu filed a consult review for similar purposes on November 17, 2009. The purpose of the original consultation was to make comments about, and recommendations to evaluate, the propensity of SU to prolong the activated partial thromboplastin time (aPTT) and the prothrombin time (PT) for a short period of time

after its administration. The conclusions stated in the reviews were that the mechanism of the prolongations of the aPTT and PT had not been adequately determined, and that the sponsor would have to perform a clinical trial to evaluate the frequency of bleeding in patients undergoing surgery with the use of rocuronium or vecuronium, which was then reversed with SU. Subsequently, the sponsor submitted a protocol for a study (**Protocol P07038: A randomized, controlled, parallel-group, double-blind trial of sugammadex or usual care (neostigmine) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin**). We reviewed the proposed trial (see Shashaty, Consult dated October 18, 2011, suggested revisions and then agreed to the final protocol that was submitted. The sponsor has now completed and submitted the clinical study report (CSR) for the trial to the NDA (submission dated December 20, 2012).

Purpose of the Consult

The Division of Neurological Products has asked that the Division of Hematology Products review the CSR to determine whether or not the data submitted from the study address the concern for a potential increase in the frequency of bleeding related to the use of SU.

Review of the Submission of Study P07038

Background

In several clinical trials with SU, it had been noted that when the drug was administered at doses of either 4 or 16 mg/kg, there was a concomitant increase in the aPTT and PT of between 17%-22%, and that this effect lasted for approximately 30 minutes. Data for 1738 subjects from various clinical trials with SU did not appear to show an increased risk of bleeding in SU-treated subjects compared to those who had received neostigmine/placebo. Despite these latter findings, and in consultation with DHP, DNP determined that the sponsor would have to perform a study to demonstrate that there was no greater risk of bleeding in the postoperative period in patients treated with SU compared to those treated with neostigmine/placebo. In addition, since the presence of a circulating anticoagulant may cause an increase in the PT and/or the aPTT, the sponsor was requested to assess the possibility that venous thromboembolism (VTE) might be increased in SU-treated patients as has been associated with the presence of some circulating anticoagulants.

In response to this request, the sponsor submitted Protocol P07038 with the following description and rationale:

- A randomized, controlled, parallel-group, multi-site, double-blind, double-dummy trial. The study would enroll subjects who were to have major orthopedic surgery on the hip or knee. This would provide a reasonably homogeneous population.
- Enrollees would receive thromboprophylaxis using one of several approved regimens because of the high frequency (40-60%) of VTE without the use of anticoagulants. This population would provide a group whose frequency of bleeding was quite well known and was enriched for possible hemorrhagic events because of the use of drugs given for thromboprophylaxis.
- Enrollment of this population would include many elderly subjects with mild to moderate renal dysfunction (Creatinine clearance ≥ 30 ml/min and ≤ 60 ml/min). Since previous studies had shown that this degree of renal dysfunction was not associated with an increase in peak concentrations of SU (but only a somewhat longer $\frac{1}{2}$ life) and that the effect of SU on the increase in aPTT and PT was dissipated over approximately 30 minutes, it would be important to assess bleeding in such patients. The protocol was designed to assess the frequency of bleeding over the 24 hour period following administration of SU so that any effects of renal dysfunction on bleeding after SU use could be determined.
- For entry on the trial, subjects must have received anticoagulant/antiplatelet therapy prior to surgery because the effects of SU on aPTT and PT are short-lived and might not be evaluable if thromboprophylaxis were administered after surgery.

Objectives

The primary objective was to assess the effect of the reversal with SU at a dose of 4 mg/kg of rocuronium or vecuronium-induced paralysis on the incidence of adjudicated bleeding events within 24 hours in subjects after SU administration compared to in subjects receiving active reversal with neostigmine or spontaneous recovery with placebo.

Secondary objectives included the effects of SU on:

- The degree and time course of the increase in aPTT and PT/INR in enrolled subjects
- Safety in enrolled subjects
- Adjudicated postsurgical bleeding events over 14 days after surgery
- Adjudicated major postsurgical bleeding events over 24 hours and 14 days after surgery
- Adjudicated VTE over 14 days after surgery
- Anti-Xa activity up to 2 hours after SU administration
- PK/PD relationship between the plasma concentrations of SU and coagulation parameters

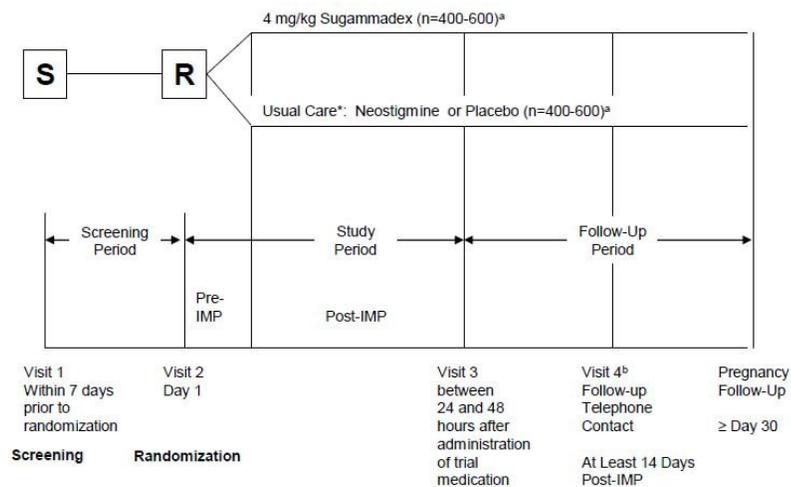
Design

This was a randomized, controlled, parallel-group, multi-site, double-blind, double-dummy trial. The study was conducted in 22 centers in Austria, Belgium and Germany from October 30, 2011 to September 26, 2012. Randomization was in a 2:1 ratio of SU to either neostigmine or placebo. Randomization was stratified on the basis of type of thromboprophylaxis (heparin, yes or no), whether subjects were to be reversed with neostigmine (yes or no) and estimated renal function (eCrCl < or ≥ 60 ml/min). After wound closure, and when the surgical team felt it was acceptable to allow spontaneous movement, trial medication was administered over 10 seconds via a flowing infusion. Subjects received follow-up assessments postoperatively for 14 days.

The schema for the trial is shown in the following diagrams.

Surgical Subjects

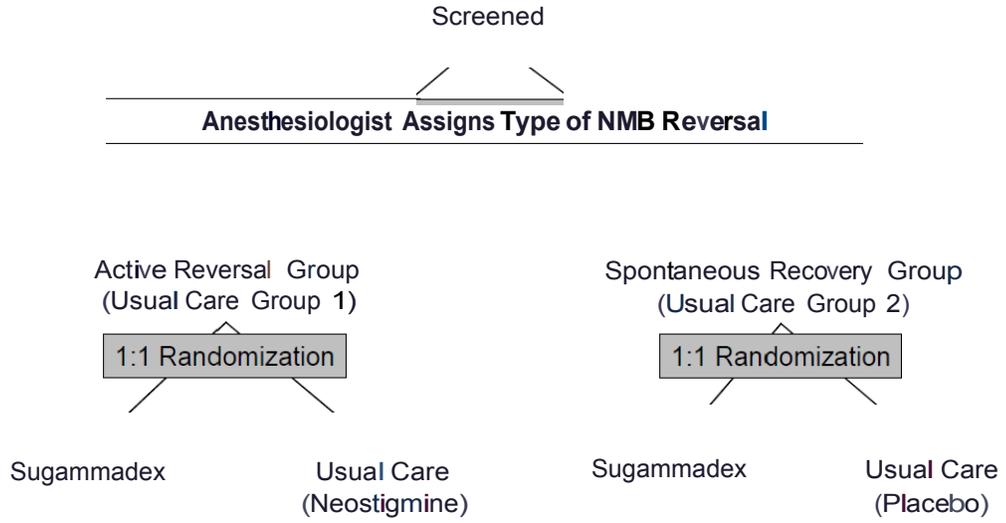
- Patients undergoing hip fracture surgery or joint (hip/knee) replacement with planned NMB administration
- ≥ 18 years
- On or planned to initiate *prior to or during* surgery single or dual thromboprophylactic therapy (LMWH, UFH, anti-platelet therapy [eg, aminosalicic acid, clopidogrel])
- Appropriate for rapid NMB reversal



*Anesthesiologist to determine Usual Care Group
Usual Care Group 1: Planned active reversal with sugammadex or neostigmine
Usual Care Group 2: Planned spontaneous reversal

- ^a Amendment #3 extended enrollment from 400 subjects up to 600 subjects per group.
- ^b Amendment #4 changed Visit 4 from 4-7 weeks to at least 14 days after administration of trial medication.

S = Screening
R = Randomization
IMP = Investigational Medicinal Product
LMWH = low molecular weight heparin
NMB = neuromuscular blockade
UFH = unfractionated heparin



The trial flow chart and schedule of events are shown in the following table.

Table 9-1 Trial Flow Chart

| | |
|--|---|
| <p>Screening Period Visit 1 (within 7 days prior to Randomization)</p> | <ul style="list-style-type: none"> • Obtain written Informed Consent (ie, enrollment, receiving a screening number) • Obtain Pharmacogenetic Consent • Issue Patient Identification Card • Obtain demographics information and record medical history • Record pre-trial medication intake (within 14 days prior to entering the trial) • Assess/record vital signs (heart rate (HR), respiratory rate (RR), and blood pressure (BP)); supine position • Perform physical examination; assess/record weight; record height • Perform, if applicable, a pregnancy test (within 24 hours before surgery) • Collect blood samples for aPTT and PT(INR) (to both central and local laboratories) using heparin-free lines/materials exactly as directed (see manual) • Collect blood samples for complete blood count (CBC), platelet count and chemistry panel (to both central and local laboratory) • Collect urine sample for urinalysis (to central laboratory) • Confirm subject meets inclusion and no exclusion criteria |
| <p>Treatment Period Visit 2 (Perianesthetic Period)</p> <p>t=0</p> | <ul style="list-style-type: none"> • Assess for adverse events • Confirm subject meets inclusion and no exclusion criteria; update medication information if any changes • Randomize to treatment (IVRS) • Insert intravenous (IV) cannula(s) and induce anesthesia (eg, propofol i/v and/or opioid) • Maintain anesthesia: propofol/ or an inhalational agent, and/or opioid • Assess/record vital signs (HR and BP) prior to administration of NMBA • Administer rocuronium or vecuronium • Secure airway • Administer maintenance doses rocuronium or vecuronium, as needed • Assess/record baseline vital signs (HR and BP) just before study medication, preferably at stable anesthesia • Record medication intake • Record time of order for any blood or coagulation-enhancing factors • Record estimated volume of actual blood loss during surgery • Assess for adverse events, including suspected unanticipated adverse events of bleeding • Collect blood samples (all subjects) just prior to study medication for aPTT, PT(INR), anti-Xa (only for subjects on UFH or LMWH), Complete Blood Count (CBC) platelet count, Chemistry panel, and tryptase and sugammadex antibodies samples for hypersensitivity evaluation (to central laboratory). For aPTT, PT(INR) and anti-Xa, use heparin-free lines/materials exactly as directed by manual. • For subset of subjects undergoing pharmacokinetic (PK) assessment collect PK, aPTT and PT(INR) samples one minute prior to study medication and just prior to study medication, including a spiking sample. For aPTT, PT(INR) and anti-Xa, use heparin-free lines/materials exactly as directed by manual. Collect PK samples from arm opposite to arm in which study medication is administered or other remote site. • After wound closure and when it is imminently acceptable for the subject to begin to move spontaneously, administer study medication sugammadex or usual care (for Usual Care Group 1: sugammadex or neostigmine; for Usual Care Group 2: sugammadex or placebo) according to the randomization schedule (and within 10 seconds into a fast running infusion) • Collect blood samples (all subjects) at 10 and 60 minutes after study medication for aPTT and PT(INR) (to central laboratory) using heparin-free lines/materials exactly as directed by manual. • For subset of subjects undergoing PK assessment: collect PK blood samples, aPTT, PT(INR), and anti-Xa activity at 3, 10, 20, 30, 60, and 120 minutes after study medication (to central laboratory). For aPTT, PT(INR) and anti-Xa, use heparin-free lines/materials exactly as directed by manual. Collect PK samples from arm opposite to arm in which study medication is administered or other remote site. • Monitor subject, including clinical signs of recovery according to routine anesthetic procedures at trial site • Assess/record HR at 2, 5, 10, 15, 25, 40, and 65 minutes and blood pressure and respiratory rate at 5 and 25 min after study medication • Record time of order for any blood products or coagulation-enhancing factors • Record study drug and medication intake, including blood products or coagulation-enhancing factors administered • Assess for potential drug interactions • Assess for adverse events, including suspected unanticipated adverse events of bleeding |

Treatment Period
Visit 3
(to occur 24 hours and
s 48 hours after IMP or at
discharge, whichever is
earlier)

- Perform physical examination and assess/record vital signs (HR, RR and BP)
- Collect blood sample for CBC/platelet count and Chemisliy (to central laboratory)
- For subjects consenting to phannacogenetic sampling, collect samples as last blood drawn for this visit
- Collect urine sample (to central laboratory)
- Record time of order for any blood products or coagulation-enhancing factors, whether surgical drain was placed, total (cumulative) drain volume.
- Record medication intake, including blood products or coagulation-enhancing factors administered
- Assess for adverse events, including suspected unanticipated adverse events of bleeding

Follow-Up Period
Telephone Contact
Visit 4
(to occur at least 14 days
after IMP administration)

- Record medication intake, including blood products or coagulation-enhancing factors administered
- Inquire about suspected unanticipated adverse events of bleeding, symptomatic VTEs and SAEs
- Inquire about possible pregnancy (female subjects of Child-bearing potential)
- End of trial

Note: if a suspected, unanticipated adverse event of bleeding occurs in the peri-anesthetic period while planned samples for aPTI and PT(INR) (and PK and anti-Xa activity in the subset of ~40 subjects) are being collected, samples for the coagulation parameters and PK will be collected as close as possible to the prespecified times. However, no additional samples to assess coagulation or PK parameters (ie, beyond the time-course samples) are required at that time. Other samples (ie, for CBC/platelet count and chemistry panel (all subjects) and an i-Xa activity and plasma for sugammadex determination (in subjects not in the subset of subjects undergoing frequent sampling)) will continue to be collected/sent to the central laboratory.

Table 9-2 Flow Chart by Assessment

ProtOCO1 No P07038

| Event/Assessment | Screening period | Treatment period | | | | | | Treatment and/or Follow-up Period | Follow up period | |
|---|---|--|------|--|--------------------------|---------------------------------|---|---|--|---|
| | Visit 1 Within 7 days prior to randomization | Visit 2 Randomization cust pOr to anesthesia in baseline | NMBA | Baseline (at wound dosure) Just prior to study medication | Study medi- cation | Me< study medi- cation | Visit J 2:24 hr and 4:8 hr aner study medication (or hospital discharge, if earlier) | Unscheduled Visit (For suspected unanticipated event of bleed ng aner study medication until end of trial) | Visit 4 Telephone Contact (lit icOst 14 dily s Ofter study medication) | PregnJncy Follow-up 30 days Ofter study medication) |
| Informed consent | X | | | | | | | | | |
| Pharmacogenetic consent | X | | | | | | | | | |
| Patient kJentification card | x (issue) | | | | | | | | X* | |
| Medical history | X | | | | | | | | | |
| Demographic info (including height) | X | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | | |
| Prior/concomitant medications | X | X | | X | | X | X | X | X | |
| Time blood or coagulation- enhancing products ordered | | X | | X | | X | X | X | X | |
| Estimated volume of actual bloodless during surgery | | | | X | | | | | | |
| Surgical drain out volume (if applicable) | | | | | | X | | | | |
| Adverse events/ | X | X | | X | | X | X | X | X | |
| Physical examination | X | | | | | X (excluding weight) | X | | | |
| Pregnancy test | < 24 hr before surgery | | | | | | | | | |

| Event/Assessment | Screening period | Treatment period | | | | | | Treatment and/or Follow-up Period | Follow up period | |
|--|---|---|-----------|---|-------------------------------|-----------------------------------|---|--|---|--|
| | Visit 1 Within 7 days prior to randomization | Visit 2 Randomization (just prior to anesthesia) until baseline | NMBA ↓ | Baseline (at wound closure) Just prior to study medication | Study medi- cation ↓ | After study medi- cation | Visit 3 ≥ 24 hr and ≤ 48 hr after study medication (or hospital discharge, if earlier) | Unscheduled Visit (For suspected unanticipated event of bleeding after study medication until end of trial) | Visit 4 Telephone Contact (at least 14 days after study medication) | Pregnancy Follow-up (≥ 30 days after study medication) |
| Vital signs | X | X | | X | | X ^a | X | X | | |
| Laboratory Data | | | | | | | | | | |
| aPTT/PT(INR) ^b | X ^c | | | X ^d | | X ^e | | X | | |
| Anti-Xa activity ^b | | | | X ^d | | X ^e | | X | | |
| CBC/Platelet count | X ^c | | | X | | | X | X | | |
| Chemistry, BUN, Creatinine | X ^c | | | X | | | X (limited) | X (limited) | | |
| Urinalysis | X | | | | | | X | | | |
| Patient randomization ^f | | X | | | | | | | | |
| NMBA administration | | | X | | | | | | | |
| Plasma sample(s) for pharmacokinetic assessments ^g | | | | X | | X ^h | | X | | |
| Trypsin and sugammadex antibodies sample for hypersensitivity assessment | | | | X | | X ⁱ | X ⁱ | X ⁱ | | |
| Sample for pharmacogenetic analysis ^j | | | | | | | X | | | |
| Study medication administered | | | | | X | | | | | |
| Interaction & recovery data | | | | | | X | | | | |
| Safety assessor blinding | | | | | | | X | X | | |
| Pregnancy follow up | | | | | | | | | X | X |
| End of trial | | | | | | | | | X | |

| Event/Assessment | Screening period | Treatment period | | | | | | Treatment and/or Follow-up Period | Follow up period | |
|------------------|---|---|-----------|---|-------------------------------|-----------------------------------|---|--|---|--|
| | Visit 1 Within 7 days prior to randomization | Visit 2 Randomization (just prior to anesthesia) until baseline | NMBA ↓ | Baseline (at wound closure) Just prior to study medication | Study medi- cation ↓ | After study medi- cation | Visit 3 ≥ 24 hr and ≤ 48 hr after study medication (or hospital discharge, if earlier) | Unscheduled Visit (For suspected unanticipated event of bleeding after study medication until end of trial) | Visit 4 Telephone Contact (at least 14 days after study medication) | Pregnancy Follow-up (≥ 30 days after study medication) |

aPTT = activated prothrombin time, CBC = complete blood count, IMP = Investigational Medicinal Product (ie, sugammadex, neostigmine, or placebo), PT(INR) = Prothrombin Time/International normalized ratio, NMBA = neuromuscular blocking agent (ie, rocuronium or vecuronium). OR = operating room. Limited chemistry: electrolytes, BUN, creatinine.

^a Heart rate at 2, 5, 10, 15, 25, 40, and 65 minutes, blood pressure and respiratory rate at 5 and 25 min after study medication.

^b Perform collection of all coagulation (aPTT, PT[INR]) and anti-Xa [only for patients on UFH or LMWH] blood samples using heparin-free lines/materials exactly as directed (see manual).

^c Screening samples sent in duplicate to central and local laboratories: aPTT, PT(INR), CBC/platelet count, serum creatinine.

^d In the subset of ~40 patients undergoing extended sampling at selected sites (ie, subset undergoing PK sampling): obtain aPTT/PT(INR), and anti-Xa at one minute prior (T₋₁) and just prior (T₀) to administration of study medication. An additional sample for future spiking experiments will be collected at T₀. For all other patients, obtain aPTT/PT(INR), and anti-Xa just prior (T₀) to administration of study medication, and at 10 and 60 minutes after initiation of study medication administration.

^e In the subset of ~40 patients undergoing extended sampling at selected sites (ie, subset undergoing PK sampling): obtain aPTT/PT(INR) and anti-Xa at 3, 10, 20, 30, 60, and 120 minutes after initiation of study medication administration. For all other patients, obtain aPTT/PT(INR) only at 10 and 60 minutes after initiation of study medication.

^f Randomization is the time point when the treatment code is appointed to a patient, ie, via the Interactive Voice Response System.

^g Pharmacokinetic assessment for determination of sugammadex concentration to be done at selected sites in subset of ~40 patients (same subset also undergoing extended aPTT, PT(INR), anti-Xa sampling). All pharmacokinetic blood samples are to be taken from the arm opposite to the arm used for drug infusion or other remote site. Plasma sample for possible sugammadex determination will also be obtained at time(s) of any suspected, unanticipated adverse events of bleeding at all study sites.

^h Obtain at 3, 10, 20, 30, 60, and 120 minutes after initiation of study medication administration.

ⁱ All patients to have sample collected at baseline for assessment related to hypersensitivity (tryptase and antibody assessment). If patient considered to have anaphylaxis/SAE related to hypersensitivity following administration of study drug, collect samples per manual immediately following reaction and at Visit 3, and Unscheduled Visit prior to Visit 4.

^j Informed consent for pharmacogenetic samples must be obtained before the DNA sample. DNA sample for analysis should be obtained at Visit 3 as the last sample drawn, for randomized patients only, or at a later date as soon as the informed consent is obtained.

^k The card must be retrieved or returned when possible after the Visit 4 telephone contact, at least 14-days post-surgery.

A Data Monitoring Committee (DMC) oversaw subject safety as outlined in the DMC charter. Two Clinical Adjudication Committees (CACs) were established, one to evaluate bleeding and venous thromboembolic events (Primary Adjudication Committee) and another to evaluate hypersensitivity or anaphylaxis (Hypersensitivity Adjudication Committee). At each institution, there was an assigned Blinded Safety Assessor who was a member of the surgical study team but who was not to be in the operating room during the surgery or recovery from neuromuscular blockade, and who was not to discuss recovery of neuromuscular blockade with anyone in the operating room. His/her function was to determine whether or not unanticipated postoperative bleeding was

occurring in the context of the nature of the surgical procedure, and to perform all subjective safety assessments.

A total of 22 trial centers participated in the trial.

Patients

The population was to include adults of ASA Class 1-3 undergoing hip surgery or hip/knee replacement surgery, who were receiving pre- or intraoperative thromboprophylaxis (heparin, fractionated heparin, vit K antagonist, antiplatelet agent) and who were planned to be treated with neuromuscular blockade with either rocuronium or vecuronium.

Inclusion criteria were:

- Age \geq 18 years
- Platelet count > lower limit of normal
- Must be a candidate for rapid reversal of neuromuscular blockade
- Written informed consent

Exclusion criteria were multiple with the following important exclusions:

- Coagulation or bleeding disorder
- Active bleeding or clotting symptoms within the 30 days prior to enrollment
- Significant hepatic or renal dysfunction
- History of hypersensitivity to any of the drugs to be used in the trial
- Use of toremifine or fusidic acid
- BMI > 35
- Presence of active hip/knee infection

Trial Endpoints

The primary endpoint was the proportion of subjects with at least one, adjudicated, major or non-major but unanticipated event of bleeding within 24 hours after trial drug administration. The initial determination of such an event was made by the Blinded Safety Assessor at each institution in concert with the surgeon. All serious unexpected adverse bleeding events (SUAEB) were forwarded to the Primary Adjudication Committee (PAC) for final decisions as to a designation of major bleeding events, non-major bleeding events or not an unanticipated bleeding event. Major bleeding events were defined as follows:

- Fatal bleeding

- Bleeding into a critical organ or area (intracranial, intraspinal, intraocular, retroperitoneal, pericardial, unoperated joint, compartment syndrome)
- Extrasurgical site bleeding with a fall in hemoglobin of ≥ 2 grams/dl or more or leading to a transfusion of ≥ 2 units of blood with 24 hours of bleeding
- Surgical site bleeding that required a second intervention or a hemarthrosis that delayed mobilization or discharge
- Surgical site bleeding that was unexpected or prolonged and/or sufficiently large to cause hemodynamic instability as determined by the surgical team.

Other prespecified endpoints evaluated included:

- aPTT, believed to be the most appropriate test to evaluate the effect of SU on Xa activity measured at baseline, at 10 minutes and at 60 minutes after trial drug administration
- Prothrombin time/INR, even though the sponsor states that Xa activity is not demonstrated via the extrinsic pathway, at baseline, at 10 minutes and at 60 minutes after trial drug administration
- Anti-Xa activity, aPTT, PT and SU serum levels were to be obtained in a subset of approximately 40 subjects at baseline, and then at 3, 10, 20, 30, 60 and 120 minutes after trial drug administration
- Adjudicated symptomatic VTE events within 14 days after trial drug administration
- Adjudicated hypersensitivity events within 14 days after trial drug administration
- The proportion of subjects with adjudicated unanticipated adverse events of bleeding within 14 days after trial drug administration
- The proportion of subjects with adjudicated unanticipated major adverse events of bleeding within 24 hours of trial drug administration
- The proportion of subjects with adjudicated unanticipated major adverse events of bleeding within 14 days after trial drug administration

Exploratory endpoints included:

- Postoperative drainage volume over the first 24 hours after surgery
- Need for postoperative transfusions
- Postoperative changes in hemoglobin level between 24-48 hours after surgery
- Incidence of postoperative anemia within 72 hours of surgery

In addition, clinical and laboratory databases were periodically reviewed blindly by the sponsor to assess changes in hemoglobin levels or the use of transfusions in order to unearth possible events that might qualify as SUAEBs for referral to the PAC. In the event of a potential clinically significant bleeding event, the Blinded Safety Assessor was to obtain blood samples as soon thereafter for CBC and platelet count; aPTT; PT; anti-Xa activity; chemistry panel; and measurement of SU level.

The sponsor also collected time-related endpoints (time of operating room admission; first incision; last stitch; extubation; etc) for assessment of time intervals.

Treatment

The trial medications for reversal of neuromuscular blockade were:

- Sugammadex given intravenously within 10 seconds at a dose of 4 mg/kg
- Neostigmine given intravenously within 10 seconds as per usual practice and the product label (maximum total dose, 5.0 mg)
- Placebo given intravenously within 10 seconds

All trial medications were to be purchased by the investigational site. Because SU may have a slightly yellowish tinge, prepared syringes were tinted to mask color differences.

Patients were first stratified on the basis of the anesthesiologist's determination as to whether each patient was to be actively reversed (usual care using neostigmine) or was to be allowed to reverse spontaneously (usual care using placebo). Subjects were then randomized in a 1:1 ratio to SU or the neostigmine arm or in a 1:1 ratio to SU or the placebo arm using an IVRS.

Treatment assignment was stratified based on the following factors:

- Prophylactic antithrombotic therapy (use of UH/LMWH or not)
- Renal function ($\text{CrCl} < 60 \text{ ml/min}$ or $\geq 60 \text{ ml/min}$ based on the Cockcroft-Gault formula)

All medications administered within the 14 days prior to the surgical procedure, as well as all treatments given in the postoperative period, were to be recorded on the eCRF.

Efficacy

No efficacy endpoints were analyzed in this trial.

Safety

The primary safety endpoint was the frequency of the development of an adjudicated, major or non-major, unanticipated adverse event of bleeding with an onset within 24 hours of trial medication administration.

Statistics

The primary safety analysis and analyses of other safety endpoints were performed on the All-Patients-as-Treated (APaT) population. The APaT population was defined as all randomized patients who received at least one dose of trial medication and were included in the treatment group corresponding to the trial medication that they actually received. The APaT population was also used for analyses of the secondary endpoints. The relative risk with associated confidence intervals for the primary endpoint was assessed using the Cochran-Mantel-Haenszel method. Analyses were stratified for renal function and type of thromboprophylactic therapy. Several additional sensitivity analyses were also to be performed.

The secondary endpoint (and other coagulation endpoints) was analyzed using a constrained data analysis method to estimate the 2-sided confidence interval for the ratio of the geometric means of the aPTT after sugammadex relative to usual care at 10 and 30 minutes after administration of trial drug. Additional adjustments to the model for other factors were also made.

A number of other statistical analyses were also to be performed, and these can be found in the Statistical Review of the submission.

The sample size for the trial was chosen to provide an estimate of the relative risk of adjudicated bleeding events with an upper bound for the confidence interval of the estimate to be no greater than a factor of 2. Based on a review of expected bleeding after hip/knee surgery of no greater than 5%, a sample size of 800 subjects was required to provide sufficient power to achieve a precision of a factor of 1.83 for the relative risk. In case the event rate was substantially lower than expected, the sponsor was to increase the sample size to achieve the desired precision by enrolling subjects until the number of primary events reached 33, or there was the enrollment of 1200 subjects.

The methods for the analysis of key safety variables are shown in the following table.

Table 9-4 Analysis Strategy for Key Safety Variables

Protocol No. P07038

| Endpoint Variable (Description, Time Point) | Primary vs. Supportive Approach ^a | Statistical Method ^b | Analysis Population | Missing Data Approach |
|---|--|--|---------------------|-----------------------|
| Primary Objective | | | | |
| Proportion of subjects with Adjudicated Bleeding event with onset within 24 hours of study medication | P | Stratified Cochran-Mantel-Haenszel ^c | APaT | NA ^d |
| Proportion of subjects with a Bleeding event with onset within 24 hours of study medication according to the investigational site | S | Stratified Cochran-Mantel-Haenszel ^c | APaT | NA ^d |
| Proportion of Subjects with Adjudicated Bleeding event with onset within 24 hours of study medication (incl. interaction model) | S | Poisson regression model ^e | APaT | NA ^d |
| Key Secondary Objective | | | | |
| aPTT values at 10 and 60 minutes post- study medication | P | cLDA ^f | APaT | Model-based |
| Secondary Objectives | | | | |
| PT(INR) values at 10 and 60 minutes post- study medication | P | cLDA ^f | APaT | Model-based |
| Proportion of subjects with adjudicated events of bleeding up to 14 days of study medication ^g | P | Difference in proportion using the Miettinen and Nurminen method | APaT | Observed data only |
| Proportion of subjects with event of bleeding as considered by the investigational site occurring up to 14 days after study medication ^g | S | Stratified Cochran-Mantel-Haenszel ^c | APaT | Observed data only |
| Proportion of subjects with adjudicated major events of bleeding with onset within 24 hours of study medication | P | Difference in proportion using the Miettinen and Nurminen method | APaT | Observed data only |
| Proportion of subjects with adjudicated major events of bleeding up to 14 days of study medication ^g | P | Difference in proportion using the Miettinen and Nurminen method | APaT | Observed data only |
| Proportion of subjects with adjudicated symptomatic VTE event up to 14 days of study medication ^g | P | Difference in proportion using the Miettinen and Nurminen method | APaT | Observed data only |
| Proportion of subjects with adjudicated events of anaphylaxis up to 14 days of study medication ^g | P | Difference in proportion using the Miettinen and Nurminen method | APaT | Observed data only |

aPTT=activate partial thromboplastin time; APaT=all subjects as treated; cLDA=constrained longitudinal data analysis; CMH= Cochran-Mantel-Haenszel; NA=not applicable; P=primary approach; PT(INR)=prothrombin time (International normalized ratio); S=secondary approach; VTE=venous thromboembolic

- ^a P=Primary approach; S=Secondary approach.
- ^b Statistical models are described in further detail below:
- ^c Stratified Cochran-Mantel-Haenszel (CMH) method was to use the $n \times 2 \times 2$ table with each identified stratum of renal function and prophylactic antithrombotic treatment as stratum n , and treatment by adjudicated event of bleeding as 2 by 2 table to estimate the relative risk of bleeding on sugammadex versus usual care treatment.
- ^d Note that it was to be assumed that if there is no record available of an adjudicated bleeding event, no such event occurred.
- ^e A Poisson regression model includes terms for treatment, renal function, and prophylactic antithrombotic treatment. This model produces an estimate that tends to be close to the stratified CMH estimate. This model was to be used to estimate the main effects of strata using 95% confidence intervals. Within this model, for each stratum, the treatment-by-stratum interaction was to be tested (ie, interaction was tested within the full model, for each stratum separately). In case of significant treatment-by-stratum interaction ($P < 0.05$), the relative risk of sugammadex versus usual care treatment was to be computed for each stratum using the Poisson regression model.
- ^f Constrained longitudinal data analysis. See text for details.
- ^g For events with an unknown start date a conservative imputation rule was to be used.

Sponsor submission, page 77-78

The primary parameter of adjudicated events of bleeding within 24 hours after trial drug administration was to be analyzed using the CMH method on the relative risk of 4 mg/kg SU versus usual care, providing an estimated relative risk and associated 95% confidence intervals. Sensitivity analyses were to be performed using the same methodology except that the primary safety endpoint was that determined by the investigator site, and an analysis using Poisson regression to assess treatment by stratum interaction terms to characterize the main effect of strata within the model.

Analyses of important secondary endpoints (particularly laboratory measures of anticoagulation) were also to be performed.

A number of descriptive analyses were to be performed for adverse events, laboratory tests and vital signs, most related to various measures of clinical bleeding and its sequelae, thromboembolic events and hypersensitivity reactions.

Demographic and baseline characteristics were tabulated to ensure comparability of patients in the two arms of the trial. PK-PD relationships (drug concentration compared to laboratory measures of anticoagulation) at various times after trial drug administration were performed in a selected group of approximately 40 subjects. Estimates of the effects of different anticoagulants used (LMWH, UH or none) and the effects of renal function on the primary endpoint were calculated.

Subjects who discontinued from the trial were not to be replaced.

The DMC was to monitor interim data. If there were a total of 6 adjudicated major bleeding events and/or SAEs of bleeding that had not yet been adjudicated, the DMC was to convene to evaluate safety based on unblinded data. If that number were not reached, the final data would be presented at a meeting for assessment.

Although this was a multicenter trial, randomization was not stratified for center, and the central IVRS provided the first available treatment code for the subject in that stratum for each randomization.

Ethics

An Independent Ethics Committee reviewed and approved the protocol and amendments.

The trial was conducted in conformance with Good Clinical Practices standards and with the standards of the countries in which they were performed. Written informed consent was required of all subjects enrolled in the trial.

Amendments to the Protocol

The protocol was amended on 4 occasions, and 2 Protocol Clarification Letters (PCL) were issued.

- PCL #1, dated February 27, 2012. This clarified the intent to have Safety Assessors report all major and non-major bleeding events deemed unusual due to the amount or length of blood loss.
- Amendment #1, dated March 2, 2012. This was designed to correct inconsistencies, but was never implemented because it was carried over to the second amendment, below.
- Amendment #2, dated March 19, 2012. This was intended to correct inconsistencies and clarify such items as postoperative bleeding events, estimation of blood loss, drainage volume, definition of suspected, unanticipated event of bleeding and exclusion of patients undergoing revision surgery.
- Amendment #3, dated May 4, 2012. This increased the sample size of the population until the number of adjudicated, suspected unanticipated adverse events of bleeding reached 33 or a total of 1200 subjects had been enrolled in the trial. The rationale for this amendment was that the number of bleeding events was lower than had been expected.
- Amendment #4, dated July 27, 2012. This increased the post-treatment follow-up period to at least 14 days, using a telephone contact to elicit adverse reactions, VTE or anaphylactic events. For any events occurring after day 14, Kaplan-Meier curves were added up to day 49 for all Tier 1 and 2 safety endpoints.

Reviewer Comments. N.B. This is extracted from the 16.1.1.5, page 2201 of the submission. There is no definition that I can find for “Tier 1”. I assume that Tier 1 is a significant bleed or an increase in aPTT, because they are the primary and “main secondary” endpoints of the trial. See copy from sponsor submission.

Statistical Methods for Descriptive Safety

The text "Adverse events (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 patients in any treatment group exhibit the event; all other adverse events will belong to Tier 3."

Now reads:

*"Adverse events (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 **or Tier-2** endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 (**if not pre-specified**) requires that at least 4 patients in any treatment group exhibit the event; all other adverse events will belong to Tier 3."*

- PCL #2, dated September 12, 2012. This clarified the process of informing and re-consenting subjects for whom Amendment 4 was applicable.

Reviewer Comments. The protocol for this study was reasonably designed to provide data for the frequency of clinically important bleeding associated with the administration of SU. The need for this study was based on the sponsor's identification of the prolongation of the aPTT and PT that had been observed during routine laboratory assessments in previous clinical trials with the use of the drug. Randomization and double-blinding features of the trial and adjudication of the endpoints by a blind Adjudication Committee were used to minimize bias. Use of a control population that was treated with standard care with or without reversal of paralysis using neostigmine provided an acceptable control population. Enrollment of subjects undergoing major orthopedic surgery of the lower limb provided a demographic group of reasonable uniformity (surgical procedure, age, associated medical conditions and treatments, etc). The requirement that all subjects enrolled were receiving thromboprophylaxis with an anticoagulant or an antiplatelet agent tended to enrich the population for the primary clinical endpoint of bleeding (although it likely reduced the possibility of observing thromboembolic events). The primary endpoint of major bleeding, the defining features of which as described are generally accepted, over the first 24 hours after trial drug administration was valid because the effects of SU on aPTT and PT dissipate over one hour. The number of secondary endpoints analyzed was useful to support the analysis of the primary endpoint, and to assess the possibility that SU might increase the frequency of venous thromboembolic disease. The statistical analysis plan appeared to be adequate to accept or reject the null hypothesis of no difference in the frequency of bleeding after the administration of SU compared to usual care.

As noted above, there were several iterations of the protocol submitted to the Agency, and the final protocol was agreed to by the sponsor and the Agency.

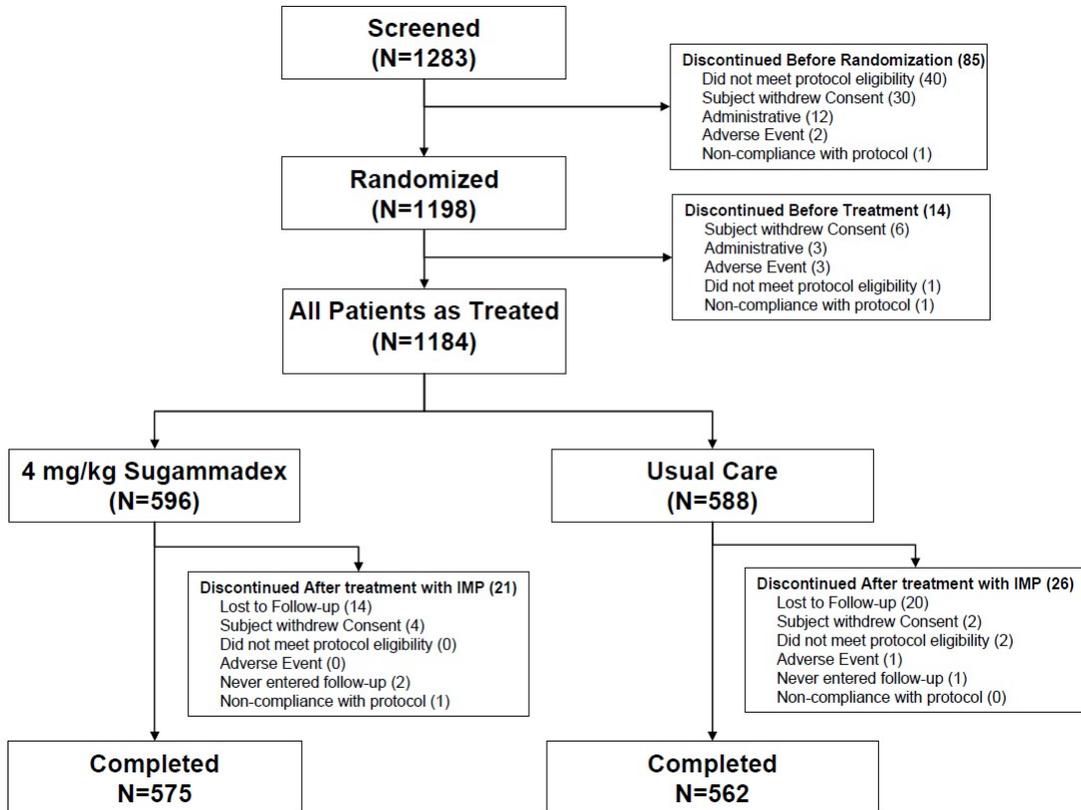
Results of the Trial

Disposition of Patients

The trial was conducted at 22 sites: 3 in Austria, 6 in Belgium and 13 in Germany.

Subject disposition is shown in the following illustration and the table that follow.

REVERSAL W/SUGAMMADEX/USUAL CARE IN HIP FRACTURE/JOINT REPLACEMENT



Sponsor submission, page 94

Table 10-1 Subject Disposition From Screening to End of Trial

Protocol No P07038

| | Number (%) of Subjects | | |
|--|--------------------------|---------------------------|--------------|
| | Sugammadex | Usual Care | Total |
| Screened | | | 1283 (100.0) |
| Discontinued before randomization | | | 85 (6.6) |
| Administrative | | | 12 (0.9) |
| Adverse Event | | | 2 (0.2) |
| Did Not Meet Protocol Eligibility | | | 40 (3.1) |
| Non-Compliance With Protocol | | | 1 (0.1) |
| Subject Withdrew Consent | | | 30 (2.3) |
| Randomized | | | 1198 (93.4) |
| Randomized | 598 (100.0) | 600 (100.0) | 1198 (100.0) |
| Discontinued before treatment with IMP | 3 (0.5) | 11 (1.8) | 14 (1.2) |
| Administrative | 1 (0.2) | 2 (0.3) | 3 (0.3) |
| Adverse Event | 1 (0.2) | 2 (0.3) | 3 (0.3) |
| Did Not Meet Protocol Eligibility | 0 | 1 (0.2) ^a | 1 (0.1) |
| Non-Compliance With Protocol | 0 | 1 (0.2) ^b | 1 (0.1) |
| Subject Withdrew Consent | 1 (0.2) | 5 (0.8) | 6 (0.5) |
| Treated ^d | 595 (99.5) | 589 (98.2) | 1184 (98.8) |
| Treated (APaT) | 596 (100.0) ^d | 588 (100.0) ^{qt} | 1184 (100.0) |
| Discontinued after treatment with IMP | 21 (3.5) | 26 (4.4) | 47 (4.0) |
| Adverse Event | 0 | 1 (0.2) | 1 (0.1) |
| Did Not Meet Protocol Eligibility | 0 | 2 (0.3) ^d | 2 (0.2) |
| Lost To Follow-Up | 14 (2.3) | 20 (3.4) | 34 (2.9) |
| Never Entered Follow Up | 2 (0.3) ^r | 1 (0.2) ^r | 3 (0.3) |
| Non-Compliance With Protocol | 1 (0.2) ^p | 0 | 1 (0.1) |
| Subject Withdrew Consent | 4 (0.7) | 2 (0.3) | 6 (0.5) |
| Completed study | 575 (96.5) | 562 (95.6) | 1137 (96.0) |

APaT=All Patients as Treated; IMP=investigational medicinal product

Subject 5/100280 decided to participate in the trial after randomization was already performed.

Subject 11/100006 was discontinued because her baseline blood sample could not be collected for technical reasons. Trial medication was not administered.

Subject 1/100016 was assigned to active reversal and randomized to receive neostigmine, but actually received sugammadex by accident.

Subject 101/200064 had significant hepatic dysfunction and did not meet inclusion criterion #5.

Subject 101/100574 had a BMI = 37.7, which exceeded the BMI specified in exclusion criterion #11.

Subject 2/200115 refused to go to the follow-up appointment. Subject 106/100565 did not enter follow-up for reasons unknown.

Subject 9/600004 did prior to the follow-up visit.

Subject 15/600002 was discontinued for non-compliance with the protocol because he was not receiving thromboprophylaxis prior to surgery and was administered succinylcholine 1 minute prior to administration of rocuronium.

Source: [Section 14.1.1.2](#)

Sponsor submission, page 96-97

There was a single subject (1/100016) who was randomized to receive standard care with neostigmine, but was given SU by error. There were no discontinuations because of adverse events in the SU arm.

Reviewer Comments. A large proportion of screened patients (93.4%) were randomized. Most of the screened patients who were not randomized were not randomized because they did not meet eligibility criteria or withdrew consent. Of the randomized subjects, 98.8% actually received trial drug (slightly more in those randomized to the SU arm compared to the usual care arm). Of the subjects randomized to the SU arm, 96.5% completed the trial while 95.6% of subjects randomized to the usual care arm completed the trial. Lost to follow up (2.3% in the SU arm and 3.4% in the usual care arm) was the most common cause for non-completion. These data support the notion that missing data were minimal, and suggest that the quality of the trial was high.

Minor deviations from, and violations of, the protocol occurred in many subjects. Most of these were due to missing information on the informed consent form, re-consenting subjects after protocol amendments were instituted, lack of preoperative use of thromboprophylactic drugs, lower than acceptable platelet counts, concomitant diagnosis of multiple sclerosis, incorrect calculation of the BMI, non-performance of a pregnancy test, use of succinylcholine in addition to other neuromuscular blocking agents, incorrect dosing, assignment to the incorrect stratum, the use of fusidic acid and a few other miscellaneous deviations. For most of the deviations or violations, it is unlikely that there was a material effect on the outcome of the trial. There was a single, accidental, retrospective unblinding of a subject at Site 9 due to the inadvertent filing of the unblinded randomization confirmation from the IVRS, which did not lead to unblinding of the Safety Assessors at that site.

Demographics

Patient characteristics are shown in the following table.

Table 10-2 Summary of Demographics and Other Subject Characteristics, Within and Across Treatment Group (All-Patients-as-Treated Population)

Protocol No P07038

| Subject Group | Number (%) of Subjects | | |
|------------------------|------------------------|---------------------|-----------------|
| | Sugammadex n=596 | Usual care n=588 | Total n=1184 |
| Sex (n,%) | | | |
| Female | 326 (55) | 340 (58) | 666 (56) |
| Male | 270 (45) | 248 (42) | 518 (44) |
| Race (n,%) | | | |
| White | 595 (100) | 584 (99) | 1179 (100) |
| Non-White | 1 (<1) | 4 (1) | 5 (<1) |
| Asian | 1 (<1) | 3 (1) | 4 (<1) |
| Multiracial | 0 | 1 (<1) | 1 (<1) |
| Ethnicity (n,%) | | | |
| Hispanic or Latino | 4 (1) | 0 | 4 (<1) |
| Not Hispanic or Latino | 592 (99) | 588 (100) | 1180 (100) |
| Age (yrs) | | | |
| Mean (SO) | 66.7 (12.0) | 66.6 (11.3) | 66.7 (11.7) |
| Median | 69.0 | 68.0 | 68.0 |
| Range | 18 - 92 | 24 - 93 | 18 - 93 |
| Age (n,%) | | | |
| 18 - <65 | 226 (38) | 237 (40) | 463 (39) |
| 65 or Older | 370 (62) | 351 (60) | 721 (61) |
| Weight (kg) | | | |
| Mean (SO) | 79.34 (13.35) | 79.09 (13.82) | 79.22 (13.58) |
| Median | 80.00 | 79.00 | 79.00 |
| Range | 43.0 - 117.0 | 47.0 - 119.0 | 43.0 - 119.0 |
| Height (cm) | | | |
| Mean (SO) | 169.30 (9.38) | 169.04 (9.02) | 169.17 (9.20) |
| Median | 168.00 | 168.00 | 168.00 |
| Range | 148.0 - 198.0 | 146.0 - 198.0 | 146.0 - 198.0 |
| BMI | | | |
| Mean (SO) | 27.61 (3.65) | 27.60 (3.79) | 27.61 (3.72) |
| Median | 27.66 | 27.53 | 27.63 |
| Range | 17.2 - 34.9 | 16.7 - 37.7 | 16.7 - 37.7 |

BMI=body mass index; SO=standard deviation

Source: [Section 14.1.2.1](#)

Sponsor submission, page 101

Reviewer Comments. The near identity between the median and mean age and BMI suggest a uniform standard demographic. This was a generally elderly population as is to be expected considering the nature of the surgery. Probably because of the geographical locale of the participating institutions, there is a virtual absence of Blacks, Hispanics and Asians. The lack of enrollment of such persons lessens the inferences that can be made for an American population. The demographic characteristics of the subjects assigned to each arm of the trial appear to be similar.

Additional baseline characteristics of the population are shown in the following table

Table 10-3 Summary of Type of Surgery, ASA Class, Creatinine Clearance Class, Prophylactic Antithrombotic Therapy, Usual Care Group, and Country Within and Across Treatment Group (All-Subjects-Treated)

Protocol No P07038

| Subject Group | Number (%) of Subjects | | |
|--|------------------------|---------------------|-----------------|
| | Sugammadex n=596 | Usual Care n=588 | Total n=1184 |
| Type of surgery (n,%) | | | |
| Hip fracture - intracapsular, dis- and replaced with total hip replacement or hemiarthroplasty | 12 (2) | 11 (2) | 23 (2) |
| Hip fracture - intracapsular, fixed with internal fixation | 6 (1) | 7 (1) | 13 (1) |
| Hip revision arthroplasty | 33 (6) | 32 (5) | 65 (5) |
| Knee revision arthroplasty | 28 (5) | 29 (5) | 57 (5) |
| Primary total hip arthroplasty | 324 (54) | 305 (52) | 629 (53) |
| Primary total knee arthroplasty | 193 (32) | 204 (35) | 397 (34) |
| ASA class (n,%) | | | |
| 1 | 92 (15) | 69 (12) | 161 (14) |
| 2 | 411 (69) | 412 (70) | 823 (70) |
| 3 | 93 (16) | 107 (18) | 200 (17) |

| | | | |
|---|----------------|----------------|----------------|
| Creatinine clearance (mL/min) | | | |
| Mean (SD) | 103.92 (36.99) | 102.49 (33.84) | 103.22 (35.47) |
| Median | 100.35 | 98.90 | 99.51 |
| Range | 33.0 - 315.8 | 33.2 - 246.4 | 33.0 - 315.8 |
| Missing | 26 | 36 | 62 |
| Creatinine clearance class, as indicated during randomization (n,%) | | | |
| < 60 mL/min | 103 (17) | 105 (18) | 208 (18) |
| >= 60 mL/min | 493 (83) | 483 (82) | 976 (82) |
| Prophylactic antithrombotic therapy, as indicated during randomization (n,%) | | | |
| Including LMWH | 581 (97) | 573 (97) | 1154 (97) |
| Including UFH | 1 (<1) | 0 | 1 (<1) |
| Including neither LMWH nor UFH | 14 (2) | 15 (3) | 29 (2) |
| Usual care group, as indicated during randomization (n,%) | | | |
| Active reversal | 292 (49) | 319 (54) | 611 (52) |
| Spontaneous recovery | 304 (51) | 269 (46) | 573 (48) |
| Country (n,%) | | | |
| Austria | 110 (18) | 113 (19) | 223 (19) |
| Belgium | 94 (16) | 84 (14) | 178 (15) |
| Germany | 392 (66) | 391 (66) | 783 (66) |

ASA=American Society of Anesthesiologist; LMWH=low molecular weight heparin; Neo=neostigmine; Plac=placebo; SD=standard deviation; UFH=unfractionated heparin

Source: [Section 14.1.2.1](#)

Sponsor submission, page 102-103

Reviewer Comments. Eighty-seven percent (87%) of subjects underwent either knee or hip arthroplasty. Most were ASA Class 2. The creatinine clearance was > 60 mL/min in 82% of subjects. Although a somewhat greater number of subjects in the usual care arm were missing data for creatinine clearance, subjects with creatinine clearances greater or less than 60 mL/min were equivalently assigned to each arm, as were type of thromboprophylactic agent received and country in which surgery was performed. Subjects in the SU arm were somewhat more likely to be allowed spontaneous recovery from muscle paralysis and somewhat less likely to be reversed with neostigmine compared to the usual care arm.

In general, the patient population in each arm had similar histories of the following medical conditions:

- **Musculoskeletal disorders**
- **Diabetes**
- **Hypertension**
- **Cardiac disorders**
- **Hypersensitivity disorders**
- **Pre-existing anemia**

- **Renal failure**
- **Use of anticoagulants, proton pump inhibitors, benzodiazepines, salicylic acid and derivatives and beta blockers**

The frequency of the use of various anesthetics and analgesics used on the day of surgery are shown in the following table.

Table 10-4 Number (%) of Subjects Exposed to Anesthetics and Analgesics on the Day of Surgery Medication Administration (All-Patients-as-Treated Population)

Protocol No P07038

| Generic Drug Name | Sugammadex N=596 | Usual Care N=588 | Total N=1184 |
|--------------------------------|---------------------|---------------------|-----------------|
| Anesthetics^a | | | |
| - Propofol | 588 (98.7) | 577 (98.1) | 1165 (98.4) |
| - Sevoflurane | 358 (60.1) | 366 (62.2) | 724 (61.1) |
| - Desflurane | 94 (15.8) | 96 (16.3) | 190 (16.0) |
| - Isoflurane | 36 (6.0) | 36 (6.1) | 72 (6.1) |
| - Ketamine | 23 (3.9) | 24 (4.1) | 47 (4.0) |
| - Etomidate | 9 (1.5) | 14 (2.4) | 23 (1.9) |
| - Esketamine | 9 (1.5) | 13 (2.2) | 22 (1.9) |
| - Thiopental | 5 (0.8) | 2 (0.3) | 7 (0.6) |
| - Anesthetics ^b | 3 (0.5) | 2 (0.3) | 5 (0.4) |
| Analgesics^c | | | |
| - Piritramide | 458 (76.8) | 457 (77.7) | 915 (77.3) |
| - Sufentanil | 305 (51.2) | 294 (50.0) | 599 (50.6) |
| - Fentanyl | 242 (40.6) | 269 (45.7) | 511(43.2) |
| - Remifentanil | 101 (16.9) | 81 (13.8) | 182 (15.4) |
| - Alfentanil | 14 (2.3) | 21 (3.6) | 35 (3.0) |
| - Dexibuprofen | 2 (0.3) | 5 (0.9) | 7 (0.6) |
| - Analgesics ^b | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| - Flupirtine | 1 (0.2) | 0 | 1 (0.1) |

ATC=Anatomical Therapeutic Chemical

^a Anesthetics based on ATC codes: N01 (anesthetics), N01AB (halogenated hydrocarbons), N01AF (barbiturates, plain), and N01AX (other general anesthetics).

^b Not otherwise specified.

^c Analgesics based on ATC codes: N01AH (opioid anesthetics), N02 (analgesics), N02AC (diphenylpropylamine derivatives), and N02BG (other analgesics and antipyretics)

Source: [Section 14.1.1.4.2](#)

Sponsor submission, page 105

Reviewer Comments. Anesthetics administered to patients in each arm of the trial were similar.

The history of the previous use of prophylactic antithrombotic agents prior to surgery is shown in the following table.

Table 10-5 Number (%) of Subjects With a History of Antithrombotic Prophylaxis (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex N=596 | Usual care N=588 | Total N=1184 |
|---|---------------------|---------------------|-----------------|
| History of prophylactic treatment ^a | 166 (27.9) | 169 (28.7) | 335 (28.3) |
| - Anti-platelet agent (ASA) ^b | 132 (22.1) | 127 (21.6) | 259 (21.9) |
| - Vitamin K antagonist ^b | 21 (3.5) | 32 (5.4) | 53 (4.5) |
| - LMWH ^b | 10 (1.7) | 5 (0.9) | 15 (1.3) |
| - Combination of Anti-platelet agent (ASA), Vitamin K, and/or LMWH | 3 (0.5) | 5 (0.9) | 8 (0.7) |
| No history of prophylactic treatment | 430 (72.1) | 419 (71.3) | 849 (71.7) |
| ASA=amino salicylic acid; ATC=anatomical therapeutic chemical; IMP=investigational medicinal product; LMWH=low molecular weight heparin ^a Based on 30 or more days of prophylactic medication before a fixed number of days (medication class dependent) before IMP: LMWH, 2 days before IMP; Anti-platelet agent (ASA), 5 days before IMP; Vitamin K antagonist, 4 days before IMP. ^b Medication class is determined using the ATC codes: LMWH, ATC code = B01AB or B01AX; Anti-platelet agent (ASA), ATC code = N02BA or B01AC; Vitamin K antagonist, ATC code = B01AA. Source: Section 14.1.1.4.3 | | | |

Sponsor submission, page 106

Reviewer Comments. Of the enrolled subjects, 28.3% were receiving anticoagulant/antiplatelet therapy within 2-5 days prior to trial drug administration. Most (21.9%) were receiving aspirin; the remainder were receiving a vitamin K antagonist (4.5%), LMWH (1.3%) or a combination of agents (0.7%). The distribution was reasonably equivalent in the two arms of the trial.

The types of antithrombotic agents received in the pre- or peri-operative period are shown in the following table.

Table 10-6 Number (%) of Subjects Receiving Pre- or Peri-Operative Antithrombotic Medication (All-Patients-as-Treated Population)

Protocol No. P07038

| Pre- or Peri-Operative Antithrombotic Medication ^a | Sugammadex n=596 | Usual Care n=588 | Total n=1184 |
|---|---------------------|---------------------|-----------------|
| LMWH ^b | 498 (83.6) | 492 (83.7) | 990 (83.6) |
| Anti-platelet agent (ASA) ^b | 15 (2.5) | 14 (2.4) | 29 (2.4) |
| LMWH and Anti-platelet agent (ASA) ^b | 73 (12.2) | 71 (12.1) | 144 (12.2) |
| No LMWH and/or Anti-platelet agent (ASA) | 10 (1.7) | 11 (1.9) | 21 (1.8) |

ASA=aminosalicylic acid; ATC=anatomical therapeutic chemical; LMWH=low molecular weight heparin

^a Defined as any antithrombotic medication in the period from 2 days (for LMWH) or 5 days (for ASA) before IMP to start of IMP.

^b Medication class is determined using the ATC codes: LMWH, ATC code = B01AB or B01AX; Anti-platelet agent (ASA), ATC code = N02BA or B01AC.

Source: [Section 14.1.1.4.4](#)

Sponsor submission, page 107

Reviewer Comments. LMWH alone was the most commonly employed anticoagulant during and immediately after surgery (83.6%) and was used in combination with aspirin in an additional 12.2% of subjects. The distribution of use was reasonably equivalent in the two arms of the trial.

The number of patients receiving heparin alone and the number who received additional agents during the day before through the 24 hours after surgery that could affect the coagulation are shown in the following table.

Table 10-7 Number (%) of Subjects Receiving Antithrombotic Medication and/or Tranexamic Acid in the Period From the Day Before to 24 Hours After Trial Medication administration (All-Patients-as-Treated Population)

Protocol No. P07038

| Medication Combination | Sugammadex n=596 | Usual Care n=588 |
|---|---------------------|---------------------|
| Heparin group | 426 (71.5) | 432 (73.5) |
| Heparin group + ASA | 56 (9.4) | 57 (9.7) |
| Heparin group + Tranexamic acid | 81 (13.6) | 59 (10.0) |
| Heparin group + ASA + Tranexamic acid | 12 (2.0) | 14 (2.4) |
| Heparin group + Other antithrombotic agents | 4 (0.7) | 7 (1.2) |
| Heparin group + Vitamin K antagonists | 7 (1.2) | 8 (1.4) |
| Heparin group + Any other combination | 5 (0.8) | 0 |
| No Heparin Group + Any other combination | 5 (0.8) | 11 (1.9) |

ASA=aminosalicylic acid; ATC=anatomical therapeutic chemical

^a Medication classes used in this table are based on the following ATC codes: B01AA, Vitamin K antagonists; B01AB, Heparin group; B01AC, Platelet aggregation inhibitors excluding heparin; B01AD, Enzymes; B01AE, Direct thrombin inhibitors; B01AX, Other antithrombotic agents; B02AA, Tranexamic acid; N02BA, ASA. Medications not explicitly mentioned in these categories are counted in the "+ any other combination" category.

Source: [Section 14.1.1.4.5](#)

Sponsor submission, page 108

Reviewer Comments. Several agents that affect bleeding/clotting were administered to subjects in the immediate pre- and post-operative period. These appeared to be equivalently given in both arms of the trial. Based on previous studies, the administration of tranexamic acid may reduce blood loss in patients during and after various surgical procedures. This raises the possibility that the use of tranexamic acid (12.4% of all subjects) might have lessened bleeding, and obscured bleeding in either or both arms. In addition, the use of tranexamic acid carries with it the possibility of an increase in the development of arterial and/or venous thromboembolic events.

Non-compliance with protocol specified doses of sugammadex (4 mg/kg \pm 10%) occurred in 13/1184 subjects (1%) with an equivalent number receiving more than and less than that dose.

Endpoints

The adjudicated events of bleeding with an onset within 24 hours after the administration of trial medication was the primary endpoint, and the adjudicated events of bleeding

within 14 days after the administration of trial medication was a secondary endpoint. The frequency of the development of these endpoints and its analysis are shown in the following two tables.

Table 11-1 Incidence (n, %) of Subjects With At Least One SUAEB^a by Adjudicated Onset, Severity, Maximum Relationship, and Treatment Group. (All-Patients-as-Treated Population)

Protocol No. P07038

| Onset | Maximum Relationship ^b | Sugammadex (N=596) | | Usual Care (N=588) | |
|---------------------------------------|-----------------------------------|--------------------|-------------------------|--------------------|-------------------------|
| | | Major | Total (Major+Non-major) | Major | Total (Major+Non-Major) |
| Within 24 hours | Unlikely | 0 | 1 (0.2) | 2 (0.3) | 3 (0.5) |
| | Possible | 12 (2.0) | 16 (2.7) | 18 (3.1) | 21 (3.6) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 12 (2.0) | 17 (2.9) | 20 (3.4) | 24 (4.1) |
| Total ^a (Up to 14 days) | Unlikely | 5 (0.8) | 7 (1.2) | 4 (0.7) | 5 (0.9) |
| | Possible | 13 (2.2) | 17 (2.9) | 19 (3.2) | 22 (3.7) |
| | Probable | 0 | 0 | 0 | 0 |
| | Overall | 18 (3.0) | 24 (4.0) | 23 (3.9) | 27 (4.6) |

SUAEB=suspected unanticipated adverse event of bleeding

^a Only events with an onset on or before Day 14 were included. Note that each subject is counted only once.

^b Maximum relationship (by adjudicator) implies that if a subject experienced, for example, 2 major adjudicated events, one unlikely and one possible related, the subject was counted in the 'possible' row, and not in the 'unlikely' row.

Source: [Section 14.2.1.1.1.1.1](#)

Sponsor submission, page 111

In an analysis of major and total bleeding within 24 hours after study drug administration, the incidence was 2.3% and 3.3%, respectively, in the stratified SU arm (N = 304) compared to the incidence of 4.1% and 4.5%, respectively, in the placebo treated arm (N = 269). Similarly, in an analysis of major and total bleeding within 24 hours after study drug administration, the incidence was 1.7% and 2.4%, respectively, in the stratified SU arm (N = 292) compared to the incidence of 2.8% and 3.8%, respectively, in the neostigmine treated arm (N = 319).

Reviewer Comments. The primary outcome endpoint was met by 2.9% of subjects randomized to the SU arm compared to 4.1% in the usual care arm. These events included both major bleeding (2.0% vs 3.4% in the SU and usual care arms, respectively) as defined in the protocol and unexpected non-major bleeding (0.9% vs 0.7% in the SU and usual care arms, respectively) as determined by the Adjudication Committee. For the majority of events, the relationship between the trial drug and bleeding was determined to be “possible”.

The frequency of the bleeding endpoint in this trial was lower than that expected from a review of the experience in patients undergoing orthopedic surgery of the lower extremity (5%), particularly for subjects assigned to the SU arm. This supports the notion that, although the administration of SU is associated with a

brief period of elevation in the aPTT and PT, these laboratory findings do not predict an increase in the frequency of bleeding.

In addition, because all of these patients were receiving other drugs designed to impair the coagulation response (particularly heparin or one of its congeners), there did not appear to be a synergistic effect on causing post-operative bleeding.

A secondary endpoint for the trial extended the time of observation for the bleeding from the first 24 hours after surgery to 14 days after surgery. There was some increase in major and unexpected non-major bleeding during the extension, but most of those events were considered to be unlikely related to trial drug administration.

Table 11-2 Analysis of Events of Bleeding Within 24 Hours of Trial Medication Administration (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Relative Risk Sugammadex vs. Usual Care (95% CI) ^a |
|--|-----------------------|-----------------------|--|
| | n (%) | n (%) | |
| Adjudicated events of bleeding with onset within 24 hours of trial medication administration | 17 (2.9) | 24 (4.1) | 0.70 (0.38, 1.29) |
| Events of bleeding with onset within 24 hours of trial medication administration according to investigator assessment ^b | 20 (3.4) | 31 (5.3) | 0.64 (0.37, 1.11) |

CI=confidence interval.

^a Primary prespecified safety event is bolded. Relative risk and associated 95% CI as computed by the Cochran-Mantel-Haenszel method stratified for renal status (< or ≥ 60 mL/min) and planned thromboprophylaxis therapy (low molecular weight heparin or other).

^b First sensitivity analysis using same method as the primary analysis. The second sensitivity analysis using Poisson regression and adjudicated SUAEBs produced identical results as the primary analysis.

Source: [Section 14.2.1.1.1.2](#)

Sponsor submission, page 112

Reviewer Comments. There was a slightly higher frequency for the determination of the primary endpoint by the primary investigators compared to that determined by the Adjudication Committee, but the relative risk of bleeding continued to favor the SU arm.

Stratification by baseline creatinine clearance for analysis of bleeding is shown in the following table.

Table 11-3 Sensitivity Analysis on Primary Endpoint: Adjudicated Events of Bleeding Within 24 Hours of Trial Medication Administration by Creatinine Clearance at Screening (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | | Usual Care (N=588) | | Relative Risk Sugammadex vs. Usual Care (95% CI) ^a | Interaction (p-value) |
|----------------------------------|--------------------|-----------|--------------------|-----------|---|-----------------------|
| | N | n (%) | N | n (%) | | |
| Creatinine clearance ≥ 60 mL/min | 493 | 11 (2.2) | 483 | 16 (3.3) | 0.67 (0.31, 1.45) | 0.85 |
| Creatinine clearance < 60 mL/min | 103 | 6 (5.8) | 105 | 8 (7.6) | 0.77 (0.27, 2.21) | |

CI=confidence interval

^a Estimated relative risk and associated 95% CI were based on the prespecified Poisson regression model.

Source: [Section 14.2.1.1.1.3](#)

Sponsor submission, page 113

Reviewer Comments. Patients with a reduced creatinine clearance appeared to have a greater frequency of bleeding than those with a normal creatinine clearance, but there was no difference in the relative risk of bleeding whether patients were treated with SU or placebo in each subgroup.

The analysis of key secondary safety endpoints (aPTT and PT) is shown in the following table.

Table 11-4 Key Secondary and Secondary Endpoint Analysis: Difference (95% CI) in APTT and PT(INR) versus Baseline by Time Point and for Sugammadex versus Usual Care (All-Patients-as-Treated Population)

Protocol No. P07038

| | | Sugammadex (vs Baseline) | | Usual Care (vs Baseline) | | Sugammadex vs Usual Care | |
|------------------------|--------|--------------------------|---------------------|--------------------------|---------------------|--------------------------|---------------------|
| | | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a | Estimate ^a | 95% CI ^a |
| aPTT ^b | 10 min | 4.7% | (3.4%, 5.9%) | -0.8% | (-2.0%, 0.4%) | 5.5% | (3.7%, 7.3%) |
| | 60 min | -1.9% | (-3.2%, -0.6%) | -2.8% | (-4.1%, -1.5%) | 0.9% | (-0.9%, 2.8%) |
| PT(INR) ^{b,c} | 10 min | 4.5% | (3.3%, 5.8%) | 1.5% | (0.3%, 2.7%) | 3.0% | (1.3%, 4.7%) |
| | 60 min | 2.7% | (1.2%, 4.1%) | 1.7% | (0.3%, 3.2%) | 0.9% | (-1.0%, 2.9%) |

aPTT=activated partial thromboplastin time; CI=confidence interval; PT(INR)=prothrombin time (international normalized ratio).

^a Estimates and confidence intervals are geometric means, adjusted for trial center, usual care group (active reversal versus spontaneous recovery), renal function (< or ≥ 60 mL/min), antithrombotic therapy (LWMH/UFH vs. other), surgical procedure (hip fracture, hip or knee replacement/revision, or hip or knee stage 1 revision [total or partial]), and treatment-by-time interaction.

^b A total of 567 subjects treated with sugammadex and 548 treated with usual care contributed to the cLDA analyses with a valid parameter value, both for aPTT as well as for PT(INR).

^c Estimates for PT and INR are identical; values for PT were used in analysis since these were provided with higher precision.

Source: [Section 14.2.1.2.1](#)

Sponsor submission, page 114

Reviewer Comments. At 10 minutes after trial drug administration, there was a small, but statistically significant, increase in the aPTT in subjects in the SU arm compared to baseline [4.7% (CI, 3.4%, 5.9%)] and in subjects in the SU arm compared to the usual care arm [5.5% (CI, 3.7%, 7.3%)]. Similar comparative increases were noted in the PT measurements [4.5% (CI, 3.3%, 5.8%) and 3.0% (CI, 1.3%, 4.7%)], respectively. At 60 minutes after trial drug administration, the laboratory findings had dissipated. These data confirm previous observations by the sponsor.

An analysis of other secondary prespecified safety bleeding endpoints is shown in the following table.

Table 11-5 Analysis of Secondary Prespecified Safety Endpoints on Bleeding (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Risk Difference ^a Sugammadex vs. Usual Care |
|---|-----------------------|-----------------------|--|
| | n (%) | n (%) | (95% CI) ^a |
| Adjudicated events of bleeding with onset within 14 days of study medication | 24 (4.0%) | 27 (4.6%) | -0.6% (-3.0 to 1.8) |
| Events of bleeding according to the investigator's assessment with onset within 14 days of study medication | 32 (5.4%) | 45 (7.7%) | -2.3% (-5.2 to 0.5) |
| Adjudicated major events of bleeding with onset within 24 hours of study medication | 12 (2.0%) | 20 (3.4%) | -1.4% (-3.4 to 0.5) |
| Adjudicated major events of bleeding with onset within 14 days of study medication | 18 (3.0%) | 23 (3.9%) | -0.9% (-3.1 to 1.2) |

CI=confidence interval.

^a Risk difference and associated 95% CI (Nurminen-Miettinen method). Positive numbers indicate a higher observed incidence for sugammadex as compared to usual care.

Source: [Section 14.3.1.5.1](#)

Sponsor submission, page 118

Reviewer Comments. All bleeding endpoints occurred at a lesser frequency in the SU treated subjects than in the usual care subjects, but these differences were not statistically significant.

The cumulative incidence of bleeding events over time according to the investigator's assessment is shown in the following graph.

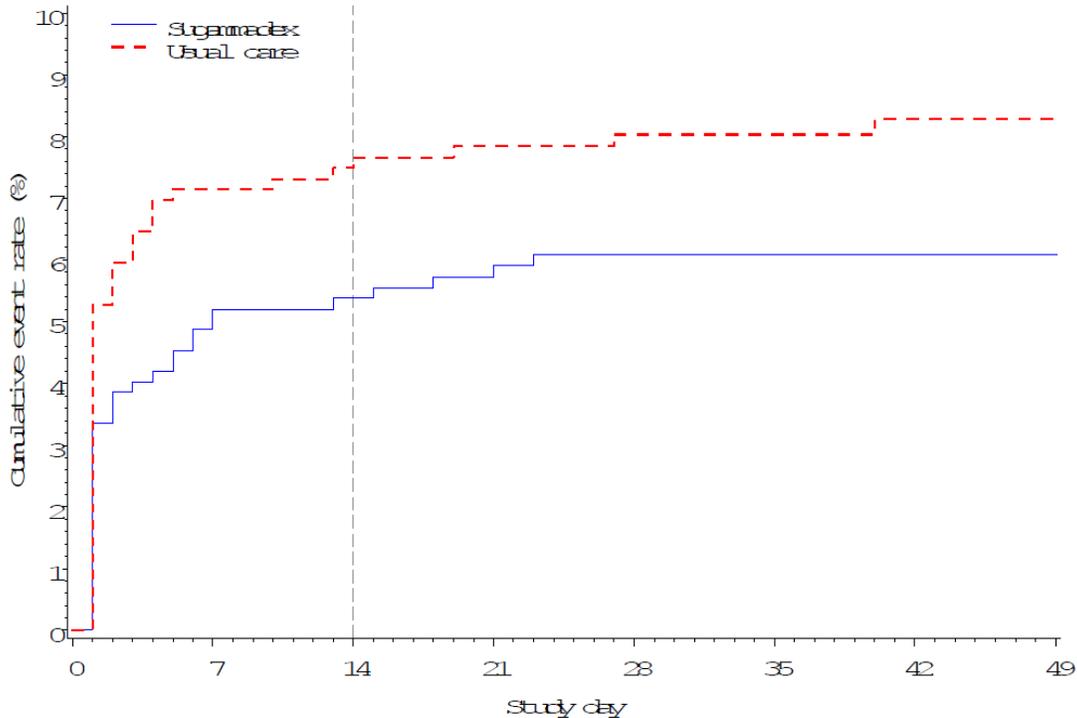


Figure 11-4 Cumulative Incidence of Events of Bleeding According to the Investigator's Assessment Over Time (All-Patients-as-Treated Population)

Source: [Section 14.2.1.1.2.4](#), [16.2.2.2]
Sponsor submission, page 120

Reviewer Comments. Most bleeding events, when they occurred, developed during the first 24 hours after trial drug administration, although a more gradual increase in bleeding events continue for several weeks following surgery. Bleeding events developing after 24 hours after surgery are not likely related to trial drug administration because its effects on measures of coagulation resolve within 60 minutes.

The analysis of prespecified blood loss endpoints is shown in the following two tables.

Table 11-6 Analysis of Prespecified Blood-Loss Endpoints (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Difference Sugammadex vs. Usual Care (95% CI) |
|--|-------------------------------|-------------------------------|--|
| Postoperative drainage volume (mL) within the first 24 hours after IMP administration – mean (SD) | 464 (367.5) | 476 (375.3) | -7.2 (-45.0, 30.5) ^a |
| Need for any postoperative transfusion – n (%) | 221 (37.1%) | 227 (38.6%) | -2.7% (-7.4, 2.0) ^b |
| For those who required postoperative transfusion the total transfusion volume (mL) – geometric mean (CV) | 335 (74.0) | 345 (84.5) | 1.10 (0.98, 1.24) ^a |
| Postoperative changes in hemoglobin concentrations (g/L) using the bleeding index ^c – mean (SD) | -15.7 (15.7) | -17.4 (17.1) | 1.4 (-0.4, 3.1) ^a |

CI= confidence interval; SD= standard deviation; CV= coefficient of variation.

^a Difference and associated 95% CI estimated using a generalized linear model, adjusted for strata and investigational site. For transfusion volume the volume was transformed to the log-scale and results were transformed back to the original scale.

^b Risk difference and associated 95% CI (Nurminen-Miettinen method, adjusted for strata and investigational site).

^c Bleeding index is the hemoglobin change adjusted for the amount of red cells transfused.

Source: [Section 14.2.1.1.4.3](#)

Sponsor submission, page 121

Reviewer Comments. Analyses of secondary endpoints of blood loss are supportive of the data reported for the primary endpoint.

Table 11-7 Analysis of Secondary Prespecified Safety Endpoints on Anemia (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Risk Difference ^a Sugammadex vs. Usual Care (95% CI) |
|--|--------------------|--------------------|---|
| | n (%) | n (%) | |
| Post-operative anemia as adverse events with an onset within 72 hours of study medication ^b | 124 (20.8%) | 132 (22.4%) | -1.6% (-6.3 to 3.1) |

CI=confidence interval.

^a Risk difference and associated 95% CI (Nurminen-Miettinen method). Positive numbers indicate a higher observed incidence for sugammadex as compared to usual care.

^b Adverse events with preferred term 'Haemorrhagic anaemia', 'Anaemia', 'Anaemia postoperative', 'Haemoglobin decreased' or 'Haemoglobin S decreased'.

Source: [Section 14.3.1.5.1](#)

Sponsor submission, page 122

Reviewer Comments. Analysis of the secondary endpoint of the development of post-operative anemia is supportive of the data reported for the primary endpoint.

The frequency of venous thromboembolic events is shown in the following table.

Table 11-8 Analysis of Secondary Safety Endpoints on Venous Thromboembolic Events (All-Patients-as-Treated Population)

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Risk Difference ^a Sugammadex vs. Usual Care (95% CI) ^a |
|--|--------------------|--------------------|--|
| | n (%) | n (%) | |
| Number of <i>potential</i> cases of VTE within 14 days of study medication as reported by the investigator | 7 (1.2%) | 7 (1.2%) | 0.0% (-1.4 to 1.4) ^b |
| Number of <i>adjudicated</i> cases of VTE within 14 days of study medication | 5 (0.8%) | 3 (0.5%) | 0.3% (-0.7 to 1.5) |

CI=confidence interval, VTE=Venous thromboembolic events.

^a Risk difference and associated 95% CI (Nurminen-Miettinen method). Positive numbers indicate a higher observed incidence for sugammadex as compared to usual care.

^b Based on post-hoc analysis.

Source: [Section 14.3.1.5.1](#)

Sponsor submission, page 123

Reviewer Comments. There was no statistically significant difference in the relative risk of developing venous thromboembolic events between the 2 arms of the study whether potential or adjudicated cases were analyzed. This suggests that SU did not induce a thrombotic potential. Additionally, the frequency of venous thromboembolism was approximately 1%, which would be considered low following orthopedic surgery of the lower extremity.

The frequency of the development of anaphylaxis is shown in the following table.

**Table 11-9 Analysis of Secondary Prespecified Safety Endpoints on Anaphylaxis
(All-Patients-as-Treated Population)**

Protocol No. P07038

| | Sugammadex (N=596) | Usual Care (N=588) | Risk Difference ^a Sugammadex vs. Usual Care (95% CI) |
|--|-----------------------|-----------------------|--|
| | n (%) | n (%) | |
| Number of <i>potential</i> cases of anaphylaxis within 14 days of trial medication as reported by the investigator | 4 (0.7%) | 3 (0.5%) | 0.2 (-0.9 to 1.3) ^b |
| Number of cases of anaphylaxis within 14 days of trial medication as <i>assessed by the investigator</i> | 0 (0%) | 1 (0.2%) | -0.2 (-1.0 to 0.5) ^b |
| Number of <i>adjudicated</i> events of anaphylaxis occurring within 14 days of trial medication | 0 (0%) | 0 (0%) | 0% (-0.6 to 0.6) |
| Number of <i>adjudicated</i> cases of hypersensitivity within 14 days of trial medication | 2 (0.3%) | 2 (0.3%) | -0.0 (-0.9 to 0.9) ^b |

CI=confidence interval.

^a Risk difference and associated 95% CI (Miettinen-Nurminen method). Positive numbers indicate a higher observed incidence for sugammadex as compared to usual care.

^b Based on post-hoc analysis. The pre-specified endpoint has been bolded.

Source: [Section 14.3.1.5.1](#)
Sponsor submission, page 124

Reviewer Comments. Evaluation of hypersensitivity reactions is not within the purview of this review.

Coagulation Endpoints

Pharmacokinetic/pharmacodynamic analyses and modeling were performed on a subgroup of 43 subjects from 2 selected sites. Blood samples were obtained just prior to trial drug administration and at 3, 10, 20, 30, 60 and 120 minutes after administration. Based on measurements of serum concentrations of SU and timed coagulation tests (aPTT, PT and anti-Xa levels), a coagulation model was constructed for surgical subjects receiving thromboprophylactic therapy. For 29 blood samples collected at unscheduled visits, only 2 contained detectable levels of SU (at 20.6 and 3.72 hours after SU administration).

The geometric mean plasma concentration 3 minutes after the administration of SU at a dose of 4 mg/kg in 20 subjects was 57.1 µg/mL with a geometric coefficient of variation of 27.9%.

Blood samples obtained prior to trial drug administration from 20 subjects receiving SU and from 23 subjects receiving placebo showed a geometric mean aPTT of 36 sec. The geometric mean aPTT was 40 sec (geometric CV, 18.2%) in the former and 36.3 sec (geometric CV, 16.3%) in the latter at 3 minutes after receiving trial drug. The geometric mean aPTT value-vs-time after trial drug administration is shown in the following figure.

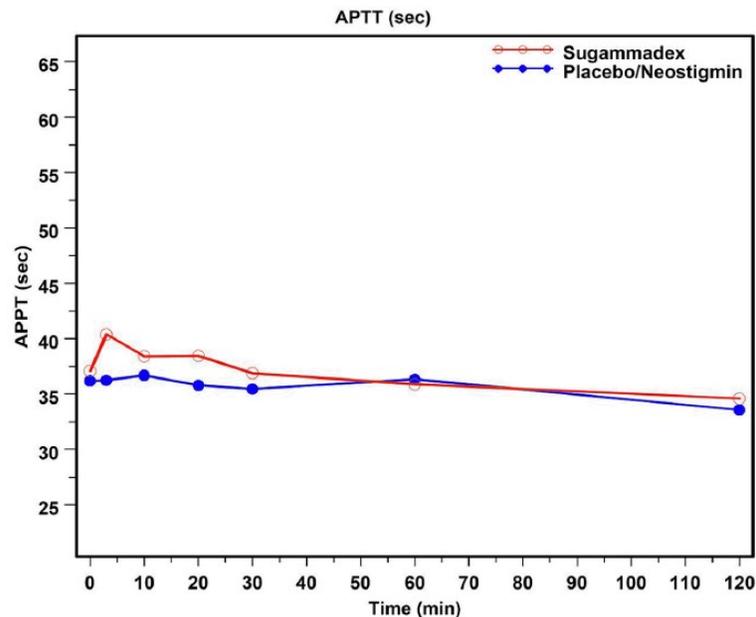


Figure 11-5 Geometric Mean aPTT Value-Versus-Time After Administration of Trial Medication

Source: [Section 14.2.2-4.2.1](#)

Sponsor submission, page 127

Reviewer Comments. There was a small, but noticeable, increase in aPTT at 3 minutes after trial drug administration in subjects who received SU but not in those

in the usual care arm. Most of the increase had dissipated by 30 minutes and was completely ablated at 60 minutes. This observation is consistent with data from other studies performed by the sponsor.

The correlation between SU concentration and aPTT is shown in the following figure.

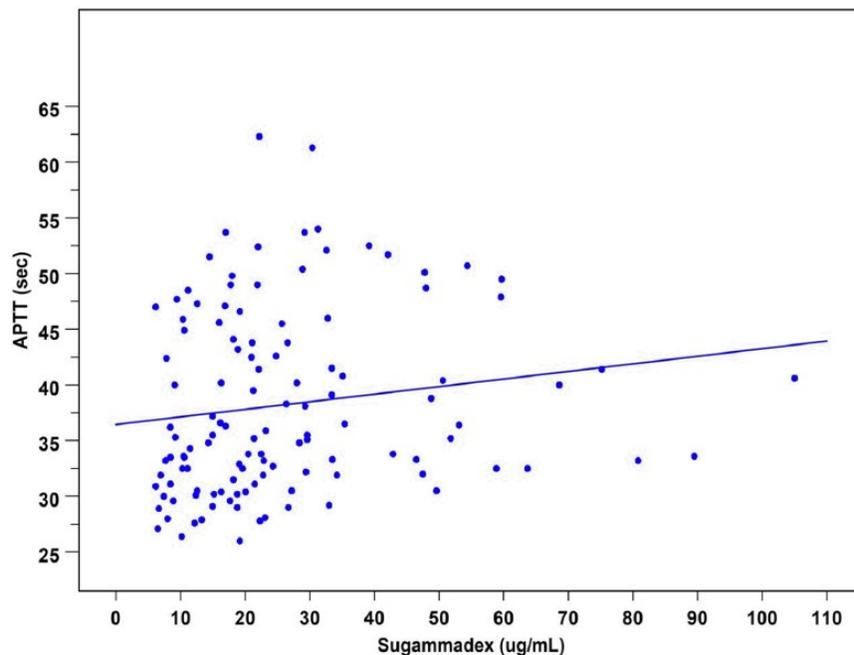


Figure 11-6 Individual Sugammadex Concentrations versus aPTT Values After Administration of Sugammadex to the 20 Sugammadex-Treated Subjects in the PK subgroup.

Source: [Section 14.2.2-5.1](#)

Sponsor submission, page 128

Reviewer Comments. Although there is some positive correlation between SU serum concentration and aPTT, the incline is very shallow, suggesting that the

relationship is weak, and the deviations from the line of correlation are large, suggesting that serum SU concentration explains only a small portion of the change in the aPTT. In addition, the graph suggests that outliers for each measure were responsible for the slope of the regression line.

The geometric mean PT value-vs-time after trial drug administration is shown in the following figure.

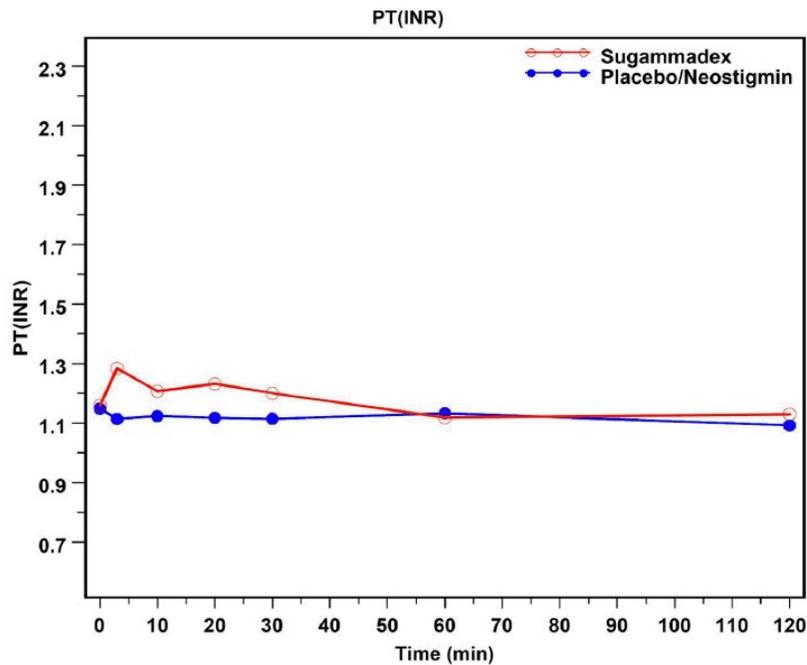


Figure 11-7 Geometric Mean PT(INR) Value-Versus-Time After Administration of Trial Medication

Source: [Section 14.2.2-4.2.1](#)

Sponsor submission, page 129

Reviewer Comments. The results for effect of SU on the PT is very similar to that of SU on the aPTT, although the effect seems to persist for a slightly longer time.

The correlation between SU concentration and PT (INR) is shown in the following figure.

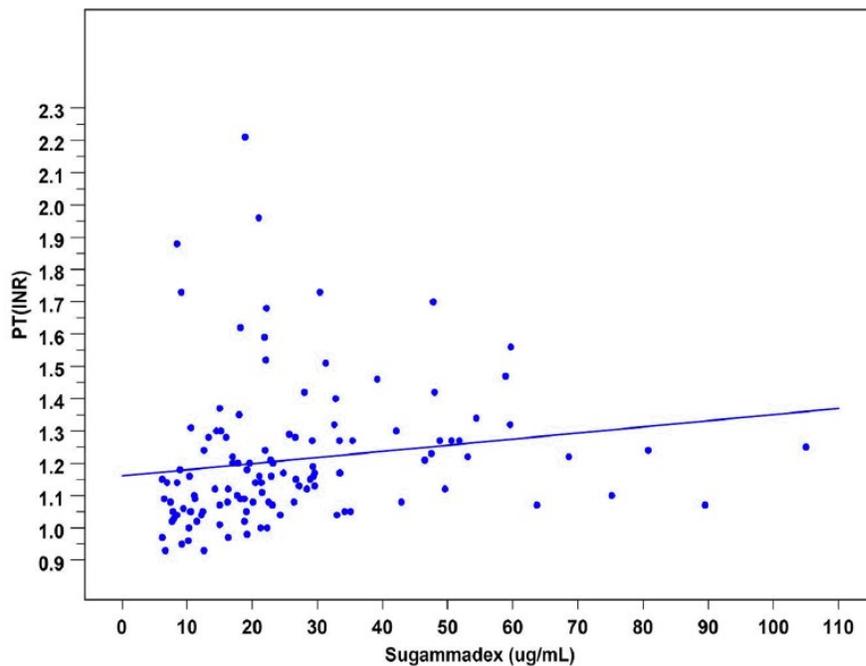


Figure 11-8 Individual Sugammadex Concentrations-Versus-PT(INR) Values After Administration of Sugammadex to the 20 Sugammadex-Treated Subjects in the PK-Subgroup

Source: [Section 14.2.2-5.2](#)

Sponsor submission, page 130

Reviewer Comments. Although there is also some positive correlation between SU serum concentration and PT, the incline is very shallow, suggesting that the relationship is weak, and the deviations from the line of correlation are large, suggesting that serum SU concentration explains only a small portion of the change in the PT. In addition, the graph suggests that outliers for each measure were responsible for the slope of the regression line.

Anti-Xa levels were below the lower limit of quantitation for all 43 subjects who were enrolled in this substudy, except for 4 samples from 3 subjects that were measured at 20 or 30 minutes after trial drug administration.

In Time in Motion studies, there were no significant differences in the time of extubation, time to become ready for operating room discharge, time to post-anesthesia care unit discharge or time to first ambulation.

Sponsor Conclusions regarding SU and bleeding

- Treatment with SU is not associated with an increase in the frequency of post-operative bleeding compared to treatment with usual care in patients undergoing major orthopedic surgery and receiving thromboprophylaxis.
- The administration of SU at a dose of 4 mg/kg causes an increase in the aPTT (5.5%) and the INR (3.0%) at 10 minutes after administration. The prolongation of coagulation times resolves by the end of 60 minutes.
- There is virtually no increase in anti-Xa levels after the administration of SU.
- The frequency of bleeding in patients with a creatinine clearance < 60 mL/min after the administration of SU is similar to the frequency of bleeding after the use of either placebo or neostigmine in similar patients treated with usual care.
- The frequency of venous thromboembolic disease is not increased in patients treated with SU compared to subjects treated with usual care.
- The administration of SU to patients undergoing major orthopedic surgery does not shorten measures of immediate post-operative events compared to subjects treated with usual care.

Reviewer Comments. Based on the data provided from this trial, I am in general agreement with the conclusions reached by the sponsor (see my Conclusions section, below).

Safety

Safety, other than for the primary endpoint, was not a main consideration for this trial, because the sponsor has submitted data for the safety profile of SU from previous trials and submissions. However, adverse events were collected during the course of the trial and are summarized below.

The number of subjects who experienced any adverse events during the trial are shown in the following table.

Table 12-2 Number (%) of Subjects With at Least One Treatment-Emergent Adverse Experience and Difference in Percentage of Subjects Between Treatment Groups (All-Patients-as-Treated Population)

Protocol No. P07038

| | Number (%) of Subjects | | |
|---|------------------------|---------------------|---|
| | Treatment Groups | | Difference Estimate (95% CI) ^a |
| | Sugammadex n=564 | Usual Care n=560 | |
| Subjects with Treatment-Emergent AEs ^b | 551 (92.4%) | 549 (93.4%) | -0.9 [-3.9 ; 2.0] |
| Subjects with SAEs | 39 (6.5%) | 40 (6.8%) | -0.3 [-3.2 ; 2.6] |
| Subjects with Treatment-Related AEs ^c | 64 (10.7%) | 72 (12.2%) | -1.5 [-5.2 ; 2.1] |
| Subjects with Treatment-Related SAEs ^c | 4 (0.7%) | 2 (0.3%) | 0.3 [-0.6 ; 1.4] |
| Deaths ^d | 0 (0.0%) | 3 (0.5%) | -0.5 [-1.5 ; 0.1] |

AE=adverse event; CI=confidence interval; SAE=serious adverse event

- ^a Risk difference and associated 95% confidence interval according to Miettinen-Nurminen method.
- ^b A treatment-emergent AE is defined as an AE occurring during or after trial medication administration up to and including 14 days after trial medication administration.
- ^c A treatment-related AE is defined as a treatment-emergent AE considered "possibly" or "probably" related to trial medication by the investigator.
- ^d Any death occurring during or after trial medication administration. A total of 4 subjects assigned to usual care group died during the trial, but one subject (Subject 1/200144) was discontinued before administration of trial medication due to a pulmonary embolism ([Section 16.2.7.2](#)) and is not accounted for in the table.

Source: [Section 14.3.1.5.1](#), [Section 16.2.7.2](#)

Sponsor submission, page 140

There were no deaths in subjects who received SU. There were 4 deaths in subjects randomized to the usual care arm. One of these patients died of pulmonary embolization prior to receiving study drug. The cause of death in the other three included ventricular fibrillation, metastatic renal cell cancer and cardiac arrest.

Serious adverse events occurred in 6.5% of SU treated subjects and in 6.8% of usual care treated subjects, of which 0.7 % and 0.3% were attributed to SU and placebo, respectively. The nature of the serious adverse events was similar between the two arms of the trial.

There were 4 serious adverse events that were considered by the investigator to be possibly related to SU administration:

- Hemorrhage at the surgical site on the 4th post-operative day that led to the need for blood transfusion and surgical revision of the wound.
- Hemorrhage at the surgical site within 24 hours after surgery that led to the need for blood transfusion and surgical revision of the wound.
- Hematoma formation at the surgical site on the 5th post-operative day that led to a delay in the date of discharge. The patient had also received enoxaparin and acenocoumarol.
- Hematoma formation at the surgical site with anemia treated with compression of the site without the need for transfusion or surgery.

There were 2 serious adverse events considered by the investigator to be possibly related to placebo administration:

- Bleeding at the surgical site within 24 hours and the need to change the dressing, and wound secretion that delayed discharge. No transfusions were given. The patient had also received aspirin, certoparin, diclofenac and heparin.
- Unexpected bleeding from the surgical site within 24 hours post-operatively with the development of a hematoma and anemia. These led to prolongation of hospitalization but no transfusions were given.

No subjects in the SU treated arm discontinued the trial because of the development of an adverse event. There were no specific adverse events that appeared to occur more frequently in SU treated subjects compared to those who were treated with usual care.

There were a total of 6 life-threatening treatment-emergent adverse events that occurred during the trial, with 3 of these in each arm. In the SU arm, there was 1 each of acute myocardial infarction, transient ischemic attack and pulmonary embolism. In the usual care arm, there was 1 each of myocardial infarction, ventricular fibrillation (with death) and apnea.

A total of 25 subjects experienced treatment-emergent severe adverse reactions that were considered to be severe: 9 in the SU arm and 16 in the usual care arm. An additional 12 subjects experienced severe serious adverse reactions that were not considered to be treatment-emergent. Of these, 3 occurred > 14 days after SU administration, 2 occurred in the usual care group before the administration of trial medication and 7 in the usual care arm > 14 days after trial drug administration. All of the severe serious adverse

reactions were stated to be possibly related to trial drug except for one subject who had developed anemia that was believed to be not related to treatment.

Three subjects who received SU had a post-operative elevation in hepatic enzymes, but in none of these subjects was the abnormality believed related to trial drug administration.

Sponsor Conclusions regarding Safety

- The incidences of treatment-emergent and treatment-related adverse events and serious adverse events were similar in the SU and placebo/neostigmine treatment groups and were mostly of mild to moderate intensity
- There were no clinically relevant differences between treatment groups in routine laboratory parameters or vital signs.

Additional Information

Besides the data from this trial, there is other information provided by the sponsor that supports the idea that SU use does not increase the frequency of post-operative bleeding, including the following:

- In Section 5.3.6 of the sponsor's submission, the sponsor provided a document entitled "CIOMS Reports: MK 8616. Hemorrhage Events Cumulative to 15-Jun-2012. I have reviewed the document, which describes a total of 5 patients. Four of the subjects developed anaphylaxis/hypersensitivity after the administration of SU. Four of the subjects developed bleeding. One of the bleeds was in the operative site (parotid gland) which was re-operated at 8 hours after administration of SU, and the reporter indicated that the cause of the bleed was "sutural insufficiency" and not due to SU. Another of the bleeds was in the operative site (tonsil), occurred several hours after the administration of SU, and was not believed to be due to SU. In two of the subjects, DIC was noted after the onset of anaphylaxis. In one of the subjects, heparin administration had led to an aPTT of > 200 sec when the bleeding was noted. In one subject, there was no indication of hemorrhage, and hypotension appeared to be related to "vascular permeability" that led to hypotension. Therefore, these reports do not appear to support the idea that SU causes bleeding.
- In a sponsor study dated April, 2009 and entitled "Assessment of possible effect of Org 25969 on the incidence of bleeding complications in patients; an analysis of adverse events", the following two tables list the frequency and types of serious bleeding events in subjects treated with SU compared to those treated with placebo.

Table 1 Number (%) of patients with a SAE indicating a bleeding complication

| GROUP | PATIENTS | % | 95% CONFIDENCE INTERVAL |
|--|----------|------|-------------------------|
| Placebo (N=130) | 2 | 1.5% | 0.2% - 5.4% |
| Org 25969 in placebo controlled trials (N=630) | 7 | 1.1% | 0.4% – 2.3% |
| Org 25969 total (N=1738) | 16* | 0.9% | 0.5% - 1.5% |

Not included: One SAE that concerned anemia without reported bleeding (subject 305111102)

Table 2 Serious Adverse Events concerning bleeding complications or indicating possible bleeding complications

| Subject number | Study | Dose group | ASA-Class | MedDRA Lowest Level Term | MedDRA Preferred Term | Intensity | Relation to IP |
|----------------|----------|------------|-----------|------------------------------------|------------------------------------|-----------|----------------|
| 105009 | P194206 | Placebo | 1 | Bleeding postoperative | Post procedural haemorrhage | Severe | None |
| 107003 | P194309 | Placebo | 3 | Intraventricular haemorrhage | Intraventricular haemorrhage | Severe | None |
| 000114 | P194207 | 0.5 mg/kg | 2 | Incision site haemorrhage | Incision site haemorrhage | Severe | None |
| 104003 | P194209B | 0.5 mg/kg | 2 | Wound haemorrhage | Wound haemorrhage | Mild | None |
| 101020 | P194208B | 0.5 mg/kg | 2 | Urinary bladder haemorrhage | Urinary bladder haemorrhage | Moderate | None |
| | | | | Bladder tamponade | Bladder tamponade | Moderate | None |
| 000097 | P194207 | 1.0 mg/kg | 1 | Haematoma muscle | Muscle haemorrhage | Severe | None |
| 201012 | P194209 | 2.0 mg/kg | 1 | Epistaxis | Epistaxis | Moderate | Unlikely |
| 103204 | P194305 | 2.0 mg/kg | 3 | Abdominal hematoma | Abdominal haematoma | Severe | None |
| 107004 | P194309 | 2.0 mg/kg | 3 | Postoperative haematoma | Post procedural haematoma | Severe | Unlikely |
| 104013 | P194301 | 2.0 mg/kg | 1 | Postoperative haemorrhage | Post procedural haemorrhage | Severe | None |
| 106012 | P194308 | 2.0 mg/kg | 3 | Operation site bleed | Operative haemorrhage | Severe | Unlikely |
| 103006 | P194301 | 2.0 mg/kg | 1 | Postoperative bleeding | Post procedural haemorrhage | Severe | None |
| 106302 | P194305 | 2.0 mg/kg | 2 | Postoperative bleeding | Post procedural haemorrhage | Severe | None |
| | | | | Upper gastrointestinal haemorrhage | Upper gastrointestinal haemorrhage | Severe | None |
| 106202 | P194305 | 2.0 mg/kg | 2 | Gastrointestinal bleeding | Gastrointestinal haemorrhage | Severe | None |
| 111102 | P194305 | 2.0 mg/kg | 2 | Anaemia | Anaemia | Moderate | None |
| 000029 | P194207 | 4.0 mg/kg | 1 | Haematoma | Haematoma | Severe | None |
| 108001 | P194309 | 4.0 mg/kg | 3 | Abdominal haematoma | Abdominal haematoma | Moderate | Unlikely |
| 101017 | P194209B | 8.0 mg/kg | 1 | Postoperative haemorrhage | Post procedural haemorrhage | Moderate | Unlikely |
| 105014 | P194206 | 16.0 mg/kg | 1 | Bleeding postoperative | Post procedural haemorrhage | Moderate | Unlikely |

Bleeding events did not appear to be dose related, and the frequency of bleeding during the 24 hours after surgery were similar in SU and placebo treated subjects as shown in the following table.

Table 7 Number (%) of patients with at least one adverse event concerning bleeding complications or indicating a possible bleeding complication, occurring within 24 hours after Org 25969 or placebo administration.

| Org 25969 (N = 630) | | Placebo (N = 130) | | Relative Risk (95% C.I.) | p |
|---------------------|-----------------|-------------------|------------------|--------------------------|-------|
| n | % (95% C.I.) | n | % (95% C.I.) | | |
| 42 | 6.7 (4.8 – 8.9) | 8 | 6.2 (2.7 - 11.8) | 1.1 (0.5 – 2.3) | 0.830 |

N.B. Clopper-Pearson confidence intervals (exact). Relative risk and 95% confidence intervals based on Cochran-Mantel-Haenszel.

Conclusions

Based on the data submitted by the sponsor from Study P07038, there is no evidence that the administration of SU to patients undergoing major orthopedic surgery of the lower limb and receiving thromboprophylaxis with heparin have a greater frequency of hemorrhage than patients receiving usual care (with neostigmine or placebo) without SU, even though patients treated with SU have some prolongation of the aPTT and the PT that lasts for less than 30 minutes after SU administration. The trial was performed in accord with the recommendations we submitted to the sponsor before the trial was initiated.

Recommendations

The sponsor should be informed that, on the basis of the data generated in Study P07038, there is no evidence that there is an increase in bleeding after the administration of sugammadex compared to neostigmine/placebo to patients who have undergone major orthopedic surgery of the lower limb and have received thromboprophylaxis with heparin or low molecular weight heparin.

----- **This is a representation of an electronic record
that was signed
electronically and this page is the manifestation of the
electronic
signature.**

/s/

GEORGE G SHASHATY
05/07/2013

KATHY M ROBIE SUH
05/07/2013

EDVARDAS KAMINSKAS
05/07/2013

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARTHUR F SIMONE
08/23/2013

CHRISTOPHER D BREDER
08/23/2013

Concur with the recommendation for Complete Response. Further comments are made in my CDTL memo.

Summary Basis for Regulatory Action

| | |
|---|--|
| Date | July 31, 2008 |
| From | Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II |
| Subject | Summary Review |
| NDA/BLA # | 22-225 |
| Supp # | |
| Proprietary / Established (USAN) Names | (b) (4) Sugammadex Sodium |
| Dosage Forms / Strength | Sterile solution, injectable 100 mg/mL |
| Proposed Indication(s) | <ol style="list-style-type: none"> 1. For routine reversal of shallow blockage following rocuronium or vecuronium 2. For routine reversal of profound blockade following rocuronium or vecuronium 3. For immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium |
| Action: | <i>Not Approvable</i> |

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding sugammadex and I refer the reader to the reviews in the action package for a more detailed discussion. Organon USA, Inc. is seeking licensing approval as a 505(b)(1) application for sugammadex for use in reversal of neuromuscular blockade (NMB) of various depths (listed above) caused by administration of specifically (and only) rocuronium (RCB) or vecuronium (VCB).

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex was designed such that the negatively charged sugar groups within its center would attract the positively charged ammonium groups of rocuronium and vecuronium and hold these neuromuscular blocking agents within its core by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of RCB and VCB within sugammadex thus renders them inactive and results in reversal of paralysis due to neuromuscular blockade.

Regarding efficacy for this application, in brief, the sponsor has demonstrated adequately that sugammadex has clinical efficacy in reversing paralysis due to NMB caused by RCB and VCB. The concept of 'shallow' and 'profound' NMB may be of importance for dosing decisions, but the use of these distinctions for indications are not warranted as the indication should relay the use of the drug, which is reversal of NMB. As such, should this application

ever proceed to approval the indication should be more general and consistent with the notion that sugammadex can be used for reversal of NMB after administration RCB or VCB. The ‘immediate reversal’ indication sought by the sponsor was not evaluated in a clinically meaningful fashion and therefore should not be included in the indications section of labeling.

Significant safety concerns were discovered late in the review that will require further elucidation and explanation prior to approval. These concerns include 1) a high rate of anaphylaxis and 2) what may be increases in coagulation parameters. These issues will need to have further characterization to allow for an adequate risk/benefit consideration prior to approval. Further safety issues that could be evaluated post approval include the potential for bone or tooth effect in pediatric patients and a questionable QT prolongation signal discussed in Dr. Simone’s review.

There is great interest in this drug by the anesthesia community and it would be considered a potentially important addition to their armamentarium as it would allow for recovery from deeper levels of NMB than that possible using existing drugs. This could allow for quicker recovery times to spontaneous respirations or, at the very least, less guessing regarding patient-to-patient variations in metabolism of neuromuscular blocking agent and the role this plays in administration of these agents and the existing drugs, used to reverse their effects. As such, this application was granted a priority review and was presented at a meeting of the Anesthesia and Life Support Drugs Advisory Committee (ALSDAC). The anaphylaxis concern was noted late in the review and did not benefit from a full analysis prior to the advisory committee meeting. Thus, committee members (mainly anesthesiologists or pain experts) had minimal information regarding anaphylactic potential upon which to make recommendations. In retrospect, recommendations made by the panel are probably not appropriate given the degree of risk (or unknown degree of risk) that may exist and the panel members not being fully apprised such that they could make an informed risk:benefit decision regarding approval.

Since there is insufficient information about the drug to determine whether the product is safe for use under the conditions sought in the proposed labeling that will require further study, and any resubmission would not be accepted as a Class I Resubmission, I am recommending a Not Approvable action.

Efficacy

This has been thoroughly covered in Dr. Shibuya’s review and will only be briefly mentioned here. Efficacy for this application was evaluated by four studies (301, 302, 310 and 303). Studies 301, 302 and 310 were similar in design and differed for the most part in how profound the NMB was and what nerve stimulator criteria were used to determine amount and timing of reversal agent administration. These details are covered in Dr. Shibuya’s review. Study 303 differed from the others and was designed to try to demonstrate that sugammadex would be effective in ‘Cannot Intubate/Cannot Ventilate (CICV) situations. The key features (along with comparator reversal agent used for comparison) are summarized in the table below from Dr. Roca’s review.

| | Study 301 | Study 302 | Study 310 | Study 303 |
|---------------------------|---|---|--|---|
| Location | Europe | United States | Europe | United States and Canada |
| Study period | November 2005 to March 2006 | November 2005 to November 2006 | November 2005 to May 2006 | February 2006 to August 2006 |
| Clinical scenario | “shallow” neuromuscular block, defined as the return of T ₂ (the second twitch in a train-of-four stimulation) | “profound” neuromuscular block, defined as 1-2 post tetanic counts | “shallow” neuromuscular block, defined as the return of T ₂ | “Immediate” reversal (defined as 3 minutes following rocuronium administration) |
| Dose of (b) (4) | 2 mg/kg | 4 mg/kg | 2 mg/kg | 16 mg/kg |
| Treatment groups | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Cis-atricurium/neostigmine | a. Rocuronium/Org25969 b. Succinylcholine/no reversal agent |
| Number of patients | 196 randomized | 182 randomized | 84 randomized | 115 randomized |
| Primary efficacy endpoint | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₁ = 0.1 |

The results of these studies are summarized in the table below, adapted from Dr. Shibuya’s review.

Summary of pivotal efficacy data, primary efficacy endpoint, means (mm:ss)

| Study # | Scenario | Org | Range | Comparator | Range | p-value |
|----------------|-----------------|----------------------|--------------------------|-------------------|-----------------------------|----------------|
| 301 | Shallow | 1:29 (R) 2:48 (V) | 0:55-5:25 1:12-64:12 | 18:30 16:48 | 3:40-106:53 2:55-76:09 | <0.0001 |
| 302 | Profound | 2:52 (R) 4:28 (V) | 1:13-16:05 1:26-68:26 | 50:22 66:12 | 13:16-145:40 4601:312:39 | <0.0001 |
| 303 | “Immediate” | 4:22* | 3:28-7:43* | 7:04 | 3:45-10:28 | <0.0001 |
| 310 | Shallow | 2:02 | 0:41-6:24 | 8:46 | 4:12-28:14 | <0.0001 |

*Time began at the administration of rocuronium. Sugammadex was administered at time=3 minutes

(R) - rocuronium
(V) - vecuronium

These data clearly indicate that sugammadex is effective in reversing NMB with RCB and VCB when compared to neostigmine. It should be noted that neostigmine is not approved for this indication but is widely used clinically and there is enough literature to at least support the concept that neostigmine would not enhance NMB such that sugammadex would be as effective, or more effective, than placebo (if neostigmine did not have an effect). Approved

agents include edrophonium and pyridostigmine, but these are not widely used. These data indicate that resolution of NMB with sugammadex occurs earlier and with less time variation when used in conjunction with RCB compared to VCB. Also noted are outliers that may not have quick resolution of NMB as the RCB group had one subject that took 16 minutes to attain the primary endpoint and VCB had one subject that took over 68 minutes (both in study 302).

Study 303 was the sponsor's attempt to try to get some type of labeling that could be interpreted as CICV. This study was designed such that subjects who were given doses of RCB that produced profound NMB were then reversed with sugammadex and were monitored to recovery of 10% of their T₁ twitch contraction of the adductor pollicis. The applicant has not provided data to support the clinical significance of this endpoint and the study did not attempt to collect what would probably be a more important endpoint, time to spontaneous ventilation. The review division feels this study is of limited clinical importance, and the advisory committee members independently concurred with this assessment and felt that labeling should not indicate "immediate" reversal or claims that could be interpreted that sugammadex was effective in CICV situations. It is instructive to note in the summary of clinical endpoints table above from the clinical studies that there were outliers that can have a prolonged recovery from NMB when sugammadex was used as the reversal agent. Therefore, to send a message to users of the drug that it may be useful and relied upon in a crisis situation could potentially lead to a catastrophic outcome. This is discussed in further detail in Dr. Shibuya's review.

Safety

The main issue with this application is whether sugammadex causes anaphylaxis and what the clinical impact of that may be if approved for the requested indications. The overall safety database consists of 2054 unique subjects including 51 pediatric subjects with 529 enrolled in pivotal efficacy trials. The sponsor listed hypersensitivity reactions in seven subjects that DAARP felt were consistent with anaphylaxis. These cases were discovered and evaluated by DAARP fairly late in the review process. However, that should be viewed in the setting of this application being granted a priority review with a shortened review time period (six-month clock) and the team simultaneously trying to get ready for an advisory committee meeting.

The aforementioned advisory committee meeting was held on March 11, 2008. In preparing for that meeting, the main issue identified for discussion by the division early on was whether the sponsor had demonstrated efficacy for the 'immediate reversal' indication that would be equivalent to CICV labeling. As stated above, DAARP discovered the possible anaphylaxis cases, but in retrospect, did not have time to adequately evaluate them or to make sure that allergy and immunology expertise was on the panel. As such, only a rudimentary presentation of this safety signal was made to the panel members, who in turn had a limited, superficial, discussion. Although some panel members stated that if the true rate of anaphylaxis was 0.1% (possible rate presented to AC panel members) that would be concerning, they also felt that the cases appeared to resolve without intervention and did not appear to be clinically life-threatening. There was not any discussion regarding the continuum of clinical presentation that one might expect would fit under the 'anaphylaxis' umbrella.

After the advisory committee meeting, as the potential impact of this safety signal became clearer, a consult was obtained from the Division of Pulmonary and Allergy Products (DPAP). This first consult was returned to DAARP on May 13, 2008 and stated that two of the subjects in the database met diagnostic criteria for anaphylaxis as proposed by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7). This would have given an incidence rate for anaphylaxis of 0.1%. The recommendations from DPAP were that the sponsor should conduct further studies to elucidate the mechanism behind the anaphylaxis and conduct studies to evaluate repeat exposure.

The sponsor conducted an additional study (19.4.110) that evaluated skin prick testing and intradermal skin testing in healthy volunteers, both with no prior sugammadex exposure, and with prior exposure sugammadex. The subjects with prior exposure to sugammadex also had clinical symptoms indicative of hypersensitivity. The results of this study were submitted to DAARP approximately two weeks prior to the advisory committee meeting. As part of the study, the sponsor also conducted two types of *in vitro* cell testing which were 1) *in vitro* basophil histamine release assay and 2) *ex vivo* mast cell mediator release assay. Included in their evaluation, the sponsor organized an independent panel of experts to review the results of Study 19.4.110 as well as the seven suspect cases and five additional cases that were identified upon a more careful search. The results of Study 19.4.110 and the sponsor organized expert panel evaluation were then submitted for our review and we extended the clock in order to afford an evaluation of this material.

The sponsor's panel of experts felt that:

- 1) Reactions were not life threatening and should be termed "hypersensitivity" instead of (b) (4).
- 2) Eleven of the 12 possible cases of drug hypersensitivity were likely related to sugammadex administration.
- 3) The most likely mechanism was nonimmunologic, non-IgE mediated histamine release
- 4) The most relevant initial test of mechanism was an *in vitro* histamine release from cultured human basophils.

Therefore, a second consult was obtained from DPAP to respond to the sponsor's expert's assertions. In the Consult dated June 16, 2008, DPAP indicated that there were three clear cases of anaphylaxis occurring in healthy volunteers and another two 'probably' cases occurring in surgical subjects. The surgical cases were listed as possible because there was confounding by polypharmacy, co-morbid conditions and the effects of surgery (e.g. abdominal pain following abdominal surgery making it difficult to use physical symptoms as an indicator). DPAP calculated that the frequency of anaphylaxis was 1.4% (3/209) in the healthy volunteer population and if the rate was calculated for the whole database it would be somewhere between 0.1 to 0.3% depending on whether the two surgical cases were included in the numerator (3/204 or 5/204). Therefore, they estimate that the rate of anaphylaxis could be anywhere from 0.1% to 1.4%. Anesthetic-induced anaphylaxis using present medications is estimated as 1:3500 to 1:20,000 with a 4% mortality rate and 2% severe brain damage rate (Sampson et.al, J Allergy Clin Immunol, March 2005; p:584-591).

The cases are reviewed quite nicely in DPAP's consult and I will not review them here with the exception of two cases that are highly instructive as well as quite concerning.

- 1) Case 106101008 was a healthy volunteer who developed paresthesias, tachycardia, blurred vision, nausea, palpitations, and stomach discomfort within 1 to 2 minutes after the initiation of a first time infusion. The infusion was stopped due to symptoms and within minutes the subject developed flushing of the arms and abdomen along with hypotension. The subject also had elevated serum tryptase levels indicating mast cell release of mediators. Follow-up intradermal skin testing (IDT) was positive. This case is quite concerning as it is clearly anaphylaxis with multisystem involvement and even an elevated serum tryptase and occurred with a first exposure. A first-exposure anaphylaxis experience would speak either against IgE mediation or pre-sensitization due to exposure to a cross-reactive allergen. The positive skin testing speaks for IgE mediation or at the very least that sugammadex sensitizes subjects or that there is cross-sensitization following exposure to another drug product.
- 2) Case 105101030 was a healthy volunteer that was exposed to escalating doses of sugammadex with a first dose of 4 mg/kg that resulted in pruritus, and while receiving a 32 mg/kg dose 13 days later had more severe symptoms of flushing, difficulty breathing, tachycardia, rash and paresthesias. This subject had negative IDT testing, which would speak against IgE mediation, but did have sensitization with worse symptoms upon re-exposure that one might expect with IgE mediation.

It should be noted that there were very little data concerning re-exposure in this development program, and the little re-exposure that occurred did so soon after the initial exposure (within a few days). This would not allow adequate evaluation regarding whether subjects would have been at risk for an antibody sensitization reaction due to IgE mediation as there would not have been enough time for the subject to develop an complete IgE response. This is because the typical lag period for IgE antibody production after first exposure to allergen is approximately six weeks.

From the data resubmitted by the sponsor, DPAP concluded that:

- 1) Results from this study indicated that sugammadex induced sensitization as none of the naïve volunteers had positive skin tests, whereas 2 of 12 subjects previously exposed did have positive skin tests.
- 2) The clinical development program did not evaluate the safety of repeat exposures after several weeks when IgE antibodies would be more fully developed.
- 3) The life-threatening potential of anaphylaxis, combined with a relatively high frequency demonstrated and expected wide usage were concerning.
- 4) The in vitro basophil histamine-release assay provided by the sponsor is primarily a research tools and of limited clinical utility for diagnosing or predicting anaphylaxis in individual patients. The ex vivo mast cell-mediator release assay also performed by the sponsor is in the preliminary stage of development and is far from being used for clinical diagnosis.

DPAP recommended the following:

- 1) Further elucidation of the underlying immunologic mechanism, e.g. development of an assay for sugammadex-specific IgE which may facilitate patient screening (if this is an IgE mediated reaction).
- 2) Formal assessment of repeat exposure of subjects from the general population and in the population of subjects that have a positive skin test to sugammadex.

We have also sought advice from external academic experts. Dr. James T. Li, M.D., Ph.D, Chair of the Division of Allergic Diseases of Mayo Clinic formal consult review was available at the time of the action and he articulated in it the following observations:

- 1) Cases 105101031 and 105101028 meet the Sampson criteria for “anaphylaxis highly likely”.
- 2) The anaphylaxis rate in healthy volunteers is about 1%. The rate in the exposed population is estimated at 0.1%. The cases did not seem life-threatening.
- 3) If the drug sensitization is immune mediated (unproven), repeated use might increase the number of sensitized individuals
- 4) There are other cases suggestive of immediate drug reactions (although not anaphylaxis).
- 5) Skin testing suggests that sugammadex causes sensitization
- 6) The clinical utility of the basophil histamine release assay in drug allergy is unknown, and probably limited.
- 7) Given the anticipated widespread use of sugammadex, caution regarding the potential for frequent drug reactions is reasonable.
- 9) Post-marketing study of reactions to sugammadex will likely be rather difficult, given the heterogeneity of patients, polypharmacy, and multiplicity of symptoms in the perioperative period.

To discuss how I evaluate the above information, I note that the sponsor’s experts contend that the reactions seen during the clinical trials were not anaphylaxis because they felt the reactions:

- 1) were not IgE mediated and
- 2) were not life-threatening

I would point out that the diagnostic criteria for anaphylaxis as proposed by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (Sampson HA et al. J Allergy Clin Immunol 2006; 117:391-7) is based on clinical presentation and not mechanism so whether these reactions are IgE mediated or not is moot. Whether the clinical presentation is the result of IgE-mediated or non-IgE mediated mechanisms is of little consequence as we have had experience where non-IgE mediated events were just as severe (heparin-NEJM 358;23 p-2457-2467) as IgE mediated events. It is difficult to tell with the information at hand, as the two cases above demonstrate, whether this is an IgE mediated reaction, a non-IgE reaction or a combination of both.

Regarding the severity of reaction, the National Institute of Allergy and Infectious Disease position paper cited states, “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.” I would contend that the contents of the paper seem to make it clear that if there is multi-system involvement it should be considered a serious reaction. That would seem to make sense and both of the cases presented above had clear multi-organ involvement and had all the features of a serious reaction. To require near-death as a diagnostic criteria seems antiquated and not a true representation of the continuum of anaphylaxis. Regarding the continuum of anaphylaxis, I would also note that for drugs that are approved and have been widely used for which we have receive reports of anaphylactic deaths (heparin, monoclonal antibodies, oncology medications etc.), we also receive reports like the ones above that did not result in near-death, so there clearly is a range of manifestations based on individual characteristics of susceptibility and semantics should not disguise the fact that there may be a significant problem associated with sugammadex. Sugammadex is clearly immunogenic, and as the position paper further points out, viewing anaphylaxis as a continuum circumvents the problem of defining a point at which an acute allergic reaction becomes anaphylaxis.

As detailed in Dr. Simone’s review, the sponsor anticipates 1.5 million exposures in the first full year of marketing increasing to 3.8 million by the fourth year of marketing. This may be a gross underestimation of use in the first year considering the considerable interest this drug has caused in the anesthesia community and considering that the sponsor also estimated that the number of cases that use steroidal NMB agents a year is 6.7 million. As such, with huge potential exposures and population consequences, should sugammadex have real anaphylaxis rates in the range demonstrated in this database, it is incumbent upon the sponsor to do an adequate evaluation prior to approval to demonstrate that the potential problem above is not, in fact, a reality. And if it is reality, experience has shown that a proper evaluation can identify patients as risk and screen them from exposure (abacavir-NEJM 358;6: p.568-579).

It is interesting to note that there are other compounds that contain cyclodextrins as detailed in the table below from Dr. Shibuya’s review. Therefore subjects do have an opportunity to be exposed to cyclodextrins prior to receiving sugammadex and one could postulate that perhaps subjects with a first time reaction may have had a prior exposure, but that would be speculation only at this point with the limited information available.

Approved products containing cyclodextrins

| Product | NDA |
|-----------------------------------|--------------|
| Caverject (alprostadil) | 20-379 |
| Daptacel (DPT vaccine) | 103666 (BLA) |
| Geodon (ziprasidone) | 20-919 |
| Sporanox IV (itraconazole) | 20-966 |
| Sporanox oral soln (itraconazole) | 20-567 |
| VFEND IV (voriconazole) | 21-267 |

Regarding other safety issues, Dr. Simone discovered that the sponsor noted in the ‘risk management plan’ that they had conducted two in-vitro studies (which did not seem to be included in the submission) that demonstrated that samples spiked with sugammadex increased aPTT, PT and INR. The sponsor, however, did not do any clinical evaluation of this finding in

subjects actually receiving the drug. The package noted an overall adverse event reporting rate for hemorrhage of 6% in sugammadex-treated subjects compared to 3% in placebo-treated subjects. I agree with him that this needs further evaluation prior to approval.

Dr. Simone also noted that there were more reports of QT prolongation in sugammadex-treated subjects compared to placebo. This is slightly perplexing as there were two negative thorough QT studies. As such, it is difficult to know what the increase in reports mean, but I would agree with him that this could be evaluated post-approval.

Finally as noted in the pharm-tox review, approximately 2% of the administered dose binds to teeth and bones with a very long half-life of 170 days. These findings have potential clinical implications in pediatric populations and perhaps in adult populations with coexisting bone trauma and will need further evaluation which could be done post-approval.

In summary, regarding safety, there are other reversal agents for non-depolarizing NMB agents (although they do not reverse the degrees of NMB that sugammadex can). These agents work through a different mechanism by indirectly inhibiting acetylcholinesterase, the enzyme that breaks down acetylcholine, allowing more acetylcholine to be available at the neuromuscular junction to cause a nerve impulse. It is important to remind ourselves that neostigmine, as well as other anticholinesterases inhibitors, has side-effects related to their indirect effects on muscarinic and nicotinic receptors. Stimulation of these receptors can result in salivation, bradycardia, tearing, miosis and bronchoconstriction. These undesirable effects are treated with antimuscarinic agents such as glycopyrrolate and do not seem to raise to the concern that anaphylaxis does. While sugammadex can reverse a deeper NMB than these agents, this advantage does not have a clinical utility such that we would tolerate the possible safety signal demonstrated in the clinical trials. As such, it would be prudent to demand that the sponsor provide a more thorough evaluation of the risks identified above.

2. Conclusions and Recommendations

As discussed above, sugammadex would be a significant advancement in anesthesia in terms of the amount of monitoring subjects would require in reversing NMB. However, it seems that this is not a clinical advancement such that sugammadex would be expected to decrease anesthetic mortality rates or cause any fewer serious adverse events than are seen at this moment with present anesthetic techniques. That combined with what could be a devastating adverse event of anaphylaxis, demonstrated at very high rates in the limited database submitted, urges caution and prudence such that further data is required.

I am well aware that there is great interest in the anesthesia community to have access to sugammadex. I am also well aware that anesthesiologists practice in a highly monitored environment, are well-trained to handle severe reactions and that the ALSDAC voted for approval of this drug. However, I do not feel that the safety was adequately explored at the AC meeting as the anaphylaxis issue was a late finding and we did not have the proper expertise to inform the discussion for our anesthesia and pain colleagues. I would also think that even if the anesthesiology community is trained to handle anaphylaxis, they should be adequately informed at what rate to expect those reactions, and have some idea as to what may

happen to patients re-exposed to sugammadex so that they can make a properly informed decision as to what drugs to use to reverse NMB.

As such, I recommend a Not Approvable action for this application.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Curtis Rosebraugh
7/31/2008 07:17:44 AM
MEDICAL OFFICER



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Summary Review for Regulatory Action

| | |
|---|--|
| Date | July 30, 2008 |
| From | Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products |
| Subject | Division Director Summary Review |
| NDA # | 22-225 |
| Applicant Name | Organon |
| Date of Submission | October 30, 2007 |
| PDUFA Goal Date | July 31, 2008 |
| Proprietary Name / Established (USAN) Name | (b) (4) sugammadex sodium injection |
| Dosage Forms / Strength | 2 ml vial: 100 mg/ml 5 ml vial: 100 mg/ml |
| Proposed Indication | 1. For routine reversal of shallow blockade following rocuronium or vecuronium. 2. For routine reversal of profound blockade following rocuronium or vecuronium. 3. For immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium |
| Recommended Action: | Not approvable |

| Material Reviewed/Consulted | |
|------------------------------------|---|
| OND Action Package, including: | |
| Medical Officer Review | Efficacy: Robert B. Shibuya, M.D. Safety: Arthur Simone, M.D., Ph.D. |
| Statistical Review | Thomas Permutt, Ph.D.; Roswitha E. Kelly, Ph.D. (CMC consult for stability) |
| Pharmacology Toxicology Review | Zengjun Xu, Ph.D.; Adam Wasserman, Ph.D.; Paul C. Brown, Ph.D. |
| CMC Review/OBP Review | Alan C. Schroeder, Ph.D.; Ali Al-Hakim, Ph.D. |
| Microbiology Review | Vinayak Pawar, Ph.D.; Stephen Langille, Ph.D. |
| Clinical Pharmacology Review | Lei Zhang, Ph.D.; Suresh Doddapaneni, Ph.D.; Venkatesh Atul Bhattaram, Ph.D.; Jogarao Gobburu, Ph.D. |
| DDMAC | Michelle Safarik, PA-C |
| DSI | Sherbet Samuels, R.N., M.P.H.; Constance Lewin, M.D., Ph.D. |
| CDTL Review | Rigoberto Roca, M.D. |
| OSE/DMEP | Judy Park, Pharm.D.; Kellie Taylor, Pharm.D., M.P.H.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph. |
| OSE/DAEA | Martin Pollock, Pharm. D. |
| OSE/DRISK | Jeanine Best, M.S.N., R.N., P.N.P; Mary Dempsey; Darrell Jenkins; Claudia Karwoski, Pharm.D. |
| DEPI | N/A |
| Renal Consult | Shen Xiao, M.D., Ph.D.; Norman Stockbridge, M.D., Ph.D. |
| Allergy Consult | Charles E. Lee, M.D.; Susan Limb, M.D.; Sally Seymour, M.D.; Badrul Chowdhury, M.D., Ph.D. |
| QT Team Consult | Christine Garnett Pharm.D.; Venkatesh Atul Bhattaram, Ph.D.; Suchitra Balakrishnan, M.D.; Joanne Zhang, Ph.D.; Ted Guo, Ph.D.; Norman Stockbridge, M.D., Ph.D. |
| Metabolic & Endocrine Consult | Gemma Kuijpers, Ph.D.; Karen Davis-Bruno, Ph.D.; Mary Parks, M.D. |
| Dental Consult | Fred Hyman, D.D.S., M.P.H.; John Kelsey, D.D.S., M.B.A.; Susan Walker, M.D. |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DAEA=Division of Adverse Event Analysis
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology

1. Introduction

(b) (4) is an aqueous formulation of the new molecular entity Org 25969, established name sugammadex sodium injection. Sugammadex is a γ -cyclodextrin designed to specifically bind the aminosteroid neuromuscular blocking agents (NMBs) rocuronium and vecuronium. This design is based on the ring-like structure of the molecule which has a lipophilic core, a hydrophilic outer surface, and negatively charged sugar groups in the interior that attract the positively charged ammonium groups of the two blocking agents. By sequestering the NMBs the drug removes enough of these agents to reverse the muscular paralysis for which they are administered during surgical procedures, and thereby reduces the time to recovery of normal ventilatory and general motor function.

Organon has submitted this application in support of the marketing of (b) (4) with three indications:

- 1) For routine reversal of shallow blockade following rocuronium or vecuronium.
- 2) For routine reversal of profound blockade following rocuronium or vecuronium.
- 3) For immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

2. Background

The Division has been working closely with Organon for four years on the development of this potentially important addition to the anesthesia armamentarium. Early studies assessing efficacy were promising and there were no safety signals noted throughout product development. The sponsor provided clear evidence that (b) (4) is effective in reversing the neuromuscular blockade induced by rocuronium and vecuronium. The application was granted a priority review status at the time it was filed and a meeting of the Anesthesia and Life Support Drugs Advisory Committee (ALSDAC) was scheduled. However, during the course of his review, Dr. Simone determined that there were clinically concerning adverse events that appeared to be cases of anaphylaxis associated with exposure to (b) (4). With the limited time available on a priority review clock, the application was presented to ALSDAC without our having completed a full analysis of this new safety concern. Thus, the committee members had minimal information regarding these events and made recommendations that now, in light of further analysis and discussion, may no longer be appropriate to the degree of risk that appears to exist for this product.

The initial decision to take this application to the ALSDAC was based on the fact that (b) (4) is a new molecular entity and the first drug in its class. Additionally, however, even at the time of filing Dr. Simone informed the review team that he did not think the sponsor had provided adequate support for their proposed indication of “immediate reversal of neuromuscular blockade...” The implication of this indication for the anesthesia community

would be that the product could be administered safely to reverse neuromuscular blockade in the emergency setting of Cannot Intubate/Cannot Ventilate (CICV). This is an uncommon but clearly life threatening situation and a product that could successfully reverse the blockade might be an extremely valuable addition to the anesthetic armamentarium. The sponsor did not actually study the use of (b) (4) in the CICV setting as it would be unethical to perform that type of study. However, the study that they did perform did not collect the most important data necessary to determine the efficacy of (b) (4) in the CICV setting, time to recovery of spontaneous ventilation.

3. CMC

I agree with the review team that there are no outstanding concerns that would preclude approval from a CMC perspective. The drug substance does contain (b) (4) Org 48302, which has an activity and pharmacological profile similar to Org 25969 and is, therefore, considered an active entity. Although it typically occurs at (b) (4) its activity has been incorporated into the efficacy evaluations and its toxicity has been adequately qualified as part of the overall developmental toxicology program.

The Office of Compliance has determined as of July 24, 2008, that the facilities used for manufacturing and control of the drug substance and drug product are acceptable.

4. Nonclinical Pharmacology/Toxicology

The general toxicology did not raise any specific concerns. While the reproductive toxicology studies did raise some concern due to increased neonatal mortality in several of the pre- and post-natal studies, there was a high safety margin for the proposed human dose and the pharmacology/toxicology review team has recommended a Pregnancy Category C. Dr. Wasserman also suggests that studies to determine the mechanism underlying this finding should be performed, but that these studies could be performed in the post-marketing period.

However, in his tertiary review, Dr. Brown has concluded that embryofetal studies have not demonstrated a clear risk to the fetus in the absence of maternal toxicity, and he (b) (4) (b) (4) for a Pregnancy Category B. He does agree with the review team that juvenile animal studies should be performed prior to approval of (b) (4) for use in the pediatric population. The reader is referred to the reviews completed by Drs. De, Wasserman and Brown for the details of their analyses.

While the initial assessment of the review team was that carcinogenicity studies were not necessary for (b) (4) as the genetic toxicology studies were negative and the drug would not be used for a total period of greater than six months, Dr. Wasserman has provided an addendum to his review addressing this issue. Based on the fact that Org 25969 binds to bone in animal models with single dose administration and is retained with a terminal half-life ranging from 60 to 210 days, he is recommending that carcinogenicity studies should be performed.

There are a number of impurities that are present in the drug substance at levels above the ICH standards requiring identification and qualification. However, due to the low toxicity potential of these (b) (4) which are γ -cyclodextran-related substances, Drs. Xu and Wasserman have determined that, as long as they remain at levels of less than or equal to (b) (4)%, identification and qualification would not be required. The sponsor will perform a partial identification should an impurity level rise above (b) (4)%, in order to determine conformance with agreed upon specifications for these impurities.

As noted above, Org 25969 binds to bone, and it binds to teeth as well. After intravenous administration in young adult rats, approximately 2% of the dose binds to teeth and bone. Binding also appears to be enhanced in regions or states of active growth. While no evidence of bone abnormalities was found in the general toxicity studies in rats and dogs, bone-specific evaluations were not performed. A bone study in adult rats demonstrated mild changes in development and structure at a very high single dose of 2000 mg/kg, not associated with evidence of compromised bone strength. However, at single doses up to 500 mg/kg, no abnormalities of bone development or structure were noted. This dose represents a single-dose NOAEL for bone integrity and structure, with an AUC-based safety margin of 26X for the proposed 4 mg/kg human dose based on the adult rat.

In a four-week toxicology study in juvenile rats dosed up to 500 mg/kg/day from Post-Natal Day 7 through 34, the NOAEL for bone was identified at 30 mg/kg/day, with a safety margin of 1X for the 4 mg/kg based on AUC though the sponsor considers the margin to be 30X for the proposed 4 mg/kg human dose based on an estimated bone concentration comparison. Doses greater than or equal to 120 mg/kg/day resulted in a number of abnormalities in bone development. Bone strength testing was not performed, as the sponsor considered the effects to be clinically insignificant.

The juvenile rats treated with 500 mg/kg/day also developed tooth discoloration after three weeks. Other dental abnormalities such as overgrown incisors and malocclusion were also noted in these animals. At doses of greater than or equal to 120 mg/kg/day, disruption of the enamel epithelial layer of the incisors with deposition of amorphous material was found. Similar findings occurred in the molars at 500 mg/kg/day. Single dose studies in juvenile rats did not find these abnormalities, although a single animal in the 500 mg/kg group did have minimal disruption of the enamel epithelium and deposition of amorphous material. Therefore, the NOAEL associated with a single-dose in the juvenile rat is 500 mg/kg and provides an AUC-based safety margin of 18X for the 4 mg/kg human dose while a bone concentration-based safety margin would be estimated at $\geq 70X$.

A consult was requested from the Division of Metabolic and Endocrine Products. As summarized on pages 17 and 18 of Dr. Roca's review (bracketed sections have been included to clarify the original quotation):

Dr. Kuijpers noted that the difference in the trabecular measurements [in the 28-day juvenile rat study] may be due to an artifact caused by the need to re-orient the treatment group femurs relative to the control femurs due to the slight difference in femur length and diameters, essentially resulting in the equivalent portions of the diaphysis were not evaluated between the groups.

Dr. Kuijpers was not convinced that the decreased bone length is due to a general toxicity and growth retardation effect as there was no clear temporal relationship, although the lack of reversibility of [effects on] longitudinal bone growth suggests a potential relationship to bone retention. No binding was observed at the growth plate; however, the Applicant did not conduct growth plate morphometry. Dr. Kuijpers also indicated that Org 25969 may possess reabsorption-inhibiting properties similar to tetracycline or bisphosphonates, but bone turnover biomarkers were not evaluated by the Applicant [in this study].

Nevertheless, her overall impression was that the safety margins supported by the [single-dose] NOAEL [in the juvenile rat] were large, > 18-fold, and supported the use in adult patients. A low AUC-based safety margin was observed in the 28-day multiple dose juvenile rat study (1X).

Dr. Kuijpers' recommendation for additional studies that would be helpful in assessing the nature of the effect of Org 25969 on bone includes:

1. Provide data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study; samples may be obtained from this study if still available.
2. Evaluation of vertebrae to interpret bone effects since they have a more homogenous trabecular structure
3. Reevaluation of the bone localization (microautoradiography) study as presentation of data was poor and errors in descriptions were noted.
4. Address the mechanism of action, including in vitro bone resorption assay (45Ca release), assessment of bone turnover markers, hydroxylapatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention.
5. Any future study should add a positive control arm of bisphosphonates to prove sensitivity of the assay and extend the period of recovery to 4-6 months (>2 times $t_{1/2\beta}$ Org 25969).
6. Fracture repair study in a nonclinical model.

A consult was also requested from the Division of Dermatology and Dental Products. Dr. Hyman noted that the rat incisors are a good model for developing human teeth as they continue to grow throughout the animal's life, and that the rat molars are a good model for permanent human teeth. As summarized on page 17 of Dr. Roca's review:

White spots on teeth appear similar in nature to that observed with dental fluorosis, which is considered a cosmetic alteration and not a pathologic finding according to the Surgeon Generals Report on Oral Health (2000). Dr. Hyman indicated that, although data for Org 25969 would suggest that it could interfere with enamelization (amelogenesis) in the juvenile rat and, therefore, may confer a theoretical risk to children with developing teeth, the extremely high doses and sustained exposure required to produce detectable adverse effects on the developing enamel provides a margin of safety for its proposed single use in patients under the age of 8, and for all children over the age of 8 regardless of the lifetime frequency of use.

Dr. Hyman agrees with the review team that the safety margins will decrease if multiple doses are [administered]; however, it was reassuring that disrupted amelogenesis and deposition of "amorphous material" was not observed until 3 weeks of daily administration at high dose levels (>30X highest planned human dose) had already taken place.

Dr. Hyman noted the low transfer of Org 25969 through the placenta to the fetus, consistent with the lack of dental findings in the reproductive toxicology studies. Furthermore, if there should be any effects on the primary teeth through gestational exposure, these would likely be replaced by normal permanent teeth later in the child's development.

Additional studies that could potentially be helpful for determining the risk profile in the pediatric population include the evaluation of extracted/shed teeth from children exposed during

development (i.e. primary teeth), and the evaluation of Org 25969's effect on the teeth of a non-human primate.

5. Clinical Pharmacology/Biopharmaceutics

(b) (4) has a volume of distribution of 12 to 15 liters, which would indicate some degree of extravascular distribution, and a mean steady-state plasma elimination half-life of approximately 1.5 to 3 hours at the proposed doses. The drug is primarily eliminated unchanged via renal excretion. No in vitro assessments of drug-drug interactions were performed as the molecule's size, structure and limited metabolism would likely preclude CYP enzyme system involvement. There was a 15-fold increase in exposure demonstrated in subjects with renal impairment, defined as a creatinine clearance less than 30 mL/min, compared to subjects with normal renal function, defined as clearance rates greater than or equal to 80 mL/min. Due to in vitro and in vivo findings that sugammadex is not efficiently removed from plasma using a low flux filter and due to inconsistent in vitro vs. in vivo findings with a high flux filter, the review team has recommended that additional studies of the use of (b) (4) in patients on hemodialysis should be undertaken. Additionally, as the sponsor's own population PK/PD interaction model predicted a prolongation of recovery time in patients with impaired hepatic function, they also recommended further study in this population.

Due to concerns raised by the Division early in development that (b) (4) might complex with drugs other than rocuronium and vecuronium, possibly resulting in displacement of the NMB or reduction in the efficacy of the complexed drug, the sponsor evaluated this potential in a series of in vitro assessments, as well as in nonclinical studies and with pharmacokinetic/pharmacodynamic modeling. These studies focused on the most frequently prescribed drugs, drugs used in the anesthetic setting and steroidal molecules. The only US marketed drug that was identified as having the potential for a displacement interaction with (b) (4) was toremifene. In addition, (b) (4) may capture hormonal contraceptives that have steroidal structures leading to decreased exposure of contraceptives. The review team has recommended that cautionary language be included in the product labeling for drugs of steroidal structures including toremifene and hormonal contraceptives.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

Four studies were submitted in support of the efficacy of (b) (4) for the proposed indications. Studies 19.4.301 (Study 301), 10.4.302 (Study 302) and 19.4.310 (Study 310) were of similar design. From Dr. Roca's review, page 9:

For the studies that were of similar design, patients were induced with a standard intravenous sequence followed by paralysis with the specified NBMA. Anesthesia was maintained with sevoflurane and parenteral agents. The level of neuromuscular blockade was monitored via a Train-Of-Four (TOF)

nerve stimulator. At the return of T₂, which was felt to approximate “shallow” blockade, the reversal agent was administered. The elapsed time between the start of administration of the reversal agent and the recovery of the T₄/T₁ ratio to 0.9, as measured by acceleromyography, was the primary endpoint. Other clinical measures of recovery were assessed including a 5-second head lift and general weakness.

Of note, compared to Study 301, in Study 302 the reversal agent was administered at 1 to 2 Post-Tetanic-Counts, to approximate “profound” block. Additionally, a higher dose of (b) (4) was used in Study 302, 4 mg/kg compared to 2 mg/kg. Study 310 differed from Studies 301 and 302 in that there were two treatment groups, rocuronium (b) (4) and cis-atricurium/neostigmine.

Study 19.4.303 (Study 303) enrolled only ASA I and II patients who were scheduled to undergo procedures requiring a short period of neuromuscular blockade. The treatment arms were: 1) rocuronium followed in three minutes by (b) (4) 16 mg/kg, and 2) succinylcholine 1 mg/kg with spontaneous recovery of neuromuscular function.

The results of these four studies are summarized in the following table, reproduced from page 10 of Dr. Roca’s review:

| Study # | Scenario | Time (in minutes) | | p-value |
|---------|--------------------|-------------------|------------|---------|
| | | Org | Comparator | |
| 301 | Routine | 1:29 (R) | 18:30 | <0.0001 |
| | Shallow | 2:48 (V) | 16:48 | |
| 302 | Routine | 2:52 (R) | 50:22 | <0.0001 |
| | Profound | 4:28 (V) | 66:12 | |
| 303 | “Immediate” | 4:22 | 7:04 | <0.0001 |
| 310 | Routine Shallow | 2:02 | 8:46 | <0.0001 |

(R) - rocuronium

(V) – vecuronium

The clinical review team questioned the use of the primary endpoint selected by the sponsor for Study 303, T₁ = 0.1. As this study was intended to provide evidence that (b) (4) would reverse a deep neuromuscular block in the setting of CICV, this endpoint may not translate to actual clinical benefit, i.e. the ability of the patient to sustain adequate spontaneous ventilation. The actual CICV scenario may be due to multiple factors, including but not limited to the patient’s underlying medical status, the other drugs that have been administered, and any structural abnormalities in the individual’s airway.

The review team has also noted that the distinction between shallow and profound neuromuscular blockade is arbitrary and of questionable clinical value. It is sufficient for labeling purposes to provide language that states that the product is capable of reversing the

neuromuscular blockade induced by rocuronium and vecuronium, and that defines the dose range available for that reversal.

8. Safety

There were two deaths in subjects exposed to (b) (4). The first was a 65 year old woman who died 42 days after surgical resection of an intestinal carcinoma. There were no immediate surgical complications, but she developed atrial fibrillation and respiratory failure that were initially noted at 23 hours post-op. Her death was attributed to myocardial infarction, cardiogenic shock and pulmonary edema. Drs. Simone and Roca have concluded that this patient's death may have been related to (b) (4). This conclusion seems to rest primarily on the fact that there is an absence of information for the period between 3 and 23 hours post-op; and since the events on Post-Op Day 42 could be related to sequelae from the events at Post-Op Hour 23, and something may have happened between Post-Op Hour 3 and 23 that would indict (b) (4) specifically as the causative agent, exposure to this drug may have lead to her death. I think this is somewhat speculative, but would agree that there is a slim chance that (b) (4) could have played some part in the ultimate outcome.

The second death was a 61 year old man who died 18 days after undergoing a radical prostatectomy with radical iliacal lymphadenectomy that was complicated by intraoperative perforation of the colon. The patient was sent home in apparent good status, but was readmitted on Post-Op Day 15 and diagnosed with a pulmonary embolus. He was treated with heparin but died a few days later. Drs. Simone and Roca concurred with the sponsor and investigator that this was unlikely to be related to (b) (4) exposure and was a typical complication of the procedure that had been performed. I agree with their conclusion.

In their reviews, Drs. Simone and Roca note that there were increased incidences QT prolongation and potentially life-threatening arrhythmias in the (b) (4) treated subjects compared to the placebo or neostigmine-treated subjects in the overall pool of comparative studies. The events occurred in close proximity to treatment with (b) (4) and were generally self limited. The events did not appear to be dose-related. QT prolongation was not noted in the two Thorough QT studies performed with (b) (4) but, of course, these studies were performed in normal volunteers. They recommended a post-marketing study to better assess the potential for cardiotoxicity due to exposure to (b) (4) vs. other reversal agents or no reversal agent.

Another safety concern raised by the clinical review team is the effect of (b) (4) on coagulation time. Standard testing of coagulation parameters was not performed in the clinical studies; however, in vitro studies did demonstrate prolongation of PT, PTT and INR due to sugammadex. Additionally, the incidence of adverse events coded as "hemorrhagic" was 6% in the (b) (4) treated subjects vs. 3% in the comparator-treated subjects. On review, Dr. Simone found that these events were typical of the post-operative setting (e.g., oozing from wounds). Although he was unable to determine whether there was a causal relationship between exposure to (b) (4) and these events, on page 30 of the sponsor's risk management plan submitted with the NDA, they state:

Since the mechanism of the interfering effect of Org 25969 on the laboratory tests is unknown, it was further investigated if Org 25969 could have an effect on hemostasis in vivo. In order to get an indication if there are any clinically relevant effects of Org 25969 on hemostasis an analysis on relevant adverse events was made. Aggregated data from phase 2 and 3 placebo controlled studies was searched for AEs of which the PT indicated any form of haemorrhage during surgery or in the post-operative period. In the group of all subjects treated with Org 25969 the combined rate for all types of haemorrhages was not statistically significant different from the placebo group (5.7% (n = 649) and 3.1% (n = 130) respectively). None of the individual AEs had a reporting rate of more than 1%. When limited to the more specific terms for surgery related bleedings, the terms Incision site haemorrhage, Post procedural haemorrhage, Haemorrhage and Operative Haemorrhage, the combined incidence for these terms was 2.8% in the total Org 25969 group, which is comparable to the 2.3% in the placebo group (no statistically significant difference). These rates are in line with the incidence of postoperative bleeding as reported in literature (0.2% - 4.7%). There was no indication for a dose response relationship in either analysis. There was no report of related AEs of which the PT indicated haemorrhage or haematoma in these trials. Based on these results it is concluded that there is no indication for clinically relevant effects of Org 25969 on hemostasis. The in-vitro studies indicate there is a potential effect on values for laboratory parameters of blood coagulation time (APTT, PT (inr), PT). It is unknown what the clinical relevance of this is. As of yet the effect on these laboratory parameters has not been investigated in treated subjects.

On page 40 of this document they provide suggestions for further investigation:

- Determine the effect of Org 25969 on APTT, PT (inr), PT by determining these parameters time as additional measurements in a volunteer study (study yet to be identified)
- Add parameters APTT, PT (inr), PT to the pre- and post operative hematology measurements in placebo controlled phase 3B trials.

Drs. Simone and Roca recommend that further study to explore these findings should be undertaken prior to approval due to the high risk associated with excessive bleeding in the surgical and post-operative settings.

The most common adverse events that appear to be related to treatment with (b) (4) included nausea and vomiting in patients, and dysgeusia and dizziness in the normal subjects in the Phase 1 studies. Headache occurred more frequently in the (b) (4) treated subjects compared to the neostigmine-treated subjects in the two major studies that employed neostigmine as the comparator; but headache occurred more frequently in the placebo-treated subjects in the pooled (b) (4) vs. placebo studies. Anesthetic complications occurred much more frequently in the (b) (4) treated subjects compared to the placebo-treated subjects, but this was likely due to the design of some of the studies during which patients were reversed with (b) (4) prior to completion of the surgical procedure in order to capture certain pharmacokinetic data, resulting in a greater incidence of movement, sucking on the endotracheal tube and similar “anesthetic complications” as defined by the coding for this event.

Late in the course of the review, Dr. Simone developed concern regarding an apparently high incidence of adverse events that had been coded as “hypersensitivity reactions,” but which appeared to be possible cases of anaphylaxis. In response to the clinical review team’s request, the sponsor submitted information on seven subjects with such adverse events. While the Division’s initial findings and analysis of this information were presented to the ALSDAC members, at that point we had had limited time to fully analyze and assess the data, and we had not yet consulted any experts on allergy and immunology. Upon review of the cases by

Drs. Lee and Chowdhury of the Division of Pulmonary and Allergy Products (DPAP), two of the subjects were determined to have had events that met the criteria for recently proposed diagnostic criteria for anaphylaxis. Based on a total of 2024 subjects exposed during the clinical development program, this would represent an incidence of anaphylaxis of 0.1%. The following comments from the Executive Summary of Dr. Lee's review summarize DPAP's assessment, conclusions and recommendations:

The sponsor conducted a skin test study with previously exposed and unexposed control patients to characterize these reactions. Of the twelve patients who were previously exposed to sugammadex, two had positive skin tests (8.3%), one who had no clinical symptoms and one who had symptoms suggestive of anaphylaxis. There were no unexposed subjects who had a positive skin test; sugammadex does not produce a non-specific positive skin test. This information suggests that exposure to sugammadex may induce sensitization and production of sugammadex-specific IgE in a percentage of those exposed. Such patients would be at risk for development of anaphylaxis if re-exposed to sugammadex.

The sugammadex drug development plan did not evaluate the safety of subsequent or repeated exposure to the drug. This is of particular concern, since wide use is anticipated and one can expect that some patients will be exposed more than once. As noted above, it appears that the product induces sensitization and production of sugammadex-specific IgE in a percentage of those exposed. It is likely that some of these sensitized patients would develop anaphylaxis or allergic reaction with subsequent exposure. The magnitude of this risk or the predictive value of skin testing in identifying patients who are at risk of such a reaction with re-exposure cannot be determined with the available information.

It is expected that the product will be used in an operating room setting, which may mitigate some risk from anaphylaxis if the event is recognized and treated appropriately. Labeling the product that it should be used only for anesthesia emergencies may increase the risk/benefit balance for the drug, but may not be practical. Labeling the product that it should only be used once may be an appropriate approach to the addressing the risk from repeat exposure until studies may be conducted to evaluate this risk.

We recommend that DARRP ask the sponsor to develop in vitro tests of sugammadex-specific IgE, IgG, IgM in order to further characterize the mechanism for these reactions. In addition, there would be benefit in asking the sponsor to evaluate the risk for reaction among subjects with subsequent exposure, both in a general population and in a population of patients who have positive skin tests to sugammadex. It would be essential to define this risk of reaction before it is widely used and patients are exposed on multiple occasions.

The sponsor convened a panel of experts to review the skin test study and the cases they had reported to the Agency. Five additional cases that had more recently been identified were also reviewed by the panel. The panel arrived at the following conclusions:

1. *The consultants were in consensus that the reactions were not life threatening and strongly preferred the term "hypersensitivity" over "anaphylaxis."*
2. *All four consultants agreed on the classification of 11 of the 12 possible cases of drug hypersensitivity related to sugammadex administration.*
3. *They also agreed that the most likely mechanism would be shown to be nonimmunologic, non-IgE mediated histamine release from tissue mast cells or basophils.*

4. *The most relevant initial test of mechanism, each recommended, was an in vitro examination of histamine release from cultured human basophils.*

DPAP was again consulted to review the additional cases and the expert panels' assessment and conclusions. Dr. Limb determined that there were at least three clear cases of anaphylaxis in healthy volunteers with another two possible cases in surgical patients. She excluded the surgical cases in her calculation of an incidence rate due to multiple confounding factors that are present in that setting. Based on the events that occurred in the normal volunteers, she calculated a frequency of anaphylaxis of 1.4% (3/209). Dr. Limb also noted that the sponsor's conclusions regarding the mechanism underlying these events, based on an in vitro basophil histamine-release assay and an ex vivo mast cell-mediator release assay, are questionable, as these types of studies are primarily used as a research tool, are technically challenging and are of limited clinical utility for diagnosing allergy in individual patients. The following is reproduced from Dr. Limb's Discussion section, pages 6 and 7 of her review:

The cases and laboratory testing show that sugammadex has allergenic potential and can cause anaphylaxis. The cases identified were serious allergic reactions with multi-organ involvement. Although the cases were not severe in the sense that the patients did not require active resuscitation, we cannot assume that sugammadex-induced anaphylaxis is minor or non-life-threatening. The most striking case of anaphylaxis with an elevated serum tryptase, Case 106101008, may have resulted in more severe injury had the infusion not been stopped. Furthermore, since the clinical development program did not evaluate the safety of repeated exposures, the potential for more serious injury and even death in sensitized patients remains a major risk that has not been formally addressed. As Case 105101030 illustrates, repeat exposures may result in more severe reactions, as is usually observed in drug hypersensitivity. We do not have any evidence to indicate that sugammadex would behave differently from other known immunogenic drugs.

The life-threatening potential, combined with a relatively high frequency of anaphylaxis and expected wide usage, are concerning. Therefore, the main recommendations outlined in DPAP's May 13, 2008, consult remain unchanged. DPAP recommends formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population, prior to widespread use of sugammadex. Further elucidation of the underlying immunologic mechanism, e.g. development of an assay for sugammadex-specific IgE, may facilitate patient screening to improve the risk:benefit ratio of elective sugammadex use.

DPAP has also consulted experts from the academic community. As of today, only one of the consultants, Dr. James T. C. Li of the Mayo Clinic, has submitted a response. Dr. Li concurs with the conclusions and recommendations of the DPAP reviewers. The reader is referred to his response for the details of his analysis.

9. Advisory Committee Meeting

(b) (4) was the subject of a meeting of the Anesthetics and Life Support Drugs Advisory Committee on March 11, 2008. Dr. Roca has reproduced the questions posed to the committee members and he has summarized the key conclusions and recommendations on pages 14 and 15 of his review. I have reproduced both the questions and his summary below:

1. The Applicant has conducted a clinical trial to evaluate the efficacy of sugammadex to effect the “Immediate Reversal” of neuromuscular blockade (NMB). The primary efficacy endpoint was the time from start of administration of rocuronium bromide (RCB) or succinylcholine (Sux) to the recovery of T1 to 10% of its baseline value. Sugammadex was administered to patients 3 minutes following administration of RCB.
 - a. Does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful?
 - b. Based on the data submitted from this study, is there sufficient clinical information to assess whether sugammadex, when used with RCB, provides a clear advantage when confronted with a “cannot ventilate/cannot intubate” situation in the clinical setting? If not, what additional information would be required to assess a possible role for sugammadex in this scenario?
2. Based on the nonclinical data submitted by the applicant from the sugammadex distribution, juvenile animal, reproductive toxicology, and dedicated bone studies:
 - a. Has the risk for adult patients, including patients with fractures or surgical injury to bone been adequately characterized?
 - b. Has the risk for pediatric patients been adequately characterized?
 - c. Does the nonclinical data support the safety of sugammadex for clinical trials in a pediatric population?
 - d. If the answers to any of the above questions is “no,” what additional information is required to support the use of sugammadex in these populations?
3. Has the applicant adequately demonstrated that sugammadex:
 - a. reverses neuromuscular blockade from rocuronium and vecuronium;
 - b. immediately reverses neuromuscular blockade from rocuronium?
 - c. can be used safely in the targeted population? Please discuss potential hypersensitivities in this population, if patients at risk can not be identified.

Highlights from the discussion at the meeting are summarized below:

1. The committee felt that the endpoint in Study 303 (T1 = 0.1) was of minimal clinical use but felt that it supported the conclusion that Org 25969 reversed paralysis more quickly than succinylcholine spontaneously resolved. The committee felt that more meaningful data for the label would consist of the time from injection that the most of patients (e.g., 95%) had responded.
2. The committee felt that rocuronium/Org25969 could not replace succinylcholine for rapid sequence induction, particularly because succinylcholine would be necessary if re-intubation was required. The committee felt that Org 25969 was an important product that could be useful in the cannot intubate/cannot ventilate scenario although it opposed the use of the words “immediate” reversal or claims that Org 25969 was effective in the cannot intubate/cannot ventilate scenario.
3. The committee was concerned about the hypersensitivity reactions although it felt that the reactions were relatively minor, self-limited, and acceptable given the known hazards of succinylcholine. The committee recommended a postmarketing surveillance program to further define the risks of hypersensitivity reactions.
4. The committee would have liked to have seen more data in the obstetric population.
5. The committee felt that the non-clinical findings regarding bone and teeth were of no concern to adults and that the current data would support a single-dose study in pediatric patients.
6. The committee felt that more data would be required for multiple-dose pediatric studies and that nonclinical studies must be conducted to assess safety in neonates or premature infants. The committee also felt that assessments of bone strength in juvenile animal models were necessary.

10. Pediatrics

(b) (4) would likely be an important addition to the pediatric anesthesia armamentarium. However, we will accept a deferral under PREA and FDAAA for pediatric studies to support the use of the product in that population until a clear picture of its immunologic potential has been defined. In addition, the sponsor will need to perform appropriate non-clinical studies to better define (b) (4) potential to cause damage to developing or healing bone in pediatric patients. Age limitations for use may also be necessary based on the effect of (b) (4) on the development of permanent teeth. Finally, additional juvenile animal studies should be performed to better understand (b) (4) potential to cause embryofetal toxicity.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

I recommend deferring labeling deliberations until the sponsor has submitted a response to our action letter. Hopefully, we will have more substantial data on the risks associated with the immunological effects of the product at that time.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action Recommended

Not approvable

- Risk Benefit Assessment

While the sponsor has provided substantial evidence that (b) (4) reverses the neuromuscular blockade induced by rocuronium and vecuronium, the data that they have provided in support of “immediate reversal” is not adequate to support that particular indication. Study 303 evaluated essentially healthy individuals undergoing short procedures and did not consider the other factors that are often at least partially responsible for the actual emergency of CICV, which is the true clinical setting that this indication is intended to address. While a study in the CICV setting itself may not be possible due to ethical considerations, Study 303 did not capture the most important outcome that would allow us to assess the ability of (b) (4) to have a significant clinical impact in this setting, return to sustained spontaneous ventilation. Until then, a specific indication for “immediate reversal” should not be granted.

Unfortunately, the finding that (b) (4) results in apparent cases of anaphylaxis raises safety concerns that, without additional data, make the risk-benefit ratio

for this drug unacceptable for approval at this time. I concur with Drs. Simone and Roca, and our colleagues from DPAP, that these are, indeed, real cases of anaphylaxis according to the most recent standards for the definition and diagnosis of anaphylaxis issued by NIH, which was based on the conclusions and recommendations of a joint government and academic expert consensus panel, and that these cases occurred at a frequency in the clinical studies that raise extremely important concerns. With the apparent frequency of 1.4% in normal volunteers exposed to (b) (4) for the first time, the incidence of anaphylaxis events per year in the community could be as high as 53,284 based on the sponsor's estimated total number of procedures with sugammadex by the year 2012, which was 3,806,000 (US Risk Management Plan, Section 1.4.1 Projected post-authorization usage data, p. 23).

While the ALSDAC members did not see this adverse event as particularly concerning due to the intensive monitoring that exists in the post-operative period and recommended approval of the product with further post-marketing evaluations of hypersensitivity and anaphylaxis, the committee received only preliminary input on this matter due to the fact that the finding surfaced late in the course of our review. We have since had the opportunity to have thorough reviews of these events performed by our expert colleagues in DPAP and, as of today, one external academic expert. (An additional academic expert has not yet responded to the consult.) These experts have determined that the events in question are clearly cases of anaphylaxis. Based on this determination, we expect that we will need to bring the sponsor's application back to an advisory committee when they resubmit in response to our current action. That committee will need to be comprised of allergy and immunology experts, and safety and risk management experts, in addition to the members of the ALSDAC. In addition, it is essential that the sponsor conduct additional studies to fully elucidate the underlying mechanism of these events and to assess (b) (4) potential to cause anaphylaxis after repeat challenge at least 6 to 8 weeks out from initial exposure. Until a clear and thorough assessment of the association between (b) (4) exposure and the development of anaphylaxis has been completed, it is not possible to make a reasoned and scientifically sound risk-benefit analysis for this product.

In addition, the sponsor should perform further evaluations to better assess the possible cardiotoxic, hepatotoxic and renal toxic effects of (b) (4) in the clinical setting and the potential for the drug to cause problems with coagulation and hemostasis in the surgical and post-operative settings. Finally, it will be necessary for the sponsor to further explore the effects of sugammadex on developing bone in appropriately designed animal studies and additional juvenile animal studies to assess its effect on embryofetal toxicity before proceeding with pediatric development.

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/s/

Bob Rappaport
7/30/2008 09:35:54 PM
MEDICAL OFFICER



Food and Drug Administration
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Cross-Discipline and Clinical Team Leader Review

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| Date | July 18, 2008 |
| From | Rigoberto Roca, M.D. |
| Subject | Cross-Discipline and Clinical Team Leader Review |
| NDA/Supplement# | 22-225/ 000 |
| Applicant | Organon USA, Inc. |
| Date of Submission | October 31, 2007 |
| PDUFA Goal Date | July 31, 2008 |
| Proprietary Name / Established (USAN) names | (b) (4) sugammadex sodium injection |
| Dosage forms / Strength | 2 ml vial: 100 mg/ml 5 ml vial: 100 mg/ml |
| Proposed Indication(s) | 1. For routine reversal of shallow blockade following rocuronium or vecuronium. 2. For routine reversal of profound blockade following rocuronium or vecuronium. 3. For immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium or vecuronium |
| Recommended Action: | Not approval |

1. Introduction

This review will provide an overview of the regulatory and scientific facts of this submission and issues that were identified during the course of the review. Aspects that will be touched upon will include the regulatory history, the adequacy of the database for an assessment of the efficacy and safety profile of the drug product, issues that were identified as warranting discussion at the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC), and the regulatory action recommended by the review team.

Particular attention will be placed on the indication requested by the Applicant, and safety issues that were identified during the course of the review.

2. Background

Sugammadex, also known as Org 25969, is a new molecular entity of the γ -cyclodextrin class. It was designed, by selective addition of functional groups around the structure, to bind rocuronium and vecuronium. It consists of ring-like structure with a lipophilic core and a

hydrophilic outer surface. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center, and then held in place by van der Waal's forces, hydrophobic and electrostatic interactions. The physical sequestration of the neuromuscular blocking agent from the neuromuscular junction will in effect reverse the paralysis. The Applicant is seeking approval for routine reversal of "shallow" and "profound neuromuscular blockade induced by rocuronium and vecuronium, and "immediate reversal" of neuromuscular blockade at 3 minutes after administration of rocuronium.

The dose of (b) (4) is dependent on the intended use. Specifically, the Applicant is proposing the following indications:

For routine reversal:

- A dose of 4.0 mg/kg (b) (4) is recommended if recovery has reached 1 – 2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.
- A dose of 2.0 mg/kg (b) (4) is only recommended if spontaneous recovery has reached the reappearance of T2 (shallow blockade) following rocuronium or vecuronium induced blockade.

For immediate reversal:

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4) is recommended.

3. Chemistry, Manufacturing, and Controls

General Product Quality Considerations

The drug substance (Org 25969), a modified γ -cyclodextrin, is an octasodium salt. The mode of action is based on the formation of 1:1 complex with rocuronium or vecuronium. The drug substance contains (b) (4) Org 48302, which has an activity and pharmacological profile similar to Org 25969; therefore, it is considered an active entity. Org 48302 is typically present at levels of (b) (4) in the representative drug substance batches. The drug substance is highly soluble in water; its hygroscopicity is managed by controlling manufacturing and storage conditions.

(b) (4)

The target concentration of the active ingredients is 100 mg/mL (b) (4). The container closure system is a type I glass vial with a latex-free, (b) (4) rubber closure and an aluminum flip off cap.

Dr. Schroeder indicates in his review that critical process steps for the manufacture of the drug product include the following: pH adjustment, adjustment to final volume, transfer to (b) (4) filling of vials, (b) (4) of vials and visual inspection. Key drug product parameters related to performance are the pH, osmolality,

particulate matter and color. And lastly, key drug product parameters related to manufacturability are solubility, hygroscopicity, polymorphism, (b) (4), and stability (temperature, metal contaminants, pH, light, oxidation, holding time, origin of color).

The drug product is sensitive to light, (b) (4). Dr. Schroeder notes that the Applicant proposes that the primary container be exposed to light no longer than 5 days, and that the (b) (4). Dr. Schroeder's review indicates that photostability data submitted in the application support the 5-day maximum limit on exposure to normal indoor lighting, (b) (4).

The application contains adequate data to support the proposed expiry period of 36 months at 25° C.

Facilities Review/Inspections

As of the date of this review, the Office of Compliance had not yet made a final determination of the cGMP status of the manufacturing and testing facilities.

Outstanding or Unresolved Issues

The only outstanding issue is the final determination of the cGMP status of the manufacturing an testing facilities by the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

General Considerations

General toxicology studies performed by the Applicant were assessed as adequate by the review team with acceptable safety margins demonstrated for human use and the identification of target organs in a single-dose and 4-week repeat-dose toxicology studies in the rat. Target organ toxicities were not identified in the dog, and although the purpose of these studies is to identify toxicity, demonstration of acceptable safety margins and the use of a maximum feasible dose are acceptable.

The target organs identified in the rat were the kidney, lung, and bladder, which are well-known toxicological findings of intravenously-administered cyclodextrins. Dr. Wasserman noted in his Supervisory memorandum that in the single-dose toxicity studies in the rat, Org 25969 was associated with renal tubular vacuoles at ≥ 600 mg/kg, foamy alveolar macrophages in the lung at 2000 mg/kg, and in the two 4-week repeat-dose toxicology studies there was an additional finding of foamy umbrella cells of the urinary bladder with Org 25969 dose levels ≥ 120 mg/kg and kidney and lung findings at ≥ 120 and 500 mg/kg, respectively. The alterations in the lung and kidney were reversible and minimal in severity with a 2-week treatment-free period, while in the 4-week repeat-dose studies these target organ findings largely reversed within the 3- or 8-week recovery period associated with each study. The review team's assessment of the lung findings were that they represented uptake and slow degradation and not indicative of an adverse effect.

Carcinogenicity

Carcinogenicity studies were not performed by the Applicant since the product is not intended for chronic use. As noted in Dr. Wasserman's addendum to his supervisory pharmacologist memorandum, after further consideration of the deposition of sugammadex into bone (bone $t_{1/2(\beta)}$ mean of 172 days), the need for the evaluation of sugammadex's potential for bone carcinogenicity may need to be reconsidered. Dr. Wasserman noted that the higher concentration that seems to be retained in this tissue, compared to adults, and the intrinsically high rate of growth of bone present in pediatric patients prior to skeletal maturation and closure of the epiphyseal plates, makes this assessment particularly relevant for the pediatric patient population.

Genotoxicity

In vitro genotoxicity studies (Ames test and chromosomal aberration test in human peripheral blood lymphocytes) were negative. These tests were performed with different batches of the drug substance, and with special batches containing relatively high levels of impurities.

Reproductive Toxicology

The Applicant submitted the results from studies evaluating fertility in rats, and there was no evidence of Org 25969-associated impairment at dose levels which afforded large safety margins. It was noted that studies which looked at degraded Org 25969 did detect apparent test-article related changes in male reproductive tissues in both single-dose (increased spermatids or hypospermia in epididymis; this was not observed in the recovery group animals) and 2-week repeat-dose studies in the rat (sperm granuloma, epididymal rupture and decreased seminal vesicle weight). These changes were not observed with the standard drug product. However, single-dose studies with degraded Org 25969 identified a safety margin for single-dose use.

Standard embryofetal development studies were conducted in both the rat and the rabbit. The review team concurred with the Applicant that no teratogenicity or embryofetal toxicity was observed in either study

Outstanding or Unresolved Issues

Drug Distribution in Bone and Teeth

After intravenous administration of Org 25969 in young adult rats, approximately 2% of the administered dose binds to teeth and bones and remains for a protracted period of time (terminal mean half-life of 170 days). Additional data indicates that binding is enhanced in regions or states where active growth is occurring. These findings have potential clinical implications for use in pediatric populations and in surgical populations with coexisting bone trauma, either as the reason for the surgical intervention (e.g., fracture) or caused by the surgical intervention (e.g., osteotomy, resection).

The Applicant attempted to address this concern by conducting four types of studies: general toxicity studies in the young adult rat and dog, toxicity studies in the juvenile rat, several dedicated studies to evaluate the effect of intravenous Org 25969 on bone quality, integrity and turnover in the young adult rat, and reproductive toxicity studies in the rat and rabbit.

Four-week general toxicity studies were conducted in young adult rats and dogs at doses up to 500 mg/kg/day and 250 mg/kg/day, respectively. No evidence of bone abnormalities were noted although bone-specific evaluations, such as μ CT, were not conducted.

Bone studies in young adult rats were conducted utilizing single-dose intravenous administration of Org 25969, 2000 mg/kg, or placebo. Evaluation of bone-specific clinical chemistry and urinalysis parameters were performed throughout the study, as well as μ CT. Sacrifice occurred on Study Day 21 or Study Day 42. There was a possible slight resorptive effect on trabecular bone on Study Day 21, without apparent effect on cortical bone, with recovery of femur trabecular bone changes by Study Day 42. With the exception of increased femur indentation, which the Applicant suggests does not reflect a meaningful weakening of bone, no evidence of compromised bone strength was noted in the majority of the 3-point bending test parameters (though stiffness was slightly reduced) and femur neck cantilever test. A subsequent study with Org 25969 administered as a single intravenous dose up to 500 mg/kg with sacrifice and evaluation of subgroups at Study Day 1, 3, 7, 14, 21, 28, 35 and 42 after single doses was negative for any of the previously described changes and was considered a single-dose NOAEL level for bone integrity and structure by the Applicant and the review team.

A 4-week toxicology study was conducted in which juvenile rats were dosed from Post-Natal Day (PND) 7 to 34 with 0, 30, 120 or 500 mg/kg/day (subcutaneous administration followed by intravenous administration as the rat matured) with sacrifice on Study Day 35, or 8-week recovery with sacrifice on Study Day 91. The NOEL for bone was identified at 30 mg/kg/day. At doses \geq 120 mg/kg/day, in-life evaluation indicated shortened ulna compared with controls; altered trabecular bone parameters (increased bone mineral density, bone volume/tissue volume ratio, trabecular number, and trabecular thickness), and mild decreased cortical thickness (no effects on cortical bone mineral density) were noted at Study Day 35 but not at Study Day 91. Decreased femur length (evaluated ex vivo) was noted at the Study Day 91 evaluation only. No bone strength measurements were conducted as the Applicant considered the effects to be insufficient to merit further evaluation. Two additional single-dose studies in juvenile rat model are less informative due to reduced (or absent) bone endpoints.

Tooth discoloration was observed beginning in the 3rd week of the 4-week dosing period for the juvenile rats receiving 500 mg/kg/day; also apparent in some of these animals were other dental abnormalities, including overgrown incisors and malocclusion. This can occur when incisors hardness is increased, such as what happens with fluoride treatment, and normal incisor wear does not occur. Disruption of the enamel epithelial layer of the incisor with deposition of “amorphous material” was noted at doses \geq 120 mg/kg/day. This “amorphous material” was not identified further by the Applicant. Molars were less affected, although similar findings were noted at 500 mg/kg/day and reversibility was noted after 8-weeks of recovery.

To examine the risk of single dose exposure to Org 25969, the Applicant conducted an extended single-dose study in which juvenile rats were administered drug intravenously on PND 7, 14, or 21 at doses of 0, 120, or 500 mg/kg and were sacrificed either acutely (1 day after dosing) or 2 weeks later. No findings were noted in juvenile rats exposed to drug on PND 7 or 14. PND 21 rats did not demonstrate drug-related effects on the teeth at 0 or 120 mg/kg;

however, a single animal (1/16) in the 500 mg/kg group was observed to have minimal disruption of the enamel epithelium with the presence of amorphous material in the incisors when it was sacrificed 2 weeks after dose administration. An additional study in which juvenile animals were dosed once on PND 7 and followed for 6 weeks did not detect defects in amelogenesis with doses as high as 500 mg/kg. The NOAEL for teeth disturbances determined from the 4-week study in juvenile rats was identified by both the Applicant and the review team as 30 mg/kg/day.

The potential clinical implications of these nonclinical observations were discussed at the Advisory committee meeting held in March of this year; the results of the discussion appear below.

Nonclinical Assessment of QT Prolongation

As noted in Dr. Wasserman's review, high concentrations of Org 25969 (1.5 mM) produced a mild inhibition (22%) of the hERG delayed inwardly-rectifying potassium channel cloned into human embryonic kidney cells; the concentration producing 50% inhibition, a standard benchmark for comparing relative propensity for block was not reached. Bath application of Org 25969 to canine purkinje fibers, which contains multiple types of ion channels involved in cardiac conduction, revealed a mild to moderate prolongation in action potential duration (APD50, APD70, and APD90: 4 – 17%) at 150 μ M and 1500 μ M tested at 1.0 [normal] or 0.3Hz [bradycardic] stimulation rates compared to baseline control. In vivo evaluation of cardiovascular safety in the dog indicated that 25 mg/kg Org 25969, with or without the presence of rocuronium, did not affect QT interval though 250 mg/kg Org 25969 did produce an increase of 6.9% over control QT duration. This dose level represents a 10-fold higher plasma concentration than is produced with clinical use of the drug; therefore, the toxicologic significance of this finding was considered negligible by the review team.

Dedicated thorough QT (tQT) studies have been conducted with clinical subjects exposed to supra-therapeutic doses of Org 25969 with or without rocuronium; in neither study was there evidence of QT prolongation.

Immunotoxicity Assessment

Three studies were conducted to assess the effects of Org 25969 on the immune system: the Plaque Forming Cell Assay, an in vitro evaluation of the immunosuppressive potential of a test compound by assessing the integrity of the T-cell Dependent Antibody Response (TDAR); a popliteal lymph node assay (PLNA) to determine if exposure to Org 25969 via injection into a foot pad would cause an increase in cellularity in the draining lymph node; and a local lymph node assay in mice after dermal application of Org 25969 to the ear to assess for evidence of contact hypersensitivity by examination of the auricular lymph node.

A mild increase in the TDAR was noted in rats administered Org 25969 up to 500 mg/kg intravenously for 2 weeks. The PLNA revealed a statistically increased level of radiolabel incorporation into cells of the PLN (~3-fold vs. control) at 278 mg/kg (NOAEL 67 mg/kg). Dr. Wasserman notes that as a signal for sensitization/immuno-stimulation this appears to be relatively mild when considering the positive control, HgCl₂ (26-fold higher than control). The third study, the auricular lymph node assay in mice after dermal application of Org 25969 to the ear did not demonstrate evidence of contact hypersensitivity. The negative results in

third study are inconsistent with the findings of the first two; however, the overall nonclinical data would appear to indicate that the possibility of sensitization and immuno-stimulation may need to be considered as a potential risk in humans.

Impurities/Degradants/Additional Active Pharmaceutical Ingredient

The manufacture of Org 25969 is

(b) (4)

A number of impurities fall above Q3A and Q3B thresholds for identification and qualification and a series of discussions with the Applicant have taken place in order to determine a path forward. Due to the low toxicity potential of γ -CDs, an agreement was reached that impurities would not require identification and qualification at levels \leq (b) (4) % when such impurities were determined to be γ -CD-related, have a molecular mass between

(b) (4)

The Applicant will perform a partial identification once an impurity rises above (b) (4) % to determine conformance to the above listed criteria.

One impurity, (b) (4) is a (b) (4) found at levels of (b) (4) % in the drug substance batches; the Applicant has requested a specification of NMT (b) (4) %. With agreement from the Division this impurity was allowed to be considere

(b) (4)

, and additional toxicology studies were conducted to qualify (b) (4) at levels which support human exposure.

Specified impurities have been qualified through general or genetic toxicology studies with inclusion in non-degraded or, where necessary to achieve acceptable exposure coverage, degraded toxicology batches of drug substance. All specified impurities in the drug product were qualified in the rat; some qualification studies for impurities in the drug substance were conducted in the dog.

5. Clinical Pharmacology/Biopharmaceutics

General Considerations

After intravenous administration, the volume of distribution is 12 – 15 liters, indicative of an element of extravascular distribution in the body. The mean steady-state plasma elimination half-life is approximately 1.5 to 3 hours at the proposed doses. The metabolism is limited, and the compound is primarily eliminated unchanged via renal excretion. Human pharmacokinetic studies indicated that the clearance of (b) (4) ranges from 97 to 138 ml/min, which is similar to the glomerular filtration and, therefore, consistent with primarily a renal route of elimination. On the average, more than 90% of the administered dose was recovered in the urine within 24 hours.

Drug-drug Interactions

In vitro metabolism assessments were not conducted by the applicant. It is unlikely that (b) (4) will be metabolized by the CYP enzyme system because of its large molecular size, its three-dimensional structure, limited hepatic distribution, and limited metabolism observed in clinical studies. Therefore, it is unlikely to affect other drugs' metabolism due to enzyme induction or inhibition, nor have its metabolism affected by other drugs that may be CYP inhibitors or inducers.

Transport-based drug-drug interactions are still possible, however, and (b) (4) may affect other drugs' transport in the kidney. This type of interaction was not evaluated by the Applicant.

Since the mechanism of action for (b) (4) is to form a 1:1 complex with rocuronium and vecuronium, it is possible that (b) (4) may form complexes with other, similar compounds resulting in displacement of the neuromuscular blocking agent. The Applicant evaluated this potential situation by a combination of in vitro assessments, nonclinical studies, and pharmacokinetic/pharmacodynamic (PK/PD) modeling, focusing on drugs that are most frequently prescribed, used in anesthesia settings, and steroidal molecules.

Under this paradigm, three products were identified as having the potential for a displacement interaction with (b) (4) toremifene, flucloxacillin, and fusidic acid. Of the three, only toremifene is currently marketed in the United States. The Applicant did not conduct specific drug interaction studies to confirm the PK/PD simulation model, and the review team's recommendation is that the package insert should include cautionary language about this potential interaction.

Critical Intrinsic Factors

The Applicant evaluated the effect of age, gender, race, renal impairment, and hepatic impairment on the exposure and pharmacodynamic response. The only factor that had an effect was renal function, with exposure increasing 15-fold in patients with renal impairment (creatinine clearance < 30 ml/min), compared to healthy subjects.

In the study that assessed the difference in exposures in patients with renal impairment, it was noted that for patients on hemodialysis, the (b) (4) rocuronium complex was not efficiently removed from the plasma using the low flux filter, a clinical finding that was consistent with the in vitro dialysis results. However, the clinical experience with the high flux filter was not as predicted by the in vitro dialysis study; it had a variable effectiveness in removing the complex.

Thorough QT Study

A formal thorough QT study was conducted by the Applicant, Study 19.4.09. A concentration-dependent increase in QTcI was noted, the mean increase in QTcI for the supratherapeutic dose that was assessed (32 mg/kg) was < 10 msec, which is considered the threshold for concern. This dose was twice the highest dose proposed by Applicant.

Outstanding or Unresolved Issues

Due to the unexpected finding in the clinical experience with patients on hemodialysis, the review team is recommending that additional clinical studies be performed with patients on hemodialysis.

With respect to patients with hepatic impairment, the expectation is that (b) (4) elimination would not be affected, since the primary mode of elimination is renal. However, hepatic impairment would affect the pharmacokinetics of rocuronium, with the applicant predicting that a prolonged recovery time would be expected, based on their population PK/PD interaction model. The review team is recommending that the additional clinical studies be performed in patients with hepatic impairment to confirm this prediction.

6. Clinical Microbiology

(b) (4) is not a therapeutic antimicrobial, therefore clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical- Efficacy

The clinical development program consisted of 28 studies, which included bioanalytical, clinical pharmacology, and safety/efficacy studies in healthy volunteers and in patients. There were four studies that were considered to be most supportive for the indication that the applicant was seeking.

Three of the Studies 19.4.301 (Study 301), 19.4.302 (Study 302), and 19.4.310 (Study 310), were of similar design; Study 19.4.303 (Study 303) differed the most from the other three.

For the studies that were of similar design, patients were induced with a standard intravenous sequence followed by paralysis with the specified neuromuscular blocking agent (NBMA). Anesthesia was maintained with sevoflurane and parenteral agents. The level of neuromuscular blockade was monitored via a Train-Of-Four (TOF) nerve stimulator. At the return of T₂, which was felt to approximate “shallow” blockade, the reversal agent was administered. The elapsed time between the start of administration of the reversal agent and the recovery of the T₄/T₁ ratio to 0.9, as measured by acceleromyography, was the primary endpoint. Other clinical measures of recovery were assessed, including a 5-second head lift and general weakness. Prior to, during anesthesia, and following recovery, the patient was monitored for safety. In these studies, the safety assessor was blinded.

The table below summarizes certain key features of the studies.

| | Study 301 | Study 302 | Study 310 | Study 303 |
|-------------------|--|---|---|--|
| Location | Europe | United States | Europe | United States and Canada |
| Study period | November 2005 to March 2006 | November 2005 to November 2006 | November 2005 to May 2006 | February 2006 to August 2006 |
| Clinical scenario | “shallow” neuromuscular block, defined as the return | “profound” neuromuscular block, defined as 1-2 post | “shallow” neuromuscular block, defined as the | “Immediate” reversal (defined as 3 minutes |

| | of T ₂ (the second twitch in a train-of-four stimulation) | tetanic counts | return of T ₂ | following rocuronium administration) |
|---------------------------|---|---|---|--|
| Dose of (b) (4) | 2 mg/kg | 4 mg/kg | 2 mg/kg | 16 mg/kg |
| Treatment groups | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Rocuronium/neostigmine c. Vecuronium./Org25969 d. Vecuronium/neostigmine | a. Rocuronium/Org25969 b. Cis-atricurium/neostigmine | a. Rocuronium/Org25969 b. Succinylcholine/no reversal agent |
| Number of patients | 196 randomized | 182 randomized | 84 randomized | 115 randomized |
| Primary efficacy endpoint | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₄ /T ₁ = 0.9 | T ₁ = 0.1 |

Additional differences between the studies are summarized in the following paragraphs, adapted from Dr. Shibuya's review.

Study 302 differed from Study 301 in two significant aspects:

1. The reversal agent was administered at 1 – 2 Post-Tetanic-Counts (PTC); this was to approximate “profound” blockade.
2. The dose of Org 25969 was 4 mg/kg (the neostigmine dose was also higher).

Study 310 differed from Study 301 in that there were two treatment groups, rocuronium/Org 25969 and cis-atricurium/neostigmine.

Study 303 differed more significantly from Studies 301, 302, and 310.

1. Patient population
 - a. Only ASA 1 and 2 patients were enrolled.
 - b. Patients would only be scheduled for a short time period of neuromuscular blockade.
2. Treatment arms
 - a. Rocuronium followed in three minutes (point of maximal blockade) by Org 25969, 16 mg/kg
 - b. Succinylcholine, 1 mg/kg. Since there is no “reversal” agent for succinylcholine, the effects of the drug were allowed to spontaneously resolve.
3. Conduct
 - a. Patient screened and randomized.
 - b. Patient induced.
 - c. Neuromuscular blockade achieved by intravenous administration of rocuronium or succinylcholine.
 - d. Three minutes following the administration of rocuronium, patients randomized to the rocuronium/Org 25969 arm were injected with Org 25969. Patients randomized to succinylcholine did not receive a sham injection.
 - e. Train-of-Four neuromuscular monitoring continuously performed until patient recovered.
 - f. Routine follow up and post-anesthesia care.

4. Since patients treated with succinylcholine do not demonstrate fade on TOF stimulation, the primary efficacy endpoint was the elapsed time from the injection of NBMA to recovery of T_1 to 0.1 (10%).

The applicant's method to assess the status of the neuromuscular blockade was the "train-of four" stimulation of the ulnar nerve to cause contraction of the adductor pollicis.

The efficacy results from the four studies are summarized in the following table, adapted from Dr. Shibuya's review.

| Study # | Scenario | Time (in minutes) | | p-value |
|---------|-------------|-------------------|------------|---------|
| | | Org | Comparator | |
| 301 | Routine | 1:29 (R) | 18:30 | <0.0001 |
| | Shallow | 2:48 (V) | 16:48 | |
| 302 | Routine | 2:52 (R) | 50:22 | <0.0001 |
| | Profound | 4:28 (V) | 66:12 | |
| 303 | "Immediate" | 4:22 | 7:04 | <0.0001 |
| 310 | Routine | 2:02 | 8:46 | <0.0001 |
| | Shallow | | | |

Study 303 was proposed by the Applicant as a study which demonstrated (b) (4) ability to rapidly reverse rocuronium, which they then proposed to extrapolate to a clinical scenario where rapid reversal of a neuromuscular blocking agent is urgently needed. The prototypical clinical situation would be where one finds that, after the neuromuscular blocking agent has already been administered, for one of various reasons, it is not possible to intubate or ventilate a patient (the CICV scenario). However, the primary endpoint selected by the Applicant for the study, $T_1 = 0.1$, is of uncertain clinical significance. It is not known whether achievement of such an endpoint actually translates to a clinical benefit; in this particular case, the ability for a patient to sustain adequate spontaneous ventilation. Furthermore, it is noted that a true CICV scenario may be multifactorial, and that simple reversal of the neuromuscular blocking agent may not be sufficient. The clinical study did not really involve patients in an emergency scenario, and as such was an artificial situation.

The concept of "shallow" and "profound" neuromuscular blockade is of questionable clinical significance; therefore the claim that a particular product is capable of reversing both types of blockade is of dubious merit. It is sufficient to note that (b) (4) is capable of reversing neuromuscular blockade secondary to rocuronium or vecuronium, and the label would reflect this.

8. Safety

The safety database consisted of data collected from 28 clinical trials, and analyzed in comparison to placebo and to neostigmine. In the trials where a comparator or anesthetic agent were not used (predominantly Phase 1 studies), safety data were collected and tabulated.

(b) (4) is intended to be administered as a single-bolus dose when reversal of neuromuscular blockade is desired, therefore the Applicant did not evaluate its efficacy or safety in the context of repeat dosing. Subsequently, safety data regarding exposure to the product is based on dosage alone.

The table below, reproduced from Dr. Simone's review, summarizes the extent to which dose was evaluated in the clinical development program. In all, 1,967 unique subjects received (b) (4) 1,754 of these received a single dose, 91 received two doses, 40 received three doses, a single subject received four doses, and 81 received eight doses. Subjects who received multiple doses are assessed in both the individual dose groups and separately. These subjects participated in the Phase 1 studies: 19.4.101, 19.4.102, 19.4.105, 19.4.106, 19.4.108 and 19.4.109.

Exposure by dose and number of unique adult subjects

| Dose (mg/kg) | Numbers of Adults Exposed to (b) (4) | | | | | | | | | | | | | | |
|--------------------|--------------------------------------|-----|-----|-----|-----|---|-----|----|-----|----|-----|----|-----|----|----|
| | 0.1 | 0.2 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 64 | 96 |
| Number of Subjects | 5 | 4 | 124 | 178 | 612 | 9 | 729 | 28 | 154 | 39 | 127 | 4 | 164 | 12 | 12 |

As noted by Dr. Simone, the clinical trials in which (b) (4) was used to reverse a NMBA provide the most clinically relevant safety data. The table below indicates the extent of exposure to (b) (4) that occurred in subjects who also received an NMBA, stratified by the phase of the clinical trial.

Adult subjects exposure to sugammadex, by dose, in pooled Phase 1-3 trials

| Trial Phase | Rocuronium, vecuronium, or pancuronium + (b) (4) (mg/kg) | | | | | | | | | | | |
|-------------|--|-----|-----|---|-----|----|-----|----|----|----|-----|---------------|
| | placebo | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32* | Total (b) (4) |
| Phase 1 | 10 | 4 | 2 | 0 | 2 | 0 | 2 | 0 | 4 | 4 | 89 | 107 |
| Phase 2 | 84 | 250 | 212 | 9 | 167 | 28 | 122 | 39 | 39 | 0 | 0 | 866 |
| Phase 3 | 46 | 11 | 392 | 0 | 413 | 0 | 0 | 0 | 56 | 0 | 0 | 872 |
| Total | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |

* The Applicant counted 81 subjects twice in the 32 mg/kg dose group as they were exposed on two different occasions, at least four days apart, to that dose. This table does not include the double count.

The number of subjects exposed to the Applicant-proposed labeled doses is greatest for the 2 mg/kg dose of (b) (4) which is recommended for reversal of "shallow" neuromuscular blockade, and least for the 16 mg/kg dose, which is recommended for the immediate reversal of neuromuscular blockade and the dose likely to be used in emergency settings.

Deaths

There were three deaths in the clinical trials following administration of study drug: two had received (b) (4) and one had received placebo. Of the two subjects who died after exposure to

(b) (4) one subject, #203104007, received a 0.5 mg/kg dose, and the other subject, #208107008, received a 2.0 mg/kg dose. In each case, the subject's death occurred after the trial was completed, and each death was judged to be unrelated to treatment with the trial medication by both the Investigator and the Applicant. Review of the case narratives led to the conclusion by the review team that not enough information was contained in the narrative to completely rule out an causal relationship for Subject #203104007, but agreement with the Applicant regarding the other two cases.

Serious adverse events

A total of 182 Serious Adverse Events (SAEs) experienced by 126 adult subjects were reported for the development program, which included 2708 exposures to (b) (4). One hundred fifty one of these SAEs occurred in 106 of the 1845 subjects who were treated with (b) (4). The table below, reproduced from Dr. Simone's review, summarizes the overall occurrences of SAEs by drug and dose.

Occurrence of SAEs among adult subjects in the clinical development program

| Treatment | Incidents of Serious Adverse Events ^A Reported for Adult Subjects | | | | | | | | | | | | |
|----------------|--|-----------------------------|----------|------------|-----------|-----------|----------|----------|----------|----------|----------|------------------------|----------|
| | Placebo N=140 | (b) (4) N=640 (mg/kg) | | | | | | | | | | Neostigmine (mg/kg) | |
| Dose | N/A | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 0.05 | 0.07 |
| Number of SAEs | 10 (7) | 13 (11) | 7 (4) | 73 (12) | 1 (11) | 41 (7) | 2 (7) | 4 (3) | 3 (8) | 6 (6) | 1 (1) | 6 (7) | 6 (8) |

^A Not included in this table are nine SAEs that occurred in subjects who did not receive (b) (4) placebo or the active comparator, neostigmine. These included one SAE that occurred with moxifloxacin, one that occurred with succinylcholine and seven SAEs, among 4 subjects, that occurred prior to and, therefore, precluded administration of study drug.

The most frequent system organ classes involved were: Respiratory, thoracic, and mediastinal disorders; Gastrointestinal disorders; Injury, poisonings, and procedural complications; and Investigation (ECG QT corrected interval prolonged, and oxygen saturation decreased).

The SAEs associated with QTc prolongation are notable because the results from the two well-designed and conducted thorough QT studies showed prolongation times of < 10 msec. While the QT studies were not conducted on patients undergoing surgical procedures, and it is acknowledged that there may be confounding factors which will not make it possible to clearly demonstrate a cause and effect relations for these events, the three-fold greater incidence of QTc prolongation in (b) (4) treated subjects than in placebo-treated subjects, 3% versus 1%, respectively, is still of concern. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in (b) (4) treated subjects than in either placebo- or neostigmine-treated subjects. These included atrial fibrillation, cardiac arrest, cardiogenic shock, electro-mechanical disjunction, myocardial infarction and ventricular tachycardia. Dr. Simone noted in his review that none of these events appeared to be dose-related and most occurred while subjects were being monitored as part of their anesthetic care, i.e., intraoperatively or in the Post Anesthesia Care Unit, where the monitoring and readily available treatments would favor a positive outcome.

Common adverse events

The overall incidence of adverse events was comparable between the subjects on (b) (4) subjects (68%) and the subjects on placebo (72%), regardless of the NMBA administered. There was slightly higher overall incidence in the vecuronium group:

- Rocuronium plus (b) (4) (67%), rocuronium plus placebo (70%);
- Vecuronium plus (b) (4) (75%), vecuronium plus placebo (83%).

A total of 58% of the 19 subjects in the uncontrolled (b) (4) plus pancuronium group experienced at least one AE.

The most frequent (i.e., $\geq 20.0\%$ incidence in either treatment group) system organ class involved included Injury, Poisoning, and Procedural Complications (36% (b) (4) 40% placebo) and Gastrointestinal Disorders (27% (b) (4) 29% placebo).

Hypersensitivity/anaphylaxis

Five subjects had experienced reactions to (b) (4) that were consistent with anaphylaxis; the Applicant identified these as hypersensitivity reactions. The Applicant conducted a hypersensitivity study to evaluate intradermal injection and skin prick responses for (b) (4) in subjects who had been previously exposed to the product, including one of whom had a hypersensitivity reaction, and (b) (4) naïve subjects. The study findings included:

1. positive test results for the subject with a previous hypersensitivity reaction;
2. positive test results for a previously exposed subject with no hypersensitivity reaction; and
3. negative test results for all subjects who had no previous exposures to (b) (4)

The Division of Pulmonary and Allergy Products was consulted for their opinion on these adverse events. Their findings are described below, in Section 8 (Other Relevant Regulatory Issues).

Coagulation Parameters

In two in-vitro studies conducted, the Applicant noted that (b) (4) caused statistically significant increases in the mean measured values of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the international normalized ratio for PT (INR); the mean values were reported to be within normal limits of the laboratory. The values were reported to be increased for concentrations of (b) (4) that were comparable to peak plasma concentrations associated with a 16 mg/kg dose; changes for the other proposed doses were not reported.

The reported rate of hemorrhagic adverse events for all doses of (b) (4) was 6% compared to 3% for placebo-treated subjects, but concurrent assessments of the coagulation parameters were not available. The in-vitro findings, combined with the differences in hemorrhage rates from the clinical studies, warrant a further clarification of the effects of (b) (4) on coagulation parameters.

9. Advisory Committee Meeting

A meeting of the Anesthetic and Life Support Drug Advisory Committee was held on March 11, 2008. The applicant presented their rationale for development of the product and the

safety and efficacy data. The Agency presented the clinical efficacy, with an emphasis on the outliers; the clinical safety, focusing on the hypersensitivity reactions; and the nonclinical data, noting the effects on bone and teeth. The questions that were posed to the committee were the following:

1. The Applicant has conducted a clinical trial to evaluate the efficacy of sugammadex to effect the “Immediate Reversal” of neuromuscular blockade (NMB). The primary efficacy endpoint was the time from start of administration of rocuronium bromide (RCB) or succinylcholine (Sux) to the recovery of T1 to 10% of its baseline value. Sugammadex was administered to patients 3 minutes following administration of RCB.
 - a. Does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful?
 - b. Based on the data submitted from this study, is there sufficient clinical information to assess whether sugammadex, when used with RCB, provides a clear advantage when confronted with a “cannot ventilate/cannot intubate” situation in the clinical setting? If not, what additional information would be required to assess a possible role for sugammadex in this scenario?
2. Based on the nonclinical data submitted by the applicant from the sugammadex distribution, juvenile animal, reproductive toxicology, and dedicated bone studies:
 - a. Has the risk for adult patients, including patients with fractures or surgical injury to bone been adequately characterized?
 - b. Has the risk for pediatric patients been adequately characterized?
 - c. Does the nonclinical data support the safety of sugammadex for clinical trials in a pediatric population?
 - d. If the answers to any of the above questions is “no,” what additional information is required to support the use of sugammadex in these populations?
3. Has the applicant adequately demonstrated that sugammadex:
 - a. reverses neuromuscular blockade from rocuronium and vecuronium;
 - b. immediately reverses neuromuscular blockade from rocuronium?
 - c. can be used safely in the targeted population? Please discuss potential hypersensitivities in this population, if patients at risk can not be identified.

Highlights from the discussion at the meeting are summarized below:

1. The committee felt that the endpoint in Study 303 (T1 = 0.1) was of minimal clinical use but felt that it supported the conclusion that Org 25969 reversed paralysis more quickly than succinylcholine spontaneously resolved. The committee felt that more meaningful data for the label would consist of the time from injection that most of the patients (e.g., 95%) had responded.
2. The committee felt that rocuronium/Org25969 could not replace succinylcholine for rapid sequence induction, particularly because succinylcholine would be necessary if re-intubation was required. The committee felt that Org 25969 was an important product that could be useful in the cannot intubate/cannot ventilate scenario although it opposed the use of the words “immediate reversal” or claims that Org 25969 was effective in the cannot intubate/cannot ventilate scenario.

3. The committee was concerned about the hypersensitivity reactions although it felt that the reactions were relatively minor, self-limited, and acceptable given the known hazards of succinylcholine. The committee recommended a postmarketing surveillance program to further define the risks of hypersensitivity reactions.
4. The committee would have liked to have seen more data in the obstetric population.
5. The committee felt that the non-clinical findings regarding bone and teeth were of no concern to adults and that the current data would support a single-dose study in pediatric patients.
6. The committee felt that more data would be required for multiple-dose pediatric studies and that nonclinical studies must be conducted to assess safety in neonates or premature infants. The committee also felt that assessments of bone strength in juvenile animal models were necessary.

10. Pediatrics

(b) (4),
due to the effects seen on the teeth and bones in juvenile animals, multiple dose studies in pediatric patients should be deferred until the potential clinical implications of these findings are better understood.

11. Other Relevant Regulatory Issues

Site Inspections by the Division of Scientific Investigations

The Division of Scientific Investigations inspected four clinical sites. All the sites were deemed acceptable.

Consult to the Division of Pulmonary and Allergy Products

A consult was requested from the Division of Pulmonary and Allergy Products for their input regarding the potential clinical significance of the adverse events reported in the clinical trials that were suggestive of anaphylaxis.

After review of the case report summaries, the results of an in vitro basophile assay testing, and the conclusion of an expert panel review organized by the Applicant, their conclusions were that sugammadex has the potential for allergic reactions, including anaphylaxis. There were several significant observations identified by Dr. Chowdhury and his team which led to different conclusions than the Applicant's.

First, it was important to ensure that a common definition of anaphylaxis be utilized in order to be able to adequately identify and assess potential cases. The most recent diagnostic criteria proposed by the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network in 2006, specifically did not identify "life-threatening" as being a condition necessary to determine whether a reaction can be classified as anaphylaxis.

Second, the frequency of this adverse event proposed by the Applicant is probably an underestimate. This is primarily because of the particular patient population studied where confounding factors, such as comorbid conditions and concomitant medications, may make

assessment of this adverse event difficult, and because the clinical development program did not assess the safety of repeated exposures.

And third, the results of the in vitro mechanistic studies reported by the Applicant (basophil histamine-release assays and ex vivo basophile histamine release assay) were insufficient. They noted that the results of the basophil histamine assays submitted by the Applicant were not suggestive of an IgE-mediated mechanism, and the mast cell skin assay did not show evidence of histamine release from mast cells in skin directly exposed to (b) (4) however the underlying mechanism cannot be determined or ruled out on the basis of these results alone due to current assay limitations.

With respect to the utility of additional mechanistic studies, Dr. Chowdhury noted that elucidation of the mechanism responsible for the hypersensitivity reaction would be helpful, as it could potentially allow patient screening and improved risk assessment. However, it was also noted that regardless of the underlying mechanism of action (i.e., whether it is IgE-mediated or not), the clinical diagnosis of anaphylaxis and the potential for serious injury or death are unchanged.

Their recommendations included that a formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population be conducted prior to widespread use.

Consult to the Division of Dermatology and Dental Products

A consult was requested from the Division of Dermatology and Dental Products for their input regarding the nonclinical findings involving the teeth. Dr. Hyman evaluated the data from the general toxicology, juvenile toxicology, and dedicated bone and teeth studies. He noted that the rat incisors, which continue to grow throughout the rat's life, are a good model for developing human teeth, and that the rat molars are a good model for permanent human teeth, equivalent to humans > 7 years of age, since they have extremely limited ability for continued growth.

White spots on the teeth appear similar in nature to that observed with dental fluorosis, which is considered a cosmetic alteration and not a pathologic finding according to the Surgeon Generals Report on Oral Health (2000). Dr. Hyman indicated that, although data for Org 25969 would suggest that it could interfere with enamelization (amelogenesis) in the juvenile rat and, therefore, may confer a theoretical risk to children with developing teeth, the extremely high doses and sustained exposure required to produce detectable adverse effects on the developing enamel provides a margin of safety for its proposed single use in patients under the age of 8, and for all children over the age of 8 regardless of the lifetime frequency of use.

Dr. Hyman agrees with the review team that the safety margins will decrease if multiple doses are used; however, it was reassuring that disrupted amelogenesis and deposition of "amorphous material" was not observed until 3 weeks of daily administration of sugammadex at high dose levels (>30X highest planned human dose) had already taken place.

Dr. Hyman noted the low transfer of Org 25969 through the placenta to the fetus, consistent with the lack of dental findings in the reproductive toxicology studies. Furthermore, if there

should be any effects on the primary teeth through gestational exposure, these would likely be replaced by normal permanent teeth later in the child's development.

Additional studies that could potentially be helpful for determining the risk profile in the pediatric population include the evaluation of extracted/shed teeth from children exposed during development (i.e., primary teeth), and the evaluation of Org 25969's effect on the teeth of a non-human primate.

Consult to the Division of Endocrine Products

A consult was requested from the pharmacology/toxicology review team in the Division of Endocrine Products for their input regarding the nonclinical findings involving the bone. Dr. Kuijpers noted that the difference in the trabecular measurements may be due to an artifact caused by the need to re-orient the treatment group femurs relative to the control femurs due to the slight difference in femur length and diameters, essentially resulting in that equivalent portions of the diaphysis were not evaluated between the groups.

Dr. Kuijpers was not convinced that the decreased bone length is due to a general toxicity and growth retardation effect as there was no clear temporal relationship, although the lack of reversibility of longitudinal bone growth suggests a potential relationship to bone retention. No binding was observed at the growth plate; however, the Applicant did not conduct growth plate morphometry. Dr. Kuijpers also indicated that Org 25969 may possess reabsorption inhibiting properties similar to tetracycline or bisphosphonates, but bone turnover biomarkers were not evaluated by the Applicant.

Nevertheless, her overall impression was that the safety margins supported by the NOAEL were large, > 18-fold, and supported the use in adult patients. A low AUC-based safety margin was observed in the 28-day multiple dose juvenile rat study (1X).

Dr. Kuijpers' recommendation for additional studies that would be helpful in assessing the nature of the effect of Org 25969 on bone included:

1. Data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study; samples may be obtained from this study if still available.
2. Evaluation of vertebrae to interpret bone effects since they have a more homogenous trabecular structure
3. Reevaluation of the bone localization (microautoradiography) study, as the presentation of the data was poor and errors in descriptions were noted.
4. Evaluation of the mechanism of action, including in vitro bone resorption assay (^{45}Ca release), assessment of bone turnover markers, hydroxylapatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention.
5. A treatment arm of bisphosphonates should be added to any future study as a positive control arm to provide assay sensitivity, and the period of recovery should be extended to 4 to 6 months (>2 times $t_{1/2\beta}$ Org 25969).
6. A fracture repair study in a nonclinical model.

Consult to the Interdisciplinary Review Team for QT Studies

Two thorough QT studies were conducted by the Applicant (Studies 19.4.109 and 19.4.105). The interdisciplinary review team concluded that the Study 19.4.109 was conducted in a satisfactory manner, and although there was a concentration-dependent increase in the QTcI, the increase for the supratherapeutic dose (32 mg/kg) did not result in a clinically significant increase.

The results for Study 19.4.105 were comparable, and the Interdisciplinary Review Team opted to not repeat their analysis, since the Applicant assessed the same doses as in the other study.

12. Labeling

The indications proposed by the Applicant are not supported by the data submitted in the application; therefore, if this product were to be approved, it would most likely be indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. (b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action
Not Approval

- Risk Benefit Assessment

The data submitted in the application does not support a favorable risk:benefit assessment. It is unclear at this time how significant is the risk of anaphylaxis, including after repeated exposures. Although the Applicant has provided data to support the efficacy of the product, and that data also demonstrated that the reversal was faster than the control, the significance of this finding with respect to the clinical benefit derived by the patient was not that clear. Even though the clinical situation proposed by the Applicant of the cannot intubate/cannot ventilate patient does exist, it was not adequately studied in the clinical development program.

- Recommendation for Postmarketing Risk Management Activities
None.

- Recommendation for other Postmarketing Study Commitments

Nonclinical

The following nonclinical data are not required for approval for an indication in adult patients; however, they would be needed prior to initiation of multiple-dose clinical studies in pediatric patients, approval of a single-dose pediatric indication, or inclusion of dosing recommendations or efficacy data on pediatric patients in the label. For that reason, they can be considered post-marketing in nature, but it is noted that if the Applicant chooses to delay their response to the deficiencies noted in the Approvable letter, these studies could be done in the pre-marketing phase.

1. An evaluation of sugammadex in a nonclinical model of bone fracture to examine potential effects of the drug on bone healing.
2. Data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study; samples may be obtained from this study if still available.
3. A repeat-dose study of sugammadex in the juvenile rat with extended period of recovery, such that bone length, material properties and integrity at full skeletal maturity may be evaluated in order to clarify the observation of slight, but lasting, decreased bone length and body weight observed in the 28-day juvenile toxicity study. Within this study, μ CT, bone turnover markers, and bone strength assessment should be obtained and evaluated; the study should incorporate positive control arms to verify assay sensitivity. The inclusion of vertebrae evaluation would be helpful to interpret bone effects since they have a more homogenous trabecular structure.
4. A reevaluation of bone localization of Org 25969 as presentation of the data was not clear and errors in descriptions were noted.

Although not required for approval in the pediatric population, studies to address the mechanism of action in bone such as an in vitro bone resorption assay (^{45}Ca release), assessment of bone turnover markers, hydroxyl-apatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention are recommended.

- Recommended Comments to Applicant

Clinical

Data from the following studies will be required prior to approval:

1. A formal assessment of the risk of an anaphylactic reaction in patients with repeated exposures, both in a general population and in a sensitized population.
2. An evaluation of the potential clinical implications of the in vitro interaction observed between (b) (4) and coagulation parameters.

Nonclinical

Further nonclinical evaluation and studies will be necessary prior to any multiple-dose pediatric trials, approval of a pediatric indication, or inclusion of dosing recommendations or efficacy data on pediatric patients in the label:

1. Provide an evaluation of sugammadex in a nonclinical model of bone fracture to examine potential effects of the drug on bone healing. You are encouraged to submit protocols of such studies to the Agency for comment prior to their conduct.
2. Provide data on growth plate morphology to help understand the longitudinal growth reduction observed in the 28-day juvenile rat study; samples may be obtained from this study if still available.

3. Provide a repeat-dose study of sugammadex in the juvenile rat with extended period of recovery, such that bone length, material properties and integrity at full skeletal maturity may be evaluated in order to clarify the observation of slight but lasting decreased bone length and body weight observed in the 28-day juvenile toxicity study. Within this study, \square CT, bone turnover markers, and bone strength assessment should be obtained and evaluated. Also, the study should incorporate positive control arms to verify assay sensitivity. Lastly, though not required, the inclusion of vertebrae evaluation would be helpful to interpret bone effects since they have a more homogenous trabecular structure. You are encouraged to consider an alternative, intermittent dosing paradigm in order to minimize effects of Org 25969 on body weight while allowing for significant drug accumulation in the skeleton.
4. Provide a reevaluation of bone localization of Org 25969 as presentation of the data was not clear and errors in descriptions were noted.

Although not required for approval in the pediatric population, the following nonclinical studies are recommended:

1. Provide additional studies to address the mechanism of action in bone such as an in vitro bone resorption assay (^{45}Ca release), assessment of bone turnover markers, hydroxyl-apatite crystal growth and dissolution assay, and effect of in vitro bone decalcification on sugammadex retention.
2. Although plasma levels of sugammadex rapidly decline with acute administration, the long retention of sugammadex in skeletal bone may be considered to be chronic exposure (i.e., greater than 6-months) and raises concern regarding the potential for development of tumors of this tissue, especially in the pediatric population which is known to develop primary bone tumors at rates which exceed that in the adult population. You will need to provide data which may be derived from published literature, in vitro and/or in vivo studies, along with a well supported rationale which is persuasive that the risk of administration and long-term retention of sugammadex in the bones of pediatric patients will not confer a risk for bone tumor development in this population. Otherwise, an evaluation of carcinogenic potential of sugammadex may be required.

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/s/

Rigoberto Roca
7/18/2008 09:24:56 AM
MEDICAL OFFICER



FDA, Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170, 10903 New Hampshire Ave., Silver Spring, MD 20993

CLINICAL REVIEW

| | |
|-------------------------|--|
| Application Type: | NDA |
| Submission Number: | 22-225 |
| Submission Code: | N-000 |
| Letter Date: | October 30, 2007 |
| Stamp Date: | October 31, 2007 |
| PDUFA Goal Date: | July 31, 2008 |
| Reviewer Name: | Arthur Simone, M.D., Ph.D. |
| Review Completion Date: | June 27, 2008 |
| Established Name: | sugammadex sodium injection |
| (Proposed) Trade Name: | (b) (4) |
| Therapeutic Class: | neuromuscular blockade reversal agent |
| Applicant: | Organon USA, Inc. |
| Priority: | P |
| Indication: | reversing neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium |
| Intended Population: | Adult surgical patients paralyzed with either rocuronium or vecuronium bromide |

Table of Contents

| | | |
|----------|---|-----------|
| 1 | EXECUTIVE SUMMARY | 4 |
| 1.1 | RECOMMENDATION ON REGULATORY ACTION | 6 |
| 1.2 | RECOMMENDATION ON POSTMARKETING ACTIONS | 8 |
| 1.2.1 | Risk Management Activity | 8 |
| 1.2.2 | Required Phase 4 Commitments | 8 |
| 1.2.3 | Other Phase 4 Requests | 8 |
| 1.3 | SUMMARY OF CLINICAL FINDINGS | 9 |
| 1.3.1 | Brief Overview of Clinical Program | 9 |
| 1.3.2 | Efficacy | 9 |
| 1.3.3 | Safety | 9 |
| 1.3.4 | Dosing Regimen and Administration | 12 |
| 1.3.5 | Drug-Drug Interactions | 13 |
| 1.3.6 | Special Populations | 13 |
| 2 | INTRODUCTION AND BACKGROUND | 14 |
| 2.1 | PRODUCT INFORMATION | 14 |
| 2.2 | CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS | 14 |
| 2.3 | AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES | 15 |
| 2.4 | IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS | 15 |
| 2.5 | PRESUBMISSION REGULATORY ACTIVITY | 15 |
| 2.6 | OTHER RELEVANT BACKGROUND INFORMATION | 15 |
| 3 | SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES | 16 |
| 4 | DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY | 16 |
| 5 | CLINICAL PHARMACOLOGY | 16 |
| 6 | INTEGRATED REVIEW OF EFFICACY | 16 |
| 7 | INTEGRATED REVIEW OF SAFETY | 17 |
| 7.1 | METHODS AND FINDINGS | 17 |
| 7.1.1 | Deaths | 20 |
| 7.1.2 | Other Serious Adverse Events | 22 |
| 7.1.3 | Dropouts and Other Significant Adverse Events | 32 |
| 7.1.4 | Other Search Strategies | 35 |
| 7.1.5 | Common Adverse Events | 35 |
| 7.1.6 | Less Common Adverse Events | 41 |
| 7.1.7 | Laboratory Findings | 41 |
| 7.1.8 | Vital Signs | 56 |
| 7.1.9 | Electrocardiograms (ECGs) | 67 |
| 7.1.10 | Immunogenicity | 81 |
| 7.1.11 | Human Carcinogenicity | 81 |
| 7.1.12 | Special Safety Studies | 81 |
| 7.1.13 | Withdrawal Phenomena and/or Abuse Potential | 83 |
| 7.1.14 | Human Reproduction and Pregnancy Data | 84 |
| 7.1.15 | Assessment of Effect on Growth | 84 |
| 7.1.16 | Overdose Experience | 84 |
| 7.1.17 | Postmarketing Experience | 85 |
| 7.2 | ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS | 85 |

| | | |
|-----------|---|------------|
| 7.2.1 | Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety | 85 |
| 7.2.2 | Description of Secondary Clinical Data Sources Used to Evaluate Safety | 92 |
| 7.2.3 | Adequacy of Overall Clinical Experience..... | 93 |
| 7.2.4 | Adequacy of Special Animal and/or In-Vitro Testing | 94 |
| 7.2.5 | Adequacy of Routine Clinical Testing | 94 |
| 7.2.6 | Adequacy of Metabolic, Clearance, and Interaction Workup | 94 |
| 7.2.7 | Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study | 95 |
| 7.2.8 | Assessment of Quality and Completeness of Data..... | 95 |
| 7.2.9 | Additional Submissions, Including Safety Update..... | 95 |
| 7.3 | SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS | 95 |
| 7.4 | GENERAL METHODOLOGY | 96 |
| 7.4.1 | Pooling Data Across Studies to Estimate and Compare Incidence | 96 |
| 7.4.2 | Explorations for Predictive Factors..... | 97 |
| 7.4.3 | Causality Determination | 98 |
| 8 | ADDITIONAL CLINICAL ISSUES | 98 |
| 8.1 | DOSING REGIMEN AND ADMINISTRATION | 98 |
| 8.2 | DRUG-DRUG INTERACTIONS | 98 |
| 8.3 | SPECIAL POPULATIONS | 98 |
| 8.4 | PEDIATRICS | 99 |
| 8.5 | ADVISORY COMMITTEE MEETING | 99 |
| 8.6 | LITERATURE REVIEW | 101 |
| 8.7 | POSTMARKETING RISK MANAGEMENT PLAN | 101 |
| 8.8 | OTHER RELEVANT MATERIALS | 101 |
| 9 | OVERALL ASSESSMENT..... | 101 |
| 9.1 | CONCLUSIONS | 101 |
| 9.2 | RECOMMENDATION ON REGULATORY ACTION | 102 |
| 9.3 | RECOMMENDATION ON POSTMARKETING ACTIONS | 102 |
| 9.3.1 | Risk Management Activity | 102 |
| 9.3.2 | Required Phase 4 Commitments | 102 |
| 9.3.3 | Other Phase 4 Requests | 102 |
| 9.4 | LABELING REVIEW | 102 |
| 9.5 | COMMENTS TO APPLICANT..... | 102 |
| 10 | APPENDICES | 103 |
| 10.1 | CONSULT FROM THE DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS – MAY 13, 2008 | 103 |
| 10.2 | CONSULT FROM THE DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS – JUNE 16, 2008 | 112 |
| 10.3 | LINE-BY-LINE LABELING REVIEW..... | 118 |

1 EXECUTIVE SUMMARY

(b) (4) is a substituted gamma-cyclodextrin that was designed to capture a molecule of the neuromuscular blocking agent (NMBA) rocuronium bromide (RCB) within its ring, thereby removing it from circulation and reversing the neuromuscular blockade it had induced. (b) (4) has been shown to be most effective with rocuronium bromide; however, it was also found to be efficacious with vecuronium bromide (VCB) in some situations, although less so with vecuronium than with rocuronium. (b) (4) does not reverse the blockade induced by other currently approved NMBAs.

In clinical trials, (b) (4) was found to be effective for reversing RCB- and VCB-induced neuromuscular blockade under two clinical conditions:

1. with the return of the second twitch (T_2) when a train-of-four (TOF) stimulus is applied to the ulnar nerve and the response of the abductor pollicis longus muscle is assessed; and
2. with the presence of one to two post-tetanic contractions following a tetanic electrical stimulus applied to the ulnar nerve and assessed by the adductor pollicis longus muscle response.

(b) (4) was also found to be effective for reversing a 1.2 mg/kg dose of RCB-induced neuromuscular blockade at three minutes following the administration, the time when the maximal pharmacodynamic effect of RCB is expected.

For the first two clinical scenarios above, (b) (4) provided a more rapid return to 90% of the ratio of the intensity of the fourth twitch (T_4) in a TOF stimulus to that of the first twitch (T_1) compared to placebo or neostigmine. (Neostigmine is the anticholinesterase agent most commonly used in clinical practice for the reversal of nondepolarizing NMBAs; however, it is an unapproved drug product.) For the third clinical scenario, (b) (4) was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied in this scenario was the return of T_1 in a TOF stimulus to 10% of its baseline value. (b) (4) reversed the NMB induced by RCB in less time than it took for the effects of succinylcholine to spontaneously resolve.

Based on these findings, the Applicant seeks the following indications for this product:

“For routine reversal:

- A dose of 4.0 mg/kg (b) (4) is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.
- A dose of 2.0 mg/kg (b) (4) is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade.

For immediate reversal:

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4) is recommended.”

While the efficacy findings for (b) (4) were robust, there were safety concerns identified in the course of the clinical development program that potentially overshadow the product's clinical utility. These include the following:

1. potentially life-threatening cardiac arrhythmias, electrocardiographic changes and events
2. potentially life-threatening anaphylactic reactions
3. the likelihood of immunogenicity
4. the effects of (b) (4) on coagulation parameters have not been fully investigated

The cardiac changes noted included QTc prolongation despite two well designed thorough QT studies that showed prolongation times of < 10 msec, the Agency's cutoff for concern. While the QT studies were not conducted on patients undergoing surgical procedures, it is not clear why there was a three-fold greater incidence of QTc prolongation in (b) (4) treated subjects than in placebo-treated subjects that rose to the level of a serious adverse event (SAE), 3% versus 1%, respectively. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in (b) (4) treated subjects than in either placebo- or neostigmine-treated subjects. These included atrial fibrillation, cardiac arrest, cardiogenic shock, electro-mechanical disjunction, myocardial infarction and ventricular tachycardia. Although it was not possible to show cause and effect for these SAEs, the greater frequency with which they occurred in (b) (4) treated subjects than those in other treatment arms in randomized studies raises a safety concern. It should be noted that none of these events occurred in a manner that appeared to be dose related and most occurred while subjects were being monitored as part of their anesthetic care, i.e., intraoperatively or in the Post Anesthesia Care Unit, where the monitoring and readily available treatments would favor a positive outcome.

The Applicant reported a number of "hypersensitivity" reactions in subjects treated with (b) (4). According to the Division of Pulmonary and Allergy Drug Products (DPADP), these reactions met the criteria for being labeled anaphylactic. In all, there were five cases that meet the diagnostic criteria for anaphylaxis. As there were 1973 adults and 51 children exposed to (b) (4) during the clinical development program; the incidence of anaphylaxis is at least 0.25% (5/2024).

While there is a possibility that the extent of the anaphylactic reactions that will occur with (b) (4) will consist only of rashes, gastrointestinal symptoms and mild to moderate changes in hemodynamic parameters, all of which will be self-limited and not require intervention, there is no evidence to support such a conclusion.

In addition, the data from the Sponsor's hypersensitivity study provides convincing evidence that (b) (4) is immunogenic. As such, the drug carries a risk for sensitization that has the potential for producing significant morbidity or mortality when the product is administered following a future surgical procedure. A study has not been conducted to assess the outcomes of second administrations of this product following a suitable time period that would allow for antibody formation. Such a study is needed to provide data that more fully characterizes the risk profile of this product.

At least one subject with no previous exposure to (b) (4) experienced an anaphylactic reaction on initial exposure and later had a positive intradermal test. This raises the safety concern over what drug or other substance may have resulted in a cross sensitization to (b) (4). While the Applicant assessed the possibility of cross reactivity with beta lactams, they did not consider the possibility of other cyclodextrins as being the offending agents. Currently, there are three beta cyclodextrins approved as antifungal agents in the United States. If there is a chance that cross sensitization occurs with these products, then the benefit of exposing millions of patients a year to (b) (4) with little or no clinical benefit to be gained by that exposure, must be weighed against the possibility of sensitizing these patients against drug products they may need for life-threatening infections at some time in the future. The possibility of such cross sensitization should be fully evaluated to more adequately characterize the risk profile of (b) (4).

Lastly, the Applicant did not assess coagulation parameters as part of the clinical laboratory investigations. In the two *in-vitro* studies that were conducted, it was noted that (b) (4) caused statistically significant increases in the mean measured values of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the international normalized ratio for PT (INR); the mean values were reported to have been within normal limits of the laboratory performing the analyses. The Applicant indicated that the values were increased for concentrations of (b) (4) comparable to peak plasma concentrations associated with a 16 mg/kg dose; however, changes for comparable concentrations of the other proposed doses were not reported. In the safety database, the reported rate of hemorrhagic adverse events for all doses of (b) (4) was 6% compared to 3% for placebo-treated subjects; however, concurrent assessments of the coagulation parameters were not made. The *in-vitro* findings combined with the differences in hemorrhage rates from the clinical studies warrant a formal investigation as to the effects of (b) (4) on coagulation in patients undergoing a variety of surgical procedures.

Based on the safety issues raised, it is recommended that an approvable action be taken, and that the Applicant provides additional data, as described below, to fully characterize the (b) (4) risks for anaphylaxis and immunogenicity.

1.1 Recommendation on Regulatory Action

The Applicant has provided sufficient evidence from adequate and well-controlled studies to demonstrate that (b) (4) reverses the neuromuscular blocking activity of rocuronium bromide (RCB) and vecuronium bromide (VCB). The data from these studies indicate that clinically relevant levels of reversal can be obtained for RCB regardless of the patient's response to electrical stimulation of the neuromuscular junction. Studies of the reversal of VCB with (b) (4) provided data that indicated clinically relevant levels of reversal could be obtained provided patients had achieved some level of spontaneous recovery from the neuromuscular blockade as assessed by electrical stimulation of the neuromuscular junction. The Applicant has adequately evaluated the dosing requirements of (b) (4) predicated on responses to electrical stimulation of the neuromuscular junction, to provide effective guidelines for clinical use.

The Applicant has not provided evidence to demonstrate that using (b) (4) to reverse the neuromuscular blockade of either RCB or VCB can result in less morbidity or mortality in situations where a patient cannot be intubated or adequately ventilated.

The analysis of the safety database has identified risks associated with the use of (b) (4) some of which currently outweigh the benefits derived from this product for any patient population.

1. A greater percentage of (b) (4) treated subjects experienced cardiac adverse events compared to placebo- and neostigmine-treated subjects. The events included potentially life-threatening arrhythmias and QTc prolongation. The number of QTc serious adverse events was unexpected as the Applicant conducted two appropriately designed thorough QTc studies, one with and one without an NMBA, which demonstrated (b) (4) to have minimal prolongation potential.
2. Upon review of the safety database, and in consultation with the Division of Pulmonary and Allergy Products, the following risks were identified that had a substantial negative impact on the benefit-risk ratio.
 - a. anaphylactic reactions
 - b. immunogenicity
 - c. potential for cross sensitization with other drugs including beta cyclodextrins
3. *In-vitro* studies have demonstrated that (b) (4) increases metrics of coagulation including PT, aPTT and INR; the clinical studies demonstrate higher rates of hemorrhagic adverse events associated with (b) (4) than with placebo. Coagulation parameters were not assessed in subjects participating in any of the clinical trials. The extent to which (b) (4) alters coagulation and affects postoperative bleeding is not currently known.

It is possible that a more complete characterization of the risk profile may help identify a population for whom the benefits outweigh the risk. The information needed to allow this reanalysis is described in more detail below. However, based on the efficacy and safety data available to date, it is recommended that an approvable action is taken for this new drug application. The following studies need to be conducted to address the safety issues raised:

1. Conduct studies to assess the presence of IgE and IgM antibodies to (b) (4) in the following populations:
 - subjects previously exposed to (b) (4) and who had signs or symptoms associated with hypersensitivity;
 - subjects with positive test results from the skin prick and intradermal injection testing study;
 - a sampling of subjects previously exposed to (b) (4) on multiple occasions, e.g., subjects in QT studies; and
 - a sampling of subjects previously exposed to each of the three doses of (b) (4) proposed for use in the label.
2. Conduct studies to assess the risk of hypersensitivity reactions and the immunogenic properties of (b) (4) by re-exposing subjects who had previously received a 16 mg/kg dose. The study must be conducted under conditions where appropriate monitoring for anaphylactic reactions can be performed and prompt treatment can be administered as needed. In this study, every effort should be made to recruit subjects previously exposed

to (b) (4) who had signs or symptoms associated with hypersensitivity and subjects who had positive test results from skin prick and intradermal injection testing in the hypersensitivity trial.

3. Conduct studies to evaluate the effects of (b) (4) on coagulation in patients undergoing surgical procedures. A substantial number of the subjects should be exposed to the 16 mg/kg dose of (b) (4) and the surgical procedures should include orthopedic, major vascular and intra-abdominal surgeries.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None is recommended at present. Depending on the findings from the Phase 4 Commitments, a Risk Evaluation and Minimization Strategy (REMS) may be required.

1.2.2 Required Phase 4 Commitments

The following Phase 4 studies will better characterize the safety profile of (b) (4) and provide additional data needed to assess safety and efficacy in the pediatric population:

1. Study the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving (b) (4) versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.
2. Conduct a study to assess clearance of (b) (4) rocuronium complexes in patients with renal failure who undergo hemodialysis using high flux filtration.
3. Conduct studies to assess safety, efficacy and dosing requirements for (b) (4) when used on patients with hepatic impairment. The studies should characterize the pharmacokinetics and pharmacodynamics of rocuronium and vecuronium in these patients following the administration of (b) (4).
4. Conduct studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. Such studies should not be started until the safety issues for the adult population have been fully vetted by the Agency.

1.2.3 Other Phase 4 Requests

None are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The following are the highlights of the drug product's clinical development program:

- Product name: (b) (4) (it has also been referred to as Org25969, sugammadex and Bridion at different points during the development program)
- Class: Gamma-cyclodextrin
- Route of administration: intravenous administered as a bolus over 10 seconds
- Indications sought: "Routine" reversal of "shallow" or "profound" neuromuscular blockade induced by rocuronium and vecuronium and "immediate" reversal of neuromuscular blockade three minutes after injection of rocuronium
- Number of pivotal efficacy trials: 4
- Number of patients enrolled in pivotal efficacy trials: 529
- Overall number of patients in safety database: 2054 unique subjects including 51 pediatric patients
- Other pertinent clinical data sources: None

1.3.2 Efficacy

The studies conducted provided strong evidence that (b) (4) effectively reverses both rocuronium- and vecuronium-induced neuromuscular blockade and does so faster than placebo and neostigmine when the study drugs were administered following either the return of T₂ in a TOF electrical stimulus or the presence of one or two twitches in response to a TOF stimulus following a tetanic electrical stimulus. All twitch-response evaluations of recovery were made by electrical stimuli applied to the ulnar nerve at the wrist and assessed by the adductor pollicis longus muscle response.

(b) (4) was also found to be effective for reversing a 1.2 mg/kg dose of RCB-induced neuromuscular blockade at three minutes following its administration, the time when the maximal pharmacodynamic effect of RCB is expected. In this trial, (b) (4) was compared to succinylcholine, a depolarizing NMBA for which there is no reversal agent. The primary efficacy endpoint studied was the return of T₁ in a TOF stimulus to 10% of its baseline value. (b) (4) reversed the NMB induced by RCB in less time than it took for the effects of succinylcholine to spontaneously resolve.

1.3.3 Safety

The extent of safety testing in the original development program was adequate. The safety database consisted of 2054 unique subjects, which included 51 pediatric subjects who were exposed to (b) (4). The clinical trials conducted by the Applicant were the only sources of

(b) (4) (sugammadex sodium injection)

human safety data for this product. In the clinical trials, subjects received only a single dose of (b) (4) which ranged from 0.1 to 96 mg/kg. The doses associated with the proposed indications, i.e., 2, 4 and 16 mg/kg were used most often in the trials.

The subjects enrolled in the Phase 2 and 3 trials were adult surgical patients, with 51 pediatric surgical subjects also enrolled in trial 19.4.306. The subjects had no known or suspected neuromuscular disorders, no personal or family history of malignant hyperthermia, and no significant hepatic or renal dysfunction except for trial 19.4.304 that included patients with impaired renal function. Female subjects were neither pregnant nor breast feeding. Subjects were excluded if they were receiving medications known to interfere with NMBAs, including anticonvulsants, aminoglycosides, and magnesium.

Overall, the incidence of adverse events in subjects who received (b) (4) was similar to those who received either placebo or neostigmine. There were two areas where the adverse-event profile of (b) (4) differed substantially from both placebo and neostigmine: cardiac serious adverse events (SAEs) and anaphylactic reactions.

The table below indicates the incidence of cardiac SAEs for the different treatment groups and doses of (b) (4). Two safety related observations can be made from the table:

1. There were a substantial number of QTc prolongation SAEs associated with (b) (4) despite two thorough QTc studies which indicated the drug does not significantly affect QTc duration.
2. None of the SAEs appears to be dose related.

Table 1: Incidence of serious cardiac adverse events

| Preferred Term | Number of Serious Adverse Events | | | | | | | | | |
|-----------------------|----------------------------------|-----------------|------------|------------|------------|------------|------------|------------|----------------------|------------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 2 | 4 | 8 | 12 | 16 | 32 | 50 | 70 |
| Total | 3 | 3 | 18 | 8 | 1 | 3 | 4 | 1 | 1 | 2 |
| N (%) | (1) | (2) | (3) | (1) | (1) | (8) | (3) | (1) | (1) | (3) |
| Atrial fibrillation | | 1 | 4 | | | | | | | |
| Cardiac arrest | | | | 1 | | | | | | |
| Cardiogenic shock | | 1 | | | | | | | | |
| EMD | | | | 1 | | | | | | |
| Myocardial infarction | | 1 | | | | | | | | |
| Vent. tachycardia | | | 1 | | | | | | | |
| QTc prolonged | 2 | | 12 | 6 | 1 | 3 | 4 | 1 | | |

These findings suggest that continued monitoring of cardiac adverse events is warranted in the post-marketing period and, therefore, a Phase 4 commitment to conduct a study comparing cardiac adverse events in patients treated with (b) (4) versus other reversal agents and no reversal agents has been recommended.

The Applicant reported a number of adverse events as hypersensitivity reactions. Further investigation into the nature of these events and consultation with the Division of Pulmonary and Allergy Products (DPAP) has led to the conclusion that these reactions met the criteria for being anaphylactic. While the reactions experienced by subjects in the clinical trial did not appear to be life threatening, the mechanism of these events has not been elucidated and there is, therefore, no way to predict who is likely to experience such reactions and whether or not life-threatening reactions will occur. Based on the size of the safety database, it would appear that, at a minimum, between 0.1 and 0.25% of patients are likely to experience anaphylaxis upon receiving (b) (4). The Applicant indicated in their Risk Management Plan that they anticipated 1.5 million exposures to (b) (4) in the first full year of marketing in the United States increasing to 3.8 million exposures by the fourth year of marketing. Such widespread use of the product makes the incidence rates for anaphylaxis observed in the clinical trials makes a source of considerable concern for safety. Therefore, further investigation is necessary to elucidate the mechanism of action for these events, to determine the level of risk posed by this reaction, and to determine whether it is possible to identify populations who may be at greatest risk for experiencing an anaphylactic reaction on exposure to (b) (4). It is recommended that the investigation into each of these areas be completed prior to further consideration of the approval of this product.

Related to the anaphylactic reactions is the potential for patients to be sensitized on their first, reaction-free, exposure to (b) (4) and then suffer an anaphylactic reaction on re-exposure some time in the future. In addition, one subject experienced an anaphylactic reaction without previous exposure to (b) (4) raising the concern that cross sensitization with other drug products may be possible. Due to the anticipated widespread use of this product, it is important that this issue also be addressed, and it is recommended that it be addressed prior to further consideration of the approval of this product including the repeat dosing study recommended by DPAP.

There is an additional safety concern related to the effects of (b) (4) on coagulation, which has not been fully vetted by the Applicant. Specifically, the Applicant has conducted two *in-vitro* studies to assess the effects of (b) (4) on aPTT, PT and INR rather than collect data from subjects undergoing surgical procedures and from whom blood samples were collected to assess other laboratory parameters. The Applicant noted that the results of those studies indicated a significant increase in each of the parameters when the samples contained concentrations of (b) (4) comparable to those seen in subject who were administered 16 mg/kg doses. The Applicant reported that the elevated values were still within the normal ranges reported for the laboratory where the measurements were made. In an effort to determine whether there was a clinical impact from these changes, aggregated data from the Phase 2 and 3 trials were evaluated for adverse events related to hemorrhage. Overall, there were such events reported in 6% of (b) (4) treated subjects but only in 3% of placebo-treated subjects. By limiting the preferred terms and expanding the (b) (4) treatment group to the Total (b) (4) group, the difference between treatment groups dropped to 0.5%. Most important however were the statements by the Applicant that the mechanism of interference is unknown and that “it is unknown what the clinical relevance of this is.” Due to the safety concerns related to postoperative bleeding and the need for some patients to be anticoagulated postoperatively, it is imperative that the

mechanism by which (b) (4) affects coagulation and the extent to which it affects bleeding in patients be elucidated prior to the product being approved for marketing.

The most frequently occurring individual adverse events with an incidence $\geq 2.0\%$ in the Total (b) (4) group included dysgeusia (12.6%), headache (4.7%), nausea (4.5%), application site irritation (3.2%), abdominal pain (2.3%), dizziness (2.0%), and pharyngolaryngeal pain (2.0%). Of these, dysgeusia, nausea, abdominal pain and dizziness occurred at least twice as frequently with (b) (4) than with placebo. Adverse events related specifically to the indication for (b) (4) include delayed reversal, inadequate reversal of the NMBA and return of neuromuscular blockade following reversal. The majority of cases of reoccurrence of blockade or residual blockade (83%) occurred in subject receiving < 2 mg/kg of (b) (4) however two subjects who received 2 mg/kg doses and one subject who received a 16 mg/kg dose had evidence of residual blockade or reoccurrence of blockade. These three cases represented 0.2% of all subjects exposed to the proposed-labeling doses. Delayed reversal was defined as a reversal time that exceeded the cutoff of three times the mean recovery time; in all, 31 subjects (2.1%) met that criterion. While the Applicant attributed some of those cases to problems with the monitoring system, the clinical significance of this finding is expected to be relatively small unless evidence can be provided that the rapid reversal of blockade in some situation(s) can reduce morbidity or mortality.

(b) (4) represents a new means of reversing the effects of two of the more commonly used NMBAs. It has been shown to significantly reduce the time to return of normal function at the neuromuscular junction; however, a clinical benefit to this reduction compared to that of the currently used products has not been demonstrated. The safety profile for (b) (4) has not been fully elucidated at this point in time, and some of the risks associated with its use could outweigh the benefit demonstrated thus far. The Applicant has proposed that (b) (4) might provide a means of dealing with one of the biggest safety concerns in anesthesia, i.e., the situation in which a paralyzed patient cannot be adequately ventilated and cannot be intubated. While there are multiple approaches to dealing effectively with this scenario, there is no evidence that reversing neuromuscular blockade will provide any benefit, even though it is widely believed, by members of the anesthesia community, members of the Advisory Committee and this reviewer. Provision of evidence in this regard could significantly alter the benefit-risk analysis for (b) (4).

1.3.4 Dosing Regimen and Administration

The Applicant has proposed the following dosing regimen:

“For routine reversal:

- A dose of 4.0 mg/kg (b) (4) is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.

(b) (4) (sugammadex sodium injection)

- A dose of 2.0 mg/kg (b) (4) is only recommended if spontaneous recovery has reached the reappearance of T₂ (shallow blockade) following rocuronium or vecuronium induced blockade.

For immediate reversal:

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4) is recommended.”

1.3.5 Drug-Drug Interactions

(b) (4) is a substituted gamma-cyclodextrin molecule that was designed to bind the steroid nucleus of rocuronium and vecuronium. It also has the ability to bind other steroid hormones and certain heavy metals, although these substances bind with a lower affinity. In his review of efficacy, Dr. Shibuya noted that some patients who had prolonged reversal times following the administration of (b) (4) were concomitantly exposed to steroid drugs. In addition, the Applicant has noted the potential for (b) (4) to interact with steroid-based contraception pills and has proposed labeling that treats exposure of (b) (4) as the equivalent of a missed dose.

1.3.6 Special Populations

(b) (4) is almost completely renally excreted thereby raising a concern for its use in patients with renal impairment. The Applicant has conducted studies involving subjects with differing degrees of renal impairment including older patients, patients with documented renal impairment, and patients with cardiac and pulmonary disease. These studies provided evidence that (b) (4) was similarly efficacious in all these subjects although the pharmacokinetics were altered (higher C_{max}, higher AUC) in the patients with renal impairment.

Subjects with hepatic impairment have not been evaluated following exposure to (b) (4). Although (b) (4) is renally excreted, rocuronium is primarily excreted by the liver and 80% of vecuronium is eliminated by hepatic excretion and metabolism. The significance of hepatic impairment on the efficacy and dosing needs of (b) (4) has not been fully elucidated.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

(b) (4) is a new molecular entity; specifically, it is a gamma-cyclodextrin structure with a lipophilic core and a hydrophilic outer surface, which has eight side-chains each connected to a sugar unit of the cyclodextrin. The ring is large enough to surround a single molecule of either rocuronium or vecuronium, both of which have a lipophilic steroidal portion that is attracted by the lipophilic core of (b) (4). Once rocuronium or vecuronium has entered the lipophilic core of (b) (4) the negatively charged sugar groups are attracted to the positively charged ammonium group of rocuronium or vecuronium. As a result of van der Waal's forces, hydrophobic and electrostatic interactions, tight binding occurs between the NMBA molecule and the (b) (4) molecule. Formation of NMBA-(b) (4) complexes reduces the amount of the NMBA available to bind to nicotinic receptors in the neuromuscular junction, and hence results in the reversal of neuromuscular blockade.

Organon is seeking approval to market (b) (4) for routine reversal of "shallow" and "profound" neuromuscular blockade (NMB) induced by rocuronium or vecuronium, and "immediate reversal" of NMB at 3 minutes after administration of rocuronium. Specifically, Organon is proposing the following indications:

For routine reversal:

- A dose of 4.0 mg/kg (b) (4) is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.
- A dose of 2.0 mg/kg (b) (4) is only recommended if spontaneous recovery has reached the reappearance of T2 (shallow blockade) following rocuronium or vecuronium induced blockade.

For immediate reversal:

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4) is recommended.

2.2 Currently Available Treatment for Indications

Two products, pyridostigmine (NDA 17-398) and edrophonium (NDA 7-959), are approved as reversal agents for the neuromuscular blocking effects of all available nondepolarizing muscle relaxants. However, these anticholinesterase agents are not widely used because of their relatively long onset of action. In the United States, neostigmine is the most commonly used reversal agent; however, it is an unapproved product. Neostigmine is preferred in clinical

practice because of its more rapid onset of action. Glycopyrrolate, an anticholinergic agent with a pharmacokinetic profile similar to that of neostigmine is frequently co-administered to counter the cholinergic effects.

2.3 Availability of Proposed Active Ingredient in the United States

This product is not currently marketed in either this country or abroad.

2.4 Important Issues With Pharmacologically Related Products

Two products are approved for the reversal of neuromuscular blockade, edrophonium and pyridostigmine; however, the most commonly used product is neostigmine, which has never been approved for use in the United States. All of these products are anticholinesterases that bind to acetylcholinesterase. They all, therefore, have muscarinic and nicotinic effects. The muscarinic stimulation leads to salivation, bradycardia, tearing, miosis and bronchoconstriction. These undesirable effects are mitigated, if not totally eliminated, by the concomitant administration often antimuscarinic agent, either atropine or, more often, glycopyrrolate.

While sugammadex is the first gamma-cyclodextrin considered for approval, there are several beta-cyclodextrin products that have been approved as antifungal agents. These agents, which include Geodon (ziprasidone hydrochloride), Sporanox IV (itraconazole), and Vfend IV (voriconazole), have all been associated with anaphylactic reactions that have been reported to the AERS database. Whether or not there is any cross reactivity between these agents and sugammadex, in terms of anaphylactic responses, has not been investigated by the Applicant.

2.5 Presubmission Regulatory Activity

Please refer to clinical review of Robert Shibuya, MD, for this information.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Please refer to clinical review of Robert Shibuya, MD, for summaries of the significant findings from these disciplines. For detailed evaluation of the NDA submission regarding the chemistry, manufacturing and controls content, the reader should consult the reviews of Drs. Alan Schroeder, Danae Christodoulou and Ali Al Hakim. For detailed evaluation regarding pharmacology-toxicology content, the reader should consult the reviews of Drs. Zenguin (Alex) Xu and Adam Wasserman.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Please refer to clinical review of Robert Shibuya, MD, for this information. Dr. Shibuya performed the clinical review of efficacy; this review is limited to evaluation of the safety data from the product's development plan and an assessment of the benefit-risk ratio based on the contents of the NDA submission, the amendments made thereto, and the input provided by the Anesthesia and Life-Support Drugs Advisory Committee and the Division of Allergy and Pulmonary Drug products.

5 CLINICAL PHARMACOLOGY

Please refer to clinical review of Robert Shibuya, MD, and the Clinical Pharmacology reviews of Drs Lei Zhang and Atul Bhattaram for this information.

6 INTEGRATED REVIEW OF EFFICACY

The evidence submitted in support of a finding of efficacy for this NDA was evaluated by Robert Shibuya, M.D. The reader is referred to his review for the information normally contained in this section and detailed reviews of the key clinical efficacy studies conducted by the Applicant.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Methods

Safety data were collected in the 28 trials conducted during the (b) (4) clinical development program. The Applicant choose to divide four of these trials into two parts (listed as: 19.4.101 part 1, 19.4.101 part 2, 19.4.109 groups A&F, 19.4.109 groups C, D &E, 19.4.208 A, 19.4.208 B, 19.4.209 A, and 19.4.209 B) referring to each as an individual trial and thereby indicating that the clinical development plan included 32 trials. From these, the Applicant generated two datasets for the integrated analysis of safety, which are described below. In addition, safety information from a pediatric trial and a sensitization study, both of which were conducted outside of the United States, were submitted with the 120-day safety update and are considered separately.

1. **Pooled Phase 1-3:** Data were pooled from the 26 trials in which (b) (4) or placebo were administered following a neuromuscular blocking agent (NMBA) (rocuronium, vecuronium or pancuronium). This dataset included 1926 subjects (1845 unique subjects) who received (b) (4) and an NMBA, and 140 unique subjects who received placebo and an NMBA and allowed for an analysis of dose response, with particular interest on the proposed marketing doses of (b) (4) 2.0 mg/kg, 4.0 mg/kg and 16 mg/kg. Within this dataset, two additional subsets were generated:
 - a. (b) (4) **vs. Neostigmine:** Data were pooled from the two Phase 3 trials in which (b) (4) (N = 179) was directly compared to neostigmine (N = 167), the most widely used NMBA reversal agent.
 - b. (b) (4) **vs. Placebo:** Data were pooled from the 10 trials that included a placebo group in order to compare the safety of (b) (4) (n=640) vs. placebo (n=140). This dataset was used by the Applicant for identifying potential adverse drug reactions.
2. **Pooled Phase 1:** The Phase 1 pooled dataset included data from six trials. All but one of these Phase 1 trials were randomized, double-blind, crossover trials in which healthy adult volunteers received single doses of trial medication but no anesthetic or NMBA. The other trial was an open-label, nonrandomized, single-center trial to determine the excretion balance, metabolite profile, and pharmacokinetics of an intravenous dose of ¹⁴C-labeled (b) (4). The pooled Phase 1 dataset includes 443 subjects (209 unique subjects) who received (b) (4) and 196 unique subjects who received placebo.

The Applicant reported that blinding for efficacy was not possible in the trials in which an NMBA was administered prior to (b) (4) since the effect of the reversal agent was observed via a twitch monitor (TOF-Watch SX®) and through visual inspection of the subjects' clinical status. However, except for two of the trials, all were safety-assessor blinded for the subjective safety assessments (i.e., the safety assessor did not administer study drug).

In general, safety was assessed across trials by the reporting of adverse events (AEs), and assessment of changes from baseline in clinical laboratory values, vital signs, and electrocardiograms (ECGs). All AEs in the integrated database were coded to MedDRA version 10.0. It was noted by the Applicant that there were some differences between the coding in the integrated database compared to some of the individual trial reports, specifically, Trials 19.4.101, 19.4.201, and 19.4.202, which were originally coded to WHO-ART.

In addition to the assessment of AEs, potential adverse drug reactions (ADRs) were identified during the (b) (4) clinical development program. These were defined as any AE that:

- was considered by the Applicant to be related to (b) (4)
- showed a dose-response;
- occurred in the Total (b) (4) group with a frequency of 2% or more and at least twice as often as compared to the placebo group (for these events a medical assessment was made taking also into consideration the Investigator's opinion of causality and the intensity of the AE);
- was biologically plausible, irrespective of incidence, including any events that were very likely to be associated with the compound based on its known pharmacological actions, preclinical experiments (animal or lab tests), or previous experience in clinical trials.; and/or
- was considered to be an SAE for which a causal relationship could not be excluded and which could be clinically relevant in the anticipated setting in which (b) (4) will be utilized.

In addition, events particularly relevant to the use of anesthesia in general and reversal agents in particular were assessed. These included:

- reoccurrence of blockade and residual blockade based on the TOF Watch SX® measurements;
- anesthetic complications, which included the following preferred terms [with examples of verbatim terms]:
 - anesthetic complication (movement [of a limb or the body], coughing during the anesthetic procedure or during surgery, grimacing, suckling the endotracheal tube, including AEs that in MedDRA versions prior to 10.0 were coded to the preferred term of "light anesthesia"),
 - airway complications of anesthesia (coughing on induction, bucking, and spontaneous breathing),
 - delayed recovery from anesthesia (delayed awakening from anesthesia or extended recovery from anesthesia),
 - unwanted awareness during anesthesia (awareness during anesthesia, awake during operation), and
 - anesthetic complication cardiac (changes in cardiac rate and rhythm).
- AEs associated with ventilation, i.e., preferred terms not specifically noted to involve an anesthetic complication; and
- allergic reactions.

(b) (4) (sugammadex sodium injection)

In addition to events particularly relevant to the use of anesthesia and reversal agents, special attention was also focused on the effect of (b) (4) on renal function because the drug is nearly exclusively removed via the kidneys.

In order to fulfill the requirements for a thorough analysis of (b) (4) effects on the QTc interval, two prospective, thorough, QTc trials (Trials 19.4.109 and 19.4.105) were conducted as part of the clinical development program. Trial 19.4.109 was conducted in non-anesthetized healthy volunteers who received (b) (4) both with and without an NMBA. Trial 19.4.105 was conducted in non-anesthetized healthy volunteers who received (b) (4) without an NMBA. In addition to the two QTc interval trials, electrocardiographic data were collected in ten of the 26 trials in which subjects received an NMBA in addition to the trial medication. Electrocardiographic data from eight of these trials (Trials 19.4.101 [Part II only], 19.4.202, 19.4.204, 19.4.205, 19.4.206, 19.4.210, 19.4.306, and 19.4.309) were pooled and analyzed for treatment related abnormalities.

Findings

Safety data collected across all 30 trials conducted during the clinical development program suggest that (b) (4) is generally safe and well tolerated. Two deaths occurred in (b) (4) treated subjects following their trial participation; neither death was considered to be related to (b) (4). The pattern and incidence of serious adverse events (SAEs) did not appear to be notably different in (b) (4) treated subjects compared with placebo- and neostigmine-treated subjects. The most commonly reported AEs in (b) (4) treated subjects were routinely managed events that were typically seen in a surgical or a post-surgical population. Four out of 1926 subjects treated with (b) (4) experienced reoccurrence of blockade (based on TOF Watch SX[®] measurements) at the proposed marketed doses (two subjects treated with 2.0 mg/kg and two subjects treated with 16.0 mg/kg); all other cases occurred at sub-optimal doses (< 2.0 mg/kg) of (b) (4).

With two exceptions, the incidence of AEs and SAEs did not appear to be related to the dose of (b) (4) administered. The adverse events “anesthetic complication” and dysgeusia were reported by the Applicant as drug-related AEs that appeared to be dose-related. Dysgeusia was reported primarily among healthy non-anesthetized volunteers enrolled in the Phase 1 trials.

Three percent of all subjects in the Total (b) (4) group experienced an “anesthetic complication.” These typically occurred during trials in which (b) (4) was administered during the surgical procedure, thereby removing one of the components of balanced anesthesia. As a result, the level of anesthesia may not have been deep enough for the ongoing surgical procedure. Airway complications, delayed recovery from anesthesia, unwanted awareness during anesthesia, and cardiac-related anesthetic complications in (b) (4) treated subjects occurred at low incidences and/or occurred at incidences that were comparable to or lower than incidences observed in neostigmine-treated subjects. Few AEs (and SAEs) related to ventilation were reported. One subject (a healthy volunteer) had a possible allergic reaction following his first exposure to (b) (4) and six Phase 1 subjects showed signs of possible hypersensitivity to (b) (4) one of whom had a known allergy to penicillin. Additional subjects exhibited signs of hypersensitivity in trials completed abroad following the original submission of the NDA.

Overall in the development program, there were large imbalances in the numbers of subjects across demographic subgroups. However, the incidences of AEs of special interest that the Applicant considered as adverse drug reactions (ADRs) [anesthetic complications, dysgeusia, allergic reactions, hypersensitivity reactions, and reoccurrence of blockade/residual blockade] were similar with respect to age, gender, ethnicity, and race among subgroups who received (b) (4). Subjects with impaired renal function were also studied. (b) (4) is predominantly cleared via the kidneys; therefore, renal impairment would be expected to increase subjects' exposure to (b) (4) and the NMBA. In Trial 19.4.304, renally impaired subjects had a prolonged and 17-fold higher exposure to (b) (4) and a prolonged and 4-fold higher exposure to rocuronium compared to subjects with normal renal function. The Applicant reported that the safety profiles between subjects with normal renal function versus subjects with impaired renal function were not appreciably different. This was an important finding as effective dialysis was not consistently demonstrated in the trial.

Extensive data collected from nonclinical trials and the population PK-PD simulations only identified three specific drugs (toremifene, flucloxacillin and fusidic acid) and a class of compounds (hormonal contraceptives) that may potentially interact with (b) (4). No potential drug interactions were reported in any of the clinical trials.

The Applicant reported that clinical laboratory assessments revealed changes in hematological parameters in subjects who received an NMBA in the pooled Phase 2 and Phase 3 trials. The Applicant indicated that the observed changes occurred in a direction and of a magnitude as would be expected for a population of surgical subjects. This observation was supported in part in that no dose trends were observed for any of the hematology parameters, and the incidence of hematology-related AEs was low overall. In addition, no dose trends were observed for any of the biochemistry parameters assessed, and the incidence of biochemistry-related AEs was low overall. Laboratory data indicative of kidney function showed no evidence of renal damage in subjects after the administration of (b) (4). In addition, biochemistry results showed no clinically important effects of (b) (4) on the liver.

The Applicant indicated that no clinically relevant findings related to the administration of (b) (4) were observed on vital signs. Based on the pooled Phase 1-3 data, as well as the two thorough QTc trials, the Applicant concluded that it is unlikely that (b) (4) will have a clinically important effect on the ECG.

7.1.1 Deaths

Three subjects in the clinical trials died following administration of study drug: two had received (b) (4) and one had received placebo. Of the two subjects who died after exposure to (b) (4) one subject, #203104007, received a 0.5 mg/kg dose, and the other subject, #208107008, received a 2.0 mg/kg dose. The subject who received placebo was #309107003. In each case,

the subject's death occurred after the trial was completed, and each death was judged to be unrelated to treatment with the trial medication by both the Investigator and the Applicant.

Subject 203104007 participated in trial 19.4.203 ((b) (4) 0.5 mg/kg dose group) and was a 65-year-old Caucasian female who died 42 days after surgery and the administration of (b) (4). She presented for an anterior resection of carcinoma of the large intestine. Her past medical history was significant only for hypertension, peptic ulcer and rheumatoid arthritis. From the data in her Case Report Form (CRF), it appears there were no surgical complications and the procedure lasted approximately 3 hours. At approximately 23 hours following the end of surgery, the patient experienced atrial fibrillation and respiratory failure. She was reported to have "recovered with sequelae" from these events. The list of concomitant medications administered following surgery included therapies for post-operative pain (including epidural infusions of fentanyl and levobupivacaine) and nausea, prophylaxis for deep vein thrombosis, and treatment of adrenal suppression (dexamethasone 5 mg IV administered 3 hours after the (b) (4) no medications for the treatment of either atrial fibrillation or respiratory failure were listed. Her death was attributed to a combination of factors, including myocardial infarction, cardiogenic shock, and pulmonary edema. According to the investigator, these post-trial SAEs were unlikely related to the trial medication. The Investigator and the Applicant judged the subject's death as not related to the trial medication; however, this reviewer believes that (b) (4) cannot be ruled out for having contributed to the subject's demise. This belief is based on the lack of data between 3 and 23 hours postdose during which time the subject began to experience atrial fibrillation and respiratory failure. As she experienced sequelae from these events, to the extent that (b) (4) contributed to the occurrence of either adverse event, it was related to the outcome.

Subject 208107008 in trial 19.4.208B ((b) (4) 2 mg/kg dose group), a 61-year-old male Caucasian, died 18 days after surgery and the administration of (b) (4) due to a pulmonary embolus. The subject had no previous medical history except for his diagnosis of prostate cancer. He underwent a radical prostatectomy with radical iliacal lymphadenectomy that were complicated by an intraoperative 1-cm perforation of the colon. The perforation was surgically repaired and the patient was prophylactically treated with antibiotics. The patient was discharged 6 days following surgery with a surgical drain *in situ*. The drain was reported to have been removed a "few days" after surgery. The subject was reported to have "felt tired" 11 or 12 days post-operatively and was ultimately hospitalized on post-operative day 15, at which time he was diagnosed as having a pulmonary embolus. Due to his recent surgery, he was considered to have unacceptable risks for thrombolytic therapy and was, therefore, treated with low molecular weight heparin. The subject died two days later. According to the Investigator, thrombosis and embolus were complications of the subject's surgical procedure, and pelvic thrombosis was a known complication of surgery of the lower abdomen. Given the nature of the surgery and the reported time sequence, the causal relationship for this SAE and death were assessed as "not related" by the Applicant. This reviewer concurs with the Applicant's assessment.

Subject 309107003 in trial 19.4.309 (placebo group) was a 73-year-old male Caucasian who died 12 days after surgery and the administration of the trial medication. He had undergone a craniotomy for resection of a cerebral meningioma. His past medical history was significant for myocardial infarction, post-infarction angina pectoris, status post CABG, hypertension,

(b) (4) (sugammadex sodium injection)

meningioma with visual deficits, headache, and reduced cognitive functioning. On post-operative day 1, the patient was reported to have had a > 60 msec prolongation of QTc, which was not treated. CT scans performed at 2, 5, 9 and 10 days post-operatively showed edema, intraventricular and subarachnoidal blood, and midline shifts which worsened to the point of suspected subfalx and transtentorial herniation. He died on post-operative day 11; the cause of death was listed as cerebral edema and ventricular bleeding with hydrocephalus. Autopsy results showed a lesion in the left middle cerebral artery that had been caused by the surgery during removal of a meningioma. The Investigator and the Applicant judged the subject's death as not related to the trial medication. This reviewer concurs with the Applicant's assessment.

(b) (4)

7.1.2 Other Serious Adverse Events

A total of 182 Serious Adverse Events (SAEs) experienced by 126 adult subjects were reported for the development program, which included 2708 exposures to (b) (4). One hundred fifty one of these SAEs occurred in 106 of the 1845 subjects who were treated with (b) (4). SAEs were categorized by the Applicant as treatment-emergent, i.e., those that occurred within seven days of the administration of the study medication, or not treatment emergent. SAEs were evaluated by temporal relation to study drug (treatment emergent or not treatment emergent), as well as in the context of the type of comparator used (placebo versus neostigmine), whether a neuromuscular blocking agent (NMBA) was used (rocuronium, vecuronium, or pancuronium), and pooled Phase 1-3 dose responses. These categories are utilized in this review as well. In the two tables below, the SAEs are summarized by drug and dose for occurrences overall (Table 2) and by the preferred terms for the adverse events (Table 3).

Table 2: Occurrence of SAEs among adult subjects in the clinical development program

| | | Incidents of Serious Adverse Events ^A Reported for Adult Subjects | | | | | | | | | | | |
|----------------|------------------|--|----------|------------|-----------|-----------|----------|----------|----------|----------|----------|------------------------|----------|
| | | N (%) | | | | | | | | | | | |
| Treatment | Placebo N=140 | (b) (4) N=640 (mg/kg) | | | | | | | | | | Neostigmine (mg/kg) | |
| Dose | N/A | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 0.05 | 0.07 |
| Number of SAEs | 10 (7) | 13 (11) | 7 (4) | 73 (12) | 1 (11) | 41 (7) | 2 (7) | 4 (3) | 3 (8) | 6 (6) | 1 (1) | 6 (7) | 6 (8) |

^A Not included in this table are nine SAEs that occurred in subjects who did not receive (b) (4) placebo or the active comparator, neostigmine. These included one SAE that occurred with moxifloxacin, one that occurred with succinylcholine and seven SAEs, among 4 subjects, that occurred prior to and, therefore, precluded administration of study drug.

Table 3: Serious Adverse Events by System Organ Class and Preferred Term

| System Organ Class Preferred Term | Number of Serious Adverse Events | | | | | | | | | | | | |
|---|----------------------------------|-----------------|----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------------------|----------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Blood and lymphatic system disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Anemia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Disseminated intravascular coagulation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>1</i> | <i>3</i> | <i>0</i> | <i>6</i> | <i>0</i> | <i>2</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Acute myocardial infarction | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atrial fibrillation | 0 | 1 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiac arrest | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cardiogenic shock | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Coronary artery disease | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Electromechanical dissociation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Myocardial infarction | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ventricular tachycardia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Vertigo | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Eye disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Retinal detachment | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastrointestinal disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>1</i> | <i>3</i> | <i>3</i> | <i>10</i> | <i>0</i> | <i>4</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>1</i> | <i>2</i> |
| Abdominal hematoma | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal hernia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Constipation | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gastric perforation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Gastrointestinal hemorrhage | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Glossodynia | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ileus | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ileus paralytic | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intestinal perforation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Large intestine perforation | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(b) (4) (sugammadex sodium injection)

| System Organ Class Preferred Term | Number of Serious Adverse Events | | | | | | | | | | | | |
|---|----------------------------------|-----------------|----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------------------|----------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Mechanical ileus | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Small intestinal perforation | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Subileus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Swollen tongue | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Upper gastrointestinal hemorrhage | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| General disorders and administration site conditions | | | | | | | | | | | | | |
| Total | 0 | 0 | 0 | 3 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Catheter related complication | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Localized edema | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Pyrexia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and infestations | | | | | | | | | | | | | |
| Total | 1 | 0 | 1 | 4 | 0 | 6 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Abdominal abscess | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Candidiasis | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cellulitis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Device related infection | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infection | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intrauterine infection | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Labyrinthitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Meningitis | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pneumonia hemophilus | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post procedural infection | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Sepsis | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Splenic abscess | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | | | | | | | | | | | |
| Total | 2 | 2 | 0 | 16 | 0 | 5 | 0 | 2 | 0 | 2 | 0 | 2 | 2 |
| Airway complication of anesthesia | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| Anastomotic complication | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Anastomotic leak | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Colon injury | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(b) (4) (sugammadex sodium injection)

| System Organ Class Preferred Term | Number of Serious Adverse Events | | | | | | | | | | | | |
|--|----------------------------------|-----------------|----------|-----------|----------|----------|----------|----------|----------|----------|----------|----------------------|----------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Contusion | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Forearm fracture | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Incision site hemorrhage | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Operative hemorrhage | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Overdose | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Peroneal nerve injury | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post procedural complication | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post procedural diarrhea | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post procedural hematoma | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Post procedural hemorrhage | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |
| Postoperative fever | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Postoperative ileus | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Procedural complication | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 |
| Procedural hypotension | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Procedural pain | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Seroma | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Investigations | | | | | | | | | | | | | |
| <i>Total</i> | 2 | 0 | 0 | 14 | 0 | 6 | 0 | 1 | 3 | 4 | 1 | 0 | 0 |
| ECG QT corrected interval prolonged | 2 | 0 | 0 | 12 | 0 | 6 | 0 | 1 | 3 | 4 | 1 | 0 | 0 |
| Oxygen saturation decreased | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | | | | | | | | | | | |
| <i>Total</i> | 0 | 0 | 0 | 1 | 0 | 0 |
| Hypocalcaemia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | | | | | | | | | | | |
| <i>Total</i> | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Compartment syndrome | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Muscle hemorrhage | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified | | | | | | | | | | | | | |
| <i>Total</i> | 0 | 0 | 0 | 1 | 0 | 0 |
| Metastatic carcinoma of the bladder | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nervous system disorders | | | | | | | | | | | | | |
| <i>Total</i> | 3 | 0 | 0 | 3 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

(b) (4) (sugammadex sodium injection)

| System Organ Class Preferred Term | Number of Serious Adverse Events | | | | | | | | | | | | |
|--|----------------------------------|-----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------------------|----------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Brain edema | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cerebral infarction | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Convulsion | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysphasia | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemiparesis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hydrocephalus | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Intraventricular hemorrhage | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Radiculitis brachial | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Psychiatric disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>4</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Delirium | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Suicidal ideation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Violent ideation | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal and urinary disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>2</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>1</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Bladder tamponade | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Renal failure acute | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Urinary bladder hemorrhage | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Urinary retention | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> |
| Pelvic hematoma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | | | | | | | | | | |
| <i>Total</i> | <i>0</i> | <i>2</i> | <i>0</i> | <i>9</i> | <i>0</i> | <i>6</i> | <i>1</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>0</i> | <i>1</i> |
| Apnea | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Atelectasis | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Bronchospasm | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dyspnea | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Epistaxis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypoxia | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Laryngeal edema | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary embolism | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(b) (4) (sugammadex sodium injection)

| System Organ Class Preferred Term | Number of Serious Adverse Events | | | | | | | | | | | | |
|--|----------------------------------|-----------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------------------|----------|
| | Placebo | (b) (4) (mg/kg) | | | | | | | | | | Neostigmine (mcg/kg) | |
| | | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 32 | 50 | 70 |
| Pulmonary edema | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory depression | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory distress | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory failure | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sleep apnea syndrome | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tracheal stenosis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Surgical and medical procedures | | | | | | | | | | | | | |
| Total | 0 | 0 | 0 | 1 | 0 | 0 |
| Intubation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vascular disorders | | | | | | | | | | | | | |
| Total | 0 | 1 | 0 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Deep vein thrombosis | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hematoma | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypotension | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Peripheral arterial occlusive disease | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Peripheral ischemia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Poor peripheral circulation | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Wound hemorrhage | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

(b) (4) vs. placebo

In studies involving the use of (b) (4) and a placebo, a total of 37 subjects (6%) who received (b) (4) experienced at least one SAE, and six subjects (4%) who received placebo were reported to have experienced at least one SAE. There were no non-treatment-emergent SAEs in these studies. The most frequently reported SAE was QTc prolongation [(b) (4) 16/640 (3%); placebo: 2/140 (1%)]. This was the only difference of consequence between the two treatment groups. The individual SAEs are listed in the table below.

Table 4: Serious Adverse Events in Studies comparing (b) (4) to placebo (based on Table 55 from the NDA ISS)

| Serious Adverse Events | | Subjects with SAE N (%) | |
|--|------------------------------|----------------------------|--------------------|
| | | (b) (4) (N=640) | Placebo (N=140) |
| System Organ Class | Preferred Term | | |
| All | Total | 37 (6) | 6 (4) |
| | | | |
| Investigations | Total | 16 (3) | 2 (1) |
| | QTc interval prolonged | 16 (3) | 2 (1) |
| Gastrointestinal disorders | Total | 7 (1) | 1 (1) |
| | Small intestinal perforation | 2 (0) | 0 (0) |
| | Constipation | 1 (0) | 1 (1) |
| | Abdominal hematoma | 1 (0) | 0 (0) |
| | Glossodynia | 1 (0) | 0 (0) |
| | Ileus paralytic | 1 (0) | 0 (0) |
| | Large intestine perforation | 1 (0) | 0 (0) |
| | Swollen tongue | 1 (0) | 0 (0) |
| Injury, poisoning and procedural complications | Total | 4 (1) | 1 (1) |
| | Post procedural hemorrhage | 1 (0) | 1 (1) |
| | Incision site hemorrhage | 1 (0) | 0 (0) |
| | Post procedural diarrhea | 1 (0) | 0 (0) |
| | Post procedural hematoma | 1 (0) | 0 (0) |
| Infections and infestations | Total | 3 (0) | 1 (1) |
| | Intrauterine infection | 1 (0) | 0 (0) |
| | Labyrinthitis | 1 (0) | 0 (0) |
| | Pneumonia hemophilus | 1 (0) | 0 (0) |
| | Post procedural infection | 0 (0) | 1 (1) |
| Nervous system disorders | Total | 1 (0) | 1 (1) |
| | Cerebral infarction | 1 (0) | 0 (0) |
| | Dysphasia | 1 (0) | 0 (0) |
| | Hemiparesis | 1 (0) | 0 (0) |

(b) (4) (sugammadex sodium injection)

| | | | |
|--|-----------------------------|-------|-------|
| | Brain edema | 0 (0) | 1 (1) |
| | Hydrocephalus | 0 (0) | 1 (1) |
| | Intraventricular hemorrhage | 0 (0) | 1 (1) |
| | | | |
| Cardiac disorders | Total | 2 (0) | 1 (1) |
| | Cardiac arrest | 1 (0) | 0 (0) |
| | Ventricular tachycardia | 1 (0) | 0 (0) |
| | Acute myocardial infarction | 0 (0) | 1 (1) |
| | | | |
| Vascular disorders | Total | 2 (0) | 0 (0) |
| | Hematoma | 1 (0) | 0 (0) |
| | Hypotension | 1 (0) | 0 (0) |
| | | | |
| Renal and urinary disorders | Total | 1 (0) | 0 (0) |
| | Bladder tamponade | 1 (0) | 0 (0) |
| | Urinary bladder hemorrhage | 1 (0) | 0 (0) |
| | | | |
| Ear and labyrinth disorders | Total | 1 (0) | 0 (0) |
| | Vertigo | 1 (0) | 0 (0) |
| | | | |
| Musculoskeletal and connective tissue disorders | Total | 1 (0) | 0 (0) |
| | Muscle hemorrhage | 1 (0) | 0 (0) |
| | | | |
| Respiratory, thoracic and mediastinal disorders | Total | 1 (0) | 0 (0) |
| | Pulmonary embolism | 1 (0) | 0 (0) |

Due to the relatively low number of SAEs, it was not possible to judge if the incidence of SAEs was influenced by the type of neuromuscular blocking agent (NMBA) administered. All SAEs of “electrocardiogram QT corrected interval prolonged” (in both treatment groups) occurred only in subjects who received rocuronium. However, ECG data were not collected in three of the four trials in which subjects received the trial medication plus vecuronium as an NMBA (19.4.207, 19.4.208A, and 19.4.208B). Among the available data for (b) (4) plus vecuronium, there were no SAEs of QTc prolongation in any (b) (4) or placebo-treated subjects who received vecuronium in trial 19.4.109 (although one incident of prolongation was reported in subject 109101064 following the infusion of moxifloxacin).

In the small, uncontrolled (b) (4) plus pancuronium treatment arm in study 19.4.207, two (11%) subjects experienced SAEs. These included abdominal abscess, candidiasis, and small intestinal perforation. None was considered as related to the trial medication per the Investigator.

(b) (4) vs. neostigmine

In the Phase 3 trials comparing (b) (4) to neostigmine (19.4.301 and 19.4.302), the incidence of SAEs was similar for (b) (4) (3%) and neostigmine (4%). Only one of the SAEs was reported as

(b) (4) (sugammadex sodium injection)

“not treatment-emergent;” this was a post-procedural infection in a 4 mg/kg (b) (4) treated subject. The table below lists the SAEs by neuromuscular blocking agent and reversal agent used.

Table 5: Serious Adverse Events in studies involving neostigmine as a comparator (based on table 58 from NDA ISS)

| Serious Adverse Event | | Rocuronium + | | Vecuronium + | | Rocuronium or Vecuronium + | |
|---|---------------------------------------|-------------------|--------------------|-------------------|--------------------|----------------------------|---------------------|
| SOC | PT | (b) (4) (N=85) | Neostig. (N=86) | (b) (4) (N=94) | Neostig. (N=81) | (b) (4) (N=179) | Neostig. (N=167) |
| Total with at least one SAE | | 4 (5) | 6 (7) | 2 (2) | 0 (0) | 6 (3) | 6 (4) |
| Injury, poisoning and procedural complications | Total | 3 (4) | 3 (3) | 0 (0) | 0 (0) | 3 (2) | 3 (2) |
| | Post procedural hemorrhage | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 2 (1) | 0 (0) |
| | Post-operative ileus | 1 (1) | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 1 (1) |
| | Procedural complication | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 2 (1) |
| Infections and infestations | Total | 1 (1) | 1 (1) | 1 (1) | 0 (0) | 2 (1) | 1 (1) |
| | Post procedural infection | 1 (1) | 1 (1) | 0 (0) | 0 (0) | 1 (1) | 1 (1) |
| | Splenic abscess | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 1 (1) | 0 (0) |
| Respiratory, thoracic and mediastinal disorders | Total | 0 (0) | 1 (1) | 1 (1) | 0 (0) | 1 (1) | 1 (1) |
| | Atelectasis | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 1 (1) | 0 (0) |
| | Dyspnea | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Gastrointestinal disorders | Total | 0 (0) | 3 (3) | 0 (0) | 0 (0) | 0 (0) | 3 (2) |
| | Gastric perforation | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| | Nausea | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| | Sub-ileus | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| Vascular disorders | Total | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| | Peripheral arterial occlusive disease | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| | Peripheral ischemia | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| General disorders and administration site conditions | Total | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |
| | Pain | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 (1) |

In summary, SAEs with an incidence $\geq 1.0\%$ were observed in the Injury, Poisoning, and Procedural Complications SOC (2% (b) (4) 2% neostigmine), Infections and Infestations SOC (1% (b) (4) 1% neostigmine), and Gastrointestinal Disorders SOC (0% (b) (4) 2% placebo). Individual SAEs by PT most often occurred in only one subject in a treatment group. Only two SAEs, post-procedural hemorrhage and procedural complication, occurred in more than one subject per group. Due to the relatively low number of SAEs, it is difficult to determine if the

incidence of SAEs was influenced by the type of NMBA administered. None of the SAEs was considered to be related to the trial medication by either the Investigator or the Applicant.

Pooled Phase 1-3 Dose Response

Overall, 5% of all subjects exposed to any dose of (b) (4) plus an NMBA (rocuronium, vecuronium, or pancuronium) experienced at least one SAE. No dose response was apparent for the overall incidence of SAEs (7.3% in the 2 mg/kg group, 4.8% in the 4 mg/kg group, and 5.1% in the 16 mg/kg group).

Drug-related (in the Investigator's opinion) SAEs were reported in 7 (0.4%) of the (b) (4) subjects in the following dose groups: < 2 mg/kg (1 subject), 2 mg/kg (1 subject), 3 mg/kg (1 subject), and 4 mg/kg (4 subjects).

The related (per the Investigator) SAEs in (b) (4) subjects included the following:

- Electrocardiogram QT corrected interval prolonged (one 2-mg/kg subject and two 4-mg/kg subjects),
- Bronchospasm (two 4-mg/kg subjects),
- Respiratory failure (one < 2-mg/kg subject),
- Hypotension (one 3-mg/kg subject), and
- Atrial fibrillation (one < 2-mg/kg subject).

The majority of the SAEs were treatment-emergent. In addition to two deaths in (b) (4) treated subjects and one in a placebo-treated subject, the following six (b) (4) treated subjects experienced a non-treatment-emergent SAE.

- Subject 308105007 (2 mg/kg) - poor peripheral circulation from Day 8 to Day 9;
- Subject 210102003 (2 mg/kg) - urinary retention from Day 9 to Day 13; (this subject also had a treatment-emergent SAE of QTc prolongation);
- Subject 308106012 (2 mg/kg) - operative hemorrhage from Day 9 to Day 11;
- Subject 302105010 (4 mg/kg) - post procedural infection from Day 10 to Day 20;
- Subject 209104001 (4 mg/kg) - meningitis from Day 11 to Day 38; (this subject also had treatment-emergent SAEs of convulsion and hypoxia); and
- Subject 209104003 (0.5 mg/kg) - wound hemorrhage from Day 32 to Day 35.

Pooled Phase 1 trials

There was one SAE (treatment-emergent) in the pooled Phase 1 trials. Subject 109101173 (a female subject who received 32 mg/kg (b) (4) alone in the third of four periods of the trial) experienced an "increase in QTcB exceeding 60 msec" (i.e., 62 msec) two minutes after the extravascular injection of 16.0 mg/kg of the intended (b) (4) dose. It was noted that the administration of the trial medication for this subject was stopped due to the extravascular injection; therefore, the subject did not receive the full randomized dose of 32 mg/kg. The SAE resolved completely after one minute. According to the Investigator, the SAE was mild and

possibly related to the administration of (b)(4). However, the Applicant assessed this SAE as unlikely related to the trial medication indicating that a more likely cause was that the subject was in pain due to the extravascular administration. Also, the subject's increase in QTcF was < 60 msec.

(b)(4)

(b)(4)

(b)(4)

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

According to the Applicant, "discontinuation of trial medication due to AE" in the clinical trials program can be applied only to the Phase 1 trials, 19.4.108 and 19.4.109, in which trial drug was infused over four minutes rather than administered as a bolus. The infusion of (b)(4) was not discontinued in any subject in 19.4.108 or 19.4.109 (Groups A and F); therefore, the data presented below represent subject withdrawal from the trial (not the trial medication) due to an AE.

Overall, 14 subjects withdrew from the trials in which they were enrolled due to adverse events; however, there were also 9 discontinuations for protocol violations, 8 subjects who withdrew consent, and 26 subjects who were lost to follow up. The table below provides summary information for those subjects who discontinued due to adverse events.

(b) (4) (sugammadex sodium injection)

Table 6: Summary data for subjects who withdrew from the trials due to adverse events

| Subject Number | Study Drug and Dose (mg/kg) | NMBA | Most Important Reason for Discontinuation |
|----------------|-----------------------------|------|---|
| 101000013 | (b) (4) (2) | -- | Wolf-Parkinson-White Syndrome (SAE) |
| 105101019 | (b) (4) (4) | -- | Elevated creatine phosphokinase (SAE) |
| 106101008 | (b) (4) (32) | | Paresthesia (SAE) |
| 109101073 | (b) (4) (32) | | Hypersensitivity (SAE) |
| 204103001 | (b) (4) (1) | RCB | Neuromuscular block prolonged (SAE) |
| 204103009 | (b) (4) (0.5) | RCB | Neuromuscular block prolonged (SAE) |
| 205000042 | (b) (4) (16) | RCB | Awareness during anesthesia (SAE) |
| 302105006 | None | VCB | Deep vein thrombosis |
| 302110014 | Neostigmine | RCB | Gastric perforation (SAE) |
| 308110003 | None | RCB | Decreased oxygen saturation |
| 311112011 | (b) (4) (4) | RCB | Large intestine perforation, sepsis, electromechanical dissociation (SAE) |
| 311118001 | None | RCB | Airway complication of anesthesia |
| 311122006 | None | RCB | Nausea |
| 312105008 | None | RCB | Nausea and vomiting |

(b) (4) **vs. placebo**

One (0.2%) (b) (4) subject (who received rocuronium) withdrew from a trial due to an AE (unwanted awareness during anesthesia). The Investigator considered this AE related to the trial medication. No placebo-treated subjects withdrew from a trial.

(b) (4) **vs. neostigmine**

One (0.6%) neostigmine subject (who received rocuronium) withdrew from a trial due to multiple AEs. These AEs were considered to be unrelated to the trial medication by the investigator. No (b) (4) subject withdrew from a trial due to an AE.

Pooled Phase 1-3 dose response

Four (0.2%) of all subjects who received (b) (4) plus an NMBA withdrew from a trial due to an AE. Two subjects were in the < 2-mg/kg dose group, one was in the 4-mg/kg dose group, and one was in the 16-mg/kg dose group. The most frequent AE leading to trial discontinuation was neuromuscular block prolonged (2 subjects in the < 2-mg/kg dose group). Adverse events leading to trial discontinuation that were considered by the investigator to be related to treatment with (b) (4) included unwanted awareness during anesthesia (one 16 mg/kg subject) and neuromuscular block prolonged (one < 2 mg/kg subject). An additional subject who received < 2 mg/kg of (b) (4) also had an adverse event labeled as “neuromuscular block prolonged,” but this event was not attributed to (b) (4) by the investigator and no alternative cause was ascribed.

7.1.3.2 Adverse events associated with dropouts

Subject 106101008 experienced a number of adverse events considered by the Investigator to be related to the study drug, (b) (4) 32 mg/kg. Soon after the start of the infusion, the subject experienced paresthesia in the skin of the hands and face, visual disturbance, dysgeusia (a metallic taste), nausea, tachycardia and stomach discomfort. The paresthesia and visual disturbance were reported as moderate in intensity. The paresthesia was described as a tingling and then later as a cramping sensation. The sudden onset and combination of the adverse events prompted the Investigator to stop the infusion. Later, flushing was noted on arms, and an erythematous rash was observed on the abdomen. The rash was neither elevated nor pruritic. These symptoms were considered a possible allergic reaction; all resolved without further treatment.

Subject 204103001 in Study 19.4.204 was a 46-year old male Caucasian with a history of mild anemia and lymphoma who underwent a scheduled splenectomy on 04-Nov-2004. Following a bolus intubation dose of 0.6 mg/kg rocuronium, a single bolus dose of 1.0 mg/kg (b) (4) was administered at 1-2 post-tetanic contractions (PTCs). Following the administration of (b) (4) the train-of-four (TOF) watch showed a maximum recovery of the TOF ratio to 20% followed by increased neuromuscular block. Approximately 30 minutes later, at TOF count 2, the investigator administered neostigmine (2 doses 10 minutes apart, as shown below) for reversal of NMB due to “safety concerns” because the TOF ratio didn’t recover to at least 90% by the time the subject arrived in the post-anesthesia care unit. Recovery was observed within about 1 hr after the second dose of neostigmine. This event was reported as the AE “neuromuscular block prolonged”, and it was reported by the Applicant as the most important of several AEs that led to the patient’s withdrawal from the trial. The other AEs leading to trial discontinuation included electrocardiogram QT prolonged (starting 1 minute following study drug administration), blood albumin decreased, hematocrit decreased, protein total decreased, and beta-N-acetyl-D-glucosaminidase increased (on post-operative Day 1).

Subject 204103009 in Study 19.4.204 was a 33-year old male Caucasian with a history of bilateral varicoceles and testes pain who underwent a scheduled bilateral varicocelectomies on (b) (6). Following a bolus intubation dose of 0.6 mg/kg rocuronium, a single bolus dose of 0.5 mg/kg (b) (4) was administered at 1-2 PTCs. In this subject, the TOF watch results demonstrated slow recovery of the train-of-four ratio, and the patient remained anesthetized throughout recovery. Therefore, the investigator administered neostigmine for reversal of NMB due to safety concerns. Recovery to the reappearance of T2 was observed within about 8 minutes of the administration of neostigmine. This event was reported as the AE “neuromuscular block prolonged”, and it led to the subject’s discontinuation from the trial.

Subject 2041004007 in Study 19.4.204 was a 42-year old female Caucasian with a history of uterine myoma who underwent a scheduled total abdominal hysterectomy on (b) (6). Following a bolus intubation dose of 1.2 mg/kg of rocuronium, a single bolus dose of 0.5 mg/kg of (b) (4) was administered at 1-2 PTCs. In this subject, the TOF watch showed a T4/T1 ratio of only 20% at 49 minutes after the administration of (b) (4). Recovery was observed about 25 minutes later. This event was reported as the AE “neuromuscular blockade prolonged”.

7.1.3.3 Other significant adverse events

Five subjects had experienced reactions to (b) (4) that were consistent with current NIH definition for anaphylaxis. These subjects had adverse events that were labeled by the Applicant as hypersensitivity reactions. The Applicant conducted a hypersensitivity study to evaluate intradermal injection and skin prick responses for (b) (4) in subjects who had been previously exposed to the product, including one of whom had a hypersensitivity reaction, and (b) (4) naïve subjects. The study findings included:

- Positive test results for the subject with a previous hypersensitivity reaction
- Positive test results for a previously exposed subject with no hypersensitivity reaction
- Negative test results for all subjects who had no previous exposures to (b) (4)

The Division of Pulmonary and Allergy Products (DPAP) has reviewed the clinical trial database and the hypersensitivity protocol. They have rendered the following conclusions:

- sugammadex is allergenic with the potential to cause anaphylaxis
- the estimated anaphylaxis frequency of 1.4% may be a significant underestimate of the true frequency, since the clinical development program did not assess the safety of repeat exposures

Based on these findings, DPAP recommended that, prior to widespread use, a formal assessment of the risk of reaction in patients with repeat exposures, both in a general population and in a sensitized population. They indicated that further elucidation of the underlying immunologic mechanism may facilitate patient screening to minimize the risk of anaphylaxis should the product ultimately be approved.

7.1.4 Other Search Strategies

Other search strategies were not indicated and none were conducted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The Applicant stated that in all trials, an adverse event (AE) was defined as any untoward medical occurrence in subject who received a study drug regardless of whether there was a causal relationship with the treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of an investigational product, whether or not related to the investigational product. Abnormal laboratory or vital sign measurements or complaints from the quality of recovery questionnaire (QoR40) were recorded as AEs at the Investigator's discretion.

At all contacts, AE data were to have been obtained by examining the subject and/or by questioning the subject in a non-suggestive manner. Symptoms that were present at screening but increased in severity and/or frequency during the treatment-emergent period were to be reported as AEs. On the AE case report form (CRF), the Investigator was to report the start date, stop date, start time, stop time, maximum intensity, action taken, relationship to trial drug, and outcome. The Investigator was also to have noted if the AE was an SAE, or if it led to the discontinuation of the subject from the trial.

Subjects were to be asked about adverse events up to the end of their participation in the trial which was 7 days after receiving the study medication for most of the trials including the pivotal studies.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Applicant reported that all AEs in the integrated database are coded to MedDRA version 10.0. However, there were some differences between the coding in the integrated database compared to some of the individual trial reports, specifically, studies 19.4.101, 19.4.201, and 19.4.202 that were originally coded to WHO-ART. Tabular summaries of MedDRA-coded data for trials originally coded to WHO-ART were provided. For all other Phase 1-3 trials, any differences between earlier MedDRA versions used for the trial reports compared to the 10th version used for the integrated database were also provided.

The preferred term (PT), "anesthetic complication," included the following Investigator verbatim terms:

- movement (of a limb or the body)
- coughing during the anesthetic procedure or during surgery
- grimacing
- suckling on the endotracheal tube
- AEs listed under the PT, "light anesthesia," in studies that used MedDRA versions prior to version 10.0

7.1.5.3 Incidence of common adverse events

(b) (4) *versus Placebo*

The incidence of subjects with at least one AE was similar for (b) (4) subjects (68%) and placebo subjects (72%). The overall incidence of AEs was similar between the two groups

regardless of the NMBA administered, although it was slightly higher overall in the vecuronium group:

- Rocuronium plus (b) (4) (67%), rocuronium plus placebo (70%);
- Vecuronium plus (b) (4) (75%), vecuronium plus placebo (83%). The higher percentage in the vecuronium plus placebo group might have been influenced by the smaller group size.

A total of 58% of the 19 subjects in the uncontrolled (b) (4) plus pancuronium group experienced at least one AE.

Adverse event incidence according to system organ class (SOC) was generally similar for (b) (4) subjects and placebo subjects. The most frequent (i.e., $\geq 20.0\%$ incidence in either treatment group) SOCs included Injury, Poisoning, and Procedural Complications (36% (b) (4) 40% placebo) and Gastrointestinal Disorders (27% (b) (4) 29% placebo).

The preferred term (PT) anesthetic complication occurred only in subjects who received rocuronium (vs. vecuronium). Other complications of anesthesia occurred infrequently and included the following:

- Airway complication of anesthesia (1% (b) (4) 0% placebo),
- Delayed recovery from anesthesia (1% (b) (4) 0% placebo),
- Unwanted awareness during anesthesia (0.3% (b) (4) 0% placebo), and
- Anesthetic complication cardiac (0.2% (b) (4) 0% placebo).

The group of anesthetic complications observed with rocuronium or vecuronium was not reported in the small subset of 19 subjects who received pancuronium and (b) (4). There was no corresponding pancuronium and placebo group for comparison.

(b) (4) *versus Neostigmine*

The Applicant reported that the incidence of subjects with at least one AE was similar for (b) (4) subjects (88%) and neostigmine subjects (89%). The overall incidence of AEs was similar between the two groups regardless of the NMBA administered, although it was slightly higher overall in the rocuronium group:

- Rocuronium plus (b) (4) (90.6%), rocuronium plus neostigmine (93.0%);
- Vecuronium plus (b) (4) (85.1%), vecuronium plus neostigmine (85.2%).

Adverse events that occurred in at least 2.0% of (b) (4) subjects in the Phase 3 controlled trials 19.4.301 and 19.4.302 were summarized by system organ class (SOC) and preferred term (PT). Adverse event incidence based on SOC was similar for (b) (4) subjects and neostigmine subjects. The most frequent (i.e., $\geq 20.0\%$ incidence in either treatment group) SOCs included the following:

- Injury, Poisoning, and Procedural Complications (67% (b) (4) 68% neostigmine)
- Gastrointestinal Disorders (46.9% (b) (4) 53.3% neostigmine),
- General Disorders and Administration Site Conditions (22% (b) (4) 21% neostigmine)
- Nervous System Disorders (18% (b) (4) 20% neostigmine)

Airway complication of anesthesia occurred in one subject (1%) in each treatment group of the rocuronium subset, and in one (1%) (b) (4) subject and 3 (4%) neostigmine subjects in the vecuronium subset. No other anesthetic complications (including the PT “anaesthetic complication”) were reported.

7.1.5.4 Common adverse event tables

The Applicant provided the following tables of adverse events. Pooled Phase 1-3 trials were used to generate the first table, which compares (b) (4) to placebo; the second compares (b) (4) to neostigmine with data from studies 19.4.301 and 19.4.302. A $\geq 2\%$ incidence in one of the treatment arms was used as the cutoff for inclusion in the tables. The adverse events are listed in the order of decreasing incidence in the (b) (4) group.

Table 7: Adverse events in Pooled Phase 1-3 studies with a placebo (Modified Table 12 from ISS, p. 56)

| Adverse Event preferred term | Rocuronium or vecuronium + | |
|---|----------------------------|-----------------|
| | (b) (4) (N=640) | Placebo (N=140) |
| | n (%) | n (%) |
| Total with at least one AE | 437 (68.3) | 101 (72.1) |
| Procedural pain | 134 (20.9) | 43 (30.7) |
| Nausea | 106 (16.6) | 25 (17.9) |
| Vomiting | 61 (9.5) | 11 (7.9) |
| Anesthetic complication | 51 (8.0) | 2 (1.4) |
| Pain | 37 (5.8) | 7 (5.0) |
| Pyrexia | 34 (5.3) | 11 (7.9) |
| Procedural hypotension | 31 (4.8) | 4 (2.9) |
| Headache | 29 (4.5) | 11 (7.9) |
| Pharyngolaryngeal pain | 28 (4.4) | 8 (5.7) |
| Chills | 20 (3.1) | 3 (2.1) |
| Back pain | 20 (3.1) | 3 (2.1) |
| Cough | 18 (2.8) | 2 (1.4) |
| Procedural hypertension | 16 (2.5) | 4 (2.9) |
| Electrocardiogram QT corrected interval prolonged | 16 (2.5) | 2 (1.4) |
| Constipation | 15 (2.3) | 7 (5.0) |
| Abdominal pain | 15 (2.3) | 3 (2.1) |
| Diarrhea | 14 (2.2) | 4 (2.9) |
| Hypertension | 14 (2.2) | 4 (2.9) |
| Vertigo | 14 (2.2) | 4 (2.9) |
| Dizziness | 13 (2.0) | 4 (2.9) |

(b) (4) (sugammadex sodium injection)

| Adverse Event preferred term | Rocuronium or vecuronium + | |
|---|----------------------------|-----------------|
| | (b) (4) (N=640) | Placebo (N=140) |
| | n (%) | n (%) |
| Postoperative wound complication | 13 (2.0) | 3 (2.1) |
| Beta 2 microglobulin urine increased ^A | 15 (2.3) | 4 (2.9) |
| Insomnia | 11 (1.7) | 3 (2.1) |
| Dysuria | 9 (1.4) | 5 (3.6) |
| Procedural complication | 6 (0.9) | 3 (2.1) |
| Paresthesia | 6 (0.9) | 3 (2.1) |
| Malaise | 5 (0.8) | 3 (2.1) |
| Procedural nausea | 4 (0.6) | 5 (3.6) |
| Pruritus | 2 (0.3) | 4 (2.9) |
| Anemia | 2 (0.3) | 3 (2.1) |
| Ventricular extrasystoles | 0 (0.0) | 3 (2.1) |

^A Includes AEs coded to beta 2 microglobulin urine increased (13 (b) (4) subjects, 2 placebo subjects) plus AEs coded to beta 2 microglobulin increased (2 (b) (4) subjects, 2 placebo subjects).

Note: Pediatric subjects from trial 19.4.306 are excluded from this table.

Table 8: Adverse events in studies 19.4.301 and 19.4.302 [where neostigmine was the comparator] (Modified Table 14 from ISS, pp. 59-60)

| Adverse Events preferred term | Rocuronium or vecuronium + | |
|-------------------------------|----------------------------|---------------------|
| | (b) (4) (N=179) | Neostigmine (N=167) |
| | n (%) | n (%) |
| Total with at least one AE | 157 (87.7) | 149 (89.2) |
| Procedural pain | 98 (54.7) | 85 (50.9) |
| Nausea | 63 (35.2) | 61 (36.5) |
| Vomiting | 28 (15.6) | 22 (13.2) |
| Headache | 21 (11.7) | 13 (7.8) |
| Incision site pain | 19 (10.6) | 14 (8.4) |
| Pain | 18 (10.1) | 14 (8.4) |
| Pharyngolaryngeal pain | 16 (8.9) | 17 (10.2) |
| Procedural nausea | 14 (7.8) | 13 (7.8) |
| Chills | 12 (6.7) | 7 (4.2) |
| Flatulence | 10 (5.6) | 4 (2.4) |
| Insomnia | 10 (5.6) | 9 (5.4) |
| Procedural hypertension | 9 (5.0) | 9 (5.4) |
| Constipation | 9 (5.0) | 11 (6.6) |
| Pruritus | 8 (4.5) | 6 (3.6) |
| Dizziness | 7 (3.9) | 11 (6.6) |
| Back pain | 7 (3.9) | 7 (4.2) |
| Muscular weakness | 7 (3.9) | 5 (3.0) |

(b) (4) (sugammadex sodium injection)

| Adverse Events preferred term | Rocuronium or vecuronium + | |
|---|----------------------------|------------------------|
| | (b) (4) (N=179) | Neostigmine (N=167) |
| | n (%) | n (%) |
| Procedural complication | 6 (3.4) | 14 (8.4) |
| Retching | 6 (3.4) | 8 (4.8) |
| Pyrexia | 6 (3.4) | 8 (4.8) |
| Blood creatine phosphokinase increased | 6 (3.4) | 3 (1.8) |
| Abdominal pain | 5 (2.8) | 6 (3.6) |
| Myalgia | 5 (2.8) | 6 (3.6) |
| Gastrointestinal disorder postoperative | 4 (2.2) | 0 (0.0) |
| Dry mouth | 4 (2.2) | 14 (8.4) |
| Hypocalcaemia | 4 (2.2) | 2 (1.2) |
| Anxiety | 3 (1.7) | 8 (4.8) |
| Oral pain | 3 (1.7) | 6 (3.6) |
| Sleep disorder | 3 (1.7) | 4 (2.4) |
| Procedural hypotension | 2 (1.1) | 11 (6.6) |
| Procedural vomiting | 2 (1.1) | 5 (3.0) |
| Dyspepsia | 2 (1.1) | 5 (3.0) |
| Airway complication of anesthesia | 2 (1.1) | 4 (2.4) |
| Post procedural complication | 2 (1.1) | 4 (2.4) |
| Erythema | 2 (1.1) | 4 (2.4) |
| Anemia | 1 (0.6) | 6 (3.6) |
| Neuromuscular block prolonged | 0 (0.0) | 4 (2.4) |

7.1.5.5 Identifying common and drug-related adverse events

From the Pooled Phase 1-3 (b) (4) vs. placebo studies, the Applicant reported slightly more (b) (4) subjects (13.3%) than placebo subjects (7.9%) had related AEs per the Investigator, regardless of the NMBA administered. Most related AEs occurred in 1% or less of either treatment group. One related AE, anesthetic complication, occurred at a two-fold higher incidence in the r group (3.3%) compared to the placebo group (0.0%).

From the Pooled Phase 1-3 (b) (4) vs. neostigmine studies, the Applicant reported that slightly more neostigmine subjects (25.1%) than (b) (4) subjects (18.4%) had related AEs per the Investigator, regardless of the NMBA administered. Most of these related AEs occurred in 1% or less of either treatment group. One related AE, vomiting, occurred at a two-fold higher incidence in the (b) (4) group (3.9%) compared to the neostigmine group (1.8%).

From the Pooled Phase 1 (b) (4) vs. placebo studies, the Applicant reported that related occurrences of dysgeusia, nausea, and dizziness were twice as frequent in (b) (4) subjects compared to placebo subjects, as follows:

- Dysgeusia (12.6% (b) (4) 1.5% placebo);
- Nausea (4.3% (b) (4) 0% placebo); and
- Dizziness (2.0% (b) (4) 0% placebo).

In addition, in the (b) (4) group, all occurrences of dysgeusia (n=56) and dizziness (n=9) and most occurrences of nausea (19/20) and abdominal pain (7/10) were considered to be related.

7.1.5.6 Additional analyses and explorations

No additional analyses were indicated and none were performed.

7.1.6 Less Common Adverse Events

Less common adverse events, i.e., those occurring in less than 2% of subjects, which warrant special consideration, include anesthetic complications, adverse events related to neuromuscular blockade and hypersensitivity. Each of these is considered in other sections of this review.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The Applicant combined trial for the purposes of analyzing laboratory testing in the same manner that was used for analyzing adverse event data. Pooled Phase 1 trials and pooled Phase 1-3 trials were analyzed separately as described in the sections that follow. For both sets of trials, hematology, biochemistry and urinalysis data were collected and evaluated. The Applicant used descriptive statistics, shift tables, and markedly abnormal post-baseline values to assess differences between treatment groups. Only those out-of-range values deemed to be clinically significant by the Investigators were recorded as adverse events. Notably missing from the clinical laboratory assessments were the coagulation parameters: activated partial thromboplastin time (aPTT), prothrombin time (PT), and the international normal ratio of the PT (INR). The need for assessment of these parameters is discussed in Section 1 of this review.

The table below indicates the numbers of subjects exposed to study drug who had baseline and follow-up laboratory assessments.

Table 9: Subject exposures for purposes of clinical laboratory assessments

| Data Set | Trial Number | Number of Subjects Exposed | |
|-------------------------|-------------------------------|----------------------------|--------------------|
| | | (b) (4) | Comparator |
| Pooled Phase 1 Trials | 19.4.101 (Part 1) | 31 | 10 placebo |
| | 19.4.102 | 84 | 28 placebo |
| | 19.4.105 | 120 | 57 placebo |
| | 19.4.106 | 37 | 12 placebo |
| | 19.4.109 (Groups C, D, and E) | 165 | 82 placebo |
| Pooled Phase 1-3 Trials | 19.4.101 (Part 2) | 10 | 10 placebo |
| | 19.4.108 | 12 | NA |
| | 19.4.109 (Groups A and F) | 321 | 83 placebo |
| | 19.4.201 | 22 | 5 placebo |
| | 19.4.202 | 88 | 10 placebo |
| | 19.4.203 | 30 | NA |
| | 19.4.204 | 43 | NA |
| | 19.4.205 | 37 | 6 placebo |
| | 19.4.206 | 157 | 16 placebo |
| | 19.4.207 | 91 | 7 placebo |
| | 19.4.208A | 78 | 20 placebo |
| | 19.4.208B | 78 | 20 placebo |
| | 19.4.209A | 99 | NA |
| | 19.4.209B | 101 | NA |
| | 19.4.210 | 42 | NA |
| | 19.4.301 | 96 | 93 neostigmine |
| | 19.4.302 | 83 | 74 neostigmine |
| | 19.4.303 | 56 | 54 succinylcholine |
| | 19.4.304 | 30 | NA |
| | 19.4.305 | 150 | NA |
| | 19.4.306 | 22 | 6 placebo |
| | 19.4.308 | 77 | NA |
| | 19.4.309 | 76 | 40 placebo |
| | 19.4.310 | 33 | 39 neostigmine |
| 19.4.311 | 197 | NA | |
| 19.4.312 | 51 | NA | |

Hematology, biochemistry and urinalysis data from the pooled Phase 1 and pooled phase 1-3 trials were collected at the time points noted below.

- Hematology and biochemistry data were collected at the following time points:
 - baseline, i.e., the last measurement before the administration of the trial medication,
 - 20 min, 60 min (except in the Pooled Phase 1 trials), 4-6 hr, 8 hr, and 24 hr post-baseline,
 - minimum and maximum values,

(b) (4) (sugammadex sodium injection)

- endpoint values, and
 - the final visit (i.e., the post-anesthetic visit for surgical subjects).
- Urinalysis data were collected at the following time points:
 - baseline (i.e., the last measurement before the administration of the trial medication),
 - 4-6 hr, 8 hr (except in the Pooled Phase 1 trials), and 24 hr post-baseline,
 - minimum and maximum values,
 - endpoint values, and
 - the final visit (i.e., the post-anesthetic visit for surgical subjects).

Follow-up urinalysis data (collected 2 weeks after the administration of (b) (4) from the Phase 3 trial 19.4.304 (in subjects with normal renal function and impaired renal function) were summarized by the Sponsor from the clinical trial report (after the presentation of urinalysis data according to dose response). The Sponsor indicated that these data were not pooled with the other Phase 1-3 urinalysis data in order to more clearly evaluate any delayed effects of (b) (4) on the kidney in renally-impaired versus normal subjects.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Analyses were conducted utilizing data from the controlled trials. Separate comparisons were made for studies using placebo and those using neostigmine as the comparator. The Applicant also analyzed the data comparing the different doses of (b) (4) utilized in the clinical development program.

7.1.7.3 Standard analyses and explorations of laboratory data

The Applicant analyzed the laboratory data using measures of central tendency, shift tables, and comparisons of marked outliers. Each analysis is considered separately in the sections that follow.

7.1.7.3.1 Analyses focused on measures of central tendency

Descriptive statistics used by the Applicant included the mean, standard deviation (SD), median, minimum, and maximum observed values, and absolute and percent mean (SD), median, minimum, and maximum changes from baseline.

Biochemistry ((b) (4) vs. placebo)

The Applicant reported that the two treatment groups were well-matched at baseline for all biochemistry parameters. Mean and median changes from baseline to the minimum and maximum values for all parameters were similar between the two groups. The largest treatment

group differences were observed for creatine phosphokinase (CK) and creatinine. For CK, median change (median percent change) to the maximum reported value was 2.0 U/L (3.0%) in the (b) (4) group and -2.0 U/L (-2.5%) in the placebo group. For creatinine, median change (median percent change) to the maximum reported value was 5.3 μ mol/L (7.6%) in the (b) (4) group and 1.8 μ mol/L (2.3%) in the placebo group.

Within the first 24 hr after dosing, the median percent changes from baseline for the renal parameters BUN, total protein, and albumin were similar in the two treatment groups at each timepoint. At 60 min and at 4-6 hr post-dose, median percent changes from baseline for creatinine were slightly higher in the (b) (4) group (9% at 60 min, 6% at 4-6 hr) compared to the placebo group (5% at 60 min, 0% at 4-6 hr). However, at 24 hr post-dose, the median percent changes from baseline were again similar in the two groups (0% (b) (4) -3% placebo).

Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined.

Biochemistry ((b) (4) vs. neostigmine)

In trials 19.4.301 and 19.4.302, biochemistry tests were measured post-baseline at approximately 4-6 hr post-dose and at the post-anesthetic visit at least 10 hr post-dose. The Applicant indicated that the two treatment groups were well-matched at baseline for all biochemistry parameters. Mean and median changes from baseline for all parameters were similar between the two groups at 4-6 hr post-dose. In particular, serum creatinine increased by 4% (median percent change) in the (b) (4) group and by 3% in the neostigmine group, while BUN decreased by 5% in the (b) (4) group and by 6% in the neostigmine group. Total protein and albumin each decreased by 2% to 3% in both treatment groups.

Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined.

Biochemistry (dose response)

Baseline values for all biochemistry parameters were similar across dose groups, and there were no dose trends for mean and median changes from baseline. However, when only the 2 mg/kg, 4 mg/kg, and 16 mg/kg dose groups were considered, there was a dose trend for CK for median change from baseline to the maximum reported value (7 U/L, 11 U/L, and 13 U/L, respectively) and for median percent change from baseline in serum creatinine at 4-6 hr (1%, 2%, and 3%, respectively). There were no other dose trends at 20 min, 60 min, 4-6 hr, or 24 hr post-dose for the renal function parameters including serum creatinine, BUN, total protein, and albumin.

Hematology ((b) (4) vs. placebo)

The Applicant reported that the two treatment groups were well-matched at baseline for all hematology parameters. For each parameter, they reported that there was no clinically relevant difference between the treatments for mean and median changes from baseline.

Hemoglobin, hematocrit, and red blood cell count decreased in each group. The median changes from baseline to the minimum reported values for these parameters were:

- Hemoglobin: -5 g/dL (b) (4) -7 g/dL placebo;
- Hematocrit: -0.01 (b) (4) -0.02 placebo; and
- Red blood cell count: $-0.15 \times 10^{12}/L$ (b) (4) $-0.20 \times 10^{12}/L$ placebo.

The total white blood cell count and absolute neutrophil count increased in each group; there was little change in absolute lymphocyte count. The median changes from baseline for these parameters were:

- White blood cell count (to maximum value): $2.40 \times 10^9/L$ (b) (4) $1.50 \times 10^9/L$ placebo;
- Absolute neutrophil count (to maximum value): $2.10 \times 10^9/L$ (b) (4) $1.30 \times 10^9/L$ placebo;
- Absolute lymphocyte count (to minimum value): $0.05 \times 10^9/L$ (b) (4) $-0.05 \times 10^9/L$ placebo.

Results for subjects who received rocuronium or vecuronium were consistent with the data for all the combined results for the two NMBAs.

Hematology ((b) (4) vs. neostigmine)

The Applicant indicated that the two treatment groups were well-matched at baseline for all hematology parameters evaluated. For all parameters, there were no clinically relevant differences between the treatments for mean and median changes from baseline. In both groups, there were very small mean and median changes in hemoglobin, hematocrit, and red blood cell count. The median changes from baseline to the minimum reported values for these parameters were:

- Hemoglobin: -1 g/L (b) (4) 0 g/L neostigmine;
- Hematocrit: 0.0 (b) (4) 0.0 neostigmine; and
- Red blood cell count: $-0.04 \times 10^{12}/L$ (b) (4) $-0.01 \times 10^{12}/L$ neostigmine.

Total white blood cell count and absolute neutrophil count increased in each treatment group, while absolute lymphocyte count and platelet count decreased slightly. The median changes from baseline for these parameters were:

- White blood cell count (to maximum value): $5.7 \times 10^9/L$ (b) (4) $5.2 \times 10^9/L$ neostigmine;
- Absolute neutrophil count (to maximum value): $5.9 \times 10^9/L$ (b) (4) $5.0 \times 10^9/L$ neostigmine;
- Absolute lymphocyte count (to minimum value): $-0.40 \times 10^9/L$ (b) (4) $-0.40 \times 10^9/L$ neostigmine; and
- Platelet count (to minimum value): $-10 \times 10^9/L$ (b) (4) $-11 \times 10^9/L$ neostigmine.

Results for subjects who received rocuronium or vecuronium were consistent with the data for all the rocuronium and vecuronium subjects combined.

Hematology (dose response)

Small changes were observed in the hematology parameters for the three studied doses of (b) (4) however, for the parameters studied, there were no changes noted that appeared to be dose dependent.

Urinalysis ((b) (4) vs. placebo)

The Applicant reported that the two treatment groups were well-matched at baseline for beta-2-microglobulin, urine creatinine, microglobulin (creatinine-dependent), and NAG. For microalbumin (non-creatinine-dependent), the mean baseline value was higher in the placebo group (45 ± 204 mg/L) than in the (b) (4) group (18 ± 44 mg/L), but median values were equivalent (5 mg/L in each group). At 4-6 hr post-baseline and at 24 hr post-baseline, median percent changes in beta-2-microglobulin and microalbumin (non-creatinine-dependent) in the (b) (4) group were similar to or less than in the placebo group. At both timepoints, median percent change in NAG was less in the (b) (4) group than in the placebo group.

The following summarizes median percent change from baseline for these parameters:

- Beta-2-microglobulin:
 - 4-6 hr post-baseline: 0% (b) (4) 3% placebo
 - 24 hr post-baseline: -25% (b) (4) -21% placebo
- Microalbumin (non-creatinine-dependent):
 - 4-6 hr post-baseline: 100% (b) (4) 130% placebo
 - 24 hr post-baseline: 0%, (b) (4) 60% placebo
- NAG:
 - 4-6 hr post-baseline: 31% (b) (4) 79% placebo
 - 24 hr post-baseline: -64% (b) (4) -5% placebo

At the final visit, there was a slight increase in urine creatinine in the (b) (4) group (median percent change 1%) compared to an 8% decrease in the placebo group, and there were increases in microalbumin (creatinine-dependent) in both groups (median percent change 82% for (b) (4) and 64% for placebo). In the small group of subjects with a quantitative measurement of urine protein (N=10 each group), median percent change at 8 hr post-baseline was similar in each group (19% (b) (4) 18% placebo). Post-baseline urine pH was also similar in each group, ranging from 5 to 8.5 in the (b) (4) group, and from 5.5 to 8 in the placebo group.

Results for subjects whose NMBA was rocuronium or vecuronium (Appendix Table 91) were consistent with the data for the rocuronium and vecuronium subjects combined.

Urinalysis ((b) (4) vs. neostigmine)

In trials 19.4.301 and 19.4.302, post-baseline urinalysis was performed only at the post-anesthetic visit at least 10 hr post-dose.

The two treatment groups ((b) (4) and neostigmine) were well-matched at baseline for urine creatinine, NAG, and urine pH. For beta-2- microglobulin, the mean baseline value was higher in the (b) (4) group than in the neostigmine group; for microalbumin, the mean baseline value was higher in the neostigmine group than in the (b) (4) group. However, the median baseline values for these parameters were similar between the two treatment groups. In both groups, there was little change in urine pH and beta-2-microglobulin, and small decreases from baseline to the final visit in urine creatinine and NAG. In both treatment groups, post-baseline urine pH ranged from 5 to 8. Microalbumin was increased in the (b) (4) group at the final visit (median percent change was 30%) compared to no change in the median of the neostigmine group.

Urinalysis (dose response)

The dose groups were well-matched for median baseline values; mean baseline values were more variable, especially those for beta-2-microglobulin and microalbumin. However, no dose trends or trends by timepoint were observed for mean or median changes from baseline.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Based on the specified safety and normal ranges, the results of the clinical laboratory tests were classified by the Sponsor into the following categories:

- Category A: value \leq lower safety range,
- Category B: value $>$ lower safety range and value \leq lower normal range,
- Category C: value $>$ lower normal range and value $<$ upper normal range,
- Category D: value \geq upper normal range and value $<$ upper safety range, and
- Category E: value \geq upper safety range.

Shift tables were constructed to determine the categorical shifts from baseline to post-baseline. Each shift was designated by a code. For example, code "AD" denoted a shift of a value from Category A (below or equal to the lower safety range) at baseline to Category D (above or equal to the upper normal range but below the upper safety range) at post-baseline assessment. The percentage of subjects with categorical shifts was presented by treatment group. Shifts of particular interest were called "notable shifts" by the Sponsor. Notable shifts in downward direction were defined as those downward shifts resulting in a value belonging to Category A or B (i.e., EA, DA, CA, BA, EB, DB, or CB). Notable shifts in upward direction were defined as those upward shifts resulting in a value belonging to Category D or E (i.e., AD, BD, CD, AE, BE, CE, or DE). The notable shift categories are listed in the table below.

Table 10: Notable shift categories (Table 24 from NDA ISS, p.112)

| Baseline Category | Post-baseline Category | | | | |
|-------------------|------------------------|----------|----|--------|--------|
| | A | B | C | D | E |
| A | -- | -- | -- | Upward | Upward |
| B | Downward | -- | -- | Upward | Upward |
| C | Downward | Downward | -- | Upward | Upward |
| D | Downward | Downward | -- | -- | Upward |
| E | Downward | Downward | -- | -- | -- |

Biochemistry ((b) (4) vs. placebo)

Overall, the Applicant indicated that there were more notable downward shifts than notable upward shifts in albumin, alkaline phosphatase, calcium, haptoglobin, lactate dehydrogenase (LDH), magnesium, potassium, total protein, sodium, and blood urea nitrogen (BUN). Also, there were more notable upward shifts in alanine aminotransferase (ALT), aspartate aminotransferase (AST), chloride, CK, creatinine, fasting glucose, and triglycerides. For most of these parameters, the percent of subjects with notable shifts was similar in the two treatment groups. The largest treatment group differences were observed for the following:

- Albumin (notable downward shifts): 12% (b) (4) 23% placebo
- Sodium (notable downward shifts): 4% (b) (4) 9% placebo
- Triglycerides (notable upward shifts): 10% (b) (4) 7% placebo

In both treatment groups, all upward shifts in total cholesterol and triglycerides were observed only in subjects who received rocuronium as the NMBA. In addition, subjects of both groups who received rocuronium (compared to those who received vecuronium) had more upward shifts in CK and more downward shifts in sodium. Conversely, subjects of both treatment groups who received vecuronium (compared to those who received rocuronium) had more downward shifts in albumin, haptoglobin, magnesium, and total protein, and more upward shifts in fasting glucose.

Biochemistry ((b) (4) vs. neostigmine)

The Applicant reported that overall, there were more notable downward shifts than notable upward shifts in albumin, alkaline phosphatase, calcium, haptoglobin, magnesium, total protein, sodium, and BUN. Also, there were more notable upward shifts in ALT, AST, total bilirubin, chloride, total cholesterol, CK, and creatinine. For most of these parameters, the percent of subjects with notable shifts was similar in the two treatment groups. The largest treatment group differences were observed for the following:

- Total bilirubin (notable upward shifts): 3% (b) (4) 8% neostigmine
- Total protein (notable downward shifts): 27% (b) (4) 32% neostigmine
- Sodium (notable downward shifts): 6% (b) (4) 11% neostigmine
- CK (notable upward shifts): 15% (b) (4) 11% neostigmine

Subjects of both groups who received rocuronium (compared to those who received vecuronium) had more downward shifts in albumin and magnesium, and more upward shifts in creatinine. Conversely, subjects of both treatment groups who received vecuronium (compared to those who received rocuronium) had more upward shifts in ALT and AST.

Biochemistry (dose response)

According to the Applicant, no dose trends were detected in the shift analysis. Overall, there were more notable downward than upward shifts in albumin, calcium, haptoglobin, haptoglobin type 2-1, magnesium, potassium, total protein, sodium, and BUN. There were also more notable upward than downward shifts in ALT, AST, chloride, CK, creatinine, fasting glucose, and triglycerides.

Hematology ((b) (4) vs. placebo)

The Sponsor indicated that the results of the shift analysis were generally consistent with the observed changes from baseline. In both treatment groups, there were more notable downward shifts than notable upward shifts in hemoglobin, hematocrit, red blood cell count, and absolute lymphocyte count. Also, there were more notable upward shifts in total white blood cell count, absolute neutrophil count, and absolute monocyte count. For each of these parameters, the percent of subjects with notable shifts was similar in the two treatment groups. The largest treatment group differences were observed for the following:

- Hemoglobin (notable downward shifts): 24% (b) (4) 31% placebo;
- Hematocrit (notable downward shifts): 26% (b) (4) 30% placebo;
- Red blood cell count (notable downward shifts): 20% (b) (4) 19% placebo;
- Total white blood cell count (notable upward shifts): 21% (b) (4) 15% placebo;
- Absolute lymphocyte count (notable downward shifts): 18% (b) (4) 18% placebo;
- Absolute neutrophil count (notable upward shifts): 19% (b) (4) 13% placebo; and
- Absolute monocyte count (notable downward shifts): 12% (b) (4) 10% placebo.

Results for subjects who received rocuronium or vecuronium were consistent with the data for all of the rocuronium and vecuronium subjects combined.

Hematology ((b) (4) vs. neostigmine)

Although there was little calculable mean or median change from baseline in hemoglobin, hematocrit, or red blood cell count, in each treatment group, there were more notable downward shifts than notable upward shifts for these parameters. In each treatment group, there were also more notable downward shifts in absolute lymphocyte count and platelet count, and more notable upward shifts in total white blood cell count and absolute neutrophil count. For each of these parameters, the percent of subjects with notable shifts were similar in the two treatment groups. The largest treatment group differences were observed for notable upward shifts in absolute neutrophil count (64% (b) (4) 55% neostigmine) and for notable downward shifts in absolute lymphocyte count (50% (b) (4) 44% neostigmine).

Results for subjects who received rocuronium or vecuronium were consistent with the data for all of the rocuronium and vecuronium subjects combined.

Hematology (dose response)

The Sponsor reported that no dose trends were detected in the shift analyses. Overall, there were more notable downward shifts than notable upward shifts in hemoglobin, hematocrit, and red blood cell count. There were also more notable downward shifts in absolute lymphocyte count, and more notable upward shifts in total white blood cell count, absolute neutrophil count, absolute monocyte count, and absolute basophil count.

Urinalysis ((b) (4) vs. placebo)

There were no shifts in urinary creatinine and microalbumin (creatinine-dependent). For NAG, the (b) (4) group had a higher percentage of notable downward shifts (21%) compared to the placebo group (4%), and a lower percentage of notable upward shifts (12%) compared to the placebo group (17%). For beta-2-microglobulin, a higher percentage of notable upward shifts were observed in the (b) (4) group (5%) compared to the placebo group (0%). For the remainder of the parameters, the incidence of notable shifts was similar between the two treatment groups:

- Microalbumin (non-creatinine-dependent) (notable upward shifts): 16% (b) (4) 19% placebo
- Urine protein (notable upward shifts): 10% (b) (4) (n=1), 10% placebo (n=1)
- Urine pH (notable upward shifts): 2% (b) (4) 0% placebo.

Urinalysis ((b) (4) vs. neostigmine)

There were no shifts in urinary parameters from baseline to the final visit.

Urinalysis (dose response)

No dose trends were detected in the shift analysis. There were no shifts in urinary creatinine and microalbumin (creatinine-dependent). There were only notable upward shifts for beta-2-microglobulin (in 5% of the Total (b) (4) group) and microalbumin (non-creatinine-dependent) (in 24% of the Total (b) (4) group). For NAG, there more notable downward shifts (20%) than notable upward shifts in the Total (b) (4) group.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Biochemistry ((b) (4) vs. placebo)

The percent of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was similar between the two treatment groups (see the tables below).

(b) (4) (sugammadex sodium injection)

In both treatment groups, all markedly high total cholesterol, creatinine, and BUN values were observed only in subjects who received rocuronium as the NMBA. In addition, subjects in both treatment groups who received rocuronium, compared to those who received vecuronium, had more markedly high values for gamma glutamyltransferase (GGT) and fasting triglycerides. Conversely, subjects in both treatment groups who received vecuronium, compared to those who received rocuronium, had more markedly low values for albumin and total protein.

Within the first 24 hr post-dose, 2 (3%) placebo subjects and no (b) (4) subjects had markedly high creatinine values (at 4-6 hr post-dose), and few subjects in either treatment group had markedly high BUN values (1 [1%] (b) (4) subject at 60 min post-dose, 2 [1%] (b) (4) subjects and 1 [2%] placebo subjects at 4-6 hr postdose). The percent of subjects with markedly low total protein or albumin values was higher overall, but always less in (b) (4) treated subjects compared to placebo subjects.

Table 11: Incidence of markedly high biochemistry values after treatment with (b) (4) or placebo (from Table 32 of ISS, p. 126)

| Biochemistry parameter (units) | Rocuronium or vecuronium + | | | | | |
|-----------------------------------|----------------------------|---------|---------|-----------------|----------------------|---------|
| | (b) (4) (N=409) | | | Placebo (N=116) | | |
| | N | n (%) | Maximum | N | n (%) | Maximum |
| Liver function: | | | | | | |
| GGT (U/L) | 407 | 11 (3) | 765 | 116 | 4 (3) | 742 |
| AST (U/L) | 407 | 7 (2) | 309 | 116 | 1 (1) | 129 |
| Total bilirubin (µmol/L) | 407 | 7 (2) | 68.4 | 116 | 4 (3) | 85.5 |
| ALT (U/L) | 407 | 3 (1) | 239 | 116 | 2 (2) | 173 |
| Kidney function: | | | | | | |
| BUN (mmol/L) | 407 | 4 (1) | 15.34 | 116 | 2 (2) | 17.50 |
| Creatinine (µmol/L) | 407 | 1 (< 1) | 172.4 | 116 | 2 (2) | 258.1 |
| Other parameters: | | | | | | |
| Fasting glucose (mmol/L) | 332 | 74 (23) | 16.04 | 77 | 11 (15) | 22.03 |
| CK (U/L) | 407 | 57 (14) | 2896 | 116 | 11 (9) | 740 |
| Haptoglobin type 2-2 (g/L) | 45 | 3 (7) | 1.43 | 9 | 2 (22 ^A) | 1.11 |
| Fasting triglycerides (mmol/L) | 332 | 9 (3) | 24.17 | 77 | 3 (4) | 10.86 |
| Haptoglobin type 2-1 (g/L) | 32 | 1 (3) | 1.68 | 9 | 0 (0 ^A) | 1.21 |
| Total cholesterol (mmol/L) | 407 | 9 (2) | 13.70 | 116 | 3 (3) | 7.82 |
| Potassium (mmol/L) | 407 | 3 (1) | 7.8 | 116 | 1 (1) | 6.5 |
| Calcium (mmol/L) | 407 | 0 (0) | 2.55 | 116 | 1 (1) | 3.35 |
| Magnesium (mmol/L) | 397 | 0 (0) | 1.00 | 106 | 1 (1) | 2.57 |

^A This result should be interpreted with caution since there were only 9 subjects in the treatment group.

(b) (4) (sugammadex sodium injection)

Notes: Pediatric subjects from trial 19.4.306 are excluded from this table. ALT=alanine aminotransferase. AST=aspartate aminotransferase. BUN=blood urea nitrogen. CK=creatinine phosphokinase. GGT=gamma glutamyltransferase.

Table 12: Incidence of markedly low biochemistry values after treatment with (b) (4) or placebo (from Table 33 of ISS, p. 127)

| Biochemistry parameter (units) | Rocuronium or vecuronium + | | | | | |
|-----------------------------------|----------------------------|----------|--------------|-----------------|----------------------|--------------|
| | (b) (4) (N=409) | | | Placebo (N=116) | | |
| | N | n (%) | Mini- mum | N | n (%) | Mini- mum |
| Kidney function: | | | | | | |
| Total protein (g/L) | 407 | 73 (18) | 31 | 116 | 23 (20) | 31 |
| Albumin (g/L) | 407 | 15 (4) | 18.8 | 116 | 7 (6) | 20.5 |
| Other parameters: | | | | | | |
| Haptoglobin (g/L) | 328 | 107 (33) | 0.10 | 96 | 26 (27) | 0.29 |
| Calcium (mmol/L) | 407 | 12 (3) | 1.38 | 116 | 7 (6) | 1.75 |
| Potassium (mmol/L) | 407 | 9 (2) | 2.9 | 116 | 0 (0) | 3.3 |
| Magnesium (mmol/L) | 397 | 5 (1) | 0.40 | 106 | 1 (1) | 0.55 |
| Haptoglobin type 2-2 (g/L) | 45 | 0 (0) | 0.14 | 9 | 1 (11 ^A) | 0.26 |

^A This result should be interpreted with caution since there were only 9 subjects in the treatment group.

Notes: Pediatric subjects from trial 19.4.306 are excluded from this table.

The incidence of AEs related to abnormalities of biochemistry clinical laboratory tests was low overall, and the differences in incidence between the (b) (4) and the placebo treatment arms were not deemed clinically relevant by the Applicant.

Biochemistry (b) (4) vs. neostigmine)

The percent of subjects with markedly abnormal post-baseline biochemistry values that met the pre-specified criteria was similar between the two treatment groups. In particular, only 1% of subjects in either treatment group had a markedly high value for serum creatinine (1% (b) (4) 0% neostigmine) or BUN (0% (b) (4) 1% neostigmine), and similar percentages had markedly low values for total protein (16% (b) (4) 20% neostigmine) or albumin (3% (b) (4) 2% neostigmine). Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined.

The incidence of AEs was low overall (0% to 3.4% (b) (4) 0% to 1.8% placebo), and the Applicant indicated that there were no clinically significant treatment group differences.

Biochemistry (dose response)

There were no dose trends for the percent of subjects with markedly abnormal post-baseline biochemistry values that met the Applicant's pre-specified criteria. In particular, there were no

dose trends at 20 min, 60 min, 4-6 hr, or 24 hr post-dose for the renal function parameters: serum creatinine, BUN, total protein, or albumin.

Most of the AEs related to abnormalities of biochemistry clinical laboratory tests occurred in 1.0% or less of the Total (b) (4) group, and no dose trends were observed. The biochemistry-related AEs that occurred in more than 1.0% of the Total (b) (4) group were hypokalemia (1.6%), blood creatine phosphokinase increased (1.5%), and hypocalcaemia (1.2%).

Hematology ((b) (4) vs. Placebo)

The percent of subjects with markedly abnormal post-baseline hematology values that met the pre-specified criteria was relatively similar between the two treatment groups. Greater percentages of (b) (4) treated subjects had markedly high values for total white blood cell count, neutrophil count and monocyte count than placebo-treated subject: 6% vs. 3%; 35% vs. 29%; and 7% vs. 3%; respectively. The maximum values for each of these parameters were also greater in the (b) (4) treated subjects; although, the clinical relevance, if any, of the differences observed is uncertain.

Results for subjects who received rocuronium or vecuronium were consistent with the combined population of rocuronium and vecuronium subjects.

Hematology ((b) (4) vs. neostigmine)

The percent of subjects with markedly abnormal post-baseline hematology values that met the pre-specified criteria was similar between the two treatment groups. Results for subjects who received rocuronium or vecuronium were consistent with the combined population of rocuronium- and vecuronium-treated subjects.

The incidence of AEs related to abnormalities of hematology clinical laboratory tests was low overall. However, incidents of anemia were reported more often in neostigmine-treated subjects (6%) compared to (b) (4) subjects (4%).

Hematology (dose response)

There were no dose trends for the percent of subjects with markedly abnormal post-baseline hematology values that met the Applicant's pre-specified criteria. Most of the AEs related to abnormalities of hematology clinical laboratory tests occurred in 1.0% or less of the Total (b) (4) group, and no dose trends were observed. The only hematology-related AE that occurred in more than 1.0% of the Total (b) (4) group was anemia (2.0%).

Urinalysis ((b) (4) vs. placebo)

The Applicant reported that for microalbumin, urine creatinine, and urine protein, the percent of subjects with markedly abnormal post-baseline values at any timepoint was similar between the two treatment groups. As shown in the table below, more (b) (4) treated subjects than placebo-

treated subjects had markedly high beta-2-microglobulin values at 4-6 hr post-baseline. At 24 hr post-baseline and at the final visit, the percentage of subjects with markedly high values for beta-2-microglobulin was similar in the two groups. For NAG, fewer (b) (4) subjects compared to placebo subjects had markedly high values at any timepoint, and more (b) (4) subjects compared to placebo subjects had markedly low values at most timepoints. Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the combined population of rocuronium and vecuronium subjects.

Table 13: Incidence of markedly high urinalysis values and corresponding maximum values (from Table 39 of ISS, p. 139)

| Urinalysis parameter (units) | Rocuronium or vecuronium + | | | |
|-----------------------------------|----------------------------|---------|--------------------|---------|
| | (b) (4) (N=409) | | Placebo (N=116) | |
| | n (%) | Maximum | n (%) | Maximum |
| Beta-2-microglobulin (mg/L): | N=378 | -- | N=100 | -- |
| 4-6 hr | 6 (10) | 24.04 | 0 (0) | 0.23 |
| 24 hr | 1 (3) | 1.79 | 0 (0) | 0.28 |
| Final visit | 56 (16) | 48.70 | 16 (16) | 13.10 |
| Microalbumin (mg/mmol creatinine) | N=78 | -- | N=20 | -- |
| Final Visit | 8 (10) | 161.21 | 1 (5) | 5.75 |
| Microalbumin (mg/L): | N=298 | -- | N=81 | -- |
| 4-6 hr | 9 (16) | 196 | 2 (22) | 101 |
| 24 hr | 1 (3) | 448 | 0 (0) | 12 |
| Final visit | 55 (20) | 1972 | 18 (23) | 861 |
| NAG (U/L): | N=386 | -- | N=110 | -- |
| 4-6 hr | 22 (37) | 28.52 | 5 (50) | 12.10 |
| 8 hr | 0 (0) | 3.86 | 0 (0) | 4.98 |
| 24 hr | 0 (0) | 3.63 | 2 (33) | 6.59 |
| Final visit | 60 (17) | 27.69 | 24 (22) | 18.08 |
| Urine protein (mg/L): | N=10 | -- | N=10 | -- |
| 8 hr | 2 (20) | 150 | 1 (10) | 120 |
| Final visit | 1 (10) | 130 | 1 (10) | 120 |

Notes: Pediatric subjects from trial 19.4.306 are excluded from this table.

The incidence of AEs related to abnormalities of the urinalysis was low overall and similar for the two treatment groups.

Urinalysis ((b) (4) vs. neostigmine)

The percent of subjects with markedly abnormal post-baseline values at the final visit that met the pre-specified criteria was similar between the two treatment groups. Results for subjects

whose NMBA was rocuronium or vecuronium were consistent with the combined population of rocuronium and vecuronium subjects.

The incidence of AEs related to abnormalities of the urinalysis was low overall and similar between the two treatment groups.

Urinalysis (dose response)

There were no dose trends for the percent of subjects with markedly abnormal post-baseline urinalysis values that met the Applicant's pre-specified criteria. In the (b) (4) subjects, there were markedly abnormal post-baseline high values for beta-2-microglobulin (in 18% of subjects overall), microalbumin (creatinine-dependent) (in 15% of subjects overall), and microalbumin (non-creatinine-dependent) (in 28% of subjects overall). In addition, there were markedly abnormal post-baseline low values for urine creatinine (in 4% of subjects overall). In the total (b) (4) group, there were similar percentages of markedly abnormal post-baseline high (24% overall) or low (18% overall) values for NAG.

Most of the AEs related to abnormalities of the urinalysis occurred in 1.0% or less of the Total (b) (4) group, and no dose trends were observed by the Applicant.

7.1.7.4 Additional analyses and explorations

(b) (4) treated subjects with AEs indicative of peri-operative decrements in renal function were selected from the group of subjects with renal AEs that were judged to be at least possibly related to (b) (4) in the opinion of the investigator. The treatment-related renal AEs in these subjects included beta-N-acetyl-D-glucosaminidase increased, beta 2 microglobulin urine increased, beta 2 microglobulin increased, albumin urine present, hematuria, blood creatinine increased, microalbuminuria, oliguria, red blood cells urine, and urinary casts. Subjects with treatment-related renal AEs that represented a single, non-specific laboratory value were excluded. All available data for the remaining subjects were then reviewed by the Sponsor's medical monitor to determine if the treatment-related renal AE represented a possible decrement in renal function in the peri-operative period.

The AEs related to abnormalities of hematology clinical laboratory tests were evaluated by the Sponsor. The incidence of these AEs was low overall, and the differences in incidence between the (b) (4) treated group and both the placebo-treated and the neostigmine-treated groups were not clinically relevant.

7.1.7.5 Special assessments

No special assessments were indicated by the laboratory results obtained by the Applicant; however, assessments of coagulation were not incorporated into any of the clinical trials as noted in Section 1 of this review. Based on the in-vitro findings and bleeding-related adverse events for (b) (4) clinical assessment of the coagulation profiles following (b) (4) treatment in surgical patients is warranted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In all trials, blood pressure and pulse rate were to be measured in the supine position after a 5-minute rest. Out-of-range vital signs values that were considered by the investigator to be clinically significant to the patient were to be recorded as AEs.

In the Phase 1-3 trials where an NMBA was administered, vital signs included systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, and core body temperature. Blood pressure and pulse rate data were summarized for the following time intervals:

- Baseline, i.e., before the administration of the trial drug
- At 2, 5, 10, and 30 min post-baseline
- At the final visit

In the pooled Phase 1-3 trials, respiratory rate data were summarized for baseline (i.e., screening) and the final visit. Core body temperature (CBT) was measured continuously throughout the anesthetic period. The “yes” or “no” responses to the question “Was the CBT maintained at ≥ 35 C during the entire NMT monitoring?” were summarized.

In the pooled Phase 1 dataset of non-anesthetized healthy volunteers who did not receive an NMBA, vital signs included SBP, DBP, pulse rate, respiratory rate, auricular body temperature, and body weight. Blood pressure and pulse rate data were summarized for the following time intervals:

- Baseline (i.e., before the administration of the trial medication)
- At 2 min, 10 min, 15 min, 30 min, 35 min, 1 hr, 2 hr, 4 hr, 6 hr, 12 hr, and 24 hr post-baseline.

Body temperature, body weight, and respiratory rate data were summarized for the Phase 1 pooled population at baseline and at follow-up. In addition, body weight, height, and body temperature data were summarized for screening and follow-up. Trial 19.4.105 was excluded from pooled Phase 1 dataset for the analysis of blood pressure and pulse rate because no post-

baseline vital signs measurements were required by protocol (but could be measured at the discretion of the investigator), and follow-up vital signs were taken at least 7 days after dosing.

Trial 19.4.107 was excluded from the pooled analysis of vital signs, but its results were summarized from the CTR. In this trial, SBP, DBP, and pulse rate data were examined for the following time intervals:

- screening, baseline (i.e., prior to drug administration)
- at 2 min, 35 min, and 60 min post-baseline
- at follow-up

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

As with the clinical laboratory investigations, the Applicant conducted analyses utilizing data from the controlled trials. Separate comparisons were made for studies using placebo and those using neostigmine as the comparator. The Applicant also analyzed the data comparing the different doses of (b) (4) utilized in the clinical development program.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Descriptive statistics include mean (SD), median, minimum, and maximum observed values, and absolute and percent mean (SD), median, minimum, and maximum changes from baseline.

Systolic blood pressure ((b) (4) vs. placebo)

The Applicant reported that the mean and median baseline systolic blood pressures (SBPs) were similar in the (b) (4) group and the placebo group (mean: 102.7 mmHg (b) (4) vs. 106.3 mmHg placebo; median 99 mmHg (b) (4) vs. 104 mmHg placebo). In both treatment groups, SBP increased after trial drug administration. Mean and median absolute increases from baseline in the placebo group were similar in magnitude across the timepoints, while the mean and median absolute increases from baseline in the (b) (4) group were more variable and were 0.5 to 7 mmHg higher compared to placebo as shown in the table below.

Table 14: Mean changes in SBP from baseline for (b) (4) and placebo

| Time from baseline assessment (minutes) | Mean SBP change from baseline | | | |
|---|-------------------------------|------|---------|-----|
| | (b) (4) | | placebo | |
| | mmHg | % | mmHg | % |
| 2 | 3.5 | 5.0 | 0.8 | 1.7 |
| 5 | -0.7 | -0.1 | 0.2 | 1.1 |
| 10 | 1.7 | 3.3 | 0.2 | 1.2 |
| 30 | 7.8 | 9.4 | 0.7 | 1.9 |

Results for subjects whose NMBA was rocuronium were consistent with the data for the rocuronium and vecuronium subjects combined. However, at the 2 and 10 minute timepoints, results for subjects whose NMBA was vecuronium were dissimilar to those of the overall group and the rocuronium subset. At both of these timepoints, mean percent change from baseline was numerically larger in the vecuronium plus placebo group than in the vecuronium plus (b) (4) group, as follows:

- 2 min: 0.7% (b) (4) + vecuronium, 5.6% placebo + vecuronium; and
- 10 min: -0.3% (b) (4) + vecuronium, 2.0% placebo + vecuronium.

The Applicant indicated it was difficult to assess the significance of the larger mean SBP increases from baseline at 30 min in the (b) (4) group compared to the placebo group due to the varied timing of the administration of (b) (4) across the protocols. When higher doses of (b) (4) were used for immediate reversal, (b) (4) was given early in the course of the procedure and at 30 minutes it was possible that the surgery was not completed, that the subject remained anesthetized, and that SBP values were therefore below pre-anesthetic levels. Conversely, when lower (b) (4) doses were administered toward the end of surgery for routine reversal, the 30 minute SBP values were likely higher because they were returning to pre-anesthetic levels in the awakening subjects.

The Applicant also stated that the difference from placebo could be partially explained by the fact that (b) (4) subjects, having received an agent that actively reverses the effects of neuromuscular blockade, were weaned from anesthesia earlier than placebo subjects. In placebo subjects, the effects of neuromuscular blockade took longer to wane naturally and thus these subjects were kept under anesthesia longer than the (b) (4) subjects. Therefore, at 30-minutes post-dose, some (b) (4) subjects were removed from anesthesia and SBP values were returning to pre-anesthetic levels, whereas most placebo subjects remained anesthetized. This was evidenced in trial 19.4.309 where 49 (of 76 total) (b) (4) subjects and 39 (of 40) placebo subjects remained under anesthesia at least until the 30-minute timepoint. The mean and median changes from baseline in this subgroup were smaller compared to those from the group who stopped anesthesia before the 30 min timepoint. The Applicant noted that the 30-minute SBP values for neostigmine were similar to those for (b) (4) which supports this explanation.

(b) (4) (sugammadex sodium injection)

Systolic blood pressure ((b) (4) vs. neostigmine)

Mean and median baseline SBPs were similar in the (b) (4) group and the neostigmine group (mean: 108.8 mmHg (b) (4) vs. 107.6 mmHg neostigmine; median 108 mmHg (b) (4) vs. 105 mmHg neostigmine). In both treatment groups, SBP increased after trial drug administration. At 2 and at 5 minutes post-baseline, mean and median increases from baseline were 4 to 7 mmHg higher in the neostigmine group than in the (b) (4) group. At 10 and 30 minutes post-baseline, mean absolute increases from baseline were 1 to 2 mmHg higher in the (b) (4) group compared to the neostigmine group. The mean percent (mean absolute) changes from baseline at each timepoint are shown in the table below.

Table 15: Mean changes in SBP from baseline for (b) (4) and neostigmine

| Time from baseline assessment (minutes) | Mean SBP change from baseline | | | |
|---|-------------------------------|------|-------------|-----|
| | (b) (4) | | Neostigmine | |
| | mmHg | % | mmHg | % |
| 2 | 0.1 | 0.3 | 6.8 | 6.9 |
| 5 | 1.9 | 2.0 | 6.2 | 6.2 |
| 10 | 5.4 | 5.9 | 4.0 | 4.7 |
| 30 | 10.8 | 11.2 | 8.8 | 9.2 |

Results for the two subsets of subjects whose NMBA was rocuronium or vecuronium were similar to the rocuronium and vecuronium combined group.

Systolic blood pressure (dose response)

In the Total (b) (4) group, mean baseline SBP was 107 mmHg, and median baseline SBP was 104 mmHg. Mean and median baseline values across the dose groups were similar, ranging from 93 mmHg to 113 mmHg (mean) and from 90 mmHg to 112 mmHg (median). No dose response was observed for change from baseline across all the dose groups. There were similar mean percent increases from baseline in the 2 mg/kg dose group and the 4 mg/kg dose group at each timepoint. The mean percent increase in the 16 mg/kg dose group at 2 min post-baseline was similar to the two other dose groups, but there were mean absolute decreases in this dose group at 5 min, 10 min, and 30 min post-baseline. The mean percent (mean absolute) changes from baseline at each timepoint in the 2 mg/kg, 4 mg/kg, and 16 mg/kg dose groups, respectively, were reported by the Applicant as follows:

- 2 min: 2.6% (2.0 mmHg); 1.9% (1.3 mmHg); 2.7% (1.9 mmHg)
- 5 min: 1.3% (0.8 mmHg); 2.5% (2.2 mmHg); -2.5% (-11.6 mmHg)
- 10 min: 4.8% (3.7 mmHg); 4.7% (4.0 mmHg); -4.7% (-8.5 mmHg)
- 30 min: 13.1% (12.3 mmHg); 13.4% (12.8 mmHg); 9.9% (-1.5 mmHg)

The fact that the 16 mg/kg group had lower SBP values than the lower dose levels of (b) (4) at 5 min and 10 min was explained by the Applicant as being related to the timing of administration of (b) (4) in trials that studied the 16 mg/kg dose (trials 19.4.108, 19.4.205, 19.4.206, and

(b) (4) (sugammadex sodium injection)

19.4.303). In trial 19.4.108, (b) (4) was administered simultaneously with the NMBA, and in the remaining trials it was administered 3 min after the NMBA (19.4.206 and 19.4.303), 5 min after the NMBA (19.4.205), or 15 min after the NMBA (19.4.206). Since (b) (4) was administered relatively early in the course of the surgeries, the subjects were likely still under anesthesia through 10 min post-dose timepoint and, therefore, the SBP values were still well below pre-anesthetic levels. In the majority of the remaining trials in this data analysis group, (b) (4) was administered at the end of the surgical procedure, at reappearance of T₂ or at 1- 2 PTCs after the last dose of NMBA and, within 5-10 min, the subjects were starting to awaken.

Diastolic Blood Pressure ((b) (4) vs. placebo)

Mean and median baseline diastolic blood pressures (DBPs) were similar in the (b) (4) group and the placebo group (mean: 58.6 mmHg (b) (4) vs. 59.3 mmHg placebo; median 58 mmHg (b) (4) vs. 58 mmHg placebo). In both treatment groups, DBP increased after trial drug administration. Mean increases from baseline in the placebo group were similar in magnitude across the timepoints, while mean increases from baseline in the (b) (4) group were more variable and 0.4 to 3.3 mmHg higher compared to placebo. The largest difference between the two groups was observed at 30 minutes post-baseline where the median increase was 4 mmHg (b) (4) and 0 mmHg for placebo. The mean percent (mean absolute) changes from baseline at each timepoint are shown in the table below.

Table 16: Mean changes in DBP from baseline for (b) (4) and placebo

| Time from baseline assessment (minutes) | Mean DBP change from baseline | | | |
|---|-------------------------------|------|---------|-----|
| | (b) (4) | | placebo | |
| | mmHg | % | mmHg | % |
| 2 | 2.8 | 7.1 | 1.0 | 3.3 |
| 5 | -0.5 | 0.2 | 0.2 | 1.1 |
| 10 | 1.3 | 4.8 | 0.9 | 3.3 |
| 30 | 4.4 | 10.4 | 1.1 | 3.9 |

Results for subjects whose NMBA was rocuronium were consistent with the data for the rocuronium and vecuronium subjects combined. At the 5 and 10 minute timepoints, results for subjects whose NMBA was vecuronium were dissimilar to those of the overall group and the rocuronium subset. At 5 minutes post-baseline, there was a mean percent increase from baseline in the vecuronium plus (b) (4) group (1%) and a mean percent decrease in the vecuronium plus placebo group (-1%). At 10 minutes post-baseline, the mean percent increase from baseline was larger in the vecuronium plus placebo group (9%) than in the vecuronium plus (b) (4) group (7%).

Diastolic Blood Pressure ((b) (4) vs. neostigmine)

Mean and median baseline DBPs were similar in the (b) (4) group and the neostigmine group (mean: 60.2 mmHg (b) (4) vs. 61.0 mmHg neostigmine; median 59 mmHg (b) (4) vs. 60 mmHg

neostigmine). In both treatment groups (except for the (b) (4) group at 2 min post-baseline), DBP increased after trial drug administration. At 2 min and 5 min post-baseline, mean and median changes from baseline were about 3 to 5 mmHg higher in the neostigmine group than in the (b) (4) group; at 10 min and 30 min post-baseline, they were about 1 to 3 mmHg higher in the (b) (4) group than the neostigmine group. The mean percent (mean absolute) changes from baseline at each timepoint are shown in the table below.

Table 17: Mean changes in DBP from baseline for (b) (4) and neostigmine

| Time from baseline assessment (minutes) | Mean DBP change from baseline | | | |
|---|-------------------------------|------|-------------|-----|
| | (b) (4) | | Neostigmine | |
| | mmHg | % | mmHg | % |
| 2 | -0.3 | -0.2 | 4.6 | 8.8 |
| 5 | 0.3 | 1.3 | 3.3 | 6.2 |
| 10 | 3.7 | 8.0 | 1.1 | 2.9 |
| 30 | 5.8 | 12.3 | 4.2 | 8.5 |

Results for the two subsets of subjects whose NMBA was rocuronium or vecuronium were similar to the rocuronium and vecuronium combined group.

Diastolic Blood Pressure (dose response)

In the Total (b) (4) group, mean baseline DBP was 61 mmHg, and median baseline DBP was 60 mmHg (Appendix Table 156). Mean and median baseline values across the dose groups were similar, ranging from 49 mmHg to 69 mmHg (mean) and from 49 mmHg to 69 mmHg (median). While there were similar mean and median changes from baseline (primarily increases) in the 2 mg/kg dose group compared to the 4 mg/kg dose group, there were mean decreases from baseline in the 16 mg/kg dose group (except for mean changes at the 2 min timepoint). The mean percent (mean absolute) changes from baseline at each timepoint in the 2 mg/kg, 4 mg/kg, and 16 mg/kg dose groups, respectively, were as follows:

- 2 min: 4.4% (1.7 mmHg); 2.0% (0.5 mmHg); 3.2% (0.8 mmHg)
- 5 min: 0.8% (-0.1 mmHg); 1.8% (0.5 mmHg); -57.0% [median -15%] (-9.6 mmHg)
- 10 min: 5.7% (2.1 mmHg); 4.5% (1.7 mmHg); -65.3 [median -11.5%] (-7.3 mmHg)
- 30 min: 13.8% (6.6 mmHg); 12.7% (6.0 mmHg); -54.1% [median -4.5%] (-2.2 mmHg)

Heart rate ((b) (4) vs. placebo)

Mean and median baseline pulse rates were similar in the (b) (4) group and the placebo group (mean: 63.3 bpm (b) (4) vs. 61.8 bpm placebo; median 62 bpm (b) (4) vs. 61 bpm placebo). Mean and median changes from baseline in each treatment group were small; at 2 min, 5 min, and 10 min post baseline, there were mean absolute decreases from baseline in the (b) (4) group. The mean percent (median absolute) changes from baseline at each timepoint were reported by the Applicant as follows:

- 2 min: 0.3% (-0.3 bpm) (b) (4) 2.8% (1.5 bpm) placebo

(b) (4) (sugammadex sodium injection)

- 5 min: -2.6% (-2.0 bpm) (b) (4) -0.6% (-0.3 bpm) placebo
- 10 min: -0.0% (-0.6 bpm) (b) (4) 3.1% (1.5 bpm) placebo
- 30 min: 3.6% (1.5 bpm) (b) (4) 1.0% (0.2 bpm) placebo

Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined, with one exception. At the 30 min timepoint, mean and median changes for subjects who received vecuronium plus (b) (4) (mean 6.8 bpm, median 3.0 bpm) were larger than for subjects who received vecuronium plus placebo (mean 0.7 bpm, median 1.0 bpm). However, this finding was not considered to be clinically significant.

Heart rate ((b) (4) vs. neostigmine)

Mean and median baseline pulse rate values were similar in the (b) (4) group and the neostigmine group (mean: 65.4 bpm (b) (4) vs. 65.6 bpm neostigmine; median 63 bpm (b) (4) vs. 63 bpm neostigmine). In the (b) (4) group, pulse rate decreased at 2 min and 5 min post-baseline; in the neostigmine group, pulse rate increased at each timepoint. At 2 min, 5 min, and 10 min post-baseline, mean and median changes from baseline were about 5 to 16 bpm higher in the neostigmine group than in the (b) (4) group; at 30 min post baseline, they were about 2 bpm (median absolute) to 3 bpm (mean absolute) higher in the (b) (4) group than the neostigmine group. The mean percent (mean absolute) changes from baseline at each timepoint were as follows:

- 2 min: -2.7% (-1.9 bpm) (b) (4) 21.8% (13.7 bpm) neostigmine
- 5 min: -1.7% (-1.3 bpm) (b) (4) 15.6% (9.8 bpm) neostigmine
- 10 min: 1.5% (0.8 bpm) (b) (4) 9.5% (5.8 bpm) neostigmine
- 30 min: 8.3% (4.7 bpm) (b) (4) 4.5% (2.1 bpm) neostigmine

Results were similar for the two subsets of subjects whose NMBA was rocuronium or vecuronium.

Heart rate (dose response)

For the Total (b) (4) group, the Applicant reported that the mean baseline pulse rate was 65.7 bpm, and the median baseline pulse rate was 64 bpm. Mean and median baseline values across the dose groups ranged from 52 bpm to 74 bpm (mean) and from 52 bpm to 70 bpm (median). Across all the dose groups, at 5 min and 30 min post-baseline there was a trend for larger mean or median absolute decreases with increasing dose of (b) (4)

There were similar, small mean decreases or increases from baseline in the 2 mg/kg dose group compared to the 4 mg/kg dose group. In the 16 mg/kg dose group, however, there were larger mean and/or median percent decreases from baseline at each timepoint (except at 2 min). The mean percent (mean absolute) changes from baseline at each timepoint in the 2 mg/kg, 4 mg/kg, and 16 mg/kg dose groups (respectively) were as follows:

- 2 min: -1.0% (-1.0 bpm); -2.6% (-2.0 bpm); -2.4% (-2.9 bpm)

(b) (4) (sugammadex sodium injection)

- 5 min: -2.1% (-1.5 bpm); -1.4% (-1.2 bpm); -43.7% [median -8.8%] (-6.6 bpm)
- 10 min: 1.3% (0.4 bpm); 1.0% (0.1 bpm); -19.7% [median -9.1%] (-6.5 bpm)
- 30 min: 7.7% (4.2 bpm); 7.4% (4.1 bpm); 10.3% [median -9.4%] (-7.3 bpm)

Respiratory rate ((b) (4) vs. placebo)

The Applicant reported that the mean and median baseline respiratory rates were similar in the (b) (4) group and the placebo group (mean: 14.5 breaths/min (b) (4) vs. 14.4 breaths/min placebo; median: 14 breaths/min (b) (4) vs. 14 breaths/min placebo). Mean and median changes from baseline to the final visit were small and, according to the Applicant, there were no clinically important treatment group differences. Mean change and mean percent change was 0.4 breaths/min (4% change) in the (b) (4) group, and 0.8 breaths/min (7% change) in the placebo group. Results for subjects whose NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined.

Respiratory rate ((b) (4) vs. neostigmine)

The Applicant reported that the mean and median baseline respiratory rates were similar in the (b) (4) group and the neostigmine group (mean: 15.7 breaths/min (b) (4) vs. 15.5 breaths/min neostigmine; median: 16 breaths/min (b) (4) vs. 16 breaths/min neostigmine). Mean and median changes from baseline to the final visit were small, and there were no clinically important treatment group differences. Mean change and mean percent change was 0.1 breaths/min (2% change) in the (b) (4) group, and 0.0 breaths/min (2% change) in the neostigmine group. Results for subjects who NMBA was rocuronium or vecuronium were consistent with the data for the rocuronium and vecuronium subjects combined.

Respiratory rate (dose response)

In the Total (b) (4) group, mean baseline respiratory rate was 15.8 breaths/min, and median baseline respiratory rate was 16 breaths/min. Mean and median baseline values across the dose groups ranged from 11.8 breaths/min to 16.7 breaths/min (mean) and from 12.0 breaths/min to 20.0 breaths/min (median). Mean and median changes from baseline to the final visit were small, and no dose trend was apparent for change from baseline. In the Total (b) (4) group, mean change from baseline was 0.1 breaths/min and mean percent change was 3%. There was a small mean increase from baseline of 0.2 breaths/min in both the 2 mg/kg and 4 mg/kg dose groups (a 3% and a 3% mean increase, respectively), while a small mean decrease of 0.5 breaths/min (2% mean decrease) was observed in the 16 mg/kg dose group.

Core body temperature (CBT)

Descriptive statistics were not reported by the Applicant. Although central body temperature was measured continuously throughout the anesthetic period; the Applicant summarized the “yes” or “no” responses to the question “Was the CBT maintained at $\geq 35^{\circ}\text{C}$ during the entire NMT monitoring” and identified those subjects who became hypothermic.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The Applicant did not conduct an analysis focused on outliers. Instead, marked outlier criteria were established and analyses based on the data collected in this manner were performed and are discussed below. Analyses focused on shifts from normal to abnormal were also not conducted. While a formal explanation was not provided for not conducting these analyses, an argument could be made that the interpretation of the findings from such analyses would be difficult as the hemodynamic changes that occur with induction, maintenance and emergence from general anesthesia can be substantial and make it difficult at best to make either intra- or inter-treatment group comparisons. The problem is magnified if the assessments are made at different stages of the anesthetic for the different treatments as noted above for the comparison of (b) (4) to placebo.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

The number and percent of subjects with markedly abnormal values according to the pre-defined safety ranges were summarized by treatment group. The subjects with markedly abnormal values were also identified. In addition, AEs related to vital signs abnormalities were summarized.

Systolic Blood Pressure

The Applicant reported that the overall percentage of subjects with treatment-emergent markedly abnormal SBP values that met the pre-specified criteria was small and similar between the two treatment groups regardless of timepoint as shown in the table below. Results for subjects whose NMBA was rocuronium were similar to the combined population of rocuronium and vecuronium subjects. In the subset of subjects who received vecuronium, 4% vecuronium plus (b) (4) subjects and no vecuronium plus placebo subjects had markedly abnormal increases in SBP.

Table 18: Incidence of markedly abnormal SBP post-baseline for (b) (4) and placebo (Table 47 from ISS p. 158)

| Parameter | Rocuronium or vecuronium + | |
|--|----------------------------|--------------------|
| | (b) (4) (N=640) | Placebo (N=140) |
| SBP markedly decreased (n [%] of subjects) | 44 (7) | 9 (6) |
| Minimum SBP value at any timepoint | 53 mmHg | 65 mmHg |
| SBP markedly increased (n [%] of subjects) | 27 (4) | 4 (3) |
| Maximum SBP value at any timepoint | 240 mmHg | 191 mmHg |

Pediatric subjects from trial 19.4.306 are excluded from this table.

(b) (4) (sugammadex sodium injection)

The overall percentage of subjects with treatment-emergent markedly abnormal SBP values that met the pre-specified criteria was small and similar between the (b) (4) versus neostigmine treatment groups regardless of timepoint or NMBA as indicated in the table below.

Table 19: Incidence and magnitudes of markedly abnormal SBP values for Trials 19.4.301 and 19.4.302 (From Table 49 of ISS, p. 160)

| Parameter | Rocuronium or vecuronium + | |
|--|----------------------------|------------------------|
| | (b) (4) (N=179) | Neostigmine (N=167) |
| SBP markedly decreased (n [%] of subjects) | 12 (7) | 7 (4) |
| Minimum SBP value at any timepoint | 68 mmHg | 69 mmHg |
| SBP markedly increased (n [%] of subjects) | 11 (6) | 11 (7) |
| Maximum SBP value at any timepoint | 204 mmHg | 210 mmHg |

The incidence of these AEs was similar between the (b) (4) and placebo treatment groups as shown in the table below.

Table 20: Incidence of adverse events for blood pressure (based on ISS Table 48)

| Adverse Event Preferred Term | Rocuronium or vecuronium + | |
|------------------------------------|----------------------------|--------------------|
| | (b) (4) (N=640) | Placebo (N=140) |
| | n (%) | n (%) |
| At least one AE | 437 (68) | 101 (72) |
| Procedural hypotension | 31 (5) | 4 (3) |
| Procedural hypertension | 16 (3) | 4 (3) |
| Hypertension | 14 (2) | 4 (3) |
| Hypotension | 12 (2) | 2 (1) |
| Blood pressure decreased | 3 (1) | 0 (0) |
| Blood pressure increased | 2 (0) | 1 (1) |
| Orthostatic hypotension | 1 (0) | 0 (0) |
| Systolic hypertension | 1 (0) | 0 (0) |
| Blood pressure diastolic decreased | 0 (0) | 1 (17) |

Note: Pediatric subjects from trial 19.4.306 are excluded from this table.

The adverse events for Trial 19.4.301 and 19.4.302 are related to abnormalities of blood pressure and are summarized by treatment group in the table below. Procedural hypotension occurred more frequently in neostigmine subjects compared to (b) (4) subjects.

(b) (4) (sugammadex sodium injection)

Table 21: Adverse Events related to blood pressure for Trial 19.4.301 and 19.4.302 (from Table 50 of ISS, p. 161)

| Adverse Event Preferred Term | Rocuronium or vecuronium + | |
|------------------------------------|----------------------------|------------------------|
| | (b) (4) (N=179) | Neostigmine (N=167) |
| | n (%) | n (%) |
| At least one AE | 157 (88) | 149 (89) |
| Procedural hypertension | 9 (5) | 9 (5) |
| Procedural hypotension | 2 (1) | 11 (7) |
| Hypertension | 2 (1) | 0 (0) |
| Blood pressure diastolic decreased | 1 (1) | 0 (0) |
| Blood pressure diastolic increased | 1 (1) | 0 (0) |
| Blood pressure systolic increased | 1 (1) | 0 (0) |

Diastolic Blood Pressure

The overall percentage of subjects with treatment-emergent, markedly abnormal DBP values that met the pre-specified criteria was small and similar between the two treatment groups regardless of timepoint. Results for subjects whose NMBA was rocuronium were similar to the combined population of rocuronium and vecuronium subjects. In the subset of subjects who received vecuronium, 6% vecuronium plus (b) (4) subjects and no vecuronium plus placebo subjects had markedly high post-baseline DBP values.

Table 22: Incidence of markedly abnormal SBP post-baseline for (b) (4) and placebo (Table 52 from ISS p. 165)

| Parameter | Rocuronium or vecuronium + | |
|--|----------------------------|--------------------|
| | (b) (4) (N=640) | Placebo (N=140) |
| DBP markedly decreased (n [%] of subjects) | 37 (6) | 7 (5) |
| Minimum DBP value at any timepoint | 20 mmHg | 24 mmHg |
| DBP markedly increased (n [%] of subjects) | 33 (5) | 5 (4) |
| Maximum DBP value at any timepoint | 120 mmHg | 114 mmHg |

Note: Pediatric subjects from trial 19.4.306 are excluded from this table.

The AEs related to abnormalities of blood pressure were presented in Table 48 Adverse events specific to DBP included blood pressure diastolic decreased (1 [1%] placebo subject and no (b) (4) subject).

Core body temperature ((b) (4) vs. placebo)

The incidence of subjects whose central body temperature was not maintained at ≥ 35 °C during the entire neuromuscular transmission monitoring was 4% in the (b) (4) group and 1% in the placebo group. Results for subjects whose NMBA was rocuronium or vecuronium were similar

to the results for the combined population of rocuronium and vecuronium subjects. The AE pyrexia occurred in similar percentages of (b) (4) and placebo subjects. Other AEs related to abnormalities of body temperature were rarely reported.

Core body temperature ((b) (4) vs. neostigmine)

The incidence of subjects whose central body temperature was not maintained at $\geq 35^{\circ}\text{C}$ during the entire neuromuscular transmission monitoring was higher in the (b) (4) group (12%) compared to the neostigmine group (5%). The lowest central body temperature recorded for nine of the 22 (b) (4) subjects ranged between $33\text{-}34.9^{\circ}\text{C}$ and for three of the nine neostigmine subjects ranged between $32.5\text{-}34.9^{\circ}\text{C}$. The reason for the difference in incidence between the two treatment groups was attributed by the Applicant to several factors including technical issues such as drapes or Bair huggers being inappropriately placed or the operating room being too cold. For some subjects it was not possible to discern when the central body temperature decreased in relation to the administration of the trial medication. Most of the (b) (4) subjects had received vecuronium rather than rocuronium, whereas the placebo subjects were more equally distributed between the rocuronium and vecuronium subsets. The incidence of AEs related to abnormalities of body temperature was similar in each treatment group.

Core body temperature (dose response)

The incidence of subjects whose central body temperature was not maintained at $\geq 35^{\circ}\text{C}$ during the entire neuromuscular transmission monitoring was 9% in the Total (b) (4) group, and no dose trend was apparent. The incidence was similar in the 4 mg/kg (12%) and 16 mg/kg (11%) dose groups, and less in the 2 mg/kg dose group (8%). Pyrexia (7.4% of the Total (b) (4) group) was the most frequent AE related to abnormalities of body temperature; all others were reported in less than 1.0% of the Total (b) (4) group.

7.1.8.4 Additional analyses and explorations

No additional analyses were indicated or conducted. No other explorations were performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical testing of (b) (4) provided no basis for concern in human administration. Clinical testing of the effects of (b) (4) on the cardiac conduction system included the recording and

analysis of electrocardiograms in 10 of the clinical trials and the completion of two thorough QTc studies. The findings from the clinical studies are discussed in detail in the sections below.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Two prospective, thorough, QTc studies (19.4.105 and 19.4.109) were conducted using the therapeutic dose (4 mg/kg) and the supra-therapeutic dose (32 mg/kg) of (b) (4) alone (19.4.105) or in combination with rocuronium or vecuronium (19.4.109). In addition, electrocardiographic data were collected in 10 of the 26 trials in which subjects received an NMBA in addition to the trial medication. The pooled analysis included data from the following eight trials: 19.4.101 (Part 2), 19.4.202, 19.4.204, 19.4.205, 19.4.206, 19.4.210, 19.4.306, and 19.4.309. Data from trials 19.4.108 and 19.4.109 were excluded from the pooled analysis for the following reasons:

- Trial 19.4.108 had no post-baseline measurements at the same times as the other trials. No ECGs were recorded immediately after the administration of the trial medication, and the post-anesthetic recording was not taken until 3 days post-trial drug. In addition, all individual values for ECG parameters were reported by the Applicant to be within normal limits, so ECG results from this trial were not discussed further.
- Trial 19.4.109 was a thorough QTc trial and was analyzed and discussed separately along with Trial 19.4.105.

The times of ECG recording after the administration of the trial medication ((b) (4) or placebo) are shown in table below for the eight trials included in the pooled Phase 1-3 analysis. These data were summarized for the 2-minute and 30-minute post-(b) (4) administration timepoints and for the remaining post-(b) (4) administration timepoints combined. The baseline ECG in these trials was taken at the time of “stable anesthesia,” prior to the administration of the rocuronium, which was the only NMBA used in each of these trials.

Since rocuronium was the only NMBA administered in the pooled Phase 1-3 trials ECG dataset, and since there was no active comparator in these trials, the ECG data for the pooled Phase 1-3 trials are presented only by Org 25959 mg/kg dose group. It was noted by the Applicant that there were approximately 5 times as many Org 25959 + rocuronium subjects (n=475) compared to placebo + rocuronium subjects (n=88) in these trials.

Table 23: Pooled Phase 1-3 trials: Time of ECG recording (Table 66 from ISS)

| Trial | Time of ECG recording post-administration of study drug | | | | | | |
|-----------------------|---|-------|--------|--------|------|------|------------------------|
| | 2 min | 5 min | 10 min | 30 min | 1 hr | 2 hr | Follow-up ^B |
| 19.4.101 (Part 2) | X | | X | X | X | X | |
| 19.4.202 | X | | | X | | | |
| 19.4.204 ^A | X | | | X | | | |
| 19.4.205 | X | | | X | | | |
| 19.4.206 | X | | | X | | | X ^B |

(b) (4) (sugammadex sodium injection)

| Trial | Time of ECG recording post-administration of study drug | | | | | | |
|-----------------------|---|-------|--------|--------|------|------|------------------------|
| | 2 min | 5 min | 10 min | 30 min | 1 hr | 2 hr | Follow-up ^B |
| 19.4.210 ^A | X | | | X | | | |
| 19.4.306 | X | | | X | | | |
| 19.4.309 | X | X | X | X | | | X ^B |

^A Placebo was used in all trials except for 19.4.204 and 19.4.210.

^B In 19.4.206, follow-up occurred during post-anesthesia while the subject was in the recovery room; in 19.4.309, follow-up took place at the post-anesthetic visit at least 10 hr after the administration of the trial medication, or on the post-operative day.

Electrocardiographic data were collected in each of the six trials in which subjects did not receive an NMBA. The pooled analysis included data from trials 19.4.101 (Part 1), 19.4.102, and 19.4.106. Data from the thorough QTc trials, 19.4.105 and 19.4.109, were summarized from their respective CTRs. Study 19.4.107 was excluded from the pooled analysis of ECGs; however, the results were summarized from the CTR.

The times of ECG recording after the administration of the trial medication ((b) (4) or placebo) are shown in table below for the three trials included in the pooled Phase 1 analysis. These data are summarized for the following timepoints: 2 min, 10-15 min, 30-35 min, 1 hr, 2 hr, and 12-24 hr. The baseline ECG in these trials was the last ECG recorded prior to the administration of the trial medication.

Table 24 Pooled Phase 1 trials: Time of ECG recording (Table 67 from ISS)

| Trial | Time of ECG recording post-administration of (b) (4) or placebo ^A | | | | | | | | | | | | |
|-------------------|--|--------|--------|--------|--------|------|------|------|------|------|-------|-------|------------------------|
| | 2 min | 10 min | 15 min | 30 min | 35 min | 1 hr | 2 hr | 3 hr | 4 hr | 6 hr | 12 hr | 24 hr | Follow-up ^B |
| 19.4.101 (Part 1) | X | X | | X | | X | X | | | | | | X |
| 19.4.102 | X | X | X | X | | X | X | | | | X | | X |
| 19.4.106 | X | | | | | X | X | X | X | X | X | X | X |

^A Placebo was used in all trials.

^B In 19.4.101 (Part 1), 7-10 days post-dose; in 19.4.102, 3-7 days post-dose; in 19.4.106, not defined.

7.1.9.3 Standard analyses and explorations of ECG data

ECG acquisition and interpretation

12-lead ECGs were obtained using standard ECG recorders and were evaluated onsite by the Investigator for immediate safety assessments. Digital ECGs were then over-read in a blinded, random order by the core ECG laboratory (Covance Central Diagnostics Inc., Reno, NV). Each ECG was then reviewed by a single qualified cardiologist for qualitative (morphology and diagnostic) findings, and post-baseline ECGs were compared to the baseline ECG for qualitative findings.

QT interval correction methods

The following three correction methods were used to calculate QTc duration:

- Bazett’s formula (QTcB): $QTc = QT/(RR)^{0.5}$,
- Fridericia’s formula (QTcF): $QTc = QT/(RR)^{0.333}$, where RR = 60/heart rate, and
- Trial specific formula based on linear regression (QTcL): First, the linear regression model $QT = a + b(RR)$ was fitted to the baseline QT:RR data. Then, the estimated slope “b” was then used to derive a trial-specific QT correction using the following formula: $QT + b(1-RR)$.

In the pooled analyses, the Fridericia correction, but not the Bazett correction, produced a slope which was nearly zero and was, therefore, considered to be the most appropriate correction method for these trial populations. Also, the trial-specific linear correction provided the best fit to these data by design. Therefore, the discussion of QTc data, by the Applicant and in this review, is focused on QTcF and QTcL rather than QTcB.

The definitions of normal and abnormal values for the categorical analysis of ECG parameters are shown in the table below. The criteria for markedly abnormal ECG HR values were the same as those for markedly abnormal pulse rate values.

Table 25 Definition of normal and abnormal values for the categorical analysis of pooled ECG data (Table 68 from ISS)

| Variable | Category/ rating | Criterion | |
|------------------------------|---|--|--|
| Heart rate (bpm) | A: Low B: Normal C: High | ≤ 50 51 – 119 ≥ 20 | |
| PR interval duration (msec) | A: Normal B: Prolonged | < 210 ≥ 210 | |
| QRS interval duration (msec) | A: Short B: Normal C: Prolonged | ≤ 50 51 – 119 ≥ 120 | |
| QT interval duration (msec) | A: Short B: Normal C: Prolonged | ≤ 200 201 – 499 ≥ 500 | |
| QTc duration (msec) | | Male | Female |
| | A: Normal B: Borderline C: Prolonged D: Abnormal | < 430 430 – 450 451 – 480 > 480 | < 450 450 – 470 471 – 500 > 500 |

| Variable | Category/ rating | Criterion |
|---------------------------------|--|-------------------------|
| QTc change from baseline (msec) | A: Normal B: Borderline C: Prolonged | < 30 30 – 60 > 60 |

The core ECG laboratory assessed the presence or absence of pathological U waves (i.e., U waves that reached an amplitude of 25% of the T wave in any lead), and classified T-wave morphology according the criteria shown in the table below.

Table 26 Description of T wave morphology for pooled ECG data (Table 69 from ISS)

| T Wave Morphology | Description |
|------------------------------|---|
| Tall | Any T wave > 10 mm |
| Notched | Any transient change in the sign of the slope of the T wave reverting to the previous slope |
| Low | T/R ratio less than approximately 1/10 |
| Flat | T amplitude < positive 1 mm to < negative 1 mm |
| Diphasic (positive-negative) | T amplitude > positive 1 mm followed by amplitude > negative 1 mm but < negative 5 mm |
| Diphasic (negative-positive) | T amplitude > negative 1 mm but < negative 5 mm followed by amplitude > positive 1 mm |
| Slightly negative | T amplitude > negative 1 mm but < negative 5 mm without diphasic T wave |
| Deeply negative | T amplitude > negative 5 mm with or without diphasic T waves |

QTc duration: statistical analysis of dose response (pooled data)

In order to more formally explore any possible effect of (b) (4) on QTc duration, the Applicant performed a statistical analysis of dose response for ECG heart rate, QTcB, QTcF, and QTcL. This analysis was similar to the ECG analyses conducted for the ECG expert reports for trials 19.4.202, 19.4.204, 19.4.205, 19.4.206, 19.4.210, 19.4.306, and 19.4.309. This analysis was exploratory in nature.

Statistical tests were two-sided and p-values less than or equal to 0.05 were considered to be statistically significant. There were no adjustments for multiplicity. Where applicable, estimates of within-dose group and between-dose group differences, with their 95% confidence intervals (95% CIs), were presented.

Within-dose group comparisons

For each dose group, the Applicant performed a paired t-test to compare the baseline value to each post-baseline value.

Between-dose group comparisons

For each post-baseline timepoint, the Applicant compared the dose groups using analysis of variance (ANOVA), with dose as an independent variable and the baseline value as a covariate. The Applicant also used a linear regression analysis to investigate possible dose trends.

7.1.9.3.1 Analyses focused on measures of central tendency

The table below summarizes the results as reported by the Applicant for the various ECG parameters and pooled data sets.

Table 27: Summary ECG data from pooled trials (based on Table 70 of ISS)

| ECG Parameter | Trial Population | Summary of Results |
|---------------|------------------|--|
| QTc | Pooled Phase 1-3 | Changes from baseline were similar for (b) (4) and placebo at 2 min and 30 min post-dose. Regression analysis showed no statistically significant effect of (b) (4) dose. One (0.2% of 468) (b) (4) subject (4 mg/kg) and no placebo subject (of 88 subjects) shifted from a normal value at baseline to an abnormal value post-baseline (at 30 min). Six (1.3%) (b) (4) subjects (three 2 mg/kg, two 4 mg/kg, one 16 mg/kg) and one (1.1%) placebo subject had a > 60 msec change from baseline for QTcF. |
| | Pooled Phase 1 | Changes from baseline were similar for (b) (4) and placebo at each post-dose timepoint (2 min, 10-15 min, 30-35 min, 1 hr, 2 hr, and 12-24 hr). There was no apparent dose trend for change from baseline at any timepoint. No subject had a >60 msec change from baseline for QTcF. |
| QT | Pooled Phase 1-3 | Changes from baseline were similar for (b) (4) and placebo at 2 min and 30 min post-dose. There was no apparent dose trend for change from baseline at any timepoint. |
| | Pooled Phase 1 | Changes from baseline were similar for (b) (4) and placebo at each post-dose timepoint (2 min, 10-15 min, 30-35 min, 1 hr, 2 hr, and 12-24 hr). There was no apparent dose trend for change from baseline at any timepoint. |
| ECG HR | Pooled Phase 1-3 | In each treatment group changes from baseline were small and clinically unimportant. Regression analysis showed no statistically significant effect of (b) (4) dose. No subject had a treatment-emergent markedly high value at any timepoint, and a similar percentage of subjects in each treatment group had treatment-emergent markedly low values at 2 min (6% (b) (4) and 4% placebo) and 30 min (7% (b) (4) and 9% placebo). |

(b) (4) (sugammadex sodium injection)

| ECG Parameter | Trial Population | Summary of Results |
|---------------|------------------|---|
| | Pooled Phase 1 | In each treatment group, changes from baseline were small and clinically unimportant. There was no apparent dose trend for change from baseline at any timepoint. No subject had a treatment-emergent markedly high value at any timepoint. At timepoints from 2 min through 1 hr, the percentage of subjects with treatment-emergent markedly low ECG HR was higher in the (b) (4) group compared to the placebo group. Treatment group differences were most pronounced at 2 min (21% (b) (4) and 11% placebo) and at 10-15 min (30% (b) (4) and 6% placebo). However, the magnitude of maximum decrease from baseline was similar for (b) (4) (range across all timepoints and doses -13.0 bpm to -16.3 bpm) and placebo (range across all timepoints -11.0 bpm to -17.0 bpm). |
| PR | Pooled Phase 1-3 | In each treatment group changes from baseline were small and clinically unimportant. There was no apparent dose trend for change from baseline at any timepoint. |
| | Pooled Phase 1 | In each treatment group changes from baseline were small and clinically unimportant. There was no apparent dose trend for change from baseline at any timepoint (2 min, 10-15 min, 30-35 min, 1 hr, 2 hr, and 12-24 hr). No subject had a treatment-emergent markedly high value at any timepoint. Shifts from a normal baseline value to a prolonged value post-baseline were observed only in the placebo group, at 2 min (one subject), at 10-15 min (one subject), and at 1 hr (one subject). |
| U waves | Pooled Phase 1-3 | A shift in U waves from absent at baseline to present post-baseline was observed in 3 (1%) (b) (4) subjects and in no placebo subject. There were too few observations to judge dose-response. |
| T waves | Pooled Phase 1-3 | The percentage of subjects with shifts in T-wave morphology from normal at baseline to abnormal post-baseline was low and similar for the (b) (4) group and the placebo group at all timepoints. No dose trends were observed. |
| QRS | Pooled Phase 1-3 | Changes from baseline were similar for (b) (4) and placebo at 2 min and 30 min post-dose. There was no apparent dose trend for change from baseline at any timepoint. |
| | Pooled Phase 1 | Changes from baseline were similar for (b) (4) and placebo at each post-dose timepoint (2 min, 10-15 min, 30-35 min, 1 hr, 2 hr, and 12-24 hr). There was no apparent dose trend for change from baseline at any timepoint. No clinically significant ECG abnormalities were observed in the pharmacokinetics trial 19.4.107. |

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The table below summarizes the results for the various ECG parameters and pooled data sets.

Table 28: Summary ECG data from pooled trials (based on Table 70 of ISS)

| ECG Parameter | Trial Population | Summary of Results |
|---------------|------------------|---|
| QTc | Pooled Phase 1-3 | One (0.2% of 468) (b) (4) subject (4 mg/kg) and no placebo subject (of 88 subjects) shifted from a normal value at baseline to an abnormal value post-baseline (at 30 min). |
| | Pooled Phase 1 | No subject shifted from a normal value at baseline to a prolonged or abnormal value post-baseline. |
| QT | Pooled Phase 1-3 | Few subjects shifted from a normal value at baseline to a prolonged value post-baseline (1% (b) (4) and 2% placebo at 2 min, 1% (b) (4) and 3% placebo at 30 min, 4% (b) (4) and 6% placebo at other timepoints). |
| | Pooled Phase 1 | Few subjects shifted from a normal value at baseline to a prolonged value post-baseline (two (b) (4) subjects at 2 min [one 64 mg/kg, one 96 mg/kg], and one (b) (4) subject [96 mg/kg] at 30-35 min). |
| ECG HR | Pooled Phase 1-3 | In each treatment group changes from baseline were small and clinically unimportant. Regression analysis showed no statistically significant effect of (b) (4) dose. No subject had a treatment-emergent markedly high value at any timepoint, and a similar percentage of subjects in each treatment group had treatment-emergent markedly low values at 2 min (6% (b) (4) and 4% placebo) and 30 min (7% (b) (4) and 9% placebo). |
| | Pooled Phase 1 | According to the Applicant, in each treatment group, changes from baseline were small and clinically unimportant. There was no apparent dose trend for change from baseline at any timepoint. No subject had a treatment-emergent markedly high value at any timepoint. At timepoints from 2 min through 1 hr, the percentage of subjects with treatment-emergent markedly low ECG HR was higher in the (b) (4) group compared to the placebo group. Treatment group differences were most pronounced at 2 min (21% (b) (4) and 11% placebo) and at 10-15 min (30% (b) (4) and 6% placebo). However, the magnitude of maximum decrease from baseline was similar for (b) (4) (range across all timepoints and doses -13.0 bpm to -16.3 bpm) and placebo (range across all timepoints -11.0 bpm to -17.0 bpm). |
| PR | Pooled Phase 1-3 | Few subjects shifted from a normal value at baseline to a prolonged value post-baseline (1% (b) (4) and 2% placebo at 2 min, < 1% (b) (4) and 2% placebo at 30 min). |
| | Pooled Phase 1 | Shifts from a normal baseline value to a prolonged value post-baseline were observed only in the placebo group, at 2 min (one subject), at 10-15 min (one subject), and at 1 hr (one subject). |

| ECG Parameter | Trial Population | Summary of Results |
|---------------|------------------|---|
| U waves | Pooled Phase 1-3 | A shift in U waves from absent at baseline to present post-baseline was observed in 1% (3) (b) (4) subjects and in no placebo subject. There were too few observations to judge dose-response. |
| T waves | Pooled Phase 1-3 | The percentage of subjects with shifts in T wave morphology from normal at baseline to abnormal post-baseline was low and similar for the (b) (4) group and the placebo group at all timepoints. No dose trends were observed. |
| QRS | Pooled Phase 1-3 | Few subjects shifted from a normal value at baseline to a prolonged value post-baseline (1% (b) (4) and 0% placebo at 2 min, 1% (b) (4) and 1% placebo at 30 min). |
| | Pooled Phase 1 | The percentage of subjects with shifts from a normal baseline value to a prolonged value post-baseline was higher in the (b) (4) group compared to the placebo group at 30-35 min (respectively, 4% vs. 0%) and at 2 hr (respectively, 3% vs. 0%), but was low and similar at the other timepoints. |

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

There were two dropouts related to ECG abnormalities. One was for electromechanical dissociation (EMD) and the other was for electrocardiogram QT prolonged; the subjects experienced their adverse events following 1 mg/kg and 4 mg/kg doses of (b) (4) respectively.

The incident of QT prolongation occurred on the day of surgery; it's duration was not captured and it was not treated. The Applicant and Investigator judged the event to be unlikely related to (b) (4) however, in the absence of another cause or reason not to suspect (b) (4) I would judge the event to be related to the study drug.

The incident of EMD occurred on postoperative day 4 and was associated with a perforated colon and sepsis. It was considered by the Investigator and Applicant as unrelated to (b) (4) I concur with this assessment based on the timing of the event and the concomitant diagnoses.

7.1.9.3.4 Thorough QTc Study 19.4.105

Title: "Randomized, double-blind, placebo-controlled five-period cross-over study to investigate the effect on the QT/QTc interval of IV single doses of Org 25969 and an open label active control part consisting of a single IV dose of moxifloxacin in healthy volunteers."

Objectives:

- Primary objectives
 - To investigate if single dose IV treatment with 4 mg/kg and 32 mg/kg (b) (4) do not clinically significantly prolong the QTc interval as compared to placebo.

(b) (4) (sugammadex sodium injection)

- To establish assay sensitivity by demonstrating QT/QTc interval prolongation as compared to placebo after single dose IV treatment with 400 mg moxifloxacin.
- Secondary objectives
 - To relate the plasma concentrations of (b) (4) after single dose administration of 4 mg/kg and 32 mg/kg with the QTc intervals.
 - To investigate safety and tolerability of the various treatments.

Design: This was a single center, randomized, placebo-controlled five-period cross over study. The trial was open-label for moxifloxacin and double-blind for (b) (4) and placebo. (b) (4) and placebo were administered as single dose, intravenous (IV) infusions over 2 minutes (double blind treatments). Moxifloxacin was to be given as a single dose IV infusion over 60 minutes (open label treatment). In total 62 subjects were randomized (including two replaced subjects) to ten treatment sequences. All subjects received at least one dose of moxifloxacin, 4 mg/kg of (b) (4) 32 mg/kg of (b) (4) and placebo. In total, 31 females and 31 males were treated; they ranged in age from 22 to 65 years old. All subjects were Caucasian.

Entry Criteria:

- Subject (male or female) was to be at least 18 but not older than 65 years of age at the day of the first dosing.
- Subject had to have a normal 12-lead automatic electrocardiogram (ECG) (incomplete right bundle branch block can be accepted) with
 - $120 \text{ ms} \leq \text{PR} \leq 210 \text{ ms}$,
 - $\text{QRS} < 120 \text{ ms}$, and
 - $\text{QTcB} \leq 430 \text{ ms}$ in males, $\text{QTcB} \leq 450 \text{ ms}$ in females.
- Subject was to have a body weight resulting in a Body Mass Index (BMI) between 18 and 30 kg/m^2 (extremes included).
- Subject was to be in a good age-appropriate, healthy condition as established by medical history, physical examination, electrocardiogram, and results of biochemistry, hematology and urinalysis testing within 3 weeks prior to the first dose.
- Results of biochemistry, hematology and urinalysis testing were to have been within the laboratory's clinical tolerance ranges or producing no clinically relevant deviations.
- Subject should have a normal blood pressure ($<90 \text{ mmHg}$ diastolic and $<150 \text{ mmHg}$ systolic) and pulse rate ($60 \text{ bpm} < \text{pulse rate} < 90 \text{ bpm}$) at screening
- Subject was to be able to refrain from all use of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) from 48 hours prior to each dose until the last pharmacokinetic blood sample had been taken for each period.
- Subject was to be able to refrain from all use of grapefruit containing products from 14 days prior to the first dose until the last pharmacokinetic blood sample had been taken.

Endpoints:

- Primary Endpoints:
 - Calculation of the largest time-matched mean difference in individual corrected QT interval (QTcI) as compared to placebo across timepoints.
- Secondary Endpoints:
 - Comparison of other ECG parameters between subjects receiving (b) (4) and subjects receiving placebo.
 - Safety evaluation including adverse events, laboratory safety, 12-lead ECGs, and vital signs.
 - Pharmacokinetic evaluation including (b) (4) plasma and -urine concentrations up to Day 30 to determine: C_{max} , t_{max} , λ_z , $t_{1/2}$, AUC, CL_{app} , CLR, and weight-normalized (wn) CLR.

Summary of Findings:

ECG Effects

For each timepoint of ECG assessment, the time-matched mean QTcI difference of moxifloxacin to placebo was above 10 msec and the one-sided 95% lower-confidence limit was above 5 msec, thus demonstrating assay sensitivity according to the Applicant.

The time-matched mean QTcI difference between the (b) (4) and placebo groups was close to zero for each timepoint. In addition, for the therapeutic (4 mg/kg) and suprathreshold (32 mg/kg) (b) (4) dosages the one-sided 95% upper-confidence limits for the largest time-matched mean QTcI differences compared to placebo were below the 10 msec margin. Therefore, according to the criteria of the ICH E14 guideline, (b) (4) was not considered to affect QTc.

The conclusions obtained from the sensitivity analyses and secondary QTc evaluations were consistent with the conclusions that resulted from the primary analyses. QTc-PK analysis showed a statistically significant relation between (b) (4) levels and QTcI. However, at the mean maximal concentration for both the therapeutic and supra-therapeutic dose level of (b) (4) the upper limit of the one-sided 95% confidence interval for dQTcI was less than 10 msec.

Safety

For 66% of the subjects in the 32 mg/kg (b) (4) group, one or more AEs were reported. The percentages of subjects for whom an AE occurred in the other treatment groups were all less than half of that: 37% in the moxifloxacin group; 31% in the 4 mg/kg (b) (4) group; and 16% in the placebo group. The percentage of subjects with drug-related (per the Applicant) AEs was also higher in the 32 mg/kg (b) (4) group (61%) compared to the other treatment groups: 28% in the moxifloxacin group, 22% in the 4 mg/kg (b) (4) group, and 7% in the placebo group. The most frequently reported drug-related AEs in the 4 mg/kg (b) (4) group were: dry mouth, salivary hypersecretion, and headache (all 3%). The most frequently reported drug-related AEs in the 32 mg/kg (b) (4) group were: dysgeusia (38%), nausea, paresthesia oral, salivary hypersecretion, sensation of foreign body, headache and somnolence (all 5%), and feeling hot, hypersensitivity, dizziness, paresthesia, and rash (all 3%). In the moxifloxacin group, the most frequently

reported drug-related AEs were headache (9%), nausea (7%), injection site pruritus (5%), dysgeusia (4%) and dizziness (4%).

One subject (4 mg/kg (b) (4)) discontinued from the trial due to an AE (increased ASAT and CK values, unlikely to be related to study drug according to the Investigator). In one subject in the 4 mg/kg group and two subjects from the 32 mg/kg (b) (4) group, an AE was reported of severe intensity (increased CK value for two subjects and increased heart rate for one subject). For one of these subjects (32 mg/kg (b) (4)) the event reported (increased heart rate) was considered by the Investigator to be possibly related to the study drug administration. The subject recovered from the event. None of the subjects experienced an SAE after administration of study drug.

There was no indication that clinically relevant drug-related differences existed between the treatment groups in hematology and urinalysis variables.

7.1.9.3.5 Thorough QTc Study 19.4.109

Title: “Randomized, double-blind, placebo-controlled, six-period, cross-over study to investigate the effect of intravenous single doses of Org 25969/rocuronium, Org 25969/vecuronium and Org 25969 alone on the QTc interval and an open label active control part consisting of a single intravenous dose of moxifloxacin in healthy volunteers.”

Objectives:

- Primary objectives
 - To investigate if i.v. single dose treatment with 32 mg/kg (b) (4) and 1.2 mg/kg rocuronium does not clinically significantly prolong the QTc interval as compared to placebo.
 - To investigate if i.v. single dose treatment with 32 mg/kg (b) (4) and 0.1 mg/kg vecuronium does not clinically significantly prolong the QTc interval as compared to placebo.
 - To investigate if i.v. single dose treatment with 32 mg/kg (b) (4) does not clinically significantly prolong the QTc interval as compared to placebo.
 - To investigate if i.v. single dose treatment with 4 mg/kg (b) (4) does not clinically significantly prolong the QTc interval as compared to placebo.
 - To establish assay sensitivity by demonstrating QT/QTc interval prolongation as compared to placebo after single dose i.v. treatment with 400 mg moxifloxacin.
- Secondary objectives
 - To relate the plasma concentrations of (b) (4) vecuronium and rocuronium with the QTc intervals.
 - To investigate safety and tolerability of the various treatments.

Design: This was a single center, randomized, double-blind, placebo-controlled, six-period cross-over trial. The trial was open-label for moxifloxacin and double-blind for (b) (4) alone, (b) (4) in combination with rocuronium/vecuronium and placebo. (b) (4) alone, (b) (4) in combination with rocuronium/vecuronium and placebo were administered as

single dose, intravenous (IV) infusions over a period of four minutes (double-blind treatments). Moxifloxacin was given as a single dose IV infusion over 60 minutes (open label treatment). In total, 84 subjects (including four replaced subjects) were randomized to six treatment sequences. All treated subjects received at least one dose of moxifloxacin, 4.0 mg/kg (b) (4), 32.0 mg/kg (b) (4), 32.0 mg/kg (b) (4) + 1.2 mg/kg rocuronium, 32.0 mg/kg (b) (4) + 0.1 mg/kg vecuronium or placebo on Day 1. In total 42 female and 41 male subjects were treated. They were in the age range of 19 to 45 years (inclusive). Most of the subjects were Caucasian, two subjects were Asian and two subjects were black. In total, 80 subjects completed the trial.

Entry Criteria:

- Subject (male or female) was to be at least 18 but not older than 45 years of age at the day of the first dosing.
- Subject had to have a normal 12-lead automatic electrocardiogram (ECG) (incomplete right bundle branch block can be accepted) with
 - $120 \text{ ms} \leq \text{PR} \leq 210 \text{ ms}$,
 - $\text{QRS} < 120 \text{ ms}$, and
 - $\text{QTcB} \leq 430 \text{ ms}$ in males, $\text{QTcB} \leq 450 \text{ ms}$ in females.
- Subject was to have a body weight resulting in a Body Mass Index (BMI) between 18 and 30 kg/m^2 (extremes included).
- Subject was to be in a good age-appropriate, healthy condition as established by medical history, physical examination, electrocardiogram, and results of biochemistry, hematology and urinalysis testing within 4 weeks prior to the first dose.
- Subject should have a normal blood pressure ($<90 \text{ mmHg}$ diastolic and $<150 \text{ mmHg}$ systolic) and pulse rate ($50 \text{ bpm} < \text{pulse rate} < 90 \text{ bpm}$) at screening
- Subject was to be able to refrain from all use of (methyl)xanthines (e.g. coffee, tea, cola, chocolate) from 48 hours prior to each dose until the last pharmacokinetic blood sample had been taken for each period.
- Subject was to be able to refrain from all use of grapefruit containing products from 14 days prior to the first dose until the last pharmacokinetic blood sample had been taken.

Summary of Findings:

ECG Effects

For moxifloxacin, the estimate for the largest time-matched QTcI mean difference to placebo was 21 ms (90% confidence interval (CI): 19 – 23 ms). In addition, the lower limit of the two-sided 99.6% CI (Bonferroni α - adjustment) of the difference between moxifloxacin and placebo was above 5 ms at several timepoints. Based on these findings, the Applicant determined that assay sensitivity was demonstrated.

Data for the administration of 4 and 32 mg/kg doses of (b) (4) in absence of an NMBA indicated that there was, at most, a “shallow” relationship between plasma concentrations of (b) (4) and QTcI prolongation. Co-administration of rocuronium or vecuronium had a negligible effect on this relationship. Correlation plots of the time-matched baseline-corrected QTcI interval difference between the active doses and placebo (dQTc) and the plasma concentrations of (b) (4)

were also evaluated. The plots of the individual maximum dQTc and the (b) (4) plasma concentrations at 5 minutes after start of the injection (C_{5min}) and versus the AUC_{0-inf} did not show a relationship between dQTc and (b) (4) exposure.

Since the therapeutic (4 mg/kg (b) (4)) and supratherapeutic doses (32 mg/kg (b) (4)) alone and in combination with rocuronium or vecuronium) did not lead to QTc interval prolongations of > 10 ms, the Applicant concluded that this study of (b) (4) used alone and in combination with rocuronium or vecuronium did not provide evidence of QTc prolongation according to the criteria of the ICH E14 guidelines. The Applicant also indicated that the robustness of the primary analysis results was confirmed by the sensitivity analysis and secondary QTc evaluations.

Safety

The highest percentage of subjects who experienced one or more AEs was observed after administration of 32 mg/kg (b) (4) rocuronium: 52%. For the other treatments these percentages were: 31% after moxifloxacin; 31% after 4 mg/kg (b) (4) 40% after 32 mg/kg (b) (4) 36% after 32 mg/kg (b) (4) vecuronium and 28% after placebo.

The percentage of subjects with drug-related AEs was higher after administration of 32 mg/kg (b) (4) rocuronium (43%) compared to administration of the other treatments: 0% after moxifloxacin, 13% after 4 mg/kg (b) (4) 27% after 32 mg/kg (b) (4) 28% after 32 mg/kg (b) (4) vecuronium and 7% after placebo.

Two subjects experienced QTc prolongation that fulfilled the pre-determined criteria of an SAE (QTcBazett change from baseline > 60 ms). Both SAEs were of mild intensity, one after moxifloxacin (not considered, by the Applicant, to be related to the study drug) and one after a dose of 32 mg/kg (b) (4) (considered, by the Applicant, to be possibly related to study drug). A different subject experienced ventricular tachycardia of moderate intensity which was observed after treatment of 32 mg/kg of (b) (4). All these subjects recovered from their SAEs.

The most frequently reported drug-related AEs were dysgeusia (52 times for 32 subjects), followed by parosmia (9 subjects), headache and nausea (8 subjects) and dizziness (6 subjects). One subject discontinued from the trial three days after administration of 32 mg/kg (b) (4) due to hypersensitive reaction and reported seven AEs which contributed to the subjects' discontinuation in the trial, all of which were judged by the Applicant as possibly related to trial medication. Due to a technical problem with one infusion pump, one subject experienced two AEs with severe intensity: dizziness which was considered, by the Investigator, as possibly related and heavy eyelids which was considered unlikely related.

No clinically relevant abnormal values related to the trial medication or procedure were reported for hematology, biochemistry, urinalysis variables, and vital signs.

7.1.9.4 Additional analyses and explorations

None were indicated and none were performed.

7.1.10 Immunogenicity

With the occurrence of anaphylactic reactions in several subjects, the potential for (b) (4) to be immunogenic was investigated. A summary of that study is provided in Section 7.1.12 below. The study was evaluated by the Division of Pulmonary and Allergy Products. Their review and comments in response to a request for consultation are included in the Appendices.

7.1.11 Human Carcinogenicity

Carcinogenicity studies were not required of this product due to the acute indication and the relatively short half-life. Although (b) (4) is absorbed by bone, in adults, the amount absorbed is small and the duration of its presence in bone is short enough that preclinical and clinical assessment of carcinogenicity are not indicated. For pediatric patients, the amount of bone absorption and its persistence in bone warrant, at a minimum, preclinical evaluation for carcinogenicity.

7.1.12 Special Safety Studies

Following submission of the NDA, the Applicant conducted a trial in Europe to further assess the “hypersensitivity” reactions observed in the previous clinical trials. The trial is summarized below.

Study Number: Trial 19.4.110

Study Design: single center, placebo-controlled, study with an open-label control phase (Phase A) and a single-blind testing phase (Phase B) to evaluate hypersensitivity reactions to (b) (4)

Primary Objectives:

- To evaluate the skin prick test (SPT) and intradermal skin test (IDT) with (b) (4) in healthy volunteers who were not previously exposed to (b) (4)
- To investigate the hypersensitivity status of exposed alleged hypersensitive volunteers of the 19.4.105, 19.4.106 and 19.4.109 trials Secondary objectives
- To investigate whether volunteers who have a positive skin prick test or intradermal test for (b) (4) are hypersensitive to penicillin

Study Population:

(b) (4) (sugammadex sodium injection)

Three groups of subjects were enrolled.

- Subjects who were not previously exposed to (b) (4) (Phase A)
- Subjects who were previously exposed to (b) (4) without clinical symptoms of hypersensitivity to (b) (4) (control subjects of Phase B)
- Subjects who were previously exposed to (b) (4) with clinical symptoms indicative of hypersensitivity to (b) (4) (Phase B)

Methods:

(b) (4) was given as a solution in increasing concentrations following a dilution scheme using stock 100 mg (b) (4) mL and diluting it with NaCl 0.9% solution (the negative control). The dilutions used in the study were 1:100000, 1:10000, 1:1000, 1:100, 1:10 and 1:1. The table below summarizes the timing of the study procedures.

Table 29: Procedures for Phases A and B (Table 3 from 4-month Safety Update Report)

| Activity | Screening | Admission Day -1 | Day 1 | Day 2 | Follow-up (6 hours after last application) |
|---|-----------|------------------|----------------|-------|--|
| Medical history | X | Update | | | |
| Physical examination | X | Update | | | X |
| Clinical laboratory ¹ | X | | | | X |
| Tryptase and methylhistamine ² | | | | X | |
| Hypersensitivity blood sampling ³ | | | X | | |
| Pregnancy test (for females) | X | X | | | |
| Drug and alcohol screen | X | X | | | |
| Serology (hepatitis B/C, HIV) | X | | | | |
| Vital signs (BP, pulse rate, height, weight) ⁴ | X | | X | X | X |
| SPT with (b) (4) | | | X | | |
| IDT with (b) (4) | | | | X | |
| Penicillin allergy test ⁵ | | | X ⁷ | X | |
| (Serious) adverse event questioning | X | X | X | X | X |
| Co-medication check | X | X | X | X | X |
| Hospitalization ⁸ | | X | X | X | |

¹ Blood and urine samples were drawn/collected for safety laboratory (standard hematology, chemistry and urinalysis (dipstick) at screening and follow-up.

² On Day 2 of Phase B a tryptase blood sample and a methylhistamine urine sample was taken (bladder was emptied) prior to the first IDT. Based on the results of the IDT, the investigator could decide to take another tryptase sample approximately 30 minutes after the last IDT and/or a methylhistamine sample approximately 1 hour after the last IDT for further analysis.

³ Prior to the first SPT on Day 1 of Phase B a pre-dose blood sample was taken. In case of positive SPT or IDT result another blood sample was taken approximately 30 minutes after the last SPT or IDT. These samples will be used for possible future hypersensitivity research.

(b) (4) (sugammadex sodium injection)

⁴ BP, pulse rate weight and height were recorded at screening and follow-up, except for weight and height which were only recorded at screening. BP and pulse rate were measured pre-dose and within 20 minutes after application and next application step on Day 1 and Day 2.

⁵ If the result of SPT was positive, no IDT for (b) (4) was performed. In this case the subjects of Phase A proceeded with the follow-up assessment (6 hours after last application) For subjects of Phase B a blood sample was taken for the Phadia ImmunoCAP test for penicillin allergy if no previous documented test results were available.

⁶ In case the result of IDT was negative for subjects included in Phase B, the Phadia ImmunoCAP test for penicillin allergy was not applicable and subjects could proceed with the follow-up assessment.

⁷ Not required in Phase A; subject could proceed to the follow-up assessment. In Phase B only required for those subjects who showed positive results at the SPT or IDT with (b) (4) (on Day 1) and in case no documented penicillin results were available.

⁸ Hospitalization: depending on the allocation to treatment (Phase A or Phase B) and the outcome of the SPT or IDT with (b) (4) subjects were 1.5 to 2.5 days in the Institute of CRS MG.

Results as reported by Applicant:

- All subjects, who were not previously exposed to (b) (4) showed no positive reaction to (b) (4) according to both SPT and IDT
- All subjects, who were previously exposed to (b) (4) tested negative to (b) (4) based on the SPT results
- Based on the SPT and IDT results, hypersensitivity for (b) (4) was confirmed for Subject 12, who was previously tested as probably hypersensitive to (b) (4) in a previous study
- No other allegedly hypersensitive subjects were hypersensitive to (b) (4) based on the SPT and IDT results
- One control subject, who was previously exposed to (b) (4) without previous clinical allergy symptoms, had a positive IDT for (b) (4) However, this subject had increased and comparable levels of urine methylhistamine both at baseline and post treatment, which may indicate a false positive outcome

The interpretation of these results by the Division of Pulmonary and Allergy Products can be found in the Appendix of this review.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Neither withdrawal phenomena nor incidents of abuse were reported by the Applicant, and none would be expected for a product such as this. Given its anticipated use as an NMB reversal agent (typically administered as a single dose), the potential for dependence is not applicable to (b) (4). Additionally, the Applicant indicates that the administration of (b) (4) does not affect a patient's mental ability or the ability to drive or operate machinery.

7.1.14 Human Reproduction and Pregnancy Data

Reproduction trials have been performed in rats and rabbits at doses up to 500 and 200 mg/kg/day, respectively. These dose levels represent an approximately 6 to 50-fold exposure ratio compared to the recommended human doses. According to the Applicant, no evidence of impaired fertility or relevant harm to the fetus and newborn pups due to (b) (4) was revealed. There were no trials conducted that involved pregnant women.

The effects of (b) (4) on labor and delivery in pregnant woman are unknown. There were no drug-related effects on labor and delivery in preclinical prenatal and postnatal development trials.

(b) (4) is excreted into milk in rats with a maximum level of 0.22% of the dose per gram of milk, which decreases when plasma levels drop. Oral exposure via milk did not induce any effects on survival, body weight and physical or behavioral developmental parameters monitored in rats in perinatal and postnatal development trials. Excretion of (b) (4) in human milk has not been studied, but can be expected based on the preclinical data.

7.1.15 Assessment of Effect on Growth

No assessments of the effects of (b) (4) on growth were made as a pediatric indication is not sought at present. Such assessments may be required if the product is approved for use in adults and a clinical benefit is thought to be likely in the pediatric population.

7.1.16 Overdose Experience

The Applicant reported two incidents of unintentional overdoses of (b) (4)

1. In subject 306104001 (randomized to the 4 mg/kg (b) (4) group), the actual dose administered was 20 mg/kg, which is above the dose recommended for “immediate reversal,” 16 mg/kg. The Applicant indicated that the subject reported no AEs during the trial.
2. In subject 205000004 (randomized to the 4 mg/kg (b) (4) group), the actual dose administered was 40 mg/kg, which is above the dose recommended for “immediate reversal,” 16 mg/kg, but less than the two highest doses administered to subjects in clinical trials. According to the Applicant, the subject experienced no adverse events or other safety concerns after receiving the higher dose of (b) (4). It should be noted that no ECGs were recorded in this subject.

The highest (b) (4) dose studied in the clinical trials was 96 mg/kg (N=12 in Phase 1 trial 19.4.106). The most frequent AE in subjects who received this dose was dysgeusia (8 subjects, 66.7%). Other AEs included headache (2 subjects, 16.7%), nausea (2 subjects, 16.7%), fatigue (2 subjects, 16.7%), pharyngolaryngeal pain (2 subjects, 16.7%), dizziness postural (1 subject,

8.3%), abdominal pain (1 subject, 8.3%), and micturation urgency (1 subject, 8.3%). In addition, the Applicant indicated that no clinically relevant effects on vital signs, clinical laboratory tests, or the ECG were observed at this dose.

The Applicant reported that (b) (4) can be removed by hemodialysis. Nine renally-impaired subjects in trial 19.4.304 received hemodialysis within the first 72 hr after surgery, either with a high flux filter (4 subjects) or with a low flux filter (5 subjects). Low flux filters appeared to be almost ineffective for removing (b) (4) from circulation as plasma levels appeared to be unaffected by dialysis in these cases. High flux filters showed variable effectiveness with uncorrected dialysis half-lives ranging between 5 and 27 hr (in 4 subjects). Dialysis half-lives were consistently shorter for rocuronium than for (b) (4) for both low and high flux filters.

7.1.17 Postmarketing Experience

(b) (4) has not been marketed in either the United States or elsewhere; therefore, there is no postmarketing experience for this product.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data sources to evaluate the safety of (b) (4) were the studies conducted by the Applicant as part of the clinical development program; indeed, these were the only sources of safety data for this drug product. The (b) (4) clinical development program consisted of 30 clinical trials, including seven Phase 1 trials (Trials 19.4.101, 19.4.102, 19.4.105, 19.4.106, 19.4.107, 19.4.108, and 19.4.109), twelve Phase 2 trials (Trials 19.4.201 through 19.4.207, Trials 19.4.208 A and B, Trials 19.4.209 A and B, and Trial 19.4.210), and eleven Phase 3 trials (Trials 19.4.301 through 19.4.306 and 19.4.308 through 19.4.312). (b) (4) was administered following neuromuscular blockade (NMB) induced by rocuronium, vecuronium or pancuronium in at least parts of 26 of the 30 trials, including all of the Phase 2 (n=12) and Phase 3 (n=11) trials and in three of the Phase 1 trials (Trials 19.4.101 [Part II only], 19.4.108 and 19.4.109 [Groups A and F only]). (b) (4) was administered to healthy volunteers with no concurrent anesthetic or neuromuscular blocking agent (NMBA) in at least parts of six of the seven Phase 1 trials (Trials 19.4.101 [Part I only], 19.4.102, 19.4.105, 19.4.106, 19.4.107 and 19.4.109 [Groups C, D and E only]). Three of the 30 trials (Trials 19.4.201, 19.4.204 and 19.4.306) were terminated prematurely for what the Applicant has called “logistical reasons.”

Safety data (with a cut-off date of 30 April 2007) from all 30 trials were analyzed and included in the NDA. Twenty-three of these 30 trials assessed the efficacy of (b) (4) As described in

(b) (4) (sugammadex sodium injection)

Section 7.1 above, the Applicant analyzed safety by dividing the clinical trials into groups based on whether (b) (4) was administered following the use of a neuromuscular blocking agent and whether an active comparator (i.e., neostigmine) or placebo was utilized in the trial. This organization of the safety database is also used in the subsections that follow. The electronic, Applicant-generated, case report tabulations submitted with the NDA as well as the narratives and case report forms for subjects who experienced serious adverse events were reviewed and formed the basis on which the overall assessment of safety was made.

7.2.1.1 Study type and design/patient enumeration

The table below summarizes the clinical trials, their objectives, and the extent of (b) (4) exposures that comprised the clinical development program.

Table 30: Trials included in safety database (based on Appendix Table 1 in ISS)

| Trial | Phase | Number of (b) (4) subjects | Total number of subjects | (b) (4) dose(s) evaluated (mg/kg) | Objectives |
|-----------------------|-------|----------------------------|--------------------------|-----------------------------------|---|
| 19.4.101 ^A | 1 | 29 | 29 | 0.1, 0.5, 1, 2, 4, 8 | Safety, pharmacokinetics, renal excretion, dose-response and tolerability of (b) (4) given alone (Part 1) and given 3 minutes after rocuronium (Part 2) |
| 19.4.102 | 1 | 28 | 28 | 1, 8, 16 | Safety, PK and dose proportionality of (b) (4) in Japanese and Caucasian subjects |
| 19.4.105 | 1 | 62 | 26 | 4, 32 | Effect of IV single doses of (b) (4) on the QT/QTc interval |
| 19.4.106 | 1 | 12 | 12 | 32, 64, 96 | Safety and tolerability of high doses of (b) (4) |
| 19.4.107 | 1 | 6 | 6 | 4 | Excretion balance, metabolite profile and pharmacokinetics of (b) (4) |
| 19.4.108 | 1 | 16 | 16 | 16, 20, 32 | Safety, tolerability and pharmacokinetics of (b) (4) in combination with rocuronium or vecuronium |
| 19.4.109 | 1 | 83 | 83 | 4, 32 | Effect of IV single doses of (b) (4) rocuronium, (b) (4) vecuronium and (b) (4) alone on the QTc |
| 19.4.201 | 2 | 27 | 27 | 0.5, 1, 2, 3, 4 | Dose-response, PK/PD and safety of (b) (4) after rocuronium |
| 19.4.202 ^C | 2 | 98 | 98 | 1, 2, 4, 6, 8 | Dose response, PK/PD and safety of (b) (4) after rocuronium |
| 19.4.203 | 2 | 30 | 30 | 0.5, 1, 2, 4, 6 | Dose response of (b) (4) following deep block induced by rocuronium and safety |
| 19.4.204 | 2 | 43 | 43 | 0.5, 1, 2, 4, 8 | Dose-finding, efficacy and safety of 5 doses of (b) (4) after rocuronium |
| 19.4.205 | 2 | 43 | 43 | 2, 4, 8, 12, 16 | Dose-finding, safety and PK |

| Trial | Phase | Number of (b) (4) subjects | Total number of subjects | (b) (4) dose(s) evaluated (mg/kg) | Objectives |
|-----------------------|-------|----------------------------|--------------------------|-----------------------------------|--|
| 19.4.206 ^C | 2 | 173 | 173 | 2, 4, 8, 12, 10 | Dose-response relation of (b) (4) after rocuronium and safety |
| 19.4.207 | 2 | 98 | 98 | 0.5, 1, 2, 3, 4, 6, 8 | Dose-response of (b) (4) after vecuronium, pancuronium or rocuronium, and safety, PK, and PK/PD after vecuronium or pancuronium |
| 19.4.208 ^A | 2 | 98 | 98 | 0.5, 1, 2, 4 | Safety of (b) (4) after rocuronium or vecuronium in Japanese subjects |
| 19.4.208 ^B | 2 | 98 | 98 | 0.5, 1, 2, 4 | Efficacy, safety and PK of (b) (4) after rocuronium or vecuronium in Caucasian subjects |
| 19.4.209 ^A | 2 | 99 | 99 | 0.5, 1, 2, 4, 8 | Safety of (b) (4) after rocuronium or vecuronium in Japanese subjects |
| 19.4.209 ^B | 2 | 101 | 101 | 0.5, 1, 2, 4, 8 | Efficacy and safety of (b) (4) after rocuronium or vecuronium in Caucasian subjects |
| 19.4.210 | 2 | 42 | 42 | 2 | Efficacy of (b) (4) after rocuronium in subjects on propofol or sevoflurane anesthesia, and evaluation of safety |
| 19.4.301 | 3 | 189 | 189 | 2 | Demonstrate faster recovery with (b) (4) compared to neostigmine as reversal agents after rocuronium or vecuronium |
| 19.4.302 | 3 | 157 | 157 | 4 | Demonstrate faster recovery with (b) (4) compared to neostigmine as reversal agents after maintenance dosing of rocuronium or vecuronium |
| 19.4.303 | 3 | 110 | 110 | 16 | Demonstrate faster recovery with (b) (4) compared to succinylcholine from rocuronium induced NMB |
| 19.4.304 | 3 | 15 | 30 | 2 | Efficacy, PK and safety of (b) (4) after rocuronium in subjects with normal or impaired renal function |
| 19.4.305 | 3 | 150 | 150 | 2 | Efficacy, safety, and PK of (b) (4) after rocuronium in elderly subjects with adult subjects |
| 19.4.306 | 3 | 91 | 91 | 0.5, 1, 2, 4 | Efficacy, safety and PK of (b) (4) after rocuronium in pediatric and adult subjects |
| 19.4.308 | 3 | 77 | 77 | 2, 4 | Safety and efficacy of (b) (4) after rocuronium in pulmonary patients |
| 19.4.309 | 3 | 116 | 116 | 2, 4 | Safety and efficacy of (b) (4) after rocuronium in cardiac patients |
| 19.4.310 | 3 | 73 | 73 | 2 | Demonstrate faster recovery from NMB with (b) (4) after rocuronium as compared to neostigmine after cis-atracurium |
| 19.4.311 | 3 | 197 | 197 | 4 | Efficacy and safety of (b) (4) after rocuronium when used at the end of surgical procedure following routine |

(b) (4) (sugammadex sodium injection)

| Trial | Phase | Number of (b) (4) subjects | Total number of subjects | (b) (4) dose(s) evaluated (mg/kg) | Objectives |
|----------|-------|----------------------------|--------------------------|-----------------------------------|--|
| | | | | | anesthesia |
| 19.4.312 | 3 | 51 | 51 | 4 | Efficacy of (b) (4) after rocuronium continuous infusion in subjects on propofol or sevoflurane anesthesia, and evaluation of safety |

A (b) (4) administered after rocuronium in Part II for Trial 19.4.101.

B (b) (4) administered at the same time as rocuronium or vecuronium.

C Studies 19.4.202 and 19.4.206 investigated immediate reversal at 3 minutes as well as routine reversal at 15 minutes; therefore, these studies are listed twice.

7.2.1.2 Demographics

Phase 1 trials were conducted in healthy adult subjects with no clinically significant diseases and no allowed concomitant medications (with the exception of paracetamol). Phase 2-3 trials, with two exceptions, were conducted in adult surgical subjects with no known or suspected neuromuscular disorders, no personal or family history of malignant hyperthermia, and no significant hepatic or renal dysfunction. The exceptions were trial 19.4.306 in which pediatric patients were also enrolled and trial 19.4.304 that was conducted in patients with impaired renal function.

Female subjects were enrolled provided they were not pregnant or breast feeding. Subjects were excluded for known or suspected allergies to narcotics, muscle relaxants, or other medication used during general anesthesia. In addition, subjects were excluded if they were receiving medication known to interfere with neuromuscular blocking agents, such as anticonvulsants, aminoglycosides, or magnesium.

The demographic parameters collected and summarized by the Applicant included age, gender, race, and ethnicity. In the Phase 3 trials, race was categorized as American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, or White/Caucasian, whereas ethnicity was categorized as Hispanic/Latino or Not Hispanic/Latino. In the Phase 1 and 2 trials, however, race was categorized only as Caucasian, Black, and Other. Therefore, the race categories for the Phase 1 and 2 trials were mapped to the Phase 3 race and ethnicity categories. Other baseline characteristics collected included the following:

- Baseline body weight and height.
- American Society of Anesthesiologists (ASA) classification of physical status.
- For Phase 2-3 trials only, clinically significant preexisting medical conditions. These were defined as either past or ongoing medical conditions:
 - That would lead to an adjustment of the anesthetic regimen
 - That proved the eligibility/non-eligibility of the subject
 - That proved the subject to be more susceptible to adverse events known to be related to the NMBA and/or (b) (4)

(b) (4) (sugammadex sodium injection)

- Concomitant medications defined as either chronic-use medications that were started before the trial and that the subject continued to use after the surgical procedure, or any medications given after the start of the trial, including those given to treat adverse events.

(b) (4) *vs. placebo*

In pooled Phase 1-3 trials with a placebo group (NMBA was rocuronium or vecuronium), the (b) (4) and placebo groups were similar with respect to age, gender, race, ethnicity, and baseline body weight and height. Most subjects in each group were between the ages of 18 and 64 years, male, Caucasian, and non-Hispanic/Latino. Median body weight was 75 kg in the (b) (4) group and 76 kg in the placebo group. More (b) (4) subjects were ASA class 1 than ASA class 2, while similar percentages of placebo subjects were ASA class 1 or ASA class 2. There was only one class 4 subject (in the (b) (4) group, from trial 19.4.309). The demographic profiles of subjects who received either rocuronium or vecuronium were similar to the profile for the combined group of rocuronium plus vecuronium subjects.

Table 31: Demographics of adult subjects in pooled Phase 1 - 3 trials involving the use of an NMBA and containing a placebo treatment arm (from Table 4 of ISS)

| Parameter | Statistic/Category | Rocuronium or vecuronium + | |
|--|---------------------------|----------------------------|--------------------|
| | | (b) (4) (N = 640) | Placebo (N=140) |
| Overall Age (yrs) | Mean (SD) | 49 (16) | 51 (16) |
| | Median | 48 | 52 |
| | Min. - max. | 18 - 90 | 19 - 86 |
| Stratified Age [n (%)] ^A | 18-64 yr | 531 (83) | 113 (81) |
| | 65-74 yr | 61 (10) | 15 (11) |
| | ≥ 75 yr | 48 (8) | 12 (9) |
| Gender [n (%)] | Male | 392 (61) | 85 (61) |
| | Female | 248 (39) | 55 (39) |
| Race [n (%)] | Asian | 80 (13) | 22 (16) |
| | Black or African American | 2 (< 1) | 0 (0) |
| | White/Caucasian | 556 (87) | 117 (84) |
| | Other | 2 (< 1) | 1 (1) |
| Hispanic or Latino Ethnicity [n (%)] | Yes | 2 (1) | 3 (3) |
| | No | 252 (99) | 83 (97) |
| | Missing | 386 | 54 |
| Weight (kg) | Mean (SD) | 75 (15) | 76 (16) |
| | Median | 75 | 76 |
| | Min. - max. | 40 - 145 | 45 - 135 |
| ASA Classification (n [%]) | 1 | 330 (52) | 56 (40) |
| | 2 | 227 (35) | 58 (41) |
| | 3 | 82 (13) | 26 (19) |

(b) (4) (sugammadex sodium injection)

| Parameter | Statistic/Category | Rocuronium or vecuronium + | |
|-----------|--------------------|----------------------------|--------------------|
| | | (b) (4) (N = 640) | Placebo (N=140) |
| | 4 | 1 ^B (<1) | 0 (0) |
| | Missing | 0 | 0 |

^A All percentages were based on non-missing data.

^B Subject 309110003 from trial 19.4.309

(b) (4) *vs. neostigmine*

In the pooled Phase 3 controlled trials 19.4.301 and 19.4.302 (NMBA was rocuronium or vecuronium), the (b) (4) and neostigmine groups were similar with respect to age, gender, race, ethnicity, and baseline body weight and height, and ASA classification. Most subjects in each group were between the ages of 18 and 64 years, Caucasian, and non-Hispanic/Latino, and there was an equal percentage of males and females in each group. Median weight was 78 kg in the (b) (4) group and 79 kg in the neostigmine group. Most subjects in each group were ASA class 2, and the distribution of subjects according to ASA class was similar for each group. There were no ASA class 4 subjects. The demographic profiles of subjects who received either rocuronium or vecuronium were similar to the profile for the combined group of rocuronium plus vecuronium subjects.

Table 32: Demographics of adult subjects in pooled Phase 1-3 trials 19.4.301 and 19.4.302 (from Table 6 of ISS)

| Parameter | Statistic/Category | Rocuronium or Vecuronium + | |
|-------------------|---------------------------|----------------------------|-------------|
| | | (b) (4) | Neostigmine |
| Overall Age (yrs) | n | 179 | 167 |
| | Mean (SD) | 50 (15) | 52 (14) |
| | Median | 51 | 54 |
| | Min. - max. | 19-85 | 18-81 |
| Age (no. [%]) | n | 179 | 167 |
| | 18-64 yr | 145 (81) | 141 (84) |
| | 65-74 yr | 25 (14) | 24 (14) |
| | ≥ 75 yr | 9 (5) | 2 (1) |
| Gender (n [%]) | n | 179 | 167 |
| | Male | 90 (50) | 83 (50) |
| | Female | 89 (50) | 84 (50) |
| Race (n [%]) | n | 179 | 167 |
| | Asian | 1 (1) | 6 (4) |
| | Black or African American | 10 (6) | 2 (1) |
| | White/Caucasian | 164 (92) | 159 (95) |
| | Other | 4 (2) | 0 (0) |

(b) (4) (sugammadex sodium injection)

| | | | |
|---|-------------|----------|----------|
| Ethnicity Hispanic or Latino (n [%]) | n | 179 | 167 |
| | Yes | 18 (10) | 22 (13) |
| | No | 161 (90) | 145 (87) |
| Weight (kg) | n | 179 | 167 |
| | Mean (SD) | 82 (22) | 81 (18) |
| | Median | 78 | 79 |
| | Min. - max. | 42-182 | 46-146 |
| ASA Class (n [%]) | n | 179 | 167 |
| | 1 | 48 (27) | 45 (27) |
| | 2 | 111 (62) | 99 (59) |
| | 3 | 20 (11) | 23 (14) |
| | 4 | 0 (0) | 0 (0) |

Dose Response

In pooled Phase 1-3 trials overall (NMBA was rocuronium, vecuronium, or pancuronium, and excluding the crossover thorough QTc trial 19.4.109), most subjects in the Total (b) (4) group were between the ages of 18 and 64 years, Caucasian, non-Hispanic/Latino, and ASA class 1 or 2. The percentages of male and female subjects were similar. There was only one ASA class 4 subject. Median body weight for the Total (b) (4) group was 72 kg. The demographic profiles of the 2 mg/kg and 4 mg/kg dose groups were similar to each other and also to the Total (b) (4) group. In comparison, the 16 mg/kg dose group was younger, predominantly female, had a higher percentage of Hispanic/Latino subjects, and had a higher percentage of ASA Class 1 and a lower percentage of ASA Class 3 subjects.

In the crossover thorough QTc trial 19.4.109, there were 40 females and 41 males ranging in age from 19 to 45 years (inclusive) who were exposed to (b) (4) plus rocuronium or vecuronium. Most subjects were Caucasian; two were Asian, and two were Black.

7.2.1.3 Extent of exposure (dose/duration)

As an acute-use drug product, (b) (4) is intended to be administered as a single bolus dose when reversal of neuromuscular blockade is desired, generally, at the end of the surgical procedure. It was not evaluated for either safety or efficacy in the setting of repeat dosing as may occur when neuromuscular blockade was not reversed in a timely fashion following an initial dose or when a patient requires additional surgery and, therefore, anesthesia with neuromuscular blockade within a short time period following the administration of (b) (4) (e.g., to urgently treat post-operative complication such as bleeding). Thus, exposure was primarily a function of dosage alone. The table below summarizes the extent to which dose was evaluated in the clinical development program. In all, 1,967 unique subjects received (b) (4), 1,754 of these received a single dose, 91 received two doses, 40 received three doses, a single subject received four doses, and 81 received

(b) (4) (sugammadex sodium injection)

eight doses. Subjects who received multiple doses are assessed in both the individual dose groups and separately. These subjects participated in the Phase 1 studies: 19.4.101, 19.4.102, 19.4.105, 19.4.106, 19.4.108 and 19.4.109.

Table 33: (b) (4) exposure by dose and number of unique adult subjects

| Dose (mg/kg) | Numbers of Adults Exposed to (b) (4) | | | | | | | | | | | | | | |
|--------------------|--------------------------------------|-----|-----|-----|-----|---|-----|----|-----|----|-----|----|-----|----|----|
| | 0.1 | 0.2 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | 64 | 96 |
| Number of Subjects | 5 | 4 | 124 | 178 | 612 | 9 | 729 | 28 | 154 | 39 | 127 | 4 | 164 | 12 | 12 |

The clinical trials in which (b) (4) was used to reverse an NMBA provide the most clinically relevant safety data. The Applicant divided the clinical studies into groups that would facilitate this approach to the review of safety (see Section 7.1 above). This approach was also utilized in this review. The table below indicates the extent of exposure to (b) (4) that occurred in subjects who also received an NMBA.

Table 34: Adult subjects exposed to (b) (4) by dose, in pooled Phase 1-3 trials (Table 3 from the NDA ISS)

| Trial Phase | Rocuronium, vecuronium, or pancuronium + (b) (4) (mg/kg) | | | | | | | | | | | |
|-------------|--|-----|-----|---|-----|----|-----|----|----|----|-----|---------------|
| | placebo | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32* | Total (b) (4) |
| Phase 1 | 10 | 4 | 2 | 0 | 2 | 0 | 2 | 0 | 4 | 4 | 89 | 107 |
| Phase 2 | 84 | 250 | 212 | 9 | 167 | 28 | 122 | 39 | 39 | 0 | 0 | 866 |
| Phase 3 | 46 | 11 | 392 | 0 | 413 | 0 | 0 | 0 | 56 | 0 | 0 | 872 |
| Total | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |

* The Applicant counted 81 subjects twice in the 32 mg/kg dose group as they were exposed on two different occasions, at least four days apart, to that dose. This table does not include the double count.

The number of subjects exposed to the Applicant-proposed labeled doses is greatest for the 2 mg/kg dose of (b) (4) which is recommended for reversal of “shallow” neuromuscular blockade, and least for the 16 mg/kg dose, which is recommended for the immediate reversal of neuromuscular blockade and the dose likely to be used in emergency settings. In this regard, the database may be inadequate to fully assess safety at the highest proposed dose.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary sources of clinical data were submitted and none were identified independent of the submission for further evaluation of safety.

7.2.2.1 Other studies

All studies submitted to the NDA were integrated into the analysis of safety.

7.2.2.2 Postmarketing experience

(b) (4) has not been approved for use outside of the United States. Therefore, no postmarketing data are available for review.

7.2.2.3 Literature

(b) (4) is a new molecular entity. A PubMed search indicated that the published literature regarding this product comes from the studies conduct by or for the Applicant.

7.2.3 Adequacy of Overall Clinical Experience

The clinical development program provided an adequate number of subjects exposed to (b) (4) to make key assessments of safety and efficacy. The doses and durations of exposure were adequate to assess safety for intended use. However, the studies did not evaluate the safety and efficacy of reparalyzing a patient soon after the administration of (b) (4) or whether (b) (4) can be successfully and safely used to reverse NMB a second time in this situation without a dose adjustment.

Demographically, most of the subjects were Caucasian (88%) and between the ages of 18-64 years old. There were sufficient subjects over the age of 65 years to adequately assess safety and efficacy in this age group. Nearly equal numbers of males and females were included in the studies. The American Society of Anesthesiologist physical status (ASA-PS) ratings of the majority of the subjects were 1 and 2; there were 102 subjects who were identified as ASA-PS 3; however, there was only a single ASA-PS 4 subject enrolled in a clinical trial.

(b) (4) was not evaluated in a sufficient number of subjects with hepatic impairment to determine whether the predictions of the PK-PD models for this population were accurate and whether dosing adjustments were necessary for these patients. Similarly, there were too few hemodialysis patients included in the trials to determine if the modeling predictions regarding high flux filtration during dialysis treatments were accurate.

The designs of the studies were adequate to address critical issues of safety and efficacy. The use of placebo and neostigmine, as an active comparator, was particularly useful for allowing risks associated with (b) (4) to be discerned from those associated with the current standard of care. In some of the trials, (b) (4) was administered long before the surgical procedure and, therefore, the anesthetic, were over. This approach was useful for some efficacy assessments, but created difficulty in interpreting some of the safety data. This difficulty was not

insurmountable due to the relatively small changes that were observed in the safety parameters, most notably, the hemodynamic assessments.

The Applicant completed a hypersensitivity study that provided useful information regarding some of the anaphylactic reactions that were observed. However, this study did not fully address the concerns raised by the Division at the Advisory Committee meeting or in teleconferences with the Applicant. Recommendations for additional studies to resolve the remaining issues are made in Section 1 of this review.

7.2.4 Adequacy of Special Animal and/or In-Vitro Testing

The Applicant's preclinical and *in-vitro* testing of (b) (4) were adequate to explore potential adverse events. The Pharmacology-Toxicology and Clinical Pharmacology reviews provide detailed information regarding these studies.

7.2.5 Adequacy of Routine Clinical Testing

The routine testing of subjects was adequate in terms of assessing biochemistry and hematologic laboratory parameters and for monitoring of vital signs and ECG. However, the Applicant failed to perform evaluations of coagulation parameters in any of the clinical trials. These parameters are essential for a complete characterization of the risk profile for (b) (4). The Applicant's *in-vitro* study findings of the effects of (b) (4) on coagulation, described elsewhere in this review, along with the differences in hemorrhagic adverse events related to the use of (b) (4) compared to placebo raise safety concerns that make clinical assessments of these parameters imperative. It is recommended that clinical evaluations of the effects of (b) (4) on coagulation be completed prior to the approval of this product.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

(b) (4) is cleared almost entirely by the kidneys. Therefore, there was no need for additional metabolic, clearance or interaction workup.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The Applicant has conducted two adequate thorough QTc prolongation studies as required by the Division. A study was also conducted to assess the impact of renal impairment on the safety and efficacy of (b) (4)

The Applicant did not assess the effects of (b) (4) on coagulation times as part of any of the clinical trials. This represents a major deficiency in the clinical assessment of safety.

7.2.8 Assessment of Quality and Completeness of Data

Based on review of the data tables included in the appendices of the NDA submission and analyses conducted using the datasets included in the submission, the data that were available for conducting the safety review were, overall, of sufficient quality and completeness to conduct an adequate review of safety.

7.2.9 Additional Submissions, Including Safety Update

The Applicant provided a 4-month safety update as an amendment to the NDA. The update described two studies initiated since the NDA submission and the safety findings from those trials. These studies included Trial 19.4.110, which assessed skin prick and intradermal testing with (b) (4) (and is reviewed elsewhere in this review), and Trial 19.4.313, which evaluated the relationship between two types of devices for assessing the reappearance of T₄ in the train-of-four twitch response. The safety findings from these studies were not incorporated into the database as part of this review. Findings from Trial 19.4.110 are described in Section

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The key adverse events, i.e., those which preclude a recommendation that (b) (4) be approved at this time or which warrant further investigation as a Phase 4 commitment are described below.

1. *Cardiac adverse events including life-threatening arrhythmias and QTc prolongation*
These events occurred at a higher rate in (b) (4) treated subjects than in either the placebo- or the neostigmine-treatment arms. The events began shortly following the administration of (b) (4) typically minutes to hours, and were generally self-limited. However, there was one patient, who died following treatment with (b) (4) that suffered

“sequellae” related to atrial fibrillation and respiratory failure. There was insufficient data to rule out the possibility that (b) (4) was directly linked to her eventual demise. The increased incidence of QTc prolongation in (b) (4) treated subjects was an unexpected finding as the two thorough QTc studies indicated that (b) (4) had little impact on the QT interval. It was noted that there was no dose-dependent relationship to any of the cardiac events. Based on these findings, a Phase 4 study comparing cardiac events in patients treated with (b) (4) versus other reversal agents and no reversal agents is recommended.

2. *Anaphylactic reactions and the potential of (b) (4) to stimulate the immune system*
These reactions have occurred in a substantial percentage of the (b) (4) exposed subjects. While the reactions observed to date have been mild to moderate, it is not possible, without knowing the mechanism by which the reactions have occurred, to determine whether or not more severe reactions are likely to occur or whether there is a particular population that is more or less at risk of such reactions. An allergic reaction that was experienced by one subject, who had never been exposed to (b) (4) raises the possibility that another drug product may sensitize patients to (b) (4) and vice versa. The Applicant-predicted exposure rate of thousands of patients a day and the common need for multiple anesthetics in the course of a lifetime warrant further investigation of both the mechanism of the anaphylactic responses and the possibility of cross sensitization. It is recommended that these investigations be completed prior to consideration of approving (b) (4)
3. *Effect of (b) (4) on coagulation time*
The Applicant failed to perform clinical evaluations of the commonly used parameters for assessing a patient’s coagulation times. These include aPTT, PT and the INR. In *in-vitro* studies, it was noted that (b) (4) prolongs all of these parameters. The clinical implications for this effect is not know, but could have significant safety implications for patients undergoing surgical procedures with increased risk of blood loss or where post-operative anticoagulation is required. Investigations need to be undertaken to determine the effects of (b) (4) on coagulation times and the mechanism by which it affects them. Knowing the mechanism is important as it could impact how patients are treated for post-operative bleeding or anticoagulation. It is recommended that these investigations be completed prior to consideration of approving (b) (4)

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Applicant’s approach to dividing the safety database into three categories, Pooled Phase 1, Pooled Phase 1-3 and Total Org 25969/ (b) (4) permitted appropriate analyses of the data. The

specifics regarding the studies incorporated into each category is described elsewhere in this review.

7.4.1.2 Combining data

The Applicant made separate comparisons of safety based on pooling data from within each of the categories described in the section above. This allowed (b) (4) treatment safety data to be appropriately compared to the two comparators, placebo and neostigmine by clinical trial phase groupings as well as across the clinical development program. Thus, dose-response information could be considered in the context of the findings for each of the comparators.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Safety data from different studies utilizing (b) (4) were pooled to generate dose-response assessments of adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

The Applicant assessed clinical laboratory parameters and occurrence of adverse events at appropriate time points relevant to the half life and timing of Cmax for (b) (4) as to adequately evaluate time dependency for adverse reactions.

7.4.2.3 Explorations for drug-demographic interactions

The Applicant enrolled sufficient numbers of subjects to assess demographic effects based on age (18-64 and ≥ 65 years of age), gender and race (Caucasian versus Japanese).

7.4.2.4 Explorations for drug-disease interactions

These explorations were limited to subjects with renal impairments based on the mechanism of elimination for (b) (4). Subjects enrolled in the clinical trials were otherwise relatively healthy adults.

7.4.2.5 Explorations for drug-drug interactions

Drug-drug interactions were not explored in the clinical development program. The administration of (b) (4) as a single dose at the end of the surgical procedure and the end of the anesthetic suggested that this approach was acceptable barring adverse events that indicated the need for further investigations.

7.4.3 Causality Determination

Causality determination was limited to the timing of adverse events relative to the administration of (b) (4) and the presence or absence of other factors that may have caused or contributed to the events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The clinical trial program adequately assessed the dosing regimen proposed in the label and the timing of administration. Sufficient testing was performed to identify the recommended dose of (b) (4) for each of the proposed indications related to the level of neuromuscular blockade.

8.2 Drug-Drug Interactions

(b) (4) has the potential to bind other steroid-based drugs and some heavy metals. The Applicant considered some of these interactions in models that are described in the Clinical Pharmacology review. Specific drug-drug interactions were not assessed in the clinical trials.

8.3 Special Populations

The impact of renal impairment was evaluated by the Applicant; however, the impact of hepatic impairment, which relates to the elimination of the NMBAs was not assessed. Additional information may be required for renally impaired patients who are dialysis dependent as the modeling data has not resolved the issue of whether (b) (4) is filtered with high flux systems.

8.4 Pediatrics

The Applicant included pediatric subjects in a single clinical trial conducted in Europe. Prior to that trial, the Applicant was advised of the need for additional preclinical data if pediatric subjects were to be enrolled in trials in the United States. The safety data from the study were considered in this review. The Pharmacology-Toxicology review and transcripts from the Advisory Committee meeting should be consulted for other safety issues regarding this patient population.

8.5 Advisory Committee Meeting

Below are some of the summary findings of the Advisory Committee which met in March, 2008, to discuss this product. Transcripts of the discussions are available at the Agency's website.

Endpoint used for comparison of (b) (4) to Succinylcholine

The consensus of the committee was that the endpoint used, $T_1 = 0.1$ was of minimal clinical use as it did not imply that a patient was ready to be extubated. By comparison, a T_1 in the range of 0.7 to 0.9 was felt to be more clinically meaningful. The committee indicated that it would be more informative for clinicians to know the time when most (e.g., 95%) patients had fully responded. There was no consensus on this issue, but FDA was advised that obtaining this important information might be difficult.

Use of (b) (4) in dealing with the clinical scenario of cannot intubate/cannot ventilate

The committee agreed that sugammadex does offer some potential advantages in comparison to other neuromuscular blockade reversal agents in dealing with a "cannot intubate/cannot ventilate" (CICV) situation, but other factors must be considered, including the induction agents and other concomitant medications used, and whether these were likely to interfere with spontaneous ventilation. The presence of co-morbidities such as upper airway anatomical abnormalities or pulmonary insufficiency would also be relevant. In addition, new technologies such as the LMA and combitube have been demonstrated to be useful in emergency settings such as the CICV scenario. It was noted that the sponsor did not address the obstetric patient population, where failed tracheal intubation is more likely, or those with renal insufficiency, where succinylcholine remains a necessary agent. The Committee recommended strongly that the sponsor fulfill a careful post-marketing surveillance and education plan regarding the obstetric and renal impairment subpopulations.

Concerns related to the prolonged exposure of bone to (b) (4)

The consensus from the committee was that there is no evidence suggesting a problem for adult patients, but given that bone changes occurred in adult and young animals, there may be potential for risk in adults with bone fractures. A post-marketing surveillance plan should be implemented if sugammadex is approved.

The committee felt that the risk in the pediatric patient population has not been adequately characterized. They suggested that the sponsor first complete a long-term repeated-dose exposure study in young animals to understand the wash-out period better, and for a longer wash-out than 172 days, and to understand the effects of receiving the agent with some regularity over a longer time period to determine if repeated exposure over time would lead to significant risk. The committee also felt that additional studies of sugammadex's effects on bone fractures in juvenile animals would be useful, including data on the uptake of the drug, as well as the healing process, at the fracture site. Additionally, evaluation of the bone strength of mature animals after repeated juvenile exposure would be necessary to characterize and define the risk to pediatric patients.

Concerns related to renal function in the pediatric population and the use of (b) (4)

In addition, because the immature renal function in the neonatal or infant pediatric population is different from the renal function of the young rats and rabbits studied, the Committee recommended that the sponsor investigate further the effect of sugammadex on pediatric renal function and that nonclinical studies in an immature renal function model may be appropriate.

The committee felt that there are enough data on single-dose exposures to suggest that single-dose clinical trials would be reasonably safe, but clearly there are concerns about repeated exposures. Multi-dosing studies in pediatric patients should not occur until all the reproductive toxicity and juvenile studies have been thoroughly analyzed. Additional data, including a juvenile rat study with bone strength (i.e., load-bearing) assessment, would be important to support multiple-dose clinical trials.

Concerns for the proposed indications for (b) (4)

The committee agreed that studies with sugammadex do support its proposed indication of reversal from rocuronium, but the majority of the panel agreed that the word "immediately" should be replaced by a description of the clinical trials and their findings. It was felt that this would be more informative to the practitioner, who may then determine whether sugammadex is appropriate for use in an urgent circumstance.

Concerns related to the population in whom (b) (4) should be used

The "targeted population" for sugammadex was defined as adult patients receiving rocuronium or vecuronium, excluding patients with renal impairment. The Committee suggested also excluding obstetric and pediatric patient populations, until additional studies are available for these two populations. The Committee discussed the issue of the potential for hypersensitivity to the agent. The Committee agreed that the rates of potential hypersensitivity symptoms appeared to be similar between the drug and the placebo group, but because there were few patients on placebo, small differences would not be detected. It was also agreed that none of the cases identified with potential hypersensitivity required additional therapy. However, it was also agreed that the available data did not preclude the possibility of some level of hypersensitivity reaction, and that this should be carefully followed with post-marketing surveillance, if sugammadex is approved. The Committee did not indicate that the hypersensitivity reactions even if they were potentially anaphylactic reactions should restrict its use.

8.6 Literature Review

The published literature related to sugammadex comes from research conducted by or for the Applicant in support of this NDA.

8.7 Postmarketing Risk Management Plan

A risk management plan was submitted by the Applicant; however, some of the issues addressed in the plan, e.g., influence of (b) (4) on coagulation time and hypersensitivity reactions, will require further investigation prior to approval. Therefore, the need for a risk management plan will be reassessed once the additional clinical information needed for approval has been evaluated.

8.8 Other Relevant Materials

Two consultations were provided by the Division of Pulmonary and Allergy Products. The input and recommendations from these consults have been incorporated in other sections of this review. The consultations are included in the Appendix for reference purposes.

9 OVERALL ASSESSMENT

9.1 Conclusions

This reviewer concurs with the Applicant's conclusions regarding the efficacy findings for (b) (4). However, there is disagreement on the nature of the reactions which the Applicant identified as "hypersensitivity" and which the Agency maintains meet the criteria for anaphylaxis. In addition, there is need for clinical evaluation of the effects of (b) (4) on coagulation, investigation of the immunogenic potential of (b) (4) and continued monitoring of cardiac adverse events related to (b) (4) compared to those associated with other reversal agents and the use of no reversal agents. Thus, in this reviewer's opinion, the known and potential risks associated with (b) (4) use that have been identified to date have not been sufficiently delineated to allow a determination that they are outweighed by the benefits of (b) (4) as a reversal agent for rocuronium- and vecuronium-induced neuromuscular blockade.

9.2 Recommendation on Regulatory Action

Refer to Section 1 for the recommendation on regulatory action.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activity is recommended at this time.

9.3.2 Required Phase 4 Commitments

Refer to Section 1 for this information.

9.3.3 Other Phase 4 Requests

No other clinically related Phase 4 requests are indicated.

9.4 Labeling Review

Comments regarding the Applicant's are included in Dr. Shibuya's review. The clinical sections of the label, especially those pertaining to safety, may require additional changes based on findings from the recommended studies.

9.5 Comments to Applicant

Comments for the Applicant have been directly incorporated into the regulatory action letter.

See Medical Officer Consultation dated 5/13/05 was withheld as a duplicate of the 5/13/05 Consultation above.

See Medical Officer Consultation dated 6/16/08 was withheld as a duplicate of the 6/16/08 Consultation above.

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/s/

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6/27/2008 06:59:31 PM
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**Division of Cardio-Renal Drug Products
Consultation for Division of Division of Anesthetic, Analgesic
and Rheumatology Products**

From: Shen Xiao, M.D., Ph.D. Medical Officer
Division of Cardiovascular and Renal Products
Through: Norman Stockbridge, M.D., Ph.D. Division Director
Division of Cardiovascular and Renal Products

To: Alison Meyer
Division of Anesthetic, Analgesic and Rheumatology Products

Subject: NDA 22-225
Name of Drug: Bridion (Org25969)
Formulation: Intravenous solution
Related Applications: N/A
Approved Indications: None yet
Current Indication: Reversal of neuromuscular blockade (with rocuronium and vecuronium only)
Sponsor: Organon US Inc, Livingston Ave, Roseland, NJ 07068, Tel: 973-325-5303

Documents Used for Review: NDA 22-225 original submission

Date Consult assigned: October 31, 2007
Date of Desired completion: March 4, 2008
Date Consult completed:

Background Information (provided by DAARP):

Bridion is a NME of the gama-cyclodextrin class. Cyclodextrins, as a class, are known to be nephrotoxic although the beta-cyclodextrins are believed to be more nephrotoxic than the gama-cyclodextrins. This molecule has been developed to bind specifically to rocuronium and vecuronium for the indication of the reversal of neuromuscular blockade caused by rocuronium and vecuronium only. Bridion is administered via the intravenous route and is excreted, almost exclusively, by the kidneys. The proposed dosing regimen is a single IV bolus injection.

In the non-clinical studies, Vacuolization of the renal cortical tubular cells and foamy cytoplasm of the transitional epithelium of the urinary bladder were observed in a dose-dependent fashion at 120mg/kg and 500 mg/kg for 2-4 weeks. There was also a single instance of elevated BUN, creatinine, and kidney weight in a dog treated a single dose of bridion although the applicant attributes that to a high dose of rocuronium.

According to the clinical overview, no unexpected renal toxicity was observed in the safety database (N=1926). The applicant included additional markers for renal toxicity (NAG, Beta-2 microglobulin, etc) to the clinical program although, in most studies, follow up was limited to < 24 hours following dosing.

Comments: After reviewing the summary of safety data set from the original NDA, we provide the following comments:

- In the non-clinical studies, the NOEL was 200 mg/kg in rats (single dose studies) and 250 mg/kg in dogs (up to 4-week general toxicity studies). In the 2 and 4-week i.v. toxicity studies in rat, the induction of reabsorption vacuoles in the kidney cortical tubular cells (graded as minimal to occasionally moderate) and the hypertrophy/foamy cytoplasm of the urinary bladder umbrella cells were observed in dose-dependent effects at 120 mg/kg and 500 mg/kg for 4 weeks and were very mild to mild. Compared to the proposed single human dosages of 2 mg/kg to 16mg/kg for immediate reversal, this product has a wide safety margin for clinical use based on the animal data.
- In the clinical PK studies, the eliminated half life of bridion is 2.2 hours. After 24 hours, more than 90% of the product was eliminated. In the tissue distribution study with rats, no drug retention in the tissues other than bone and teeth was observed. Therefore, the possibility of delayed renal effect of this product is low.
- In clinical biochemistry analysis in the pooled phase 1 to 3 trials, there were transient, reversible, dose-dependent (2, 4, and 16 mg/kg), minor increases (<10%) of serum level of creatinine (Scr) from baseline. This change was back to baseline at the end of 24 hours of post-dose. During the same period of creatinine change, there was also a change of serum level of creatine phosphokinase (CK). There was no difference of BUN between the treated and placebo control groups. Therefore, it is possible that the transient change of Scr parallel with the CK was due to the effect of bridion on muscle not on renal function. In addition, since the measurement of Scr may be varied from 5 to 15%, the less than 10% change is not considered as clinical significance.
- In patients with renal function impairment from mild (creatinine clearance between 50 to 80 ml/min) to severe (creatinine clearance < 30 ml/min), the renal function did not get worse compared to the baseline although the eliminated half life of bridion was significantly increased.
- In the urinalysis in the pooled phase 1 to 3 trials, parameters including urine specific gravity, pH, beta-2-microglobulin, urine creatinine, microalbumin, urine protein, NAG, and sediment analysis for the analytes casts, crystals, RBC count, hyalinic cylinders, WBC count, round epithelial cells, squamous epithelial cells, and yeast, were applied. Some of these parameters may be more sensitive than the Scr to detect the renal safety signal. The specificity of these biomarkers, however, needs to be confirmed in the future clinical studies. Currently, these parameters can be used as referenced biomarkers for renal toxicity evaluation. Based on the provided safety data, there were no differences of these parameters between the treated and control groups.

Questions for Consult and addressed:

1. Were the tests of renal function sufficient to detect a renal safety signal for this NME?

In general, Scr is considered as the most dependable biomarker to detect the renal safety signal. Other parameters used by sponsor in this NDA such as urinary beta-2-microglobulin, microalbumin, urine protein, NAG, and sediment analysis may be more sensitive in some conditions than the change of Scr. However, the specificity of these biomarkers needs to be further confirmed in the future clinical studies.

Currently, it could be difficult to detect a renal safety signal for NME without the change of Scr or renal pathology examination.

2. Within the context of post-operative fluid shifts and changes in cardiopulmonary status, was the follow-up assessment for renal function sufficient to rule out delayed nephrotoxicity?

Based on the clinical PK/PD data and the pooled safety data set from Phase 1 to 3 trials, we did not observe any evidence for delayed nephrotoxicity signals related to this product. However, there were no adequate data to support that the delayed nephrotoxicity can be ruled out if patients are in the status of severe dehydration and decreased renal blood flow caused by the post-operative fluid shifts since this drug is mainly excreted by the kidneys.

3. Were the numbers of patients exposed to bridion sufficient to rule out a significant renal safety signal?

There were total of 1926 patients in the safety database. We consider that the number of patients exposed to bridion is sufficient to evaluate the renal safety.

4. Do you agree with the applicant's conclusion that no renal safety signal exists for bridion?

In the whole safety database from pooled phase 1 to phase 3 trials, there were no significant changes of renal function measured by Scr and other urinary biomarkers such as urinary beta-2-microglobulin, microalbumin, urine protein, NAG, and sediment analysis. Therefore, no significant renal safety signals were detected. However, due to the less sensitivity of Scr and the limitations of current available renal biomarkers, it is impossible to exclude absolutely the minor to mild renal toxicities which can not be detected by the change of Scr or current available renal biomarkers.

Considering this product was also tested in patients with mild, moderate and severe renal impairment, and no significant renal function changes compared to the baseline were observed, this would be reassuring that bridion may not have significant effect on the renal function.

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/s/

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CLINICAL REVIEW

Application Type NDA 22-225
Submission Number 000

Letter Date 30 October 2007
Stamp Date 31 October 2007
PDUFA Goal Date 30 April 2008

Reviewer Names Robert B. Shibuya, M.D.
Review Completion Date 29 April 2008

Established Name Org 25969 (Sugammadex sodium)
(Proposed) Trade Name ^{(b) (4)}
Therapeutic Class Neuromuscular blockade reversal agent
Applicant Organon

Priority Designation P

Formulation Sterile solution, Injectable
Strength 100 mg/mL
Dosing Regimen Single-dose
Route of Administration Intravenous
Indication Reversal of neuromuscular blockade by rocuronium or vecuronium
Intended Population Adults

Table of Contents

| | | |
|----------|---|-----------|
| 1 | EXECUTIVE SUMMARY | 4 |
| 1.1 | RECOMMENDATION ON REGULATORY ACTION | 4 |
| 1.2 | RECOMMENDATION ON POSTMARKETING ACTIONS | 5 |
| 1.2.1 | Risk Management Activity | 5 |
| 1.2.2 | Required Phase 4 Commitments | 5 |
| 1.2.3 | Other Phase 4 Requests | 5 |
| 1.3 | SUMMARY OF CLINICAL FINDINGS | 5 |
| 1.3.1 | Brief Overview of Clinical Program | 6 |
| 1.3.2 | Efficacy | 6 |
| 1.3.3 | Safety | 9 |
| 1.3.4 | Dosing Regimen and Administration | 9 |
| 1.3.5 | Drug-Drug Interactions | 9 |
| 1.3.6 | Special Populations | 10 |
| 2 | INTRODUCTION AND BACKGROUND | 10 |
| 2.1 | PRODUCT INFORMATION | 10 |
| 2.2 | CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS | 11 |
| 2.3 | AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES | 11 |
| 2.4 | IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS | 11 |
| 2.5 | PRESUBMISSION REGULATORY ACTIVITY | 12 |
| 2.6 | OTHER RELEVANT BACKGROUND INFORMATION | 13 |
| 3 | SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES | 14 |
| 3.1 | CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE) | 14 |
| 3.2 | ANIMAL PHARMACOLOGY/TOXICOLOGY | 14 |
| 3.3 | CLINICAL PHARMACOLOGY | 15 |
| 4 | DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY | 15 |
| 4.1 | SOURCES OF CLINICAL DATA | 15 |
| 4.2 | TABLES OF CLINICAL STUDIES | 15 |
| 4.3 | REVIEW STRATEGY | 16 |
| 4.4 | DATA QUALITY AND INTEGRITY | 16 |
| 4.5 | COMPLIANCE WITH GOOD CLINICAL PRACTICES | 17 |
| 4.6 | FINANCIAL DISCLOSURES | 17 |
| 5 | CLINICAL PHARMACOLOGY | 17 |
| 5.1 | PHARMACOKINETICS | 17 |
| 5.2 | PHARMACODYNAMICS | 17 |
| 5.3 | EXPOSURE-RESPONSE RELATIONSHIPS | 18 |
| 6 | INTEGRATED REVIEW OF EFFICACY | 18 |
| 6.1 | INDICATION | 18 |
| 6.1.1 | Methods | 19 |
| 6.1.2 | General Discussion of Endpoints | 19 |
| 6.1.3 | Study Design | 20 |
| 6.1.4 | Efficacy Findings | 21 |
| 6.1.5 | Clinical Microbiology | 39 |
| 6.1.6 | Efficacy Conclusions | 39 |
| 7 | INTEGRATED REVIEW OF SAFETY | 40 |
| 8 | ADDITIONAL CLINICAL ISSUES | 40 |

| | | |
|-----------|---|-----------|
| 8.1 | DOSING REGIMEN AND ADMINISTRATION | 40 |
| 8.2 | DRUG-DRUG INTERACTIONS | 40 |
| 8.3 | SPECIAL POPULATIONS..... | 41 |
| 8.4 | PEDIATRICS | 41 |
| 8.5 | ADVISORY COMMITTEE MEETING | 41 |
| 8.6 | LITERATURE REVIEW | 42 |
| 8.7 | POSTMARKETING RISK MANAGEMENT PLAN | 42 |
| 9 | OVERALL ASSESSMENT..... | 42 |
| 9.1 | CONCLUSIONS | 42 |
| 9.2 | RECOMMENDATION ON REGULATORY ACTION | 42 |
| 9.3 | RECOMMENDATION ON POSTMARKETING ACTIONS | 42 |
| 9.3.1 | Risk Management Activity | 42 |
| 9.3.2 | Required Phase 4 Commitments..... | 42 |
| 9.3.3 | Other Phase 4 Requests..... | 43 |
| 9.4 | LABELING REVIEW | 43 |
| 9.5 | COMMENTS TO APPLICANT..... | 43 |
| 10 | APPENDICES | 44 |
| 10.1 | REVIEW OF INDIVIDUAL STUDY REPORTS | 44 |
| 10.2 | LABELING REVIEW..... | 83 |

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer limited his review to the efficacy and administrative sections of this application. From the perspective of efficacy, this reviewer recommends that sugammadex be approved for the indication of the reversal of neuromuscular blockade induced by rocuronium and vecuronium.

Sugammadex sodium (aka Org25969 or (b)(4) is a new molecular entity (NME) that was developed to bind the neuromuscular blocking agents (NMBAs) rocuronium or vecuronium, therefore clearing the neuromuscular junction and reversing the paralysis induced by the NMBA. Subsequent to binding NMBA, the sugammadex-NMBA should be excreted renally. Because the applicant indicated that it would prefer that the product be referenced as sugammadex after most of this review was written, this review will usually reference the product as Org25969, the name used during most of the development.

The applicant is seeking three indications. It considers two of the indications to be “routine” reversal of neuromuscular blockade which correspond to the clinical scenario of the predictable end of surgery. The applicant has further subdivided “routine” reversal into “shallow” meaning that more of the NMBA has been metabolized and “profound” indicating more neuromuscular blockade from the last dose of NMBA. The applicant also investigated an “immediate” reversal situation where Org25969 was administered three minutes following a high dose of NMBA. The applicant purported that the “immediate” reversal situation was applicable to the “Cannot intubate/cannot ventilate” situation, a medical emergency. The Agency does not agree that the applicant showed efficacy in a medical emergency.

The applicant submitted compelling evidence of efficacy. The finding of efficacy for the reversal of neuromuscular blockade relied predominantly on three adequate and well controlled studies that explored the use of the drug at three dose regimens for the three clinical scenarios envisioned as separate indications by the applicant.

The applicant submitted 13 other studies, predominantly small Phase 2 trials, that informed to efficacy. In all 16 studies, there was evidence of treatment effect and dose-response was observed in each study where it was examined. In most of the efficacy studies, Org25969 was tested against an active comparator, neostigmine. Neostigmine is an unapproved, marketed acetylcholinesterase inhibitor that is the standard of care for the reversal of neuromuscular blockade by nondepolarizing NMBAs such as rocuronium and vecuronium. One study compared the combination of rocuronium/Org25969 to spontaneous recovery following the injection of succinylcholine.

The review of safety for this application was conducted by Dr. Arthur Simone. Please see his review for details. Dr. Simone found that the safety profile of Org25969 was acceptable for a

NMBA reversal agent with one possible exception. There was one case that appeared certainly to be anaphylactoid or possibly true anaphylaxis and several other cases of hypersensitivity. The other safety issues identified were related to the potential effects of sugammadex on the bones and teeth in juvenile animals.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Dr. Simone has addressed Risk Management Activity in his review of safety.

1.2.2 Required Phase 4 Commitments

The areas of concern that were identified in the Agency review of Org25969 include:

- Hypersensitivity reactions – To date, the applicant has not fully characterized these reactions, specifically whether they are IgE mediated or if any populations at risk can be identified. If the product is approved, it will be necessary to ensure that due diligence is employed in following up on this disturbing clinical safety finding.
- Effects on bone – Org25969 binds to the hydroxyapatite of bone (although not the epiphysis or callus) with a half-life in the range of 170 days. In the nonclinical studies conducted, this effect did not appear to affect bone function or fracture healing although the evaluation was not as complete as the Agency requires.
- Effects on teeth – Juvenile rat studies showed rare defects in enamel formation.

Because surgery in the pediatric population is frequently staged and multiple and the fact that bone and tooth formation are more susceptible in the pediatric population, the applicant would have to conduct certain studies to further understand the risks suggested in the nonclinical studies.

1.2.3 Other Phase 4 Requests

From the efficacy perspective, no further postmarketing studies are necessary.

1.3 Summary of Clinical Findings

Org25969 is a NME of the gamma-cyclodextrin class. Beta-cyclodextrins have been used in approved pharmaceutical products but as excipients. Org25969 is first in class and is using a novel mechanism of action to scavenge the NMBAs rocuronium and vecuronium when they are no longer needed therapeutically.

1.3.1 Brief Overview of Clinical Program

As a New Molecular Entity, this initial NDA submission was substantial. Following, are the key features of the clinical research program.

- Product name: Org25969 aka sugammadex
- Class: Gamma-cyclodextrin
- Route of administration: intravenous
- Indications: “Routine” reversal of “shallow” or “profound” neuromuscular blockade induced by rocuronium and vecuronium and “Immediate” reversal of neuromuscular blockade after injection of rocuronium
- Number of pivotal efficacy trials: Four
- Number of patients enrolled in pivotal efficacy trials: 529
- Overall number of patients in safety database (single exposure): 2054 unique patients and subjects
- Other pertinent clinical data sources: None

1.3.2 Efficacy

The applicant conducted 28 clinical studies. The applicant considers four studies to be pivotal. Three pivotal studies were highly similar in design. One was significantly different. Studies 19.4.301 (Study 301), 19.4.302 (Study 302), and 19.4.310 (Study 310) were of similar design. Study 301 enrolled adults without renal disease or other serious systemic disease who were scheduled for surgery requiring general anesthesia in the supine position. Following screening, patients were randomized 1:1:1:1 to one of the following treatment groups

Table 1: Treatment groups, Study 301

| Group Number | Neuromuscular Blocking Agent (NBMA) | “Reversal”* agent |
|---------------------|--|--------------------------|
| 1 | Rocuronium | Org25969 |
| 2 | Rocuronium | Neostigmine |
| 3 | Vecuronium | Org25969 |
| 4 | Vecuronium | Neostigmine |

*Quotation marks used because neostigmine is a marketed, unapproved drug and Org25969 is investigational

Patients were induced with a standard intravenous sequence followed by paralysis with the specified NBMA. Anesthesia was maintained with sevoflurane and parenteral agents. The level of neuromuscular blockade was monitored via a Train-Of-Four (TOF) nerve stimulator. At the return of T₂, which was felt to approximate “shallow” blockade, the reversal agent was administered. The dose of Org25969 was 2 mg/kg. The elapsed time between the start of administration of the reversal agent and the recovery of the T₄/T₁ ratio to 0.9, as measured by acceleromyography, was the primary endpoint. Other clinical measures of recovery were assessed including a 5-second head lift and general weakness. Prior to, during anesthesia, and following recovery, the patient was followed for safety. In these studies, the safety assessor was blinded.

Study 302 differed from Study 301 in two significant aspects.

1. The reversal agent was administered at 1-2 Post-Tetanic-Counts (PTC). This was to approximate “profound” blockade.
2. The dose of Org25969 was 4 mg/kg (the neostigmine dose was also higher).

Study 310 differed from Study 301 in that there were two treatment groups, rocuronium/Org25969 and cis-atricurium/neostigmine. This reviewer notes that this study design was not properly controlled because the neuromuscular blocking agent used was cis-atricurium, not rocuronium.

Study 303 differed more significantly from Studies 301, 302, and 310.

1. Patient population
 - a. Patients had to be somewhat healthier because only ASA 1 and 2 patients could be enrolled.
 - b. Patients would only be planned for a short period of neuromuscular blockade.
2. Treatment arms
 - a. Rocuronium followed in three minutes (point of maximal blockade) by Org25969, 16 mg/kg
 - b. Succinylcholine, 1 mg/kg. Since there is no “reversal” agent for succinylcholine, the effects of the drug were allowed to spontaneously resolve.
3. Conduct
 - a. Patient screened and randomized.
 - b. Patient induced.
 - c. Neuromuscular blockade achieved by intravenous administration of rocuronium or succinylcholine.
 - d. Three minutes following the administration of rocuronium patients randomized to the rocuronium/Org25969 arm were injected with Org25969. Patients randomized to succinylcholine did not receive a sham injection.
 - e. Train-of-Four neuromuscular monitoring continuously performed until patient recovered.
 - f. Routine follow up and post-anesthesia care.
4. Since patients treated with succinylcholine do not demonstrate fade on TOF stimulation, the primary efficacy endpoint was the elapsed time from the injection of NBMA to recovery of T_1 to 0.1 (10%).

Table 2, following, briefly summarizes the efficacy results from Studies 301-3 and 310.

Table 2: Summary of pivotal efficacy data, primary efficacy endpoint, means (mm:ss)

| Study # | Scenario | Org | Comparator | p-value |
|---------|-------------|----------|------------|---------|
| 301 | Routine | 1:29 (R) | 18:30 | <0.0001 |
| | Shallow | 2:48 (V) | 16:48 | |
| 302 | Routine | 2:52 (R) | 50:22 | <0.0001 |
| | Profound | 4:28 (V) | 66:12 | |
| 303 | “Immediate” | 4:22 | 7:04 | <0.0001 |
| 310 | Routine | 2:02 | 8:46 | <0.0001 |
| | Shallow | | | |

The efficacy data all demonstrated a statistically significant treatment effect with large effect size that favored Org25969 over the active comparator. Studies 301 and 302 had been conducted in accordance with a Special Protocol Assessment (SPA) agreement.

This reviewer also notes that

Comments/Conclusions:

1. The studies submitted support a finding of substantial evidence of efficacy.
2. Org25969 appears to be somewhat more efficacious when used with rocuronium than vecuronium.
3. While the comparisons of means showed an unequivocal treatment effect that is more convincing since the studies were active controlled (albeit with an unapproved comparator), Org25969 did not work convincingly in all patients. In each pivotal trial and in certain Phase 2 studies, “outliers” were observed (defined as > 3x the mean recovery time). In rare cases the time to endpoint exceeded the median or mean for the comparator. While this does not change the conclusion that Org25969 is an effective reversal agent, this fact should be addressed in labeling.
4. Study 303 demonstrated that patients recovered 10% of their T₁ more rapidly when Org25969 was administered at maximal rocuronium effect than patients who were treated with succinylcholine recovered spontaneously. The clinical significance of a T₁ = 0.1 is uncertain. Furthermore, this reviewer notes that the applicant did not test the 16 mg/kg dose in an emergency situation, making extrapolation of the Phase 3 scenario to the cannot intubate/cannot ventilate (CICV) situation speculative.
5. As predicted by the applicant, there were technical problems with the generation of the acceleromyography data. Hence, the applicant employed an adjudication committee to provide expert interpretation of certain TOF tracings. Unfortunately, the exact wording defining those cases that would be adjudicated was vague. However, the numbers of patients that were adjudicated were small and a sensitivity analysis that excluded the adjudicated cases showed no differences in the trial outcomes.

6. While a cross-study comparison, neostigmine, administered at the return of T2, following neuromuscular blockade with cis-atricurium, appeared to be more rapidly reversed than rocuronium or vecuronium.

1.3.3 Safety

Dr. Arthur Simone conducted the review of safety. Please see Dr. Simone's review for a detailed discussion of the safety data. Briefly, the primary safety concern is hypersensitivity.

Most concerning is the healthy volunteer who developed a tryptase-positive reaction with clinical features suggestive of anaphylaxis after Org25969 had been dosed to 8 mg/kg (planned for 32 mg/kg). While this patient recovered without therapy, he was skinprick and intradermal allergy testing positive some months following the exposure. The Division has worked with and encouraged the applicant to conduct IgE testing and further define the nature of these reactions. To date, the applicant has not conducted the IgE testing nor, in the opinion of this reviewer, have they completely evaluated this and similar (albeit less severe) cases of hypersensitivity.

1.3.4 Dosing Regimen and Administration

The applicant has conducted a comprehensive Phase 2 dose-ranging program and believes that the following dosing regimens are appropriate.

Table 3: Proposed dosing regimens

| Scenario | Proposed dose |
|--|----------------------|
| "Routine/shallow" – return of the second twitch in a train-of-four | 2 mg/kg IV |
| "Routine/profound" – 1-2 post-tetanic-counts following a tetanic stimulus | 4 mg/kg IV |
| "Immediate" – three minutes after a high (1.2 mg/kg) dose of rocuronium – presumably at maximal neuromuscular blockade | 16 mg/kg IV |

This reviewer and the Office of Clinical Pharmacology are in agreement that the Phase 2 studies, as confirmed by Studies 301, 302, and 303 support these doses for these scenarios.

1.3.5 Drug-Drug Interactions

This molecule, a substituted gamma-cyclodextrin, that was designed to bind the steroid nucleus of rocuronium and vecuronium, has the ability to bind other steroid hormones and certain heavy metals, albeit with low affinity. In this reviewer's analysis of the outliers, (Section 6), many of the outliers (patients who had a delayed or unapparent response to Org25969) were on concomitant steroid drugs. Dr. Simone did not find any evidence of clinically significant drug-drug interactions in his safety review.

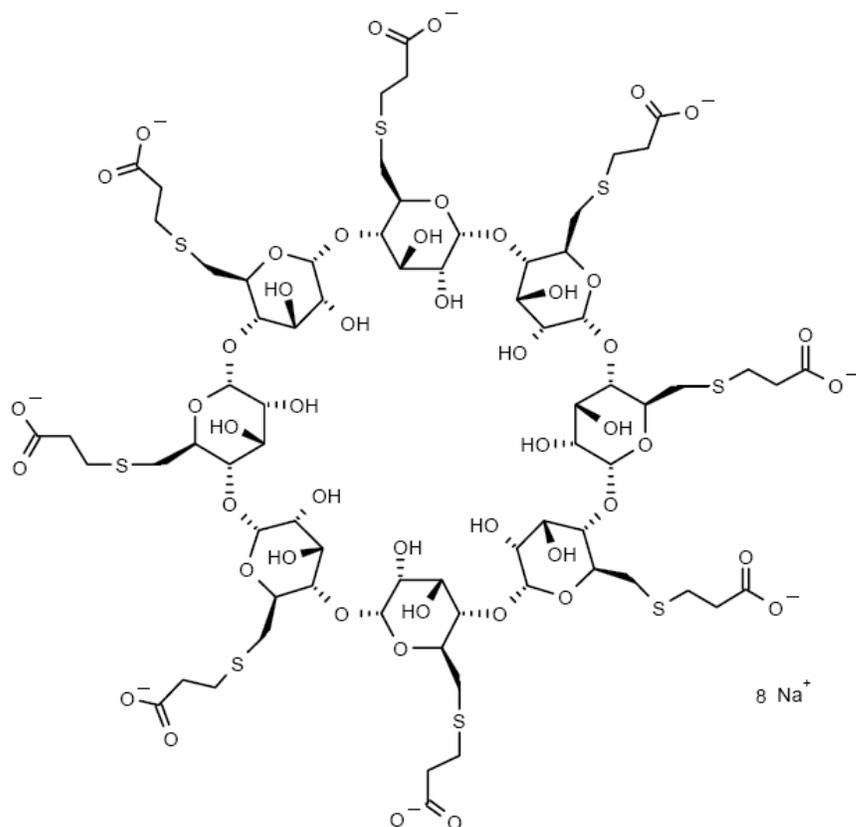
1.3.6 Special Populations

This product is almost completely renally excreted. Therefore, its use in patients with renal impairment is a concern and is addressed in the labeling. The applicant conducted studies in older patients, patients with renal impairment (CHECK THIS), patients with cardiac and pulmonary disease and showed that the drug performed similarly in all patients although the pharmacokinetics were altered (higher C_{max}, higher AUC) in the patients with renal impairment. Please see Dr. Lei Zhang's and Dr. Atul Bhattaram's review for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Org25969 aka sugammadex is a New Molecular Entity of the gamma cyclodextrin class. The drug has been designed, by the selection of functional groups on the structure, to bind rocuronium and vecuronium. In doing so, the molecule has the ability to bind other steroid molecules albeit with lesser avidity. The structure of Org25969 is shown below.



Source: Introduction on Org 25969, page 2

Organon, the applicant, is seeking a proposed trade name of “(b) (4)” for the product. It is a sterile solution for intravenous injection. The applicant is seeking the indication of the reversal of neuromuscular blockade from rocuronium and vecuronium. While the drug to be used as a single dose, Organon is proposing three dosing schemes.

- From “shallow” neuromuscular blockade, defined as the return of T₂ in a train of four (TOF), the applicant is proposing a dose of 2 mg/kg. For this clinical scenario, the applicant believes that Org25969 will work with both rocuronium and vecuronium.
- From “profound” neuromuscular blockade, defined as 1-2 post tetanic counts, the applicant is proposing a dose of 4 mg/kg. For this clinical scenario, the applicant believes that Org25969 will work with both rocuronium and vecuronium.
- For “immediate” reversal, defined as three minutes following the injection of 1.2 mg/kg of rocuronium, the applicant is proposing a dose of 16 mg/kg. This clinical scenario is limited to rocuronium.

2.2 Currently Available Treatment for Indications

Pyridostigmine (NDA 17-398) and edrophonium (NDA 7-959) are approved as reversal agents or antagonists to the neuromuscular blocking effects of nondepolarizing muscle relaxants. These agents are not widely used because of a relatively slow onset of action.

Neostigmine is an unapproved, marketed product. While unapproved, it is the most commonly used NMB reversal agent in the United States. Neostigmine is of the acetylcholine-esterase inhibitor class, similar to pyridostigmine although it has a more rapid onset of action and its pharmacokinetic profile is similar to glycopyrrolate which is frequently co-administered to counter the cholinergic effects.

2.3 Availability of Proposed Active Ingredient in the United States

Org25969 is not approved in the United States or anywhere in the world. It is under review for marketing approval in Europe.

2.4 Important Issues With Pharmacologically Related Products

Cyclodextrins have been used in the formulations of the following approved products (Table 4).

Table 4: Approved products containing cyclodextrins

| Product | NDA |
|-----------------------------------|--------------|
| Caverject (alprostadil) | 20-379 |
| Daptacel (DPT vaccine) | 103666 (BLA) |
| Geodon (ziprasidone) | 20-919 |
| Sporanox IV (itraconazole) | 20-966 |
| Sporanox oral soln (itraconazole) | 20-567 |
| VFEND IV (voriconazole) | 21-267 |

In these products, the cyclodextrin generally acts to enhance the delivery of active drug substance, for example by formation of complexes with the API that may improve aqueous solubility and drug product stability.

2.5 Presubmission Regulatory Activity

Org25969 was developed under IND 68,029.

Following a Pre-IND meeting in July 2003, the key points pertinent to the clinical development program were documented as follows:

- Develop an adequate dose-ranging relationship for rocuronium and Org25969
- In addition to quantitative measurements of T4/T1 ratio, include clinically accessible indicators of reversal such as elapsed time to head lift and sustained tetanus, indicators of strength, ventilatory reserve, cognition, and recovery.
- Develop an argument to support the use of acceleromyography.
- Collect core temperature data.
- Sub-investigators and patients should be blinded. The use of blinded safety-assessors is acceptable.
- Studying patients with hepatic insufficiency will not be required.
- A study to validate the PK model with common steroidal, non-steroidal NMBA, and other critical drugs used concurrently with anesthesia will be required.

The IND was initially submitted in August 2003 and was placed on hold for CMC issues, insufficient nonclinical data, and inadequate clinical monitoring. In April 2004, the applicant adequately addressed the hold issues and the IND clinical was allowed to proceed.

The End-of-Phase 2 meeting occurred on May 3, 2005. Key points relating the clinical program follow:

- The applicant is to conduct a mass balance study in humans.
- A one-sided significance level of 0.025 is acceptable in clinical trials.
- Specify a plan to handle missing data.
- The clinical trials should encompass the range of clinical morbidity (ASA 1-4) and demographics likely to be encountered in this clinical setting.
- The anesthetic regimens should be comparable between treatment arms.
- Acceleromyography data to assess efficacy will be useful; however, commonly used clinical markers of muscle strength must support the AMG data.
- The Agency articulated concern regarding undesired binding to other drug moieties.
- A thorough assessment of the effect of Org25969 on QT interval will be required.
- Since full renal maturity is not seen until age 2, study of the drug in children under 2 years of age is not recommended until it has been assessed in adults with renal insufficiency. A follow up letter from FDA to Organon dated November 16, 2005 reiterated that data from adults with compromised renal function and data from a

preclinical juvenile animal study would be required prior to proceeding with trials in children.

- Test renal function for 1-3 days following exposure.

(b) (4)

On September 2, 2005, the Agency reached agreement with the applicant for Studies 19.4.301 and 19.4.302.

In a letter dated December 22, 2005, the applicant documented a teleconference that occurred on December 6, 2005. In that letter, Organon stated that the Agency agreed that it would not be necessary for the anesthesiologist to use an acceleromyography instrument to determine the timing and correct dose of Org25969 to use.

On December 15, 2006, the Agency, in denying a meeting to discuss a study entitled “Randomized, double-blind, placebo-controlled, six-period cross-over study to investigate the effect of intravenous single doses of Org25969/rocuronium, Org25969/vecuronium, and Org25969 alone on the QTc interval and an open label active control part consisting of a single intravenous dose of moxifloxacin in healthy volunteers,” indicated that it is in agreement with the proposals in the applicant’s December 4, 2006 meeting package.

The Pre-NDA meeting occurred on October 30, 2006. Pertinent highlights follow:

- The pivotal studies appear adequate for filing.
- Analyze data from studies where Org25969 was administered at 1-2 PTCs and 15 minutes after the NMBA independently.
- Studies where Org25969 was given to immediately reverse a maximum neuromuscular blockade will not be considered an evaluation of “Emergency Reversal” because the studies were not conducted under emergency conditions.
- The pediatric data will be summarized in the NDA.
- The safety evaluations appear to be adequate.
- An analysis of all cases of recurarization should be presented.
- Evidence that concomitantly administered medication required dose adjustment in clinical trials should be presented and separately analyzed.
- It may be possible to defer pediatric studies.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

At the time of the finalization of this review, the findings of the other review disciplines, except Chemistry/Manufacturing/Controls are tentative.

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review was conducted by Dr. Alan Schroeder, ONDQA/Division I/Branch II. Briefly, Dr. Schroeder found that the product is approvable pending resolution of consultant reviews and adequate responses by the applicant. Issues identified by Dr. Schroeder at the Midcycle Review included:

- There were small increases in degradation and decreases in assay over 24 months, therefore FDA consults on expiry will need to be completed before the expiration dating can be finalized.
- Dr. Schroeder has requested more information on the starting material.
- The product is packaged in clear glass vials. The product shows some degradation under (b)(4) light conditions.

3.2 Animal Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Dr. Z. Alex Xu of the Division of Anesthesia, Analgesia, and Rheumatology Products. Highlights from Dr. Xu's presentation at the Midcycle review follow.

- Toxicology studies showed minimal to mild toxicity with the target organs being the lung, urinary bladder, and kidney. The lowest NOAEL in the most sensitive species in multiple dosing was 30 mg/kg.
- Org25969 is not mutagenic or clastogenic.
- The Segment 1 (fertility and early embryonic development) reproductive toxicity studies were negative. The Segment 2 (embryonic/fetal development) studies showed decreases in fetal body weight and maternal body weight but an increase in litter size (NOAEL for maternal toxicity – 20 mg/kg, for embryofetal development – 200 mg/kg). The Segment 3 (pre and postnatal development) studies showed an increase in neonatal mortality in the F1 generation and maternal cannibalization at 30 mg/kg.
- Juvenile studies showed dose dependent minimal to slight vacuolization in renal tubules at 120 and 500 mg/kg and effects (tooth discoloration, disruption of the enamel epithelium) on dentition.
- Org25969 has been shown to bind to the hydroxyapatite in bone. The significance of this finding has not been fully characterized.

3.3 Clinical Pharmacology

The Clinical Pharmacology review was conducted by Drs. Lei Zhang of the Division of Clinical Pharmacology 2/Office of Clinical Pharmacology and Atul Bhattaram of the Division of Pharmacometrics/Office of Clinical Pharmacology.

- The applicant has conducted 17 studies (including Phase 3) where pharmacokinetic data were collected and analyzed.
- The applicant has conducted three population pharmacokinetic reports for model development and validation to predict changes in unbound drug concentration after complex formation with Org25969.
- The drug is not metabolized and mainly excreted via the kidney with a half-life of 1-4 hours.
- The drug is dose-proportional for the dose range proposed.
- Renal impairment results in greater exposure (17-fold increase in AUC).
- The presence of rocuronium or vecuronium and an anesthetic has little effect of the pharmacokinetics of Org25969.
- The applicant has used a novel pharmacometric modeling strategy to assess the potential for drug-drug interactions. As a novel approach, the acceptability of the applicant's strategy is subject to further review.
- There is evidence of dose-response for efficacy but not for safety.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The efficacy review relied upon the clinical study reports and datasets from four Phase 3 studies, Studies 301, 302, 303, and 310. Summary data from certain Phase 1 and 2 studies were also assessed. The datasets were used for certain confirmatory analyses. The applicant's summary of efficacy was also reviewed.

4.2 Tables of Clinical Studies

The applicant conducted 28 clinical studies. They fell into categories of bioanalytical, clinical pharmacology, and safety and efficacy studies in healthy volunteers and patients. The studies that directly pertain to the clinical review are noted in Table 5, following.

Table 5: Key clinical studies

| Study # | Objective | Population | N |
|----------|---|--------------------|-----|
| 19.4.101 | Safety, PK renal excretion, dose response, tolerability | Healthy volunteers | 29 |
| 19.4.105 | Effect on the QT interval | Healthy volunteers | 62 |
| 19.4.109 | Effect on the QT interval | Healthy volunteers | 83 |
| 19.4.106 | Safety and tolerability of high doses (up to 96 mg/kg) | Healthy volunteers | 12 |
| 19.4.108 | Safety, tolerability, PK when administered w/ roc/vec | Healthy volunteers | 16 |
| 19.4.201 | Dose response, PK/PD, and safety w/ roc | Patients | 27 |
| 19.4.204 | Dose finding, efficacy, safety w/ roc | Patients | 43 |
| 19.4.206 | Dose response after roc | Patients | 173 |
| 19.4.207 | Dose response after roc, vec, and pancuronium | Patients | 98 |
| 19.4.306 | Efficacy, safety, and PK after roc in adults and children | Patients | 91 |
| 19.4.301 | Efficacy and safety (“shallow” blockade) | Patients | 189 |
| 19.4.302 | Efficacy and safety (“profound” blockade) | Patients | 157 |
| 19.4.303 | Efficacy and safety (“immediate reversal”) | Patients | 110 |
| 19.4.310 | Efficacy and safety (“shallow” blockade – vs atr/neo) | Patients | 73 |
| 19.4.304 | Efficacy and safety in pts w/ nl or impaired renal fx | Patients | 30 |
| 19.4.305 | Efficacy and safety in elderly patients | Patients | 150 |
| 19.4.308 | Efficacy and safety in pulmonary patients | Patients | 77 |
| 19.4.309 | Efficacy and safety in cardiac patients | Patients | 116 |
| 19.4.311 | Uncontrolled safety study | Patients | 197 |

Extracted from Table 1, CTD Module 2.7.6

4.3 Review Strategy

For this New Molecular Entity, the applicant has generated considerable clinical data. This reviewer conducted the review of efficacy, focusing on the four studies (301-3 and 310). This review also included an assessment of the clinical pharmacology program.

Dr. Arthur Simone of the Division of Anesthesia, Analgesia, and Rheumatology Products conducted the review of safety for Org25969.

4.4 Data Quality and Integrity

The Division of Scientific Investigations was asked to inspect the sites of four clinical investigators. Two sites, Dr. Keith Candiotti and Dr. R. Kevin Jones, had been inspected at the time of finalization of this review. DSI had preliminary inspection results for Dr. Manfred Blobner, Dr. Jennifer Hunter, and the applicant. DSI opined that all of the sites were acceptable although they noted some significant protocol violations at Dr. Jones’ site. Dr. Jones participated in Study 302. There were errors in the NMBA maintenance dosing. In the opinion of this reviewer, those errors are not significant because patients were reversed when the correct level of blockade was reached, which would negate such dosing errors. Dr. Jones also had errors in the time of dosing of the reversal agent where some patients were dosed late (at 3, 4, or 5 PTCs). The predicted effect of this violation is to shorten the time from reversal to endpoint. In assessing the treatment assignments for the protocol violators, there were numerically more violators in the Org25969 group. However, most of the Org25969 violators were reversed at 3

PTCs (a slight advantage to the reversal agent) compared to the neostigmine violators where the majority were reversed at 4 or 5 PTCs (a larger advantage).

Therefore, in the opinion of this reviewer, the findings in the clinical investigator inspections are acceptable.

4.5 Compliance with Good Clinical Practices

The applicant certified that all 28 studies submitted were conducted in compliance with Good Clinical Practices. There were no issues identified to indicate to the contrary.

4.6 Financial Disclosures

According to the Financial Certification and Disclosure document, two investigators received significant payments. Those two investigators were:

- (b) (6) served on the adjudication committee, acted as a consultant, and received an institutional grant. He was an investigator in Study 301.
- (b) (6) received an educational grant and served as a investigator for Studies (b) (6).

The applicant certified that none of the financial arrangements associated with Org25969 met the reporting requirements as defined in 21 CFR 54.

5 CLINICAL PHARMACOLOGY

Please see Section 3.3 and Drs. Zhang's and Bhattaram's reviews for more detail regarding the clinical pharmacology program.

5.1 Pharmacokinetics

Key data from the clinical pharmacology program follow.

- The volume of distribution is 12-15 liters.
- The half-life is 1-4 hours.
- The drug is not appreciably metabolized but is excreted, unchanged, via the kidneys.
- Renal impairment increases exposure and half-life.
- The product is dose proportional within the planned dose range.
- Pharmacokinetic modeling was used to predict the behavior of the drug in hepatically impaired patients.

5.2 Pharmacodynamics

The pharmacodynamic effects of Org25969 have been evaluated in Phase 2 and 3. The drug appears to have no other effect except binding rocuronium and vecuronium. However, the drug

has the potential to bind other steroidal moieties, both endogenous and exogenous and certain metals (iron and magnesium). Drs. Simone and Bhattaram will further discuss this aspect of the drug.

5.3 Exposure-Response Relationships

The applicant has conducted 12 Phase 2, dose-finding studies ranging from 0.5 to 16 mg/kg. Drs. Zhang and Bhattaram concur with this reviewer that there appears to be dose response and that the applicant has adequately explored what is the appropriate dose.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant is proposing three indications (the “routine” reversal is subdivided into “shallow” and “profound”).

- A “routine” reversal described as “(b) (4)™ (sugammadex sodium) Injection is indicated for routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium.”
- An “immediate” reversal described as “(b) (4)™ (sugammadex sodium) Injection is indicated for immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.”

The generic indication of the reversal of neuromuscular blockade of nondepolarizing skeletal muscle relaxants has been granted to edrophonium and pyridostigmine. In this case, because Org25969 was “designed” to bind rocuronium and vecuronium and that is part of the indication, adding that restriction to the indication for Org25969 is appropriate.

The applicant is proposing a new clinical scenario that it refers to as “immediate reversal.” The scenario studied in Study 303 was a high dose of rocuronium followed in three minutes by a high dose of Org25969.

In certain sections of the application, the applicant appears to extrapolate the clinical scenario studied in Study 303 to an emergency cannot-intubate/cannot-ventilate scenario (page 91/99 of the Clinical Overview document). The applicant writes “As a result, use of Org 25969 in a CICV situation following rocuronium administration may prevent the need for emergency non-invasive airway ventilation including rigid bronchoscopy, combitube ventilation, or transtracheal jet ventilation, and may prevent the need for emergency invasive airway access such as surgical or percutaneous tracheostomy or cricothyrotomy. In situations where succinylcholine is used for intubation and a CICV scenario develops, there is no antagonist available... (b) (4)

.”

Furthermore, extrapolation of the use of Org25969 to an emergency situation appears to have been accomplished. White et al published a case report in recent journal (March 2007) (Lenz A, Hill G, White PF. Emergency Use of Sugammadex After Failure of Standard Reversal Drugs. *Anesthesia & Analgesia*;104(3):585-6.) where they describe rescuing a regularized patient in the PACU.

The significance of Study 303 was discussed at the Advisory Committee meeting.

6.1.1 Methods

The applicant submitted, among other studies, clinical study reports and full datasets for Studies 19.4.301-3 and 310 to support the proposed indication. Studies 301 and 302, studying reversal of “shallow” and “profound” blockade had been approved via the SPA mechanism. Study 303 had been discussed with the Agency. The Agency disagreed that the findings, if positive, could be extrapolated to an emergency or CICV situation.

This reviewer performed a complete review of Studies 301-3 and 310.

6.1.2 General Discussion of Endpoints

The applicant used a standard methodology (Train-Of-Four stimulation to the lunar nerve to cause contraction of the adductor pollicis) to assess the status of neuromuscular blockade. The applicant argued that mechanomyography, the gold standard to quantitate the strength of contraction of the adductor pollicis, was not feasible because the equipment is no longer manufactured and the technique is too complex.

Instead, the applicant proposed the use of an acceleromyograph. The Division agreed that the acceleromyograph would be acceptable to quantitate the strength of contraction.

For Studies 301, 302, and 310, the applicant selected the return of the T_4 to T_1 ratio to 0.9 as the primary endpoint. There is a substantial body of evidence in the literature that supports the conclusion that $T_4/T_1 = 0.9$ is clinically relevant and the patient should be safe to extubate.

For Study 303, the “immediate” reversal study, the applicant selected an endpoint of $T_1 = 0.1$. There was justification for not using the more established T_4/T_1 ratio since the comparator in Study 303 was succinylcholine, which does not produce fade. The applicant did not provide any references to support the clinical significance of this endpoint. A Medline search by this reviewer did not find any references to inform to this issue. While the return of some strength is certainly evidence of some degree of reversal of blockade or offset of action (for succinylcholine), the significance of the particular endpoint selected is subject to debate.

6.1.3 Study Design

Table 6 enumerates the attributes of an adequate and well-controlled study per 21 CFR 314.126 on the left column. The two adjacent columns discuss how the pivotal studies addressed these qualities.

Table 6: Comparison Of Pivotal Studies To Attributes of An Adequate And Well-Controlled Study

| Attribute per 21 CFR 314.126 | Studies 301, 302, 310 | Study 303 |
|---|--|--|
| Clear statement of objectives | The objectives were clear and appropriate. | |
| Summary of the proposed methods of analysis | The protocol contained a sufficiently detailed statistical analysis section. | |
| Valid comparison to a control | An active control was used. [†] | The study drug was compared to the spontaneous offset of succinylcholine. |
| Method of subject selection provides assurance that they have the disease being studied | The inclusion and exclusion criteria were appropriate for the proposed indication. | |
| Method of assignment to treatment or control minimizes bias | The study was randomized. Given the relatively small size of the studies, there were some imbalances in the characteristics of the cohorts as treated. However, none of the imbalances appeared to bias the study to favor or disfavor the study drug. | |
| Adequate measures are taken to minimize the bias of subjects, observers, and analysts | Patients were blinded because they had been induced. The anesthetist was not blinded, however, the primary efficacy endpoint used an objective instrument. The safety assessor was blinded.* | Since succinylcholine causes fasciculations and no sham injection was administered, the anesthetist was not blinded. Again the endpoint is objective.* |
| Methods of assessment of response are well identified and reliable. | The use of acceleromyography had been questioned but found acceptable by the Division. The primary endpoint is clinically accepted as valid. | The primary endpoint selected has not been proven to be clinically meaningful. |
| The analysis is adequate to assess the effects of the drug. | The appropriate statistical tests were applied to assess efficacy. | |

[†]Neostigmine is an unapproved, marketed drug. Nonetheless, neostigmine is the most commonly used reversal agent in this clinical scenario.

*The blinding precautions, while not perfect, are acceptable for a study of an anesthetic product.

Studies 301 and 302 meet the attributes of an adequate and well-controlled study. Study 310 was not properly controlled in that cis-atricurium was used as the NMBA. However, given that other positive studies, this reviewer believes that Study 310 is an important supportive study. Study

303 met most attributes although the relevance of the endpoint selected requires further consideration and input from the Advisory Committee.

6.1.4 Efficacy Findings

The sponsor submitted full reports for four studies that are pertinent to the proposed indication and clinical scenarios, Studies 301, 302, 303, and 310.

NB The SAS transport files for the pivotal studies contain as many as 104 data columns, many of which are data calculated from measured data. The “define.pdf” file was somewhat helpful in interpreting the pertinent data columns. However, many of the definitions are ambiguous and there appeared to have been incongruities between data present in the cells and the purported format in the define.pdf file. For instance, the define.pdf file indicated that certain columns were supposed to have data in MMSS format when they actually contained data in number of seconds.

The applicant was contacted to confirm which columns contained the primary endpoint data. In response to this query, the applicant emailed (18 January 2008) that these data were in the “ut09t” and “it09t” columns for Studies 301, 302, and 310 and the “urt10t” and “irt10t” columns for Study 303. In a teleconference held on 31 January, the applicant indicated that an error was made and the appropriate columns for Studies 301, 302, and 310 were “urt09t” and “irt09t.”

This reviewer copied and pasted data from the referenced datasets in to Excel and sorted these data. It appears that the correction made on 31 January was incorrect. For example, in Study 301, the lowest and highest “urt09t” in the Org25969 arm are “162” and “9314.” Those data are clearly not in the MMSS format as the define.pdf file indicates. If these are numbers of seconds, that would correlate with 2 minutes, 42 seconds and 155 minutes, 14 seconds. However, in the clinical study report, the range of values is noted to be 55 seconds to 64 minutes, 12 seconds. The data in the columns to which the “r” were not added (with few exceptions – treatment errors) correlated with the data presentation. Therefore, this reviewer concluded that the statements in the 18 January email were correct and the “correction” given during the 31 January telecon was erroneous.

As stated elsewhere in this review, these protocols were similar. These were multicenter, randomized, safety assessor-blinded, parallel-group, active-controlled studies. The applicant enrolled adults planned for elective surgery in the supine position. Patients could not have significant renal or other systemic disease.

With regard to study conduct, patients were screened per routine for clinical investigations. Most of the study-related activities occurred in the “perioperative” phase described following.

- Randomization
- Continuous vital sign monitoring including ECG for QT interval
- Induction with typical intravenous agents
- Maintenance of anesthesia with sevoflurane, intravenous opioid, or other conventional agents

- Affix, stabilize, and calibrate the Train-of-Four (TOF-Watch SX) device and start “continuous” neuromuscular monitoring
- Administer neuromuscular blocking agent (NMBA)
- Intubation
- Perform surgery, maintain anesthesia, monitor vital signs, administer additional NMBA as clinically indicated
- At the appointed time (protocol specific), administer study drug (Org25969 or control)
- Continue neuromuscular monitoring until the specified endpoint is reached.
- Discontinue anesthesia per standard of care, transfer to recovery room
- Continuously monitor for adverse events, vital signs, etc.

Following the operative phase, there was a post-anesthetic visit approximately 12 hours following administration of study drug and a follow-up visit 7 days later.

A brief description of key features of each study and the summary statistics follow.

Study 301

1. Location: Europe
2. Study period: November 2005 to March 2006
3. Clinical scenario: “shallow” neuromuscular block, defined as the return of T₂ (the second twitch in a train-of-four stimulation)
4. Dose of Org25969: 2 mg/kg
5. Treatment groups:
 - a. Rocuronium/Org25969
 - b. Rocuronium/neostigmine
 - c. Vecuronium./Org25969
 - d. Vecuronium/neostigmine
6. N = 196 randomized
7. Primary efficacy endpoint: T₄/T₁ = 0.9

Table 7: Summary statistics, Study 301, Time from administration of reversal agent to $T_4/T_1 = 0.9$ (primary efficacy endpoint) – patients treated with rocuronium

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=48) | Neostigmine (N=48) |
| Including imputed data | n | 48 | 48 |
| | Geometric mean | 1:29 | 18:30 |
| | Mean (SD) | 1:37 (0:50) | 26:47 (24:36) |
| | Median | 1:24 | 17:36 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |
| Complete cases | n | 47 | 45 |
| | Geometric mean | 1:28 | 18:38 |
| | Mean (SD) | 1:35 (0:49) | 27:18 (25:12) |
| | Median | 1:23 | 18:31 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |

Source: CSR, page 85 (of pdf file)

Table 8: Summary statistics, Study 301, Time from administration of reversal agent to $T_4/T_1 = 0.9$ (primary efficacy endpoint) – patients treated with vecuronium

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=48) | Neostigmine (N=45) |
| Including imputed data | n | 48 | 45 |
| | Geometric mean | 2:48 | 16:48 |
| | Mean (SD) | 4:28 (9:17) | 23:26 (18:32) |
| | Median | 2:08 | 18:56 |
| | Min. – max. | 1:12 - 64:12 | 2:55 - 76:09 |
| Complete cases | n | 46 | 34 |
| | Geometric mean | 2:41 | 17:52 |
| | Mean (SD) | 4:22 (9:28) | 24:44 (19:04) |
| | Median | 2:06 | 21:51 |
| | Min. – max. | 1:12 - 64:12 | 2:55 - 76:09 |

Source: CSR, page 88 (of pdf file)

Study 302

1. Location: U.S.
2. Study period: November 2005 to November 2006
3. Clinical scenario: “profound” neuromuscular block, defined as 1-2 post tetanic counts
4. Dose of Org25969: 4 mg/kg
5. Treatment groups:
 - a. Rocuronium/Org25969
 - b. Rocuronium/neostigmine

- c. Vecuronium./Org25969
- d. Vecuronium/neostigmine
- 6. N = 182 randomized
- 7. Primary efficacy endpoint: $T_4/T_1 = 0.9$

Table 9: Summary statistics, Study 302, Time from administration of reversal agent to $T_4/T_1 = 0.9$ (primary efficacy endpoint) – patients treated with rocuronium

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=37) | Neostigmine (N=37) |
| Including imputed data | n | 37 | 37 |
| | Geometric mean | 2:52 | 50:22 |
| | Mean (SD) | 3:17 (2:24) | 55:30 (27:06) |
| | Median | 2:42 | 49:00 |
| | Min. – max. | 1:13 – 16:05 | 13:16 - 145:40 |
| Complete cases | n | 30 | 22 |
| | Geometric mean | 2:36 | 55:59 |
| | Mean (SD) | 3:01 (2:36) | 60:57 (25:03) |
| | Median | 2:34 | 57:04 |
| | Min. – max. | 1:13 - 16:05 | 13:16 - 133:28 |

Source: CSR, page 104 (of pdf file)

Table 10: Summary statistics, Study 302, Time from administration of reversal agent to $T_4/T_1 = 0.9$ (primary efficacy endpoint) – patients treated with vecuronium

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=47) | Neostigmine (N=36) |
| Including imputed data | n | 47 | 36 |
| | Geometric mean | 4:28 | 66:12 |
| | Mean (SD) | 8:44 (14:36) | 77:48 (56:59) |
| | Median | 3:15 | 49:53 |
| | Min. – max. | 1:26 - 68:25 | 46:01 - 312:39 |
| Complete cases | n | 41 | 15 |
| | Geometric mean | 3:35 | 91:01 |
| | Mean (SD) | 6:19 (11:52) | 107:12 (72:01) |
| | Median | 3:00 | 95:47 |
| | Min. – max. | 1:26 - 63:32 | 46:01 - 312:39 |

Source: CSR, page 107 (of pdf file)

Study 310

1. Location: Europe
2. Study period: November 2005 to May 2006
3. Clinical scenario: “shallow” neuromuscular block, defined as the return of T₂
4. Dose of Org25969: 2 mg/kg
5. Treatment groups:
 - a. Rocuronium/Org25969
 - b. Cis-atricurium/neostigmine
6. N = 84 randomized
7. Primary efficacy endpoint: T₄/T₁ = 0.9

Table 11: Summary statistics, Study 310, Time from administration of reversal agent to T₄/T₁ = 0.9 (primary efficacy endpoint)

| | | Treatment group | |
|------------------------|----------------|-------------------------|---------------------------|
| | | roc/Org 25969 (N=34) | cis/Neostigmine (N=39) |
| Including imputed data | n | 34 | 39 |
| | Geometric Mean | 2:02 | 8:46 |
| | Mean (SD) | 2:18 (1:20) | 10:09 (6:10) |
| | Median | 1:55 | 7:12 |
| | Min. – max. | 0:41 - 6:24 | 4:12 - 28:14 |
| Complete cases | n | 32 | 34 |
| | Geometric Mean | 1:55 | 8:58 |
| | Mean (SD) | 2:08 (1:09) | 10:23 (6:20) |
| | Median | 1:55 | 7:15 |
| | Min. – max. | 0:41 - 6:24 | 4:12 - 28:14 |

Source: CSR, page 75 (of pdf file)

Study 303

1. Location: U.S. and Canada
2. Study period: February 2006 to August 2006
3. Clinical scenario: “Immediate” reversal (defined as 3 minutes following rocuronium administration)
4. Dose of Org25969: 16 mg/kg
5. Treatment groups:
 - a. Rocuronium/Org25969
 - b. Succinylcholine/no reversal agent
6. N = 115 randomized
7. Primary efficacy endpoint: T₁ = 0.1

Table 12: Summary statistics, Study 303, Time from administration of reversal agent to $T_1 = 0.1$ (primary efficacy endpoint)

| | | Treatment group | |
|------------------------|-------------|----------------------------------|---------------------------|
| | | Rocuronium + Org 25969 (N=55) | Succinylcholine (N=55) |
| Including imputed data | n | 55 | 55 |
| | Mean (SD) | 4:22 (0:44) | 7:04 (1:34) |
| | Median | 4:11 | 7:06 |
| | Min. – max. | 3:28 - 7:43 | 3:45 - 10:28 |
| Complete cases | n | 54 | 53 |
| | Mean (SD) | 4:21 (0:43) | 7:09 (1:33) |
| | Median | 4:11 | 7:11 |
| | Min. – max. | 3:28 - 7:43 | 3:45 - 10:28 |

Source: CSR, page 86 (of pdf file)

OUTLIERS

In assessing the efficacy data, the applicant noted that not all patients responded to Org25969 equally well. The applicant conducted a separate analysis of the outliers. The clinical definition used was a cutoff three times the mean recovery time and the applicant devised a statistical algorithm to also define outliers. A total of 31 outliers were identified out of an Intent-to-Treat database of 1470 patients. Eleven of the 31 patients were enrolled in pivotal trials.

This reviewer conducted a separate analysis of the outliers in the pivotal trials. The outlier effect is shown in Figures 1-4, following. These figures are “Kaplan-Meier-type” representations of the efficacy data for the primary efficacy endpoint limited to the Org25969-treated patients only. The abscissa is time from injection of the reversal agent and the ordinate is the proportion of patients meeting the endpoint criterion. The outliers are readily identified in circles.

Figure 1: “Kaplan-Meier” analysis, Study 301, Org25969-treated patients, pooled rocuronium and vecuronium treated patients

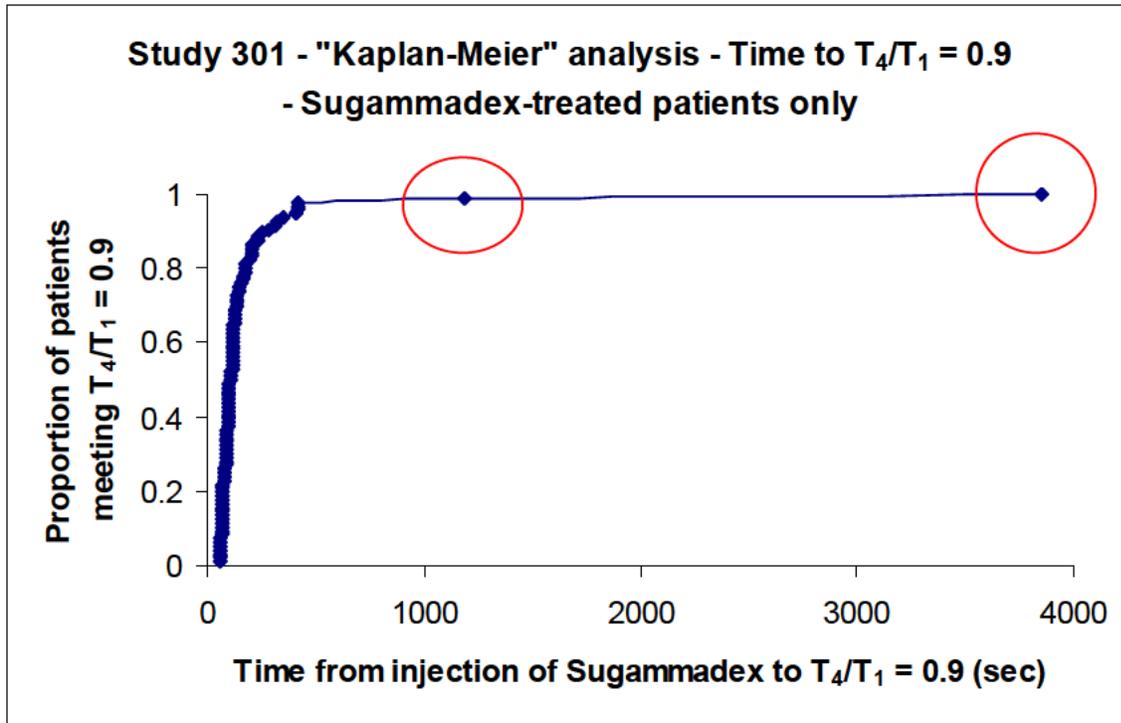


Figure 2: “Kaplan-Meier” analysis, Study 302, Org25969-treated patients, pooled rocuronium and vecuronium treated patients

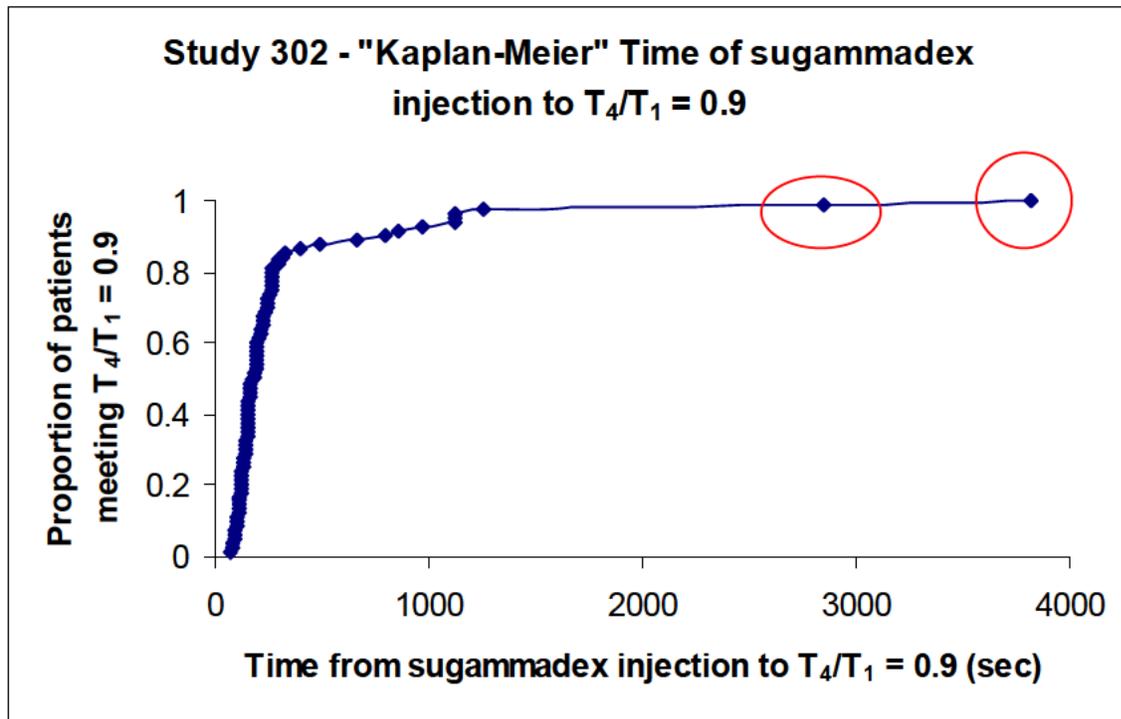


Figure 3: “Kaplan-Meier” analysis, Study 303, Rocuronium/Org25969-treated patients time to T1 = 0.1

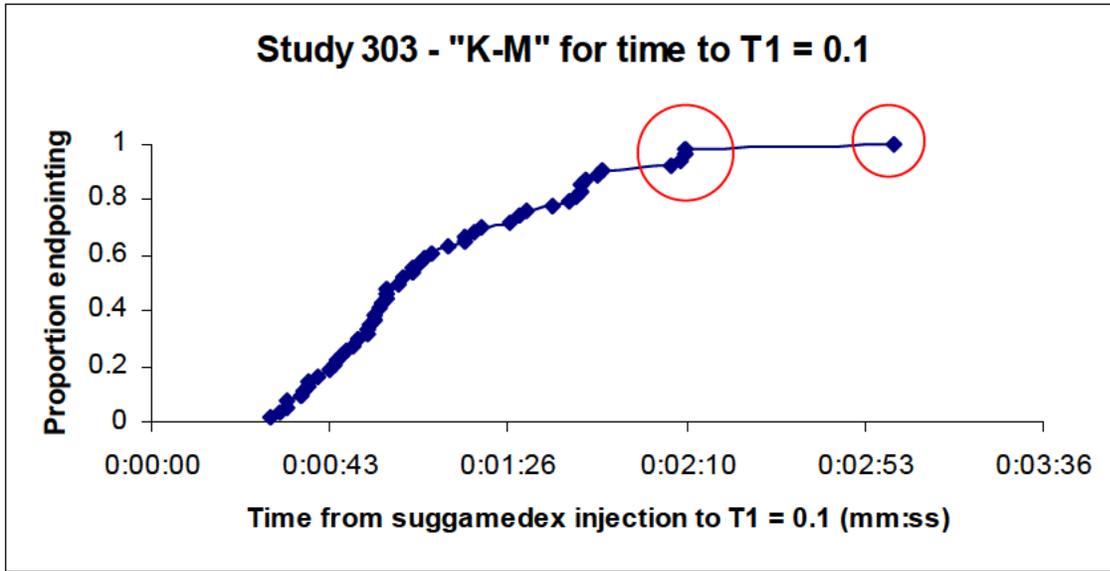
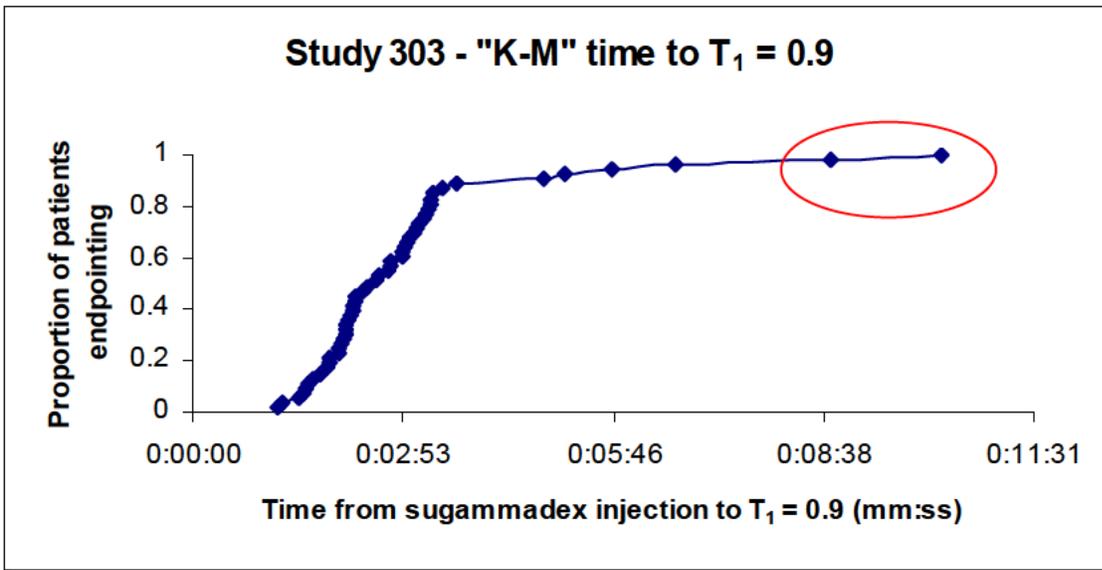


Figure 4: “Kaplan-Meier” analysis, Study 303, Rocuronium/Org25969-treated patients, time to T4/T1 = 0.9



Anesthesia products are expected to have a low failure rate. However, for the “routine” clinical scenario, if Org25969 takes an unexpectedly long time to work, there is no real harm to the patient. The critical safety issue with a lack of 100% response to the drug is in the “immediate reversal” scenario. (b) (4)

However, in other parts of the submission, the applicant proposes that the

16 mg/kg could be useful in (b) (4). Therefore, it is not unreasonable to address the outliers in Study 303 in that context.

In the CICV situation where a rocuronium block was unsuccessfully reversed with Org25969, that prolonged response time could result in anoxic encephalopathy or death unless the anesthesiologist were to successfully intervene with non-pharmacologic methods. Four patients met the applicant's definition of outlier. By comparison, none of the succinylcholine patients met the 3x the mean clinical definition.

The case report forms for the outliers in Study 303 were reviewed and summarized following.

Narratives of Outliers, Study 303:

Patient 303106007 was a 47 year old Caucasian female at the time of screening. Her past medical history was significant for bilateral breast cancer and "uterine" [endometrial?] dysplasia. She was scheduled for bilateral tissue expander placement (pectoral). Her medications at the time of screening were goserelin and tamoxifen. She received midazolam preoperatively. Her intraoperative medication included several boluses of propofol, 2 x 5 mg ephedrine (for hypotension), ondansetron, and a dose of cefazolin. She received morphine, celecoxib, oxycodone/acetaminophen postoperatively.

Key events are summarized below:

| Event | Time |
|---|-----------------|
| Start of anesthesia (fentanyl 200 mcg, propofol 130 mg) | 09:03 |
| Start sevoflurane | 09:06 |
| Rocuronium 6.7 mL | 09:18:43 |
| Administration of Org25969 | 09:21:46 |
| Return of T₁ to 10% | 09:23:04 |
| Reappearance of T ₂ | 09:23:04 |
| Reappearance of T ₃ | 09:23:04 |
| Return of T ₁ to 90% | 09:24:19 |
| Return of T ₄ /T ₁ = 0.7 | 09:23:04 |
| Return of T ₄ /T ₁ = 0.8 | 09:23:04 |
| Return of T ₄ /T ₁ = 0.9 | 09:36:04 |
| Stop sevoflurane | 10:28 |
| Extubation | 10:40 |

*HH:MM or HH:MM:SS

The site reported that reoccurarization occurred per the NMT guidelines (following return of the T₄/T₁ = 0.9, the T₄/T₁ dropped below 0.8 and did not recover again until 09:50:49). The investigator felt that the low values were due to movement or an unstable trace and did not represent reoccurarization. She experienced adverse events of postoperative pain, intraoperative hypotension, and intraoperative tachycardia and bradycardia. As stated previously, the

intraoperative hypotensive was treated with ephedrine. The rate abnormalities did not require intervention.

Patient 303106010 was a 42 year old Hispanic male at the time of screening. He had no past medical history. His indication for surgery was a repair of a quadriceps tear. He was hypertensive (151/87) on the screening physical but was not on any antihypertensive medication. He received midazolam as his premedication. He received additional propofol, a dose of ondansetron, and a dose of cephazolin intraoperatively. He also developed tachycardia and hypertension during the surgery for which he received two doses of labetalol, 5 mg IV. His postoperative medications included morphine, meperidine, and oxycodone/acetaminophen.

Key events are summarized below:

| Event | Time |
|--|-----------------|
| Start nitrous oxide | 08:46 |
| Start sevoflurane | 09:02 |
| Fentanyl 100 mcg, propofol 200 mg | 09:05 |
| Rocuronium 10 mL | 09:32:31 |
| Administration of Org25969 | 09:35:32 |
| Return of T₁ to 10% | 09:37:39 |
| Reappearance of T ₂ | 09:37:24 |
| Reappearance of T ₃ | 09:37:24 |
| Return of T₁ to 10% | 09:37:39 |
| Return of T ₄ /T ₁ = 0.7 | 09:38:39 |
| Return of T ₄ /T ₁ = 0.8 | 09:40:54 |
| Return of T ₄ /T ₁ = 0.9 | 09:40:54 |
| Return of T ₁ to 90% | 09:45:24 |
| Stop sevoflurane | 10:28 |
| Extubation | 10:48 |
| Stop nitrous oxide | 10:49 |

*HH:MM or HH:MM:SS

Recurarization occurred when the T₄/T₁ ratio dropped to 71% at 10:00:24. There was no documentation of when the T₄/T₁ ratio returned to 0.9. The case report form indicates that the patient had fully recovered strength at 13:10, upon discharge from the recovery room. He was able to perform a 5-second head lift at 10:48.

Besides the intraoperative hypertension and tachycardia and the postoperative recurarization, he reported postoperative pain and nausea as adverse events.

Patient 303112006 was a 25 year old African-American female at the time of screening. Her medical history was significant for status post right knee surgery, migraine, and mitral valve insufficiency. She was admitted for arthroscopy of the knee and excision/biopsy of intraarticular mass (presumed pigmented villonodular synovitis). Her medications upon screening were pantoprazole, acetaminophen, hydrocodone/acetaminophen, and Excedrin. She received

midazolam and ampicillin (MVP prophylaxis) preoperatively. Intraoperatively, she received cefazolin and dolesetron. Her postoperative medications included cefalexin, hydrocodone/acetaminophen, and hydromorphone.

Key events are summarized below:

| Event | Time |
|---|-----------------|
| Start of anesthesia (fentanyl 250 mcg, propofol 200 mg) | 13:10 |
| Maintenance anesthesia with propofol infusion | 13:20-14:15 |
| Rocuronium 8.7 mL | 13:35:34 |
| Administration of Org25969 | 13:38:42 |
| Return of T₁ to 10% | 13:39:26 |
| Reappearance of T ₂ | 13:39:26 |
| Reappearance of T ₃ | 13:39:26 |
| Return of T ₁ to 90% | 13:40:26 |
| Return of T ₄ /T ₁ = 0.7 | 13:39:41 |
| Return of T ₄ /T ₁ = 0.8 | 13:39:56 |
| Return of T ₄ /T ₁ = 0.9 | 13:41:26 |
| Extubation | 14:45 |

*HH:MM or HH:MM:SS

Recurarization did not occur in this patient. She was first able to perform a 5-second head lift at 14:46.

At the time of discharge from the recovery room (16:45), she was arousable with minimal stimulation, cooperative, able to perform a 5-second head lift, and did not have general muscle weakness. Her recovery was otherwise unremarkable.

Patient 303112013 was a 45 year old Caucasian male at the time of screening. His past medical history was significant for a urinary tract infection (7 days prior to surgery), tobacco use and “allergies” to oxycodone/acetaminophen and hydrocodone/acetaminophen. His medications prior to screening included levofloxacin and acetaminophen. His preoperative medications included IV levofloxacin and midazolam. He presented with nephrolithiasis for which he underwent cystourethroscopy as part of the study. His post-operative medications included furosemide, ampicillin, and oral analgesics.

Key events are summarized below:

| Event | Time |
|--|-----------------|
| Start of anesthesia (fentanyl 50 mcg, propofol 300 mg) | 07:55-08:00 |
| Maintenance anesthesia with propofol infusion | 13:20-14:15 |
| Rocuronium 10.3 mL | 08:20:34 |
| Administration of Org25969 | 08:23:17 |
| Return of T₁ to 10% | 08:26:17 |
| Reappearance of T ₂ | 08:26:17 |
| Reappearance of T ₃ | 08:26:17 |

| | |
|--|----------|
| Return of T ₁ to 90% | 08:28:17 |
| Return of T ₄ /T ₁ = 0.7 | 08:26:32 |
| Return of T ₄ /T ₁ = 0.8 | 08:26:47 |
| Return of T ₄ /T ₁ = 0.9 | 08:26:47 |
| Extubation | 09:09 |

*HH:MM or HH:MM:SS

His postoperative course was uncomplicated save a rash on both forearms and moderate proteinuria.

Narratives of Outliers, other pivotal studies:

Patient 301109001 was a 47 year old Caucasian woman at the time of her participation in Study 301. She had no past medical history and was on no medication at the time of screening. Her indication for surgery was excision of cholesteatoma.

She was randomized to the vecuronium/Org25969 arm. She received pre-operative medications consisting of mometasone furoate and midazolam and intraoperative droperidol, marcaine, betamethasone, IV ketorolac and IV acetaminophen. Her post op-medication consisted of acetaminophen.

Key events are summarized below.

| Event | Time* |
|--|-----------------|
| Start of anesthesia (2480 mcg remifentanyl, 130 mg propofol) | 07:41-3 |
| Start sevoflurane | 07:44 |
| Vecuronium dosed | 08:09 |
| Reappearance of T2 | 09:25:27 |
| Org25969 dosed | 09:26:04 |
| Reappearance of T3 | 09:26:57 |
| T ₄ /T ₁ ratio = 0.7 | 09:28:12 |
| T ₄ /T ₁ ratio = 0.8 | 09:29:42 |
| T₄/T₁ ratio = 0.9 | 10:30:12 |
| Stop sevoflurane | 11:45 |
| Extubation | 11:48 |

*MM:SS or HH:MM:SS

She experienced hypotension during the surgery (BP 70-88/39-46) treated with IV ephedrine. Her pre and post-op blood pressure was ~120/80. Otherwise, her clinical course appeared unremarkable.

Patient 301112002 was a 41 year old Caucasian female at the time of screening. Her past medical history was significant for asthma, anemia, and endometrial hyperplasia. Her medications at the start of the trial included an albuterol MDI and ferrous sulfate. She was scheduled for total abdominal hysterectomy for menorrhagia. Intraoperatively, she received

granisetron, haloperidol, morphine, and ampicillin/clavulanic acid. Paracetamol and morphine were used post operatively for analgesia.

Key events are summarized below.

| Event | Time |
|---|-----------------|
| Start sevoflurane | 09:05 |
| Start of anesthesia (500 mcg alfentanil, 160 mg propofol) | 09:06 |
| Vecuronium (3.2 mL) dosed | 09:21 |
| Vecuronium (0.6 mL) dosed | 10:26 |
| Vecuronium (0.6 mL) dosed | 11:07 |
| Reappearance of T2 | 11:33:31 |
| Org25969 dosed | 11:34:29 |
| Reappearance of T3 | 11:35:16 |
| T ₄ /T ₁ ratio = 0.7 | 11:35:46 |
| T ₄ /T ₁ ratio = 0.8 | 11:38:46 |
| T₄/T₁ ratio = 0.9 | 11:54:16 |
| Stop sevoflurane | 11:55 |
| Extubation | 12:01 |

*HH:MM or HH:MM:SS

The surgery and recovery were uncomplicated.

Patient 302102016 was a 46 year old Hispanic man at the time of screening. His past medical history was significant for prostate cancer for which he underwent radical prostatectomy as part of this trial. The patient received midazolam preoperatively. Intraoperatively, the patient received multiple boluses of fentanyl, hydromorphone, and “ketzol,” indigo carmine, ondanestron, and ketorolac. He received metoclopramide and fentanyl post-operatively.

Key events are summarized below.

| Event | Time |
|---|-----------------|
| Start of anesthesia (150 mcg fentanyl, 180 mg propofol) | 07:10-12 |
| Start sevoflurane | 07:13 |
| Vecuronium (6.65 mL) dosed | 07:26 |
| Nitrous Oxide (50%) | 07:29 |
| Vecuronium (1 mL) dosed | 08:09 |
| Vecuronium (1 mL) dosed | 08:25 |
| Vecuronium (1 mL) dosed | 08:48 |
| Vecuronium (1 mL) dosed | 09:11 |
| Vecuronium (1 mL) dosed | 09:18 |
| Vecuronium (1 mL) dosed | 09:24 |
| Vecuronium (1 mL) dosed | 09:41 |
| Org25969 dosed | 09:48:04 |
| Reappearance of T2 | 09:49:36 |
| Reappearance of T3 | 09:49:51 |

| | |
|--|-----------------|
| T ₄ /T ₁ ratio = 0.7 | 09:55:21 |
| T ₄ /T ₁ ratio = 0.8 | 10:02:21 |
| T₄/T₁ ratio = 0.9 | 10:51:36 |
| Stop sevoflurane/nitrous oxide | 10:53 |
| Extubation | 10:57 |

*HH:MM or HH:MM:SS

The patient's core temperature fell below 35°C during “part” of the case. Other than postoperative nausea, pain, and an episode of tachycardia (lasting 90 minutes, fully recovered), his surgery and postoperative recovery were unremarkable.

Patient 302103102 was a 64 year old Caucasian female at the time of screening. She had a complex medical history including hypertension, hypercholesterolemia, history of transient ischemic attack, “facial cancer,” rectocele, cystocele, and history of hysterectomy and appendectomy. Her indication for surgery was cystocele and rectocele for which she was undergoing a repair. Her medications at the start of the study were lovastatin and “afeditab CR.” She received doxusate calcium, fentanyl, ketorolac, levofloxacin, fentanyl, dolasetron, morphine, midazolam, hydrocodone/acetaminophen, and morphine postoperatively.

Key events are summarized below.

| Event | Time |
|--|-----------------|
| 500 mg propofol | 10:30 |
| Start nitrous oxide 50% | 10:35 |
| 100 mcg fentanyl | 10:40 |
| Vecuronium (7.9 mL) dosed | 11:05 |
| Start sevoflurane | 11:50 |
| Vecuronium (1.2 mL) dosed | 12:04 |
| Reappearance of T2 | 13:00:21 |
| Org25969 dosed | 12:59:28 |
| Reappearance of T3 | 13:00:21 |
| T ₄ /T ₁ ratio = 0.7 | 13:02:21 |
| T ₄ /T ₁ ratio = 0.8 | 13:20:21 |
| T₄/T₁ ratio = 0.9 | 13:46:50 |
| Stop sevoflurane | 13:40 |
| Extubation | 13:54 |
| Stop nitrous | 14:00 |

*HH:MM or HH:MM:SS

The case report form indicates that there was difficulty calibrating the TOF device. She experienced adverse events of hyperkalemia (18 hour duration, recovered completely), nausea, shivering, headache, and postop pain.

Patient 302102101 was a 53 year old Caucasian male at the time of screening. His past medical history was significant for allergic rhinitis and prostate cancer for which he was scheduled for

radical prostatectomy. His medications at the time of screening were intranasal beclomethasone, an iron supplement, and cod liver oil. He received midazolam preoperatively. Intraoperatively, he received fentanyl, morphine, “ketzol,” ketorolac, and ondansetron. He received fentanyl, famotidine, ketorolac, ondansetron, potassium chloride and meperidine postoperatively.

Key events are summarized below.

| Event | Time |
|--|-----------------|
| Start of anesthesia (200 mg propofol + 150 mcg fentanyl) | 11:50 |
| Start nitrous oxide 50%/sevoflurane | 11:51 |
| Vecuronium (7 mL) dosed | 12:07 |
| Vecuronium (1 mL) dosed | 12:35 |
| Vecuronium (1 mL) dosed | 13:09 |
| Vecuronium (1 mL) dosed | 13:33 |
| Vecuronium (1 mL) dosed | 13:59 |
| Vecuronium (1 mL) dosed | 14:09 |
| Vecuronium (1 mL) dosed | 14:27 |
| Vecuronium (1 mL) dosed | 14:35 |
| Vecuronium (1 mL) dosed | 14:47 |
| Vecuronium (1 mL) dosed | 14:54 |
| Org25969 dosed | 15:04:27 |
| Reappearance of T2 | 15:06:10 |
| Reappearance of T3 | 15:06:25 |
| T ₄ /T ₁ ratio = 0.7 | 15:09:40 |
| T ₄ /T ₁ ratio = 0.8 | 15:11:10 |
| T₄/T₁ ratio = 0.9 | 15:18:40 |
| Stop sevoflurane | 15:19 |
| Stop nitrous | 15:27 |
| Extubation | 15:30 |

*HH:MM or HH:MM:SS

His postoperative course was complicated by shivering, incisional pain, nausea, and inspiratory chest pain but was otherwise routine.

Patient 302102001 was a 63 year old Asian male with a history of hypertension, mild to moderate aortic stenosis, and prostatic carcinoma at the time of screening. His medications at the time of screening included a multivitamin. Preoperative medications included midazolam, Intraoperative medications included fentanyl, cephazolin, atropine, ketorolac, Postoperative medications included morphine, ketorolac, famotidine, cephazolin, colace, and hydrocodone/acetaminophen

Key events are summarized below.

| Event | Time |
|--|-----------------|
| Start nitrous oxide 50% | 07:15 |
| 120 mg propofol | 07:17 |
| Start sevoflurane | 07:18 |
| Vecuronium (7 mL) dosed | 07:31 |
| Vecuronium (1 mL) dosed | 08:58 |
| Vecuronium (1 mL) dosed | 09:09 |
| Vecuronium (1 mL) dosed | 09:40 |
| Vecuronium (1 mL) dosed | 10:03 |
| Vecuronium (1 mL) dosed | 10:15 |
| Org25969 dosed | 10:43:31 |
| Reappearance of T2 | 10:44:55 |
| Reappearance of T3 | 10:44:55 |
| T ₄ /T ₁ ratio = 0.7 | 10:50:40 |
| T ₄ /T ₁ ratio = 0.8 | 10:55:25 |
| T₄/T₁ ratio = 0.9 | 11:02:10 |
| Stop sevoflurane | 11:10 |
| Stop nitrous | 11:15 |
| Extubation | 11:19 |

*HH:MM or HH:MM:SS

The core body temperature fell below 35°C during the “first part” of the case. Intraoperatively, the patient experienced hypotension that was treated with ephedrine. He experienced a drop in his hematocrit, nausea, and left ankle pain as adverse events.

Patient 310102003 was a 58 year old Caucasian female at the time of screening. Her past medical history was significant for multiple drug allergies, hypertension, tuberculosis, bronchitis, “breast neoplasia,” and edema of the left arm. She was admitted for hysterectomy and bilateral salpingoophorectomy. Her medications upon study entry included tamoxifen, atenolol, lisinopril, Preoperative medications included midazolam. Intraoperatively she received amoxicillin/clavulanic acid, “perfalgan, ondansetron, dexamethasone (for “inflammation prevention”) Postoperatively she received morphine, “clexane” for DVT prophylaxis, salmeterol MDI, omeprazole, “tardyferon”, and her presurgical medical regimen.

Key events are summarized below:

| Event | Time |
|--|-----------------|
| Remifentanyl, 1200 mcg | 08:45-11:00 |
| Propofol, 750 mg | 08:50-10:55 |
| Chloral hydrate | 10:17 |
| Rocuronium 6.8 mL | 09:27:51 |
| Administration of Org25969 | 10:42:02 |
| Reappearance of T ₂ | 10:41:06 |
| Reappearance of T ₃ | 10:42:41 |
| Return of T ₄ /T ₁ = 0.7 | 10:43:11 |
| Return of T ₄ /T ₁ = 0.8 | 10:43:26 |
| Return of T₄/T₁ = 0.9 | 10:48:26 |
| Extubation | 11:00 |

*HH:MM or HH:MM:SS

The adverse events reported included upper extremity edema, mild bronchospasm, and anemia. Otherwise, her postoperative course was unremarkable. Her TOF data were reviewed by the CIAC and found to be “reliable.”

Reviewer comments – outliers:

This reviewer notes that two of the outliers in Study 303 experienced recurarization. In addition Patient 310102003 received dexamethasone intraoperatively and was on tamoxifen and Patient 303106007 was also on tamoxifen. Patient 301109001 was exposed to mometasone and betamethasone. Patient 302102101 was on intranasal beclomethasone. Dexamethasone, mometasone, beclomethasone, and betamethasone are steroid hormones and tamoxifen is an estrogen receptor modulator. These concomitant medications could have interfered with the action of Org25969. The applicant also did not propose a reasonable hypothesis.

Suffice it to say that not all patients responded as quickly as would be hoped, particularly in Study 303.

It is important to note in Study 303 that the Org25969 was administered three minutes after rocuronium, at the peak effect of the NMBA. The fastest reversal to T₁ = 0.1 was 29 seconds following Org25969 injection and longest was 2:17. If one looks at the time to T₄/T₁ = 0.9, virtually complete recovery, the range from injection of rocuronium to reversal is 03:29 to 17:21 with a mean of 05:23 and median of 04:50.

Missing, Adjudicated, and “Unreliable” Data

In reviewing the clinical study reports (CSR), tables, data listings, and datasets, it became clear that there were issues with missing and unreliable data. It also became clear that the applicant had adjudicated some data.

- The applicant addressed missing data identically in the protocols for each pivotal study. The imputation scheme was conservative. Missing data for Org25969-treated patients were imputed using the 95th percentile (long recovery times) for the Org25969 cohort. Missing data for the active comparator were imputed with data for the 5th percentile (short recovery times) for the comparator. This concept was used consistently and was approved in the Special Protocol Assessment.
- The applicant predicted that some of the acceleromyograph data would be unreliable due to issues with patient movement, calibration, etc. with the device. Hence, the applicant planned and implemented a “Central Independent Adjudication Committee” (CIAC). This was described prospectively in the protocols. Upon this reviewer’s assessment of the CIAC guide, it was noted that some of the criteria for adjudication were vague. Because of this, the Division requested that the applicant analyze the data for the pivotal studies without the adjudicated cases. Overall, the adjudicated cases that involved the primary efficacy endpoint comprised a small proportion of the cases as shown in Table 13, following.

Table 13: Adjudicated cases, pivotal studies

| Study | # adjudicated | ITT population |
|--------------|----------------------|-----------------------|
| 301 | 14 | 189 |
| 302 | 9 | 157 |
| 303 | 7 | 110 |
| 310 | 8 | 84 |

The applicant’s reanalysis, excluding the adjudicated cases, did not significantly affect the results. Therefore, while some of the wording of the adjudication document was vague, it does not appear to have affected the validity of the conclusions.

- This reviewer noted that some data were considered “unreliable.” In one instance (Study 301), those data appeared to have been handled inconsistently. The applicant was queried and asked to respond. The applicant confirmed that the two cases (Patients 104019 and 105001) had been handled differently. For Patient 104019, the applicant used the unreliable data; for the other patient, the data were imputed. The applicant conducted a sensitivity analysis that showed that imputing the data for Patient 104019 caused a negligible difference in the results. The applicant indicated that data adjudicated as “unreliable” were imputed per the protocol-specified scheme.

Other data informing to efficacy

In the entire clinical development program, there were a total of 16 studies (all previously referenced except Studies 208 and 209) that informed in some way to efficacy. Many of them were Phase 2 studies with very small numbers of patients in each treatment arm. Yet, this reviewer notes that in every study conducted, there was evidence of treatment effect. If the study conclusion were random, the likelihood that all 16 studies would be positive and none would be negative is 0.0000153 (15 in a million). The pertinent studies, total study size, control used, and results are shown in Table 14.

Table 14: All studies, regardless of sample size, informing to efficacy

| Study # | N | Control | Results |
|----------------|----------|----------------|----------------|
| 101 | 29 | Placebo | Positive |
| 201 | 54 | Placebo | Positive |
| 202 | 99 | Placebo | Positive |
| 203 | 30 | Dose | Positive |
| 204 | 50 | Dose | Positive |
| 205 | 45 | Placebo | Positive |
| 206 | 175 | Placebo | Positive |
| 207 | 98 | Placebo | Positive |
| 208 | 99 | Dose | Positive |
| 209 | 101 | Dose | Positive |
| 306 | 91 | Dose | Positive |
| 301 | 189 | Active | Positive |
| 310 | 73 | Active | Positive |
| 302 | 154 | Active | Positive |
| 303 | 110 | Active | Positive |
| 310 | 116 | Placebo | Positive |

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

In the opinion of this reviewer, the studies submitted constitute substantial evidence of efficacy for the use of Org25969 as a reversal agent when rocuronium or vecuronium are used as the neuromuscular blocking agent. It is worthwhile to note that the drug did not work consistently well in all patients. This reviewer notes that two Phase 3 studies were not conducted for each dosing paradigm. However, in light of the extensive and consistent Phase 2 results, this reviewer believes that the efficacy data support the proposed dose range of 2 mg/kg to 16 mg/kg.

The Advisory Committee (please see Section 8.5) agreed that Org25969 is an effective reversal agent for neuromuscular blockade induced by rocuronium and vecuronium in the proposed population (adults without significant renal disease). The committee felt that the outliers were significant and that the Division should consider with care how to present those data and the pertinent data might not be directly related to the means observed. The consensus seemed to be that three separate indications should not be granted (and definitely the word “immediate” should not be used).

7 INTEGRATED REVIEW OF SAFETY

Dr. Arthur Simone conducted the review of safety. Please see Dr. Simone's review for a complete discussion of the safety findings.

This review will briefly discuss the key safety findings for sugammadex. Dr. Simone found:

1. The overall exposure was 1,845 adults exposed to sugammadex and a neuromuscular blocking agent, 88% of which were ASA class 1 and 2.
2. The key safety issues identified are:
 - a. Hypersensitivity – One healthy volunteer exposed to 8 mg/kg (planned dose was 32 mg/kg) had the infusion stopped after experiencing rash, flushing, tachycardia, palpitations, nausea, visual disturbances, and paresthesias. His tryptase levels were mildly elevated (peak value 29 mcg/L, ULN, 15 mcg/L). Several months later, he was skin prick and intradermal test positive. At the time of finalization of this review, the applicant has not tested his serum for IgE. Several other patients developed adverse events coded as hypersensitivity and Dr. Simone identified several others whose symptom cluster could have represented a hypersensitivity reaction. The applicant tested several patients who experienced possible hypersensitivity reactions. Two patients were positive, one was the previously described patient.
 - b. Org25969 deposits in bone (binding to hydroxyapatite) with a long half life (approximately 6 months). While it does not bind to callus or the epiphyseal plate, these findings are not fully characterized and could represent additional hazards to pediatric patients.
 - c. Dr. Simone identified several cases of cardiac serious adverse events. He did not feel that the available data implicated Org25969 in the events.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

As stated previously, the applicant has conducted a substantial amount of dose-ranging work in Phase 2 and has confirmed the doses of 2, 4, and 16 mg/kg in the “routine/shallow,” “routine/profound,” and “immediate” scenarios in Studies 301, 302, and 303. This reviewer recommends that the references to “routine,” “shallow,” “profound,” and “immediate” be struck and replaced with a description of the level of blockade. The 16 mg/kg dose should be recommended when there is no response from peripheral nerve stimulation.

8.2 Drug-Drug Interactions

Except for the demonstrated interaction with toremifene, there are multiple potential interactions with steroid hormones and heavy metals. Dr. Simone did not find any direct evidence of drug-drug interactions. Still, it is important to recognize that that is in a database of <1900 patients.

Therefore, the potential for drug-drug interactions should figure prominently in the labeling and detailing.

8.3 Special Populations

At the time this review was written, the Office of Clinical Pharmacology (OCP) review was still pending. It is this reviewer's understanding that OCP has no substantial disagreement with the applicant's conclusions regarding the elderly, renally impaired, cardiac, and pulmonary populations. However, the applicant took a novel approach in modeling redosing of Org25969 proximate to an initial use that will require more review in that Office.

8.4 Pediatrics

The Advisory Committee opined that single-dose studies could be conducted in the pediatric population. However, because of the effects on teeth and bones seen in juvenile animals, the panel felt that more non-clinical work would have to be done to support multiple-dose studies in pediatric patients. If this product were to be approved, this reviewer recommends a waiver until the bone and teeth effects are better understood and the safety in adults is better defined.

8.5 Advisory Committee Meeting

A meeting of the Anesthetic and Life Support Drug Advisory Committee was held on March 11, 2008. The applicant presented the rationale for development and the safety and efficacy data. The Agency presented the clinical efficacy, emphasizing the outliers, the clinical safety, emphasizing the hypersensitivity reactions, and the nonclinical data, emphasizing the effects on bone and teeth. Highlights from the meeting are summarized following.

1. The committee felt that the endpoint in Study 303 (T1 = 0.1) was of minimal clinical use but felt that it supported the conclusion that Org25969 reversed paralysis more quickly than succinylcholine spontaneously resolved. The committee felt that more meaningful data for the label would consist of the time from injection that the majority (say 95%) of patients had responded.
2. The committee felt that rocuronium/Org25969 could not replace succinylcholine (sux) for rapid sequence induction, most importantly because sux would be necessary if a re-intubation was required. The committee felt that Org25969 was an important product that could be useful in the cannot intubate/cannot ventilate scenario although it opposed the use of the words "immediate" reversal or claims that Org25969 was effective in the cannot intubate/cannot ventilate scenario.
3. The committee was concerned about the hypersensitivity reactions although it felt that the reactions were relatively minor and self limited and were acceptable given the known hazards of succinylcholine. The committee recommended postmarketing surveillance to further define the risks of hypersensitivity reactions.
4. The committee would have liked to have seen more study done in the obstetric population.

5. The committee felt that the non-clinical findings regarding bone and teeth were of no concern to adults. The current data would support a single dose study in pediatric patients.
6. The committee felt that more study would be required for multiple dose pediatric studies and that nonclinical studies must be conducted to assess safety in neonates or premature infants. The committee also felt that assessments of bone strength in juvenile animal models were necessary.

8.6 Literature Review

The pertinent literature referenced by the applicant that pertained to efficacy was reviewed. No substantive differences in the assessment of the available literature were noted.

8.7 Postmarketing Risk Management Plan

Dr. Simone will cover the Post Marketing Risk Management Plan in his review of safety.

9 OVERALL ASSESSMENT

9.1 Conclusions

As this review was limited to the efficacy data and administrative issues, this reviewer recommends that, from the perspective of efficacy, the application be approved.

9.2 Recommendation on Regulatory Action

As stated previously, from the perspective of efficacy, the applicant has provided substantial evidence of efficacy for the dose range proposed.

9.3 Recommendation on Postmarketing Actions

There are no efficacy issues that require postmarketing actions.

9.3.1 Risk Management Activity

Please see Drs. Simone, Roca, Rappaport, and Rosebraugh's reviews and memoranda for recommendations on Risk Management Activity.

9.3.2 Required Phase 4 Commitments

Please see Drs. Xu, Wasserman, Simone, Roca, Rappaport, and Rosebraugh's reviews and memoranda for recommendations on Phase 4 commitments.

9.3.3 Other Phase 4 Requests

Please see Drs. Xu, Wasserman, Simone, Roca, Rappaport, and Rosebraugh's reviews and memoranda for other Phase 4 requests.

9.4 Labeling Review

Comments for the proposed package insert follow in the Appendix.

9.5 Comments to Applicant

This reviewer has no comments for the applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Number: 19.4.301

Protocol Title: A multi-center, randomized, parallel group, comparative, active controlled, safety-assessor blinded, phase IIIa, pivotal trial, in adult subjects comparing Org 25969 with neostigmine as reversal agent of a neuromuscular block induced by rocuronium or vecuronium at the reappearance of T₂.

Primary Objectives:

1. To demonstrate faster recovery from a neuromuscular block induced by rocuronium after reversal at reappearance of T₂ by 2.0 mg/kg Org 25969 compared to 50 µg/kg neostigmine.
2. To demonstrate faster recovery from a neuromuscular block induced by vecuronium after reversal at reappearance of T₂ by 2.0 mg/kg Org 25969 compared to 50 µg/kg neostigmine.

Secondary Objectives: To evaluate the safety of a single dose of 2 mg/kg of Org 25969 and 50 mcg/kg of neostigmine administered to adult patients

Study Design: Randomized, parallel-group, safety-assessor blinded, active-controlled

Duration: Patients were to receive a single dose of drug.

Sample Size: The study was to have enrolled approximately 144 patients at 9 non-US sites, including Germany, Austria, Spain, U.K, Italy, the Netherlands, and Sweden.

Inclusion Criteria: Patients were to have met all of the following criteria to be enrolled.

1. ASA class 1 to 4
2. Greater than or equal to the age of 18 years
3. Scheduled for surgical procedure with a general anesthesia with the use of rocuronium or vecuronium for endotracheal intubation and maintenance of neuromuscular block
4. Scheduled for surgical procedures in supine position
5. Willing to give written informed consent

Exclusion Criteria: Patients who met any of the following criteria were not to have been enrolled.

1. Patients in whom a difficult intubation because of anatomical malformations is expected
2. Known or suspected to have neuromuscular disorders impairing NMB and/or significant renal dysfunction
3. Known or suspected to have a (family) history of malignant hyperthermia
4. Known or suspected to have an allergy to narcotics, muscle relaxants or other medication used during general anesthesia
5. Patients receiving medication in a dose and/or at a time point known to interfere with NMBA, such as antibiotics, anticonvulsants and Mg²⁺ (See Appendix 12.5 for a complete overview)
6. Patients in whom the use of neostigmine and/or glycopyrrolate may be contra-indicated
7. Patients who have already participated in an Org 25969 trial
8. Patients who have participated in another clinical trial, not pre-approved by NV Organon, within 30 days of entering into CT 19.4.301
9. Women who are pregnant or are breastfeeding
10. Women of childbearing potential not using any method of birth control or using only hormonal contraception as birth control

Treatment Groups:

All patients were to have been induced with propofol and/or opioid and maintained with sevoflurane and/or opioid.

Patients were to have been randomized to one of the following four groups 1:1:1:1, Table A1.

Table A1: Treatment groups, Study 301

| Group | Neuromuscular blocker | Reversal agent |
|--------------|------------------------------|-----------------------|
| 1 | Rocuronium | Org 25969 |
| 2 | Rocuronium | Neostigmine |
| 3 | Vecuronium | Org 25969 |
| 4 | Vecuronium | Neostigmine |

Rocuronium dose = 0.6 mg/kg (intubation) + 0.1-0.2 mg/kg maintenance

Vecuronium dose = 0.1 mg/kg (intubation) + 0.02-0.03 mg/kg maintenance

Org25969 dose = 2.0 mg/kg

Neostigmine dose = 50 mcg/kg (+ 10 mcg/kg glycopyrrolate)

Study Conduct:

The study was to have been conducted in four periods: screening, peri-anesthetic, post-anesthetic, and follow-up. Descriptions of the key activities to have been performed in each period are summarized below.

Screening (maximum of 7 days prior to surgery): Obtain informed consent, history and physical, vital signs, pregnancy test (if applicable), pre-trial intake, inclusion/exclusion criteria, collection of urine

Peri-anesthetic: Randomize, induce anesthesia and neuromuscular blockade, maintain anesthesia with continuous ECG, vital sign, neuromuscular (Train-of-Four), body temperature monitoring.

After the last dose of roc/vec and reappearance of T₂, administer study drug (either Org 25969 or neostigmine). Continue to monitor clinical status and neuromuscular blockade until at least T₄/T₁ of 0.9. Assess clinical signs of recovery, adverse events, concomitant medications. Collect blood for safety assessment. Extubate and transfer to PACU. Patients not meeting clinical extubation criteria in the operating room were to have been transferred to the PACU, if medically appropriate and extubated in the PACU when clinically appropriate.

Post-anesthetic (at least 10 hours after administration of study drug): Conduct physical examination, assess vital signs, obtain blood and urine for safety studies, monitor for adverse events.

Follow-up: Contact patient on post-operative day 7 (telephone or visit) and assess concomitant medication use, adverse events, quality of recovery (QoR40).

Permitted Concomitant Medications:

Any medication expected to interfere with roc and vec was to be prohibited. If after administration of Org25969, muscle relaxation was required, a non-steroidal drug NMB drug was to have been used.

Outcome Measures:

1. Neuromuscular monitoring: Via acceleromyography (TOF-Watch® SX) at the adductor pollicis muscle. Neuromuscular monitoring via Train-of-Four (TOF) stimulation was to have been done every 15 seconds until the end of anesthesia.
2. Clinical signs of recovery (i.e. level of consciousness, 5 second head lift, check for general muscle weakness)
3. Health economics variables (the QoR-40)

Primary Efficacy Endpoint: Time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.9

Secondary endpoints:

- Time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.8
- Time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.7

- Assessments of clinical signs of recovery prior to PACU transfer after extubation and prior to PACU discharge

Other efficacy variables:

- T1 at the time of reappearance of T3
- Time from start of administration of the last bolus dose of NMB to recovery T_4/T_1 ratio to 0.7
- Time from start of administration of the last bolus dose of NMB to recovery T_4/T_1 ratio to 0.8
- Time from start of administration of the last bolus dose of NMB to recovery T_4/T_1 ratio to 0.9.
- Health economics variables (QoR-40)

Safety: Assessments were to have included:

1. Adverse events
2. Laboratory monitoring (blood at baseline, 4-6 hours post administration, at post-anesthetic visit; urine at screening and post-anesthetic visit). Blood was to have been analyzed for hematocrit, hemoglobin, erythrocyte count, leukocyte count, differential and platelets, sodium, potassium, chloride, calcium, ionized magnesium, creatinine, blood urea nitrogen, transaminases, gamma-GT, alk phos, CK, LDH, bilirubin, total protein, albumin, cholesterol, and haptoglobin. Urine was to be analyzed for pH, protein, glucose, blood, ketones, bile pigments, urobilinogen, N-acetyl-glucosaminidase, β 2-microglobulin, microalbumin, creatinine, casts, erythrocytes, leukocytes, epithelial cells, and crystals.
3. Physical exams
4. Vital signs
5. If a significant decrease in the T_4/T_1 ratio was observed, the time to recovery of the lowest T_4/T_1 ratio, value of lowest T_4/T_1 ratio, and time to return of T_4/T_1 ratio of 0.9 were to have been recorded.

Statistical Analysis Plan and Definition of Analyzed Study Populations:

EFFICACY

- All subjects randomized – self explanatory
- All subjects treated – all randomized patients who received a dose of study drug
- Intent to treat (ITT) – all patients in the treated group who had at least one post baseline efficacy assessment
- Per protocol (PP) – All patients from the ITT group without any major protocol violation

The primary analysis was to have been performed on the ITT group. There were to have been two analyses on the primary group, those with all data and those with imputed recovery times. The analysis using the imputed recovery times was to be the primary analysis.

The imputation scheme was to be:

1. Time to T4/T1 ratio to 0.8 is available: Org 25969 group: first calculate for all subjects randomized to receive Org 25969 and with times to recovery of the T4/T1 ratio to 0.8 and 0.9 available, the difference in time between these two recovery times. Next, add the 95% percentile (P95) of these differences to the time to recovery of the T4/T1 ratio to 0.8 of the subjects with missing times to recovery of the T4/T1 ratio to 0.9. This will be used as imputation of the missing time to recovery of the T4/T1 ratio to 0.9. Neostigmine group: same as for Org 25969 subjects but now use only subjects randomized to receive neostigmine and calculate the 5% percentile (P5) of the differences in time to recovery of the T4/T1 ratio to 0.8 and 0.9.

2. Time to T4/T1 ratio to 0.7 is available, but the time to T4/T1 ratio to 0.8 is missing: Org 25969 group: first calculate for all subjects randomized to Org 25969 and with times to recovery of the T4/T1 ratio to 0.7 and 0.9 available, the difference in time between these two recovery times. Next, add the P95 of these differences to the time to recovery of the T4/T1 ratio to 0.7. This will be used as imputation of the missing time to recovery of the T4/T1 ratio to 0.9. Neostigmine group: same as for Org 25969 subjects but now use only subjects randomized to receive neostigmine and calculate the P5 of the differences in time to recovery of the T4/T1 ratio to 0.7 and 0.9.

3. Times to T4/T1 ratio to 0.7 and to 0.8 are both missing: Org 25969 group: impute the P95 of the time to recovery of the T4/T1 ratio to 0.9 observed in all subjects randomized to receive Org 25969. Neostigmine group: impute the P5 of the time to recovery of the T4/T1 ratio to 0.9 observed in all subjects randomized to receive neostigmine.

SAFETY

- Safety data was to have been collected from the screening period up to post-operative day 7.
- No statistical tests on the safety data were to have been performed.
- Adverse events were to have been coded using the version of MedDRA current at the time of database lock.
- Laboratory data were to have been converted to SI units. Shift analyses were to have been conducted on laboratory data.
- “Markedly abnormal” vital sign data were prospectively defined as summarized below (page 356/2792 of the Clinical Study Report). Vital sign data were to have been summarized using standard statistical methods.

| Variable | Unit | Criterion value | Change from baseline |
|--------------|------|-----------------|----------------------|
| Heart rate | bpm | ≥ 120 | increase of ≥ 15 |
| | bpm | ≤ 50 | decrease of ≥ 15 |
| Systolic BP | mmHg | ≥ 160 | increase of ≥ 20 |
| | mmHg | ≤ 90 | decrease of ≥ 20 |
| Diastolic BP | mmHg | ≥ 95 | increase of ≥ 15 |
| | mmHg | ≤ 45 | decrease of ≥ 15 |

- For cases of potential reoccurarization, additional parameters were calculated as described previously in this review.

Protocol Amendments: There were no protocol amendments.

RESULTS:

Patient Exposure

Study 301 was conducted at 13 sites, all in Europe. A total of 198 patients were randomized of which 189 were treated and 185 completed. The Intent-to-Treat population (all treated patients with at least one post-baseline efficacy evaluation) was 189 patients. Patient disposition per treatment group is summarized in Table A2, following.

Table A2: Patient disposition (per treatment group)

| NMB agent | Disposition | Org 25969 | Neostigmine | Total |
|------------|-------------|-----------|-------------|-------|
| Rocuronium | Randomized | 49 | 49 | 98 |
| Rocuronium | Treated | 48 | 48 | 96 |
| Rocuronium | Completed | 47 | 47 | 94 |
| Vecuronium | Randomized | 51 | 49 | 100 |
| Vecuronium | Treated | 48 | 45 | 93 |
| Vecuronium | Completed | 47 | 44 | 91 |

Demographics/Medical History/Concomitant Medications

- Because of the small size of this study, the ability of randomization to normalize differences was limited compared to studies of larger size.
- While there were some mild imbalances in the demographic characteristics (e.g. the female:male ratio was 35:65 in the rocuronium/Org25969 cohort as opposed to nearly 1:1 in the other cohorts), none would be expected to affect the results.
- The medical histories in the cohorts were comparable.
- The anesthetic use was comparable between groups.
- None of the patients were ASA class 4.

Drop-Outs

In total, 13 patients dropped out (4 in the rocuronium group, 9 in the vecuronium group). Nine patients dropped out prior to the administration of study drug. Further descriptions of the drop-outs that were administered study drug follow.

- Patient 103007 (vecuronium/Org25969) could not be reached for follow up assessment.
- Patient 102010 (vecuronium/neostigmine) did not have a follow up assessment.
- Patient 104006 (rocuronium/Org25969) refused further trial participation following the day of surgery.
- Patient 112004 (rocuronium/neostigmine) could not be reached for the follow up assessment.

Protocol Deviations

The applicant divided protocol deviations into major and minor. Major protocol violations included

- Not meeting the inclusion criteria of ASA class 1-4, 18 or more years old, scheduled in the supine position, or without informed consent.
- Meeting such exclusion criteria such as neuromuscular disorders, significant renal dysfunction, receiving medication expected to interfere with the NMB.
- Violation of the randomization schedule.
- Administration of a dose that deviates more than 10% from the prescribed dose.
- Administration of study drug more than two minutes from the time point to be studied
- Use of concomitant medications that might be expected to interfere with the endpoint prior to scoring any efficacy variable.

Minor protocol violations included

- Use of a concomitant medication that could interfere with the endpoint after scoring the efficacy variable.
- Use of a neuromuscular block measurement device other than the TOF-Watch SX.
- Unreliability of (all of or some of) the time course of action data assessed after the reappearance of T₂.
- Occurrence of malignant hyperthermia during anesthesia.

There were a total of 12 major protocol violations, summarized in Table A3, following.

Table A3: Major protocol violations

| Patient ID | NMB | Reversal Agent | Violation |
|------------|-----|----------------|--|
| 101018 | Roc | Org25969 | Study drug administered > 2 minutes after return of T ₂ |
| 108009 | Roc | Org25969 | Study drug administered > 2 minutes after return of T ₂ |
| 105009 | Roc | Org25969 | Dose more than 10% low |
| 103002 | Roc | Org25969 | Vancomycin administered proximate to study drug |
| 103013 | Roc | Neostigmine | Erythromycin administered proximate to study drug |
| 109016 | Vec | Org25969 | Dose more than 10% low |
| 109005 | Vec | Org25969 | Clindamycin administered proximate to study drug |
| 107005 | Vec | Org25969 | Received study drug before reappearance of T ₂ |
| 101012 | Vec | Neostigmine | Received two doses of neostigmine |
| 103005 | Vec | Neostigmine | Erythromycin administered proximate to study drug |
| 112007 | Vec | Neostigmine | Gentamicin administered proximate to study drug |
| 105007 | Vec | Neostigmine | Received study drug before reappearance of T ₂ |

Given the fact that the protocol violations were reasonably balanced between the Org25969 and neostigmine arms, this reviewer does not believe that they affected the study outcome.

Minor protocol violations:

There were five patients with minor protocol violations, two in the rocuronium cohort (one reversed with Org25969 and one with neostigmine) and three in the vecuronium cohort (two with Org25969 and one with neostigmine). All five had “unreliable” data pertaining to the determination of the T₄/T₁ ratio. Please see Section 6.1.4 and the comments section for a discussion.

PRIMARY EFFICACY RESULTS

The applicant varied slightly from the protocol specified analysis plan in that the analysis plan implied that a pooled analysis (including both rocuronium and vecuronium) would be done. In the Clinical Study Report, the applicant has conducted the analysis by NMB, therefore losing statistical power. This is acceptable and preferable.

Table A4, following, is summarized data for the primary efficacy endpoint for patients treated with rocuronium. The tables show a clear and convincing treatment effect; the geometric mean for recovery of the T₄/T₁ ratio is 1:29 in the Org25969 cohort versus 18.30 in the neostigmine cohort. The “Including imputed data” section is the primary analysis per the protocol. For a

discussion of the “Completed cases” section, please see the section of this review regarding missing data.

Table A4: Summary primary endpoint data, Study 301, rocuronium-treated patients

Table 14 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, rocuronium group (ITT group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=48) | Neostigmine (N=48) |
| Including imputed data | n | 48 | 48 |
| | Geometric mean | 1:29 | 18:30 |
| | Mean (SD) | 1:37 (0:50) | 26:47 (24:36) |
| | Median | 1:24 | 17:36 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |
| Complete cases | n | 47 | 45 |
| | Geometric mean | 1:28 | 18:38 |
| | Mean (SD) | 1:35 (0:49) | 27:18 (25:12) |
| | Median | 1:23 | 18:31 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |

Source: CSR, page 79/142

Some patients required one or more maintenances of rocuronium. Table A5, following, shows that there was no difference in the time to the T₄/T₁ = 0.9 with respect to the redosing of NMB.

Table A5: Summary primary endpoint data, Study 301, rocuronium-treated patients, effect of maintenance dosing

Table 15 Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T₄/T₁ ratio to 0.9 for subjects who received an intubating dose only and those who received at least one maintenance dose, rocuronium group (ITT group)

| | | Intubating dose only | Intubating dose and maintenance dose(s) |
|------------------------|----------------|----------------------|---|
| Including imputed data | n | 33 | 15 |
| | Geometric mean | 1:28 | 1:31 |
| | Mean (SD) | 1:34 (0:47) | 1:42 (0:56) |
| | Median | 1:23 | 1:25 |
| | Min. – max. | 0:56 – 5:25 | 0:55 – 4:11 |
| Complete cases | n | 33 | 14 |
| | Geometric mean | 1:28 | 1:28 |
| | Mean (SD) | 1:34 (0:47) | 1:38 (0:56) |
| | Median | 1:23 | 1:18 |
| | Min. – max. | 0:56 – 5:25 | 0:55 – 4:11 |

Source: CSR, page 81/142

Table A6, following, is summarized data for the primary efficacy endpoint for patients treated with vecuronium. The tables show a clear and convincing treatment effect; the geometric mean for recovery of the T₄/T₁ ratio is 2:48 in the Org25969 cohort versus 16:48 in the neostigmine cohort. It is interesting to note that the time to recovery is longer with vecuronium than rocuronium, predicted on the binding affinities.

Table A6: Summary primary endpoint data, Study 301, vecuronium-treated patients
Table 16 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, vecuronium group (ITT group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=48) | Neostigmine (N=45) |
| Including imputed data | n | 48 | 45 |
| | Geometric mean | 2:48 | 16:48 |
| | Mean (SD) | 4:28 (9:17) | 23:26 (18:32) |
| | Median | 2:08 | 18:56 |
| | Min. – max. | 1:12 - 64:12 | 2:55 - 76:09 |
| Complete cases | n | 46 | 34 |
| | Geometric mean | 2:41 | 17:52 |
| | Mean (SD) | 4:22 (9:28) | 24:44 (19:04) |
| | Median | 2:06 | 21:51 |
| | Min. – max. | 1:12 - 64:12 | 2:55 - 76:09 |

Source: CSR, page 82/142

A statistically significant interaction between trial site and treatment group was observed for the vecuronium primary analysis.

Some patients required one or more maintenances of vecuronium. Table A7, following, shows that there was a small increase in the time to the T₄/T₁ = 0.9 with respect to the redosing of NMB.

Table A7: Summary primary endpoint data, Study 301, vecuronium-treated patients, effect of maintenance dosing

Table 17 Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received at least one maintenance dose, vecuronium group (ITT group)

| | | Intubating dose only | Intubating dose and maintenance dose(s) |
|------------------------|----------------|----------------------|---|
| Including imputed data | n | 28 | 20 |
| | Geometric mean | 2:21 | 3:35 |
| | Mean (SD) | 4:28 (11:46) | 4:28 (4:02) |
| | Median | 1:56 | 3:26 |
| | Min. – max. | 1:12 – 64:12 | 1:41 – 19:47 |
| Complete cases | n | 27 | 19 |
| | Geometric mean | 2:15 | 3:27 |
| | Mean (SD) | 4:22 (11:59) | 4:20 (4:06) |
| | Median | 1:56 | 3:26 |
| | Min. – max. | 1:12 – 64:12 | 1:41 – 19:47 |

Source: CSR, page 90/142

The differences in mean time to recovery were compared in a 2-way ANOVA test as summarized in Tables A8 and A9, following.

Table A8: ANOVA analysis, Study 301, rocuronium

Table 3 Summary of the time (min) from start of administration of Org 25969 or neostigmine administered at reappearance of T_2 following rocuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

| | Trial 19.4.301 ^b | |
|----------------------|---|--|
| | Rocuronium + Org 25969 (2.0 mg.kg ⁻¹) | Rocuronium + Neostigmine (50 µg.kg ⁻¹) |
| n | 48 | 48 |
| Geometric Mean | 1.5 | 18.5 |
| 95% CI | 1.3 – 1.7 | 14.3 – 23.9 |
| Median | 1.4 | 17.6 |
| Min. – max. | 0.9 – 5.4 | 3.7 – 106.9 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

^b Anesthetic regimen included induction with propofol and maintenance with sevoflurane.

Source: Clinical Overview, page 51

Table A9: ANOVA analysis, Study 301, vecuronium

Table 5 Summary of the time (min) from start of administration of Org 25969 or neostigmine administered at reappearance of T₂ following vecuronium to recovery of the T₄/T₁ ratio to 0.9 (ITT group)

| | Trial 19.4.301 ^b | |
|----------------------|--|---|
| | Vecuronium + Org 25969 (2.0 mg.kg ⁻¹) | Vecuronium + Neostigmine (50 µg.kg ⁻¹) |
| n | 48 | 45 |
| Geometric Mean | 2.8 | 16.8 |
| 95% CI | 2.3 – 3.4 | 12.9 – 21.9 |
| Median | 2.1 | 18.9 |
| Min. – max. | 1.2 – 64.2 | 2.9 – 76.2 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T₄/T₁ ratio to 0.9.

^b Anesthetic regimen included induction with propofol and maintenance with sevoflurane.

Source: Clinical Overview, page 53

These tables show a statistically significant treatment effect for both the roc and vec treated patients.

Secondary Efficacy Endpoints

The analyses of the time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.8, time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.7, and assessments of clinical signs of recovery prior to PACU transfer after extubation and prior to PACU discharge generally supported the primary endpoint.

The clinical signs of recovery data are summarized in the following tables [A10 (roc) and A11 (vec)].

Table A10: Clinical signs of recovery (rocuronium group, ITT)

| | Time point ^{a)} | | | |
|--|--------------------------|----------------------------|--------------------------|----------------------------|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | Org 25969 (N=48) n | Neostigmine (N=48) n | Org 25969 (N=48) n | Neostigmine (N=48) N |
| Subject's level of consciousness | | | c) | |
| Awake and oriented | 30 | 35 | 46 | 48 |
| Arousable with minimal stimulation | 16 | 13 | 1 | 0 |
| Responsive only to tactile stimulation | 2 | 0 | 0 | 0 |
| Subject cooperative ^{b)} | | | | |
| No | 7 | 1 | 0 | 0 |
| Yes | 41 | 47 | 47 | 48 |
| Subject able to perform the 5 s. head lift | | | | |
| No | 3 | 10 | 0 | 0 |
| Yes | 38 | 37 | 47 | 48 |
| General muscle weakness | | | | |
| No | 38 | 38 | 47 | 48 |
| Yes | 3 | 9 | 0 | 0 |

Data were taken from Appendix F, Table 6.2-R.C.1

^{a)} 1: prior to transfer to the recovery room after extubation

2: prior to discharge from the recovery room

^{b)} in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed

^{c)} no assessment was performed for Subject 108017 (Org 25969) prior to transfer to recovery room

Source: CSR, page 88

Table A11: Clinical signs of recovery (vecuronium group, ITT)

| | Time point ^{a)} | | | |
|--|--------------------------|----------------------------|--------------------------|----------------------------|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | Org 25969 (N=48) n | Neostigmine (N=45) n | Org 25969 (N=48) n | Neostigmine (N=45) n |
| Subject's level of consciousness | | | | ^{c)} |
| Awake and oriented | 29 | 26 | 48 | 43 |
| Arousable with minimal stimulation | 17 | 14 | 0 | 1 |
| Responsive only to tactile stimulation | 2 | 5 | 0 | 0 |
| Subject cooperative ^{b)} | | | | |
| No | 7 | 7 | 0 | 0 |
| Yes | 41 | 38 | 48 | 44 |
| Subject able to perform the 5 s. head lift | | | | |
| No | 1 | 6 | 0 | 0 |
| Yes | 40 | 32 | 48 | 44 |
| General muscle weakness | | | | |
| No | 37 | 32 | 48 | 44 |
| Yes | 4 | 6 | 0 | 0 |

Data were taken from Appendix F, Table 6.2-V.C.1

^{a)} 1: prior to transfer to the recovery room after extubation

2: prior to discharge from the recovery room

^{b)} in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed

Source: CSR, page 92

The clinical signs of recovery showed that the use of Org25969 resulted in clinically similar recovery from neuromuscular blockade compared to recovery using neostigmine.

Analyses of the T1 at the time of reappearance of T3, time from start administration of the last bolus dose of NMB to recovery T₄/T₁ ratio to 0.7, time from start administration of the last bolus dose of NMB to recovery T₄/T₁ ratio to 0.8, and time from start administration of the last bolus dose of NMB to recovery T₄/T₁ ratio to 0.9 also supported the primary endpoint.

Effects of missing data:

The primary cause of missing data was because the T₄/T₁ ratio failed to return to 0.9 within a reasonable time. Those data were imputed as described previously. The primary efficacy analysis, shown in Tables # and #, preceding, is based on those imputed data.

To address whether imputation affected the outcome, the applicant performed analyses of data on the basis of complete and imputed cases. This analysis is summarized below.

Table A12: Effects of missing data – patients treated with rocuronium

Table 14 Summary of the time (min:sec) from start of administration of IP to recovery of the T_4/T_1 ratio to 0.9 by treatment group, rocuronium group (ITT group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=48) | Neostigmine (N=48) |
| Including imputed data | n | 48 | 48 |
| | Geometric mean | 1:29 | 18:30 |
| | Mean (SD) | 1:37 (0:50) | 26:47 (24:36) |
| | Median | 1:24 | 17:36 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |
| Complete cases | n | 47 | 45 |
| | Geometric mean | 1:28 | 18:38 |
| | Mean (SD) | 1:35 (0:49) | 27:18 (25:12) |
| | Median | 1:23 | 18:31 |
| | Min. – max. | 0:55 - 5:25 | 3:40 - 106:53 |

Table A13: Effects of missing data – patients treated with vecuronium

Table 15 Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 for subjects who received an intubating dose only and those who received at least one maintenance dose, rocuronium group (ITT group)

| | | Intubating dose only | Intubating dose and maintenance dose(s) |
|------------------------|----------------|----------------------|---|
| Including imputed data | n | 33 | 15 |
| | Geometric mean | 1:28 | 1:31 |
| | Mean (SD) | 1:34 (0:47) | 1:42 (0:56) |
| | Median | 1:23 | 1:25 |
| | Min. – max. | 0:56 – 5:25 | 0:55 – 4:11 |
| Complete cases | n | 33 | 14 |
| | Geometric mean | 1:28 | 1:28 |
| | Mean (SD) | 1:34 (0:47) | 1:38 (0:56) |
| | Median | 1:23 | 1:18 |
| | Min. – max. | 0:56 – 5:25 | 0:55 – 4:11 |

Tables A12 and A 13 show that the imputation scheme did not change the findings.

Missing, adjudicated, and unreliable data

Please see Section 6.4.1, ~page 39 for a discussion of missing, adjudicated, and unreliable data after query and resolution with the applicant.

REVIEWER COMMENTS

This study had been reviewed and found acceptable via the Special Protocol Assessment (SPA) process.

Using the protocol-specified primary efficacy endpoint and statistical analysis plan, Org25969 demonstrated clear superiority to neostigmine in the rapidity of reversal.

Org25969 appeared slightly more efficacious when used with rocuronium although this finding should be interpreted with caution due to the small sample size.

The issues with missing, adjudicated, and unreliable data have been resolved.

SAFETY FINDINGS

Dr. Arthur Simone has completed a review of the safety findings. A brief summary of the safety data for this study follows.

- The raw adverse event rate was roughly equivalent for the Org25969 and neostigmine groups although patients treated with rocuronium (regardless of reversal agent), experienced a greater overall rate (~87% in the roc versus ~75% for the vec).
- No deaths occurred.
- The SAE rates were similar for roc/Org25969 and roc/neostigmine (no SAEs occurred in the vec group).
- Adverse events graded as severe appeared more frequently in the patients treated with Org25969.
- One patient treated with Org25969 experienced an adverse event coded as drug hypersensitivity.

Number: 19.4.302

Protocol Title: A multicenter, randomized, parallel group, comparative, active controlled, safety-assessor blinded, phase IIIa, pivotal trial in adult subjects comparing Org 25969 with neostigmine as reversal agent of a neuromuscular block induced by maintenance dosing of rocuronium or vecuronium at 1-2 PTCs.

Study 302 was identical to Study 301 with the following exceptions:

1. Org25969 or neostigmine was to be administered at 1-2 post tetanic counts (profound neuromuscular blockade).
2. The dose of Org25969 was to be 4 mg/kg and the dose of neostigmine/glycopyrrolate was to be 70 and 14 mcg/kg

3. The sample sizes were to be smaller (~36/arm)
4. One interim analysis was planned.

Protocol Amendments:

Amendment 1: (October 2005)

- All changes were administrative except a secondary endpoint that was corrected (time to reappearance of T2 to be timed from Org25969/neostigmine administration, not NMB administration), assessments of clinical signs of recovery to be done in the peri-anesthetic period

Amendment 2: (March 2006)

- Clarified that the blinded safety assessor to conduct assessments after anesthesia
- Multiplicity correction to be Hwang-Shih-deCani method (previously O'Brien-Fleming)
- Clarified that an independent CRO will perform the interim analysis

Amendment 3: (August 2006)

- Discontinue neostigmine arms (DSMB recommendation following interim analysis)
- Administrative changes to reflect the early termination.

RESULTS:

Patient Exposure

Study 302 was conducted at 8 centers, all in the United States. A total of 182 patients were randomized of which 155 completed. The Intent-to-Treat population (all treated patients with at least one post-baseline efficacy measurement) was 157 patients. Table A14, following, summarizes the patients randomized, treated, and completed.

Table A14: Patient disposition (per treatment group)

| NMB agent | Disposition | Org 25969 | Neostigmine | Total |
|------------|-------------|-----------|-------------|-------|
| Rocuronium | Randomized | 48 | 40 | 88 |
| Rocuronium | Treated | 37 | 38 | 75 |
| Rocuronium | Completed | 37 | 37 | 74 |
| Vecuronium | Randomized | 52 | 42 | 94 |
| Vecuronium | Treated | 46 | 36 | 82 |
| Vecuronium | Completed | 46 | 35 | 81 |

Demographics/Medical History/Concomitant Medications

- Because of the small size of this study, the ability of randomization to normalize differences was limited compared to studies of larger size.
- In the opinion of this reviewer, the mean differences in demographics would not have been expected to affect the outcome of the study.
- The medical histories in the cohorts were comparable.

- The anesthetic/concomitant medication use was comparable except that this reviewer notes that more doses of NMBA were used in the Org25969 arms than the neostigmine arms.
- As with Study 301, no patients were ASA class 4.

Drop-Outs

In total, 27 patients dropped out prematurely (15 in the roc group; 12 in the vec group). Only two of these patients were treated. One patient was treated with rocuronium/neostigmine and discontinued due to a SAE (gastric perforation). Another patient was treated with vec and was scheduled to be treated with Org25969. She developed a deep venous thrombosis prior to reversal and was discontinued.

Patients who discontinued prior to treatment (N = 25) dropped out for reasons such as equipment malfunction, administrative issues, and change in surgical plan.

Protocol Violations

The applicant divided protocol violations into major and minor as in Study 301. There were a total of 26 patients meeting the definition of major protocol violators as summarized in Table A15, below.

Table A15: Major protocol violators

| NMB Agent | Reversal Agent | N |
|------------|----------------|---|
| Rocuronium | Org25969 | 5 |
| Rocuronium | Neostigmine | 6 |
| Vecuronium | Org25969 | 9 |
| Vecuronium | Neostigmine | 6 |

The majority of protocol violations occurred due to administration of a prohibited (potentially interfering) drug proximate to study drug (20 patients). Other reasons included meeting one or more exclusion criteria, administering the reversal agent at the wrong time, or an error in dosing of the reversal agent or randomization schedule. Given the fact that the protocol violations were fairly balanced between the Org25969 and neostigmine arms, this reviewer does not believe that they affected the study outcome.

As with the major protocol violators, Study 302 had a higher rate of minor protocol violators compared to Study 301. As in Study 301, all minor protocol violations were related to “unreliability” of the neuromuscular monitoring data. In Study 302, the proportion of treatment allocations was more unbalanced with 8 patients in the Org25969 group (6 rocuronium, 2 vecuronium) compared to 2 patients in the neostigmine group (both vecuronium) having some or all of the TOF data being “unreliable.”

Missing, adjudicated, and unreliable data

Please see Section 6.4.1, ~page 39 for a discussion of missing, adjudicated, and unreliable data after query and resolution with the applicant.

PRIMARY EFFICACY RESULTS

The analysis of the primary efficacy endpoint is summarized in Table A 16, following.

Table A16: Results – primary efficacy endpoint, Study 302 - rocuronium
Table 18 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, rocuronium group (Intent-to-Treat Group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=37) | Neostigmine (N=37) |
| Including imputed data | n | 37 | 37 |
| | Geometric mean | 2:52 | 50:22 |
| | Mean (SD) | 3:17 (2:24) | 55:30 (27:06) |
| | Median | 2:42 | 49:00 |
| | Min. – max. | 1:13 – 16:05 | 13:16 - 145:40 |
| Complete cases | n | 30 | 22 |
| | Geometric mean | 2:36 | 55:59 |
| | Mean (SD) | 3:01 (2:36) | 60:57 (25:03) |
| | Median | 2:34 | 57:04 |
| | Min. – max. | 1:13 - 16:05 | 13:16 - 133:28 |

Source: CSR, page 104

There was a statistically significant interaction between trial site and treatment group for this comparison for several of the analyses (imputed data, per protocol).

Table A17: Results – primary efficacy endpoint, Study 302 - vecuronium

Table 19 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, vecuronium group (Intent-to-Treat Group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=47) | Neostigmine (N=36) |
| Including imputed data | n | 47 | 36 |
| | Geometric mean | 4:28 | 66:12 |
| | Mean (SD) | 8:44 (14:36) | 77:48 (56:59) |
| | Median | 3:15 | 49:53 |
| | Min. – max. | 1:26 - 68:25 | 46:01 - 312:39 |
| Complete cases | n | 41 | 15 |
| | Geometric mean | 3:35 | 91:01 |
| | Mean (SD) | 6:19 (11:52) | 107:12 (72:01) |
| | Median | 3:00 | 95:47 |
| | Min. – max. | 1:26 - 63:32 | 46:01 - 312:39 |

Source: CSR, page 107

Tables A18 and A19 following show that the difference in the mean time to T₄/T₁ = 0.9 were highly statistically different when tested in an ANOVA model.

Table A18: Statistical analysis, primary efficacy endpoint, rocuronium

Table 6 Summary of the time (min) from start of administration of Org 25969 or neostigmine administered at 1-2 PTCs following rocuronium to recovery of the T₄/T₁ ratio to 0.9 (ITT group)

| | Trial 19.4.302 | |
|----------------------|--|---|
| | Rocuronium + Org 25969 (4.0 mg.kg ⁻¹) | Rocuronium + Neostigmine (70 µg.kg ⁻¹) |
| n | 37 | 37 |
| Geometric Mean | 2.9 | 50.4 |
| 95% CI | 2.5 – 3.4 | 43.5 – 58.4 |
| Median | 2.7 | 49.0 |
| Min. – max. | 1.2 – 16.1 | 13.3 – 145.7 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T₄/T₁ ratio to 0.9.

Source: Overview, page 54

Table A19: Statistical analysis, primary efficacy endpoint, vecuronium
Table 7 **Summary of the time (min) from start of administration of Org 25969 or neostigmine administered at 1-2 PTCs following vecuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)**

| | Trial 19.4.302 | |
|----------------------|--|---|
| | Vecuronium + Org 25969 (4.0 mg.kg ⁻¹) | Vecuronium + Neostigmine (70 µg.kg ⁻¹) |
| n | 47 | 36 |
| Geometric Mean | 4.5 | 66.2 |
| 95% CI | 3.3 – 6.0 | 55.6 – 78.9 |
| Median | 3.3 | 49.9 |
| Min. – max. | 1.4 – 68.4 | 46.0 – 312.7 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

Source: Overview, page 55

Effects of missing data:

The primary cause of missing data was because the T_4/T_1 ratio failed to return to 0.9 within a reasonable time. Those data were imputed as previously described. The primary efficacy analysis, shown in Tables # and #, preceding, is based on those imputed data.

To address whether imputation affected the outcome, the applicant performed analyses of data on the basis of complete and imputed cases. This analysis is summarized below.

Table A20: Effects of missing data – patients treated with rocuronium

Table 18 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, rocuronium group (Intent-to-Treat Group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=37) | Neostigmine (N=37) |
| Including imputed data | n | 37 | 37 |
| | Geometric mean | 2:52 | 50:22 |
| | Mean (SD) | 3:17 (2:24) | 55:30 (27:06) |
| | Median | 2:42 | 49:00 |
| | Min. – max. | 1:13 – 16:05 | 13:16 - 145:40 |
| Complete cases | n | 30 | 22 |
| | Geometric mean | 2:36 | 55:59 |
| | Mean (SD) | 3:01 (2:36) | 60:57 (25:03) |
| | Median | 2:34 | 57:04 |
| | Min. – max. | 1:13 - 16:05 | 13:16 - 133:28 |

Source CSR, page 104

Table A21: Effects of missing data – patients treated with vecuronium

Table 19 Summary of the time (min:sec) from start of administration of IP to recovery of the T₄/T₁ ratio to 0.9 by treatment group, vecuronium group (Intent-to-Treat Group)

| | | Treatment group | |
|------------------------|----------------|---------------------|-----------------------|
| | | Org 25969 (N=47) | Neostigmine (N=36) |
| Including imputed data | n | 47 | 36 |
| | Geometric mean | 4:28 | 66:12 |
| | Mean (SD) | 8:44 (14:36) | 77:48 (56:59) |
| | Median | 3:15 | 49:53 |
| | Min. – max. | 1:26 - 68:25 | 46:01 - 312:39 |
| Complete cases | n | 41 | 15 |
| | Geometric mean | 3:35 | 91:01 |
| | Mean (SD) | 6:19 (11:52) | 107:12 (72:01) |
| | Median | 3:00 | 95:47 |
| | Min. – max. | 1:26 - 63:32 | 46:01 - 312:39 |

Source: CSR, page 107

The addition of imputed data does not appear to change the results of the study.

Secondary Efficacy Endpoints

The analyses of the time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.8, time from start of administration of the reversal agent/study drug to recovery of the T₄/T₁ ratio to 0.7, and assessments of clinical signs of recovery prior to PACU transfer after extubation and prior to PACU discharge generally supported the primary endpoint. There was a statistically significant interaction between trial site and treatment group for this comparison for one of the secondary endpoint analyses (time to recovery of T₄/T₁ = 0.7, rocuronium).

The clinical signs of recovery data are summarized following [Tables A22 (roc) and A23 (vec)].

Table A22: Clinical signs of recovery - rocuronium

Table 21 Summary of the clinical signs of recovery by assessment and treatment group, rocuronium group (Intent-to-Treat Group)

| | Time point ^{a)} | | | |
|---|--------------------------|----------------------------|--------------------------|----------------------------|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | Org 25969 (N=37) n | Neostigmine (N=37) n | Org 25969 (N=37) n | Neostigmine (N=37) N |
| Subject's level of consciousness | | ^{c)} | ^{c)} | ^{c)} |
| Awake and oriented | 26 | 20 | 34 | 32 |
| Arousable with minimal stimulation | 9 | 11 | 0 | 1 |
| Responsive only to tactile stimulation | 2 | 3 | 0 | 0 |
| Subject cooperative ^{b)} | | | | |
| No | 3 | 5 | 0 | 0 |
| Yes | 34 | 30 | 34 | 33 |
| Subject able to perform the 5-sec head lift | | | | |
| No | 1 | 2 | 0 | 0 |
| Yes | 33 | 28 | 34 | 33 |
| General muscle weakness | | | | |
| No | 31 | 25 | 32 | 30 |
| Yes | 3 | 5 | 2 | 3 |

Data were taken from Appendix F, Table 6.2-R.C.1

^{a)} 1: prior to transfer to the recovery room after extubation

2: prior to discharge from the recovery room

^{b)} in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed

^{c)} No assessments were performed for Subjects 103004, 103015, & 110005 (neostigmine) prior to transfer to the recovery room after extubation and for Subjects 105002, 105010, & 105013 (Org 25969) and Subjects 103011, 105003, 105005 & 105011 (neostigmine) prior to discharge from the recovery room (Appendix G, Listing 14.A)

Source, CSR, page 113

Table A22: Clinical signs of recovery - vecuronium

Table 23 Summary of the clinical signs of recovery by assessment and treatment group, vecuronium group (Intent-to-Treat Group)

| | Time point ^{a)} | | | |
|---|--------------------------------|----------------------------------|--------------------------------|----------------------------------|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | Org 25969 (N=47) n c) | Neostigmine (N=36) n c) | Org 25969 (N=47) n c) | Neostigmine (N=36) N c) |
| Subject's level of consciousness | | | | |
| Awake and oriented | 27 | 20 | 39 | 33 |
| Arousable with minimal stimulation | 12 | 8 | 2 | 1 |
| Responsive only to tactile stimulation | 7 | 7 | 0 | 0 |
| Subject cooperative ^{b)} | | | | |
| No | 9 | 10 | 0 | 0 |
| Yes | 37 | 25 | 41 | 34 |
| Subject able to perform the 5-sec head lift | | | | |
| No | 1 | 1 | 0 | 1 |
| Yes | 36 | 24 | 41 | 33 |
| General muscle weakness | | | | |
| No | 33 | 23 | 40 | 31 |
| Yes | 4 | 2 | 1 | 3 |

Data were taken from Appendix F, Table 6.2-V.C.1

^{a)} 1: prior to transfer to the recovery room after extubation

2: prior to discharge from the recovery room

^{b)} in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed

^{c)} No assessments were performed for Subject 110024 (Org 25969) and Subject 111015 (neostigmine) prior to transfer to the recovery room after extubation and for Subjects 105004, 105012, 105014, 105102, 105104 & 110024 (Org 25969) and Subjects 105007 & 111015 (neostigmine) prior to discharge from the recovery room. (Appendix G, Listing 14.A)

Source, CSR, page 118

Other efficacy variables

The time to reappearance of T₃ and time from last bolus of NMBA to recovery of T₄/T₁ = 0.7, 0.8, and 0.9, all supported the primary analysis.

REVIEWER COMMENTS

This study was similar to Study 301, varying only in the depth of paralysis (1-2 PTCs versus return of T₂) at which a reversal agent was administered and the dose of Org25969 used (4 mg/kg versus 2 mg/kg).

The study met the protocol defined criteria for success with a p-value of < 0.0001 .

The issues with missing data, unreliable data, and outliers were successfully resolved.

SAFETY FINDINGS

Dr. Arthur Simone has completed a review of the safety findings. A brief summary of the safety data for this study follows.

- The raw adverse event rate was roughly equivalent for the Org25969 and neostigmine groups, regardless of the NMBA used.
- No deaths occurred.
- The SAE rates were similar for Org25969 and neostigmine.
- Adverse events graded as severe appeared more frequently in the patients treated with vecuronium/neostigmine than vecuronium/Org25969.

Number: 19.4.303

Protocol Title: “A multicenter, randomized, parallel group, comparative, active controlled, safety assessor blinded, phase IIIa trial in adult subjects comparing recovery from 1.2 mg/kg rocuronium followed by 16.0 mg/kg Org25969 at 3 minutes with recovery from 1.0 mg/kg succinylcholine”

Primary Objective: To demonstrate faster recovery to T1 10% after neuromuscular block induced by 1.2 mg/kg rocuronium reversed at 3 minutes by 16 mg/kg of Org25969 compared to succinylcholine

Secondary Objectives:

- To demonstrate faster recovery to T1 90% after neuromuscular block induced by roc/Org25969 versus succinylcholine
- To evaluate the safety of a single dose of roc/Org25969 vs. succinylcholine

Study Design: Randomized, active controlled, parallel group, single dose, safety-assessor blinded

Duration: This was to be a single-dose study.

Sample Size: The applicant planned to randomize 49 patients/arm.

Inclusion Criteria: Patients were to have met the following inclusion criteria.

- Between 18 and 65 years of age
- ASA Class 1–2
- Scheduled to undergo a surgical procedure under general anesthesia requiring a short duration of neuromuscular relaxation with the use of rocuronium or succinylcholine and requiring endotracheal intubation
- Scheduled to undergo surgical procedure in supine position
- Body Mass Index (BMI) of < 30
- Having given written informed consent.

Exclusion Criteria:

- Known to have ischemic heart disease or a history of myocardial infarction within the last year
- Patients in whom a difficult intubation is expected because of anatomical malformations
- Known or suspected to have neuromuscular disorders impairing neuromuscular blockade
- Known or suspected to have significant renal dysfunction
- Known or suspected to have a (family) history of malignant hyperthermia
- Known or suspected to have an allergy to narcotics, muscle relaxants, midazolam, anesthetics, or other medications used during general anesthesia
- Receiving medication in a dose and/or at a time point known to interfere with neuromuscular blocking agents such as antibiotics, anticonvulsants, and Mg²⁺
- Female subjects who are pregnant

Treatment Groups:

1. Rocuronium, 1.2 mg/kg followed by Org25969, 16 mg/kg (three minutes separating the injections)
2. Succinylcholine, 1 mg/kg

Permitted Concomitant Medications:

- If renewed muscle relaxation is needed, a non-aminosteroidal could be administered.
-

Prohibited Concomitant Medications:

- Medications known to modify the actions of non-depolarizing NMBAs during the screening or peri-anesthetic periods
- Muscle relaxants other than the assigned study drug.
- Reversal agents other than the assigned study drug.

Study Conduct:

The study was divided into four phases, summarized following.

Screening: During the screening visit (within one week of surgery), the following procedures were to have been performed

- Patient consented
- History and physical exam.
- Vital signs
- Urine sample for safety and pregnancy
- Inclusion and exclusion criteria
- Assess pre-trial medications and adverse events

Peri-anesthetic: During the time immediately prior to and during the surgery, the following procedures were to have been performed (study-specific procedures in *italics*)

- *Patient randomized*
- Routine pre-anesthetic clinical procedures (place IV cannulas)
- Continuous ECG monitoring
- *Induce anesthesia with IV opioid, propofol, or other agents appropriate to the clinical scenario*
- *Affix, stabilize, and calibrate the Train-of-Four (TOF) device and start continuous monitoring*
- Continue routine anesthetic monitoring (vital signs, body temperature, etc.)
- Administer NMBA within 10 seconds
- Intubate
- Maintain anesthesia with IV opioid, propofol, or other appropriate agent.
- Monitor adverse events
- Administer Org25969 (for patients receiving roc) three minutes following the start of roc/succinylcholine injection. NB Patients administered succinylcholine did not received placebo 3 minutes following injection of the NMBA.
- Collect blood, continue routine anesthetic and neuromuscular monitoring, collect adverse event and medication data at least until the recovery of T4/T1 = 0.9.

Post-anesthetic:

- Assess clinical signs of recovery prior to transfer to recovery room after extubation and prior to discharge from the recovery room.

Follow-up:

- Contact (in person if in hospital, by telephone if discharged)
- Assess quality of recovery (via questionnaire), concomitant medication intake, adverse events.

Outcome Measures:

Primary Efficacy Endpoint:

The primary efficacy endpoint was to be the elapsed time from administration of rocuronium or succinylcholine to recovery of T₁ to 10% of the initial T₁. This reviewer notes that 10% of the initial T₁ does not reflect full clinical reversal.

Secondary Endpoints;

- Time from administration of the NMBA to recovery of T₁ to 90% of the initial T₁
- Clinical signs of recovery

Other Efficacy Endpoints:

- Time from start of administration of rocuronium to recovery of the T4/T1 ratio to 0.7
- Time from start of administration of rocuronium to recovery of the T4/T1 ratio to 0.8
- Time from start of administration of rocuronium to recovery of the T4/T1 ratio to 0.9
- Time from start of administration of Org 25969 to the time of reappearance of T3
- T1 at the time of reappearance of T3.
- Health Economics Patient Reported Outcomes (Quality of Recovery questionnaire)

Safety: Adverse events, laboratory testing, ECGs, vital signs, physical exams

Statistical Analysis Plan and Definition of Analyzed Study Populations:

EFFICACY

The primary analysis was to be performed on the ITT population, defined as all patients who received study drug and had at least one post-baseline efficacy assessment. Imputation rules for missing data were to be:

For imputation of missing times from the start of administration of rocuronium or succinylcholine to the recovery of T1 to 10% and to 90% a worst case scenario for rocuronium/Org 25969 and a best case scenario for succinylcholine will be applied.

For the primary efficacy variable the following procedure will be followed. In case of missing data in the: • rocuronium/Org 25969 group: calculate the 95th percentile (P95) of the available times from the start of administration of rocuronium to the recovery of T1 to 10% of the baseline value in all subjects randomized to receive rocuronium and Org 25969. Impute this P95 value for the missing times in this group. • succinylcholine group: calculate the 5th percentile (P5) of the available times from the start of administration of succinylcholine to the recovery of T1 to 10% of the baseline value in all subjects randomized to receive succinylcholine. Impute this P5 value for the missing times in this group.

Data from the two treatment groups (roc/Org25969 versus succinylcholine) were to have been compared using both the completed data and those with imputed data. The analysis with imputed data was to have been the primary analysis.

Secondary efficacy data were to have been analyzed similarly to those of the primary endpoint.

SAFETY

Safety data were to have been handled identically to Studies 301 and 302.

Protocol Amendments:

Amendment 1 (March 2006) – administrative changes

Amendment 2 (May 2006) – administrative changes

Amendment 3 (June 2006) – allowed for maintenance with inhalational agents

RESULTS:

Patient Exposure

Study 303 was conducted at 13 sites, 11 in the U.S. and 2 in Canada. Two of the U.S. centers did not enroll any patients. A total of 115 patients were randomized of which 189 were treated and 108 completed. The Intent-to-Treat population (all treated patients with at least one post-baseline efficacy evaluation) was 110 patients. Patient disposition per treatment group is summarized in Table A24, following.

Table A24: Patient disposition

| | Treatment group | | Total n |
|------------|------------------------|-----------------|------------|
| | Rocuronium + Org 25969 | Succinylcholine | |
| | n | n | |
| Randomized | 57 | 58 | 115 |
| Treated | 56 | 54 | 110 |
| Completed | 55 | 53 | 108 |

Data were taken from Appendix F, Table 1.1-A

Note: The number of subjects randomized is based on the treatment group according to the randomization schedule. The number of subjects treated and completed is according to the treatment they actually received.

One (101007) subject was randomized to the rocuronium + Org 25969 group but received succinylcholine. Two (101006 and 101008) subjects were randomized to the succinylcholine group but received rocuronium and Org 25969.

Source: Table 4 of CSR, page 74

Demographics/Medical History/Physical Exam

Given the small size of the trial, the treatment groups were reasonably similar and any differences in baseline characteristics would not be expected to change the findings.

Drop-Outs

Five patients dropped out (2 in the Roc/Org group and 3 in the succinylcholine group). The Roc/Org patients withdrew consent. The succinylcholine patients had a cancellation of the surgery, surgeon's request, and due to scheduling error.

Two patients were treated but did not complete the study. One (roc/Org) was lost to follow up; one (succinylcholine) was discharged prior to completing the study and, presumably, lost to follow up.

Protocol Deviations

The major protocol violations are summarized in Table A25, taken verbatim from the clinical study report (page 76).

Table A25: Major protocol violations

| Major protocol violation | Treatment group | | | |
|---|------------------------------------|--|-----------------------------|--|
| | Rocuronium + Org 25969 (N = 55) | | Succinylcholine (N = 55) | |
| | n | (Subject no.) | n | (Subject no.) |
| One or more of the selected inclusion criteria not met | 1 | (105003) | 1 | (112004) |
| Violation of the randomization schedule | 1 | (101007) | 2 | (101006) (101008) |
| Administration of a neuromuscular blocking agent other than rocuronium or succinylcholine | 1 | (106027) | 0 | |
| Administration of a dose of rocuronium / Org 25969 / succinylcholine that deviated more than 10% from the dose prescribed in the protocol | 1 | (101011) | 0 | |
| Administration of Org 25969 more than 1 min from the time point specified in the protocol | 1 | (101002) | 0 | |
| Subject used medication expected to interfere with NMBAs, before scoring any efficacy variable | 18 | (103004) (103005) (103009) (103010) (106001) (106004) (106007) (106010) (106012) (106013) (106015) (109001) (109003) (109009) (111002) (112002) (113001) (116002) | 11 | (103002) (103003) (106005) (106006) (106008) (106009) (106014) (109002) (112001) (113002) (116001) |
| Total | 23 | | 14 | |

One patient randomized to receive roc/Org received succinylcholine and two patients assigned succinylcholine received roc/Org.

There was a numerical imbalance between the treatment assignment groups, predominantly patients who received drugs expected to interfere with NMBAs (mostly inhaled anesthetic agents). The roc/org treated patients had more interfering drugs. Since these drugs would be expected to enhance the effect of the NMBA, the fact that the Org-treated patients received more interfering drugs would have biased the study results against Org25969.

The other violations were insufficient in number to be expected to alter the results.

The majority of the minor protocol violations were due to the administration of possibly interfering drugs after some but not all of the efficacy parameters had been collected (as opposed to prior to scoring any efficacy variable). Seventeen patients in the roc/Org group were minor protocol violators compared to 11 in the succinylcholine group. For the reason stated above, this would be expected to bias against Org25969. The other two minor protocol violations were unreliable data in one patient per treatment group.

PRIMARY EFFICACY RESULTS

Table A26, below, extracted from the Clinical Study Report, shows the summary data for the primary efficacy endpoint, time from NMBA administration to recovery of T₁ to 10%.

Table A26: Primary efficacy results

| | | Treatment group | |
|------------------------|-------------|----------------------------------|---------------------------|
| | | Rocuronium + Org 25969 (N=55) | Succinylcholine (N=55) |
| Including imputed data | n | 55 | 55 |
| | Mean (SD) | 4:22 (0:44) | 7:04 (1:34) |
| | Median | 4:11 | 7:06 |
| | Min. – max. | 3:28 - 7:43 | 3:45 - 10:28 |
| Complete cases | n | 54 | 53 |
| | Mean (SD) | 4:21 (0:43) | 7:09 (1:33) |
| | Median | 4:11 | 7:11 |
| | Min. – max. | 3:28 - 7:43 | 3:45 - 10:28 |

Source: CSR, page 86

While the magnitude of the treatment effect was not as great as in Studies 301 and 302, the statistical analysis of the primary endpoint data (ANOVA) showed high statistical significance as shown in Table A27, following.

Table A27: Statistical analysis, Study 303

| | Trial 19.4.303 | |
|-------------------------------------|---|--|
| | Rocuronium + Org 25969 (16.0 mg.kg ⁻¹) | Succinylcholine (1.0 mg.kg ⁻¹) |
| Time to T₁ of 10% | | |
| n | 55 | 55 |
| Mean (SD) | 4.4 (0.7) | 7.1 (1.6) |
| Median | 4.2 | 7.1 |
| Min. – max. | 3.5 – 7.7 | 3.8 – 10.5 |
| p-value ^a | <0.0001 | |
| Time to T₁ of 90% | | |
| n | 55 | 55 |
| Mean (SD) | 6.2 (1.8) | 10.9 (2.4) |
| Median | 5.7 | 10.7 |
| Min. – max. | 4.2 – 13.6 | 5.0 – 16.2 |
| p-value ^a | <0.0001 | |

^aP-value obtained from a 2-way ANOVA on the time to T₁ 10% / 90%.

Source: Clinical Overview, page 57

Secondary Efficacy Endpoints

Summary statistics for the time from administration of the NMBA to return of T₁ to 90% is shown in Table A28, following.

Table A28: Time from the administration of NBMA to return of T₁ to 90%

| | | Treatment group | |
|------------------------|-------------|----------------------------------|---------------------------|
| | | Rocuronium + Org 25969 (N=55) | Succinylcholine (N=55) |
| Including imputed data | n | 55 | 55 |
| | Mean (SD) | 6:11 (1:50) | 10:56 (2:25) |
| | Median | 5:41 | 10:41 |
| | Min. – max. | 4:12 - 13:35 | 5:01 – 16:11 |
| Complete cases | n | 54 | 53 |
| | Mean (SD) | 6:08 (1:47) | 11:02 (2:24) |
| | Median | 5:39 | 10:53 |
| | Min. – max. | 4:12 - 13:35 | 5:01 - 16:11 |

Source: CSR, page 88

The analysis of the clinical signs of recovery showed that there was no difference between the quality of recovery between treatment groups (Table A29).

Table A29: Clinical signs of recovery

| | Time point ^{a)} | | | |
|---|--|--------------------------------|--|--------------------------------|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | Rocuronium + Org 25969 (N=55) n | Succinylcholine (N=55) n | Rocuronium + Org 25969 (N=55) n | Succinylcholine (N=55) N |
| Subject's level of consciousness | | | | |
| Awake and oriented | 25 | 27 | 50 | 53 |
| Arousable with minimal stimulation | 19 | 21 | 4 | 2 |
| Responsive only to tactile stimulation | 10 | 7 | 0 | 0 |
| Subject cooperative ^{b)} | | | | |
| No | 12 | 10 | 0 | 0 |
| Yes | 43 | 45 | 54 | 55 |
| Subject able to perform the 5-sec head lift | | | | |
| No | 5 | 3 | 0 | 0 |
| Yes | 39 | 42 | 54 | 55 |
| General muscle weakness | | | | |
| No | 38 | 39 | 54 | 54 |
| Yes | 6 | 6 | 0 | 1 |

^{a)} Data were taken from Appendix F, Table 6.2-B.1

- a) 1: prior to transfer to the recovery room after extubation
- 2: prior to discharge from the recovery room

- b) In case the subject was not cooperative, the 5-sec head lift test and general muscle weakness were not to be assessed.

Source: CSR, page 91

The other efficacy endpoints generally supported the primary.

REVIEWER COMMENTS

Study 303 studied generally healthy patients who required neuromuscular blockade for a short period of time (intubation). The study compared the offset of effect for an intubating dose of succinylcholine (1 mg/kg) versus a comparable dose of rocuronium (1.2 mg/kg) followed quickly (3 minutes, at maximum effect) by Org25969, 16 mg/kg. The depth of paralysis or intubating conditions were not systematically characterized although there is nothing to suggest that the paralysis achieved was different.

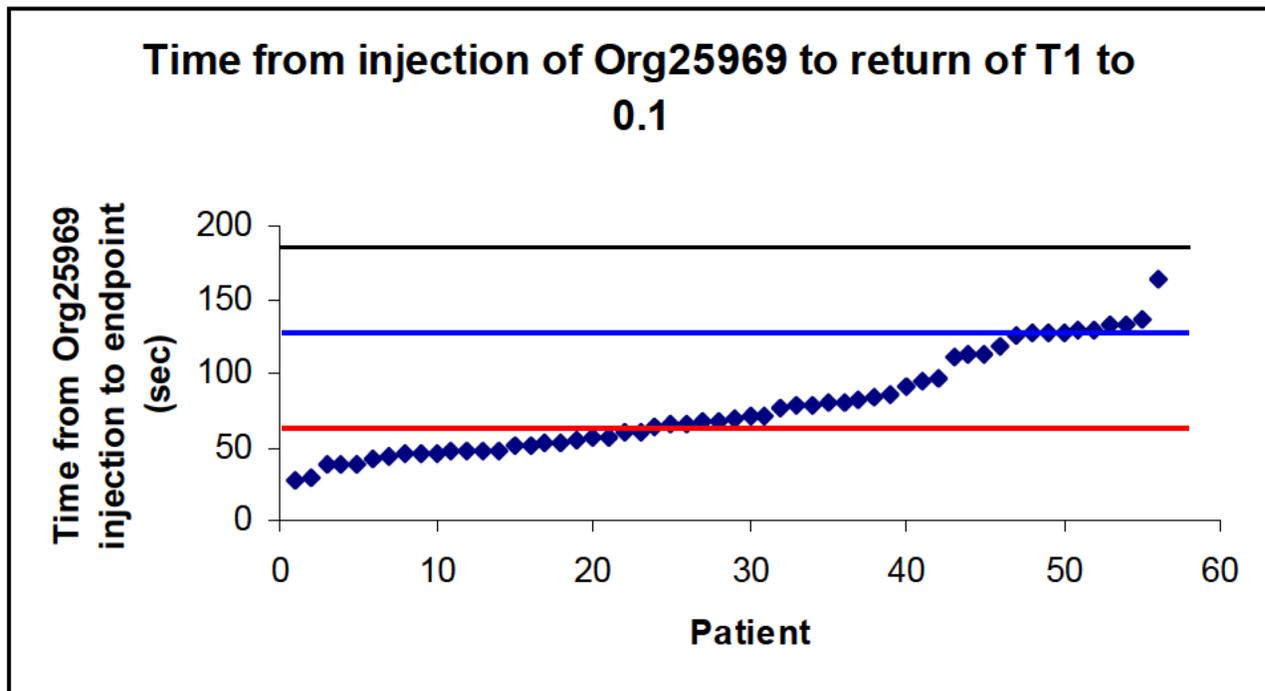
The primary efficacy endpoint was time from the NMBA administration to return of T₁ to 0.1. Because succinylcholine does not cause fade, it was not possible to assess the more clinically recognized T₄/T₁ ratio used in the other studies. Whether or not return of T₁ to 0.1 is clinically relevant is debatable.

The proportion of patients who were at risk of anoxic encephalopathy notwithstanding, this reviewer is concerned that the applicant is trying to extrapolate Study 303 to the cannot intubate/cannot ventilate (CI/CV) situation.

This reviewer notes that the mean time to return of T_1 to 0.1 was 4:22 in patients treated with rocuronium with a minimum of 3:28 and maximum of 7:43. The patient recorded as 7:43 was actually treated with succinylcholine in a treatment error.

To try to understand the data in another way, Figure A1, following, summarizes the data from the Org25969-treated patients, showing how each patient performed as a function of the time from Org25969 injection. Half of the patients endpointed in 60 seconds or less and 70% endpointed in less than 90 seconds.

Figure A1: Study 303, Time to endpoint from injection of Org25969



SAFETY FINDINGS

Again, Dr. Simone will conduct the review of safety. A brief summary of the safety data for this study follows.

- No deaths occurred.
- One serious adverse event occurred in a patient following administration of succinylcholine (pelvic hematoma).

- The adverse event rate did not appear significantly different between treatment arms from a qualitative or quantitative perspective.
 - One patient treated with Org25969 experienced an adverse event coded as ‘swelling face.’”
-

Number: 19.4.310

Protocol Title: Comparison of rocuronium and Org 25969 with cis-atracurium and neostigmine when neuromuscular block is reversed at reappearance of T₂

Primary Objective: To show a faster recovery from neuromuscular block with Org25969 after rocuronium compared to neostigmine after cisatracurium when administered at the reappearance of T₂

Secondary Objectives:

- To evaluate the safety of the 2 mg/kg Org25969 and neostigmine
- To demonstrate a faster onset of blockade after rocuronium than cisatracurium

Study Design: Randomized, safety assessor blinded, parallel group, active-controlled

Duration: This is a single dose study.

Sample Size: The sponsor planned to enroll 84 patients total.

The study was otherwise identical to Study 301 with the following notable exceptions:

- Treatment Groups:
 - Patients were randomized to one of two arms
 - Rocuronium 0.6 mg/kg and Org25969 2 mg/kg
 - Cisatracurium 0.15mg/kg and neostigmine 50 mcg/kg
- Exploratory Endpoints: Was to include a Reversal Agent Satisfaction Questionnaire (RASQ) for the person who gave anesthesia, nurse who provided care in the PACU, and all team members

Protocol Amendment:

Amendment 1 (September 2005) – Provided clarification for procedures regarding problems with successful extubation, assessment of recovery, drugs that might affect neuromuscular blockade, and assurance that continuous monitoring of the QT interval will occur.

RESULTS:

Patient Exposure

Study 310 was conducted at eight sites, all in Europe. A total of 84 patients were randomized of which 73 were treated and 72 completed. The ITT population numbered 73. Patient disposition per treatment group is summarized in Table A30, following.

Table A30: Patient disposition

| | Treatment group | | Total (n) |
|------------|----------------------|------------------------|--------------|
| | roc/Org 25969 (n) | cis/Neostigmine (n) | |
| Randomized | 40 | 44 | 84 |
| Treated | 34 | 39 | 73 |
| Completed | 33 | 39 | 72 |

Source: CSR, page 65

Demographics/Medical History/Concomitant Medications

- Because of the small size of this study, even by the standards of the Org25969 development program, the ability of randomization to normalize differences was limited.
- While there were some imbalances (e.g. the male:female ratio was 41:59 in the roc/Org arm and 59:41 in the atric/neostig arm) in the demographic characteristics, they would not be reasonable expected to affect the efficacy results.
- The medical histories were comparable between treatment groups.
- The anesthetic use was comparable between groups.
- None of the patients were ASA class 4.
- 72/73 patients were Caucasian as were 885 of the patients in the four pivotal trials.

Drop-Outs

- Twelve patients discontinued prematurely although 11 dropped out prior to treatment with study drug.
 - Reasons for dropout prior to treatment included problems with the TOF watch (N=7), withdrew consent (N = 1), lack of study drug in pharmacy (N=1), problems with laptop (N=1), surgery postponed (N=1).
 - The treated patient (110006) could not be contacted for the follow up assessment.

Protocol Deviations

Eight patients had major protocol deviations, four in each arm. The majority of the violations occurred because the study drug was not administered within the temporal constraints of the

protocol (2 in the Org arm; 3 in the neostigmine arm). Because of the balance between arms and small numbers, this reviewer does not believe that this affected the result.

Six patients had minor protocol violations, all related to unreliable data. The issues relating to unreliable data were successfully resolved as discussed in Section 6.1.4.

PRIMARY EFFICACY RESULTS

Summary statistics for the primary efficacy endpoint are in Table A31, following. It is interesting to note that the treatment effect size is considerably smaller than in Study 301 (roc/Org vs. roc/neostigmine and vec/Org vs. vec/neostigmine). In those studies, the mean recovery time for the rocuronium/Org25969-treated patients was in the range of 90 seconds compared to ~120 seconds here. The comparator group in Study 310 is cis-atracurium/neostigmine and the recovery times were approximately 8:50 compared to ~18:30 in Study 301. While the comparator group had a shorter recovery time, the statistical analysis showed a high degree of statistical significance (Table A32).

Table A31: Summary statistics for time to recovery of $T_4/T_1 = 0.9$

| | | Treatment group | |
|------------------------|----------------|-------------------------|---------------------------|
| | | roc/Org 25969 (N=34) | cis/Neostigmine (N=39) |
| Including imputed data | n | 34 | 39 |
| | Geometric Mean | 2:02 | 8:46 |
| | Mean (SD) | 2:18 (1:20) | 10:09 (6:10) |
| | Median | 1:55 | 7:12 |
| | Min. – max. | 0:41 - 6:24 | 4:12 - 28:14 |
| Complete cases | n | 32 | 34 |
| | Geometric Mean | 1:55 | 8:58 |
| | Mean (SD) | 2:08 (1:09) | 10:23 (6:20) |
| | Median | 1:55 | 7:15 |
| | Min. – max. | 0:41 - 6:24 | 4:12 - 28:14 |

Source: CSR, page 75

Table A32: Statistical analysis, time to recovery of $T_4/T_1 = 0.9$

| | Trial 19.4.310 ^b | |
|----------------------|--|--|
| | Rocuronium + Org 25969 (2.0 mg.kg ⁻¹) | Cisatracurium + Neostigmine (50 µg.kg ⁻¹) |
| n | 34 | 39 |
| Geometric Mean | 2.0 | 8.8 |
| 95% CI | 1.7 – 2.4 | 7.4 – 10.4 |
| Median | 1.9 | 7.2 |
| Min. – max. | 0.7 – 6.4 | 4.2 – 28.2 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

^b Anesthetic regimen included induction and maintenance with propofol.

Source: Clinical Overview, page 51

Similar to Study 301, efficacy of Org25969 did not appear to be affected by the use of maintenance doses of rocuronium (Table A33).

Table A33: Effect of a single versus maintenance doses of rocuronium

| | | Intubating dose only | Intubating dose and maintenance dose(s) |
|------------------------|----------------|----------------------|--|
| Including imputed data | n | 18 | 16 |
| | Geometric mean | 2:10 | 1:53 |
| | Mean (SD) | 2:33 (1:34) | 2:02 (0:58) |
| | Median | 2:16 | 1:49 |
| | Min. – max. | 0:41 - 6:24 | 1:07 - 5:07 |
| Complete cases | n | 17 | 15 |
| | Geometric mean | 2:04 | 1:45 |
| | Mean (SD) | 2:24 (1:28) | 1:50 (0:32) |
| | Median | 2:11 | 1:43 |
| | Min. – max. | 0:41 - 6:24 | 1:07 - 3:05 |

Source: CSR, page 77

Secondary Efficacy Endpoints

The secondary endpoints supported the primary endpoint.

Table A34, following, shows that there was no significant difference in the quality of the recovery from neuromuscular blockade between the treatment groups.

Table A34: Clinical signs of recovery, Study 310

| | Time point ^{a)} | | | |
|--|------------------------------|--------------------------------|------------------------------|--|
| | 1 | | 2 | |
| | Treatment group | | Treatment group | |
| | roc/Org 25969 (N=34) n | cis/Neostigmine (N=39) n | roc/Org 25969 (N=34) n | cis/Neostigmine (N=39) n ^{c)} |
| Subject's level of consciousness | | | | |
| Awake and orientated | 22 | 27 | 33 | 35 |
| Arousable with minimal stimulation | 7 | 7 | 1 | 2 |
| Responsive only to tactile stimulation | 5 | 5 | 0 | 0 |
| Subject cooperative | | | | |
| Yes | 26 | 31 | 34 | 37 |
| No | 8 | 8 | 0 | 0 |
| Subject able to perform the 5 s. head lift ^{b)} | | | | |
| Yes | 25 | 31 | 34 | 37 |
| No | 1 | 0 | 0 | 0 |
| General muscle weakness ^{b)} | | | | |
| No | 23 | 29 | 34 | 37 |
| Yes | 3 | 2 | 0 | 0 |

Data were taken from Appendix F, Table 6.2-C.1

a) 1: prior to transfer to the recovery room after extubation, 2: prior to discharge from the recovery room

b) If subject was not cooperative, the headlift test and general muscle weakness were not assessed

c) for two subjects, Subjects 107001 and 107003 (both cis/neostigmine) the clinical signs of recovery prior to discharge are missing.

Source: CSR, page 80

REVIEWER COMMENTS

Study 310 was identical to Study 301 with the exception of the control group. It demonstrated that Org25969, 2 mg/kg reversed a neuromuscular blockade (return of T2) more rapidly than neostigmine when cis-atracurium was used as the NMBA. The study provides replication of the efficacy observed in Study 301.

SAFETY FINDINGS

Dr. Simone has completed a review of the safety findings. A brief summary of the study data for this study follows:

- The raw adverse event rate was similar in both treatment groups.
- No deaths or serious adverse events occurred.
- There was an imbalance (12% for Org25969 versus 3% for neostigmine) in adverse events believed to be drug-related.
- One patient in the Org group experienced a “swelling face.”

REFERENCES

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Robert Shibuya
6/24/2008 11:55:35 AM
MEDICAL OFFICER

Rigoberto Roca
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