FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Background Materials

Meeting of the
Anesthetic and Analgesic Drug Products Advisory Committee
(AADPAC)

FDA White Oak Campus,
10903 New Hampshire Ave.
Bldg. 31 Conference Center
The Great Room (Rm.1503)
Silver Spring, MD 20993–0002

November 6, 2015

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 022225 to this Advisory Committee in order to gain the Committee's insights and opinions concerning the proposed drug product, Sugammadex injection for the reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

M E M O R A N D U M

DATE: October 9, 2015

FROM: Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

RE: Overview of the November 6, 2015, AADPAC Meeting to Discuss NDA 022225 (Sugammadex)

At this meeting of the AADPAC, we will be discussing Organon's NDA 022225 for sugammadex sodium injection and their submission in response to the Not Approvable action letter issued on July 31, 2008. The originally proposed indications were for the routine reversal of what the Applicant referred to as "shallow" and "profound" neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at three minutes after administration of rocuronium for the clinical scenario of "cannot intubate/cannot ventilate." With this submission, the Applicant has modified the proposed indication to:

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

Although the Applicant has modified the indication as noted above, they are proposing to describe the use of the highest dose in the Dosing and Administration section of the label for the purpose of "an urgent or emergent need to reverse neuromuscular blockade following administration of rocuronium."

During the first review cycle, this application was presented at the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) meeting held on March 11, 2008. This background package will include a brief review of the prior discussions during that advisory committee meeting, and an update of the data from new studies that have been added to the safety database. The primary focus of this background package will be on the safety issues communicated to the Applicant during the first review cycle, which included signals for hypersensitivity/anaphylaxis and cardiac dysrhythmias.

With respect to the issue of hypersensitivity/anaphylaxis, the Agency and the Applicant will each present their analyses of a repeat-dose clinical study conducted in healthy volunteers that was designed to evaluate the risks of hypersensitivity reactions with repeat exposure to sugammadex (Trial P101). Analyses of the Applicant's post-marketing safety database and the updated pooled clinical study database will also be presented.

Issues related to cardiac dysrhythmias emerged as a potential safety signal following the first review cycle. The Applicant has performed an evaluation of their pooled and integrated analysis of adverse events across the Phase 1 to 3 studies, and an analysis of cases in their post-marketing database. The Applicant and Agency will present their perspectives on the updated safety information.

At the November 6, 2015, meeting, the Committee will be asked to consider the following discussion points:

1. **Whether the Applicant presented sufficient information to characterize the risk of hypersensitivity / anaphylaxis.**

2. **Whether the Applicant presented sufficient information to characterize the risk of cardiac dysrrythmias.**

3. **Whether there are issues not addressed in the supportive data that warrant the need for additional studies and, if so, should these studies be conducted before or after approval.**

4. **Whether the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of this application.**

The Division and the Agency are grateful to the members of the committee and our invited guests for taking time from your busy schedules to participate in this important meeting. Thank you in advance for your advice, which will aid us in making the most informed and appropriate decision possible.

2. Executive Summary

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 a 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 reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.

The proposed dosing regimens, which are to be administered as a single bolus injection, are as follows:

- A dose of 4 mg/kg is recommended if recovery has reached 1 to 2 post tetanic counts (PTC) (deep blockade) following administration of rocuronium- or vecuronium-induced blockade.

- A dose of 2 mg/kg is only recommended if spontaneous recovery has reached the reappearance of T2 (moderate blockade) following rocuronium- or vecuronium-induced blockade.

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

This background document will briefly chronicle the development and regulatory history of sugammadex, including the contents of the original NDA submission, and the issues raised by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) during the course of the NDA review, and by members of the Anesthetic Life Support Drugs Advisory Committee (ALSDAC) during the meeting held on March 11, 2008. This document will also highlight the Applicant's response to key outstanding issues, including hypersensitivity/anaphylaxis, cardiac dysrhythmias, and coagulation disorders that were noted in the original NDA review. Finally, while DAAAP's review of these issues is still ongoing, highlights of our perspective on these issues will be presented.

3. Summary of FDA Review of Clinical Efficacy and Safety

A. Preliminary Findings from NDA 022225 prior to the March 2008 Meeting of the Anesthetic and Life Support Drug Advisory Committee (ALSDAC)

Efficacy

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). The Applicant's method to assess the status of the neuromuscular blockade was the evaluation of the degree of contraction of the adductor pollicis after a "train-of-four" (ToF) stimulation of the ulnar nerve.

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

	Study 301	Study 302	Study 310	Study 303
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.

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 NDA 022225 Submission

Study #	NMB	Time to ToF = 0.9 (m:sec)		p-value
		Sugammadex	Neostigmine	
301	Roc Vec	1:29 2:48	18:30 16:48	<0.0001
302	Roc Vec	2:50 4:28	50:22 66:12	<0.0001
310	Roc Cis-Atr	2:02 -	- 8:46	<0.0001
303	Roc Succinylcholine - (no reversal)	4:22 7:04	- -	<0.0001

Abbreviations: Cis-atr = Cis-Atracurium, m:sec = time in minutes:seconds to primary outcome was achieved, NMB = neuromuscular blocking agent, Roc = Rocuronium, Vec = Vecuronium.

Safety

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 NDA 022225 by Dose

	Pbo	Sugammadex (mg/kg)										Neostigmine (mcg/kg)	
Dose	**N/A**	**0.5**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**32**	**50**	**70**
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**

Pbo = Placebo
N/A = not applicable

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 appropriately designed and conducted thorough QT studies, which 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 March 2008 ALSDAC meeting

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" (CICV) 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 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 (*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.

The ALSDAC unanimously recommended approval of sugammadex. However, a detailed review of the drug hypersensitivity data were 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.

C. Division's Assessment of the Original 2007 NDA Submission

DAAAP agreed with the finding of the 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.

This section describes events following the ALSDAC meeting related to the two main safety issues described above, as well as a potential issue related to coagulation that was identified during the first review cycle, but after the ALSDAC meeting, and therefore not discussed at the ALSDAC meeting. Also described is the communication of deficiencies sent to the Applicant on July 31, 2008.

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 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[1] criteria for anaphylaxis (see Table 5 on p. 14), 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 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.

[1] The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network

The consultants 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.

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 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, and another 2 possible cases in surgical patients identified from the overall sugammadex clinical database. The safety database in the original NDA submission 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).

Due to the number of confounding factors present in the Phase 2 and Phase 3 data, which made adjudication of the 2 cases difficult, DPARP only included the data from the Phase 1 studies in their calculation of the anaphylaxis rate. 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’s conclusion was that this was a relatively high frequency of anaphylaxis. Furthermore, there was concern that this might actually be an underestimate, 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.

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 meeting, the Division noted that a substantial number of post-marketing 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. 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.

Coagulation Parameters

A third issue arising from the first review cycle, but after the meeting of the 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 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 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. 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 warranted a formal investigation as to the effects of sugammadex on coagulation in patients undergoing a variety of surgical procedures.

The Not Approvable letter requested that the Applicant provide studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures in their Complete Response submission. The studies were to 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.

D. Applicant's Complete Response and the Division's Preliminary Assessment

The updated sugammadex clinical development program submitted in the Complete Response on June 19, 2015, consisted of 58 studies. The cumulative database for sugammadex contains a total of 5,999 subject exposures to IV sugammadex in 4453 unique subjects as reported by the applicant. 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 urgent reversal of rocuronium.

The Applicant's response and DAAAP's preliminary reviews follow. Further consultative input was provided on the hypersensitivity issue by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) and input on the coagulation issue was provided by the Division of Hematology and Oncology Products (DHOP) at the FDA.

Hypersensitivity/Anaphylaxis

To address the hypersensitivity issue, the Applicant conducted a trial in healthy volunteers to evaluate the risk 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 (Trial P06042). Adjudication of hypersensitivity cases was reportedly performed by a blinded, independent group. Additional assessments 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) were also included in Trial P06042.

During a routine inspection by the Office of Scientific Investigations, the monitoring and documentation of the trial raised concerns about the potential unblinding of investigators to treatment assignment, limiting the utility of the data from the study. Subsequently, the Applicant conducted another repeat-dose hypersensitivity study (Trial P101). Section 3.G of this document contains a summary of the inspections conducted by the team from the Office of Scientific Investigations.

The results from Trial P101 were reviewed by members of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). Their overall conclusions can be found in their consultation report in Section 6 of this document.

The Applicant and DPARP will present their perspectives on these recent data and analyses. The Committee will be asked to discuss whether the risk of these events has

been adequately characterized and, if not, what additional information should be required to support the approval of this application.

Cardiac adverse events

Based on their integrated analysis of AEs across the Phase 1 to 3 studies, the Applicant concluded that sugammadex did not show any increase in the incidence of arrhythmia-related AEs in healthy subjects and surgical patients when compared to placebo. The Applicant also conducted an analysis with respect to neostigmine, and drew similar conclusions from that analysis.

The Applicant noted that sugammadex is marketed in more than 50 countries, and the reports of post-marketing AEs that were identified as arrhythmias are consistent with what one might expect for peri/post-operative patients and with what has been observed in the clinical studies. Thus, they concluded that sugammadex does not pose an increased risk for cardiac arrhythmias when compared to placebo.

Regarding bradycardia, there appears to be a small mean overall decrease of heart rate when sugammadex is administered for the reversal of some NMBAs, and it is more consistently observable with rocuronium than in the setting of vecuronium neuromuscular blockade. Furthermore, this effect seems to translate into rare bradycardic events that would be readily detected in the peri-operative setting. Importantly, the post-marketing safety surveillance data suggest that rapid resolution occurs after intervention with an anticholinergic agent (e.g., atropine).

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.

The Applicant also 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 the 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 preanesthesia 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.

FDA's Interdisciplinary Review Team (IRT) 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 Division also sought input from the IRT regarding other arrhythmias observed in the clinical trials. They noted that, with respect to the other serious cardiac AEs, other than bradycardia in the pooled Phase 1-3 data compared to placebo and atrial fibrillation in the pooled Phase1-3 trials, it is hard to come to a conclusion regarding the other isolated events with no dose-response. The Division considered the Applicant's explanation of the incidence being representative of the post-surgical population to be reasonable.

Given that the clinical trials were not designed to compare the incidence of cardiac arrhythmias between treatment with sugammadex, placebo, and neostigmine, it is not possible to attribute causality of the arrhythmias to the individual treatments as opposed to an underlying medical condition, the effects of other anesthetic agents, or a complication from the surgical procedure. Furthermore, the evidence from the clinical trials: the timing of the arrhythmias relative to administration of sugammadex (i.e., usually up to several minutes), the clinical setting in which they occurred (i.e., with cardiac monitoring and well qualified medical staff immediately available to intervene),

and that most resolved with minimal to no intervention and without sequelae, does not warrant further evaluation of these adverse events provided clinicians are made aware of their possibility and the Applicant continues to monitor them in the post-marketing setting.

The Applicant states that, since its approval for marketing outside the U.S. in 2008, more than 12.1 million vials of sugammadex have been sold, and estimates that approximately 11.5 million patients have been exposed as of March 2015. During this period, the Applicant's post-marketing adverse event database has accumulated 1200 case reports describing 2,301 adverse events associated with the administration of sugammadex. Among the reported adverse events were the 152 cardiac arrhythmias listed in the table below (Table 4).

Table 4 Number of Cardiac Rhythm Abnormalities Reported in Post-marketing database

Cardiac Rhythm Abnormality (preferred term)	Number of events
Atrial fibrillation	4
Atrialventricular block	13
Bradycardia	61
Cardiac/cardiorespiratory arrest	35
ST segment changes	5
Supraventricular tachycardia/extrasystoles	5
Tachycardia	20
Ventricular fibrillation	6
Ventricular tachycardia	3
Total	**152**

The post marketing data somewhat mimic the data from the clinical trials in that bradycardia and tachycardia were the most common AEs. Given the limitations associated with the reporting of post-marketing data (e.g., underreporting of adverse events, unknown number of exposures, and provision of limited information regarding concomitant medications, comorbidities, outcomes, and other relevant medical information in many of the reports) and the lack of alternative treatment data for comparison, it is not possible to draw any solid conclusions with the information. However, several observations can be made:

1. Some of these arrhythmias occurred in conjunction with anaphylactic reactions.
2. Most of the reactions occurred within minutes of sugammadex administration.
3. Most of the reactions resolved with limited or no intervention.
4. Of the 11 fatalities reported in the post-marketing database, three were associated with arrhythmias and cardiac arrest.

a. A 90-year-old female dialysis patient died 5 days after her surgery to remove a peritoneal catheter.
b. A 76-year-old female with a history of gastric cancer and pulmonary edema who presented for surgical removal of blood clots from a chest tube. She experienced cardiac arrest 2 minutes after sugammadex injection; however, the reporter attributed the cardiac arrest to massive pulmonary edema, which in turn was attributed to the sugammadex.
c. A 72-year-old male underwent a pancreaticoduodenectomy for cancer of duodenal papilla. Experienced a hypertensive episode and subsequent myocardial infarction.

At this juncture, it appears the Applicant has adequately demonstrated that sugammadex treatment does not cause significant QTc prolongation and is not associated with cardiac arrhythmias to a clinically relevant degree compared to placebo and neostigmine. The post-marketing safety data for sugammadex do not appear to provide any evidence to the contrary. Given the occurrence of any arrhythmias following administration of sugammadex, it seems appropriate to inform clinicians of the possibility to assure an adequate level of vigilance and to continue to monitor for these adverse events in the post-marketing setting to determine whether any additional actions may be required in the future.

Coagulation/Bleeding

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 post-marketing 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 5). 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 5 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 n (%)	Total (Major + Non-major) n (%)	Major n (%)	Total (Major + Non-major) n (%)
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 unl kely and one possible related, the subject was counted in the 'possible' row, and not in the 'unlikely' row.
Source: Applicant's Study Report submission, page 111

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 6). 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 6 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: Applicant's Study Report submission, page 114

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 7).

Table 7 Number of Subjects with at Least One Treatment Emergent Adverse Event

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 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: Applicant's Study Report submission, page 140

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 (≤ 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 post-marketing cases of hemorrhage events cumulative to April 2015. There were a total of 12 reports. 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 post-marketing 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. We agree with these conclusions and do not think that additional discussion or analyses are necessary at this time.

E. Post-Marketing Safety Findings

Sugammadex was first authorized for use on July 25, 2008, in the European Union. Since that time, it has received marketing authorization in over 50 countries including Japan, Australia, New Zealand, and nations in Central and South America, Asia, the Middle East, and Africa. During the period from July 25, 2008 through March 31, 2015, the Applicant estimates that a total of 12,106,246 vials of sugammadex have been distributed. During this period, the Applicant's post-marketing adverse event database has accumulated 1200 case reports describing 2,301 adverse events associated with the administration of sugammadex. Three observations were made in the high level review of this database:

1. There were approximately 300 hypersensitivity reactions reported. Some of these were associated with cardiac arrhythmias, cardiac arrest, shock, and the need for infusions of vasoactive drugs, reintubation with mechanical ventilation, and admission to the intensive care unit. None of the events were reported to have resulted in fatality. Most of these adverse events occurred within minutes of the administration of sugammadex.
2. There were over 150 adverse reactions related to cardiac rate and rhythm abnormalities. These included potentially life-threatening supraventricular and ventricular arrhythmias, cardiac arrest, and reports of fatal outcomes. A substantial number of these reactions were associated with the cases of anaphylactic reactions.
3. There were more than 75 adverse reactions related to sugammadex being ineffective, having a delayed effect, or having a decreased effect. Seven of these met the criteria for serious adverse events. Most of these events required prolonged ventilation and resolved without subsequent morbidity or mortality.

There are a number of shortcomings associated with post-marketing safety data that limit their utility in characterizing the risks associated with a drug product. Some of these include: the under-reporting of adverse events, the inability to accurately assess the number of exposures to the drug product, and the limited amounts of information provided in many of the adverse reactions. These make it difficult, at best, to accurately determine incidence rates for adverse reactions and to be able to ascribe, with certainty, a reaction to a particular drug product. Given these limitations, the review of the post-marketing data to date did not identify any new safety concerns associated with the use of sugammadex or any evidence that the risks of anaphylaxis or cardiac arrhythmias was greater than observed in the clinical development program.

F. Clinical Trial Comparing Outcomes for Sugammadex and Neostigmine

The Applicant has conducted a clinical trial (P07981) designed 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 neostigmine. The trial also investigated whether there was a difference between the two treatments for the following:

1. time from start of study medication administration to operating room (OR) discharge
2. time from start of study medication administration to extubation
3. time from start of study medication administration to PACU discharge readiness
4. time from PACU entry to PACU discharge ready
5. time from PACU entry to hospital discharge
6. grip strength
7. pulmonary function tests, including:
    - forced inspiratory volume in 1 second (FIV_1)
    - forced expiratory volume in 1 second (FEV_1)
    - maximal expiratory flow and maximal inspiratory flow at 50% (MEF_{50}/MIF_{50})
    - Forced vital capacity (FVC)

From this randomized, parallel-group, single-site trial, the Applicant found that the incidences of residual neuromuscular blockade at entry to the PACU was 0% for sugammadex and 43% for neostigmine ($p<0.0001$). They also found there was a 17% reduction in the time from administration of the reversal agent to the time the patient was ready for discharge from the OR for patients treated with sugammadex (the geometric means were 15 minutes and 18 minutes for sugammadex and neostigmine, respectively). There was also a 4 minute difference in the geometric mean time to extubation favoring treatment with sugammadex.

Beyond the differences noted above, the trial results demonstrated no significant difference between the treatments for:

1. time from administration of reversal agent to PACU discharge readiness
2. time spent in the PACU
3. time from PACU entry to hospital discharge
4. grip strength both on the initial measurement made in the PACU and that made when the RASS returned to 0 ± 1
5. all PFT parameters, both on the initial measurement made in the PACU and that made when the RASS returned to 0 ± 1
6. treatment emergent adverse events and serious adverse events

In summary, the trial demonstrated that, on entry to the PACU, significantly less residual paralysis is associated with reversal from neuromuscular blockade using sugammadex compared to neostigmine. However, there were no significant differences between the two treatments for measures of strength, pulmonary function, or adverse event profiles indicating that the differences in residual paralysis are not associated with a clinically relevant benefit and that incomplete reversal of neuromuscular blockade with neostigmine does not pose a clinically relevant risk.

G. Summary of Inspection Findings

Second Review Cycle (December 21, 2012 to September 20, 2013)
The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) had requested a consult with the Office of Scientific Investigations (OSI) for clinical site inspections as part of the December 21, 2012, NDA submission. The clinical site inspections covered two studies. During the inspection of Study P06042, "*A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Incidence of Hypersensitivity after Repeated Single Dose Administrations of Sugammadex (SCH 900616) in Healthy Subjects*", the inspections found protocol deviations and other objectionable findings that could impact the validity, reliability, and integrity of the data. One of the four study sites, the single US site, was no longer in existence but source records (with the exception of data for 10 subjects) were available for inspection. This inspection resulted in a Warning Letter (link: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm408996.htm) and the data were considered unreliable. The inspection of the UK site revealed several objectionable conditions and the data were also deemed unreliable. An OAI-Untitled Letter was issued (in lieu of a Warning Letter because the investigator is located outside of the United States and did not conduct the study under an IND). The site in the Netherlands was also no longer in existence but source records were available for inspection. At the Netherlands site and at the site in Germany, there were cases where the dosing investigator made an initial inquiry as to potential adverse events and instances where the investigator who evaluated adverse events also dosed the subjects. These protocol violations potentially resulted in biased reporting of primary endpoint data at the site level. The Applicant failed to report significant protocol violations in the Clinical Study Report submitted to FDA. The inspection of the Applicant resulted in an OAI-Untitled Letter (in lieu of a Warning Letter because the Applicant's written response completely addressed all of the violations and detailed the corrective actions that had already been taken).

Third Review Cycle (October 22, 2014 to April 22, 2015)
The Applicant received a Complete Response letter on September 20, 2013, and in order to address the deficiencies identified in Study P06042, the Applicant conducted a new study, Study P101 "*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*". DAAAP requested a consult with OSI for clinical site inspections as part of the October 22, 2014, resubmission of NDA 22225. Study P101 was conducted at six trial centers, four in the United States and two in Belgium. Two US sites and the Applicant, Merck, were inspected. During the inspection of the Applicant, it was discovered that, contrary to the protocol requirement, the Applicant granted one clinical site a general authorization regarding site-staff study conduct, permitting staff responsible for dosing to perform adverse event assessments and hypersensitivity assessments. It was also discovered that the Applicant's staff from the Department of Biostatistics and Research Decision

Sciences (BARDS) had access to the randomization allocation of all 375 subjects in the treatment phase of Study P101 while the study was ongoing and prior to database lock. The Applicant failed to provide a complete description of the extent of the unblinding in the Clinical Study Report to FDA. Attestations of the statisticians and programmers could not be confirmed due to the deletion of the data files in question, lack of an audit trail of their activities involving the unblinded variable, and the inability to interview all staff involved. The inspection of the Applicant resulted in an OAI-Untitled Letter, in lieu of a Warning Letter because there was no evidence that the Applicant changed any data after the unblinding. Because of the potential unblinding of data prior to database lock, OSI recommended that the review team consider requesting sensitivity analyses with a set of plausible possibilities, including analyses of the data for the time period before and after the date of potential unblinding. In addition, although no significant issues were noted at the two clinical sites initially inspected, it was recommended that the additional four clinical sites be inspected to determine whether there was any evidence of unblinding at the site level.

Current Review Cycle (June 19, 2015 to the present)

The Applicant received a CR letter on April 22, 2015, and DAAAP consulted OSI for clinical site inspections as part of the June 19, 2015, resubmission of NDA 22225. There were no new Applicant-initiated clinical studies. Inspection of the four remaining sites involved with Study P101 was requested. All inspections have been concluded. There was no documentation at the sites of any discussion of allocation by the site and Applicant staff. There was no evidence of unblinding at the sites. The inspections did not uncover any serious deviations/findings that would impact the validity or reliability of the submitted data. OSI has concluded that the inspectional findings of these sites support validity of data as reported by the Applicant under NDA 22225.

4. Overall Summary

Materials submitted by Organon USA Inc., a subsidiary of Merck & Co., Inc., to address issues related to safety of sugammadex will be presented and discussed at this meeting of the AADPAC. A summary of the efficacy program and updated safety database will precede discussion on specific safety topics. The safety discussion will focus primarily on concerns related to hypersensitivity/anaphylaxis and cardiac dysrhythmias. Following the discussion, the panel will vote on questions related to these topics as well as on the overall risk benefit of sugammadex.

5. Topics for Advisory Committee Discussion

At the November 6, 2015, meeting, the Committee will be asked to consider the following discussion points:

1. **Whether the Applicant presented sufficient information to characterize the risk of hypersensitivity / anaphylaxis.**

2. **Whether the Applicant presented sufficient information to characterize the risk of cardiac dysrrythmias.**

3. **Whether there are issues not addressed in the supportive data that warrant the need for additional studies and, if so, should these studies be conducted before or after approval.**

4. **Whether the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of this application.**

6. Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Consultation

Date:	September 16, 2015
To:	Rigoberto Roca, MD, Deputy Director, 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 for injection (Org 25969, SCH 900616, MK-8616)

General Information

NDA#:	22225
Applicant:	Merck & Co., Inc., (on behalf of Organon USA, Inc., a subsidiary of Merck)
Drug Product:	Sugammadex for injection (Org 25969, SCH 900616, MK-8616)
Request From:	Diana Walker, Regulatory Project Manager, DAAAP
Request Date:	June 25, 2015
Date Received:	June 25, 2015
Materials Reviewed:	NDA 22225 Sensitivity Analysis June 19, 2015, Resubmission October 22, 2014, Resubmission December 20, 2012, DPARP Medical Officer Consultations dated May 2008, Jun. 2008, Nov. 2008, Apr. 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 (MK-8616) for injection, which is being proposed for marketing in the US as a selective relaxant binding agent indicated for reversal of moderate neuromuscular blockade (sugammadex dose: 2 mg/kg at the reappearance of T2) and deep neuromuscular blockade (sugammadex dose: 4 mg/kg at 1-2 post-tetanic counts [PTCs]) induced by rocuronium- or vecuronium. A higher sugammadex dose of 16 mg/kg is only recommended if there is an urgent or emergent need to reverse NMB following administration of rocuronium. 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 Applicant submitted a Complete Response on December 20, 2012, having conducted a repeat-dose hypersensitivity study (Study P06042) to evaluate the risk of anaphylaxis with sugammadex; however, this submission was not approved as concerns related to potential unblinding of investigators to treatment assignment limited the utility of the data. The Applicant then submitted a new repeat-dose hypersensitivity study (Study P101) on October 22, 2014; however, there were concerns regarding the potential unblinding of statisticians to treatment assignment identified during the review cycle and the application was not approved. Most recently, the Applicant submitted a Complete Response on June 19, 2015, which included a sensitivity analysis, of Study P101 data, which will be briefly described in the body of this consultative review. Both the sensitivity analysis performed and the additional site inspections conducted did not reveal any significant concerns regarding the data integrity of Study P101; accordingly, the original data and analysis from Study P101 was deemed valid and is the focus of this 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 the repeat-dose hypersensitivity 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 April 22, 2015, over 12 million doses of sugammadex are estimated to have been distributed worldwide. Therefore, a brief summary of post-marketing reports will 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 had 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 <u>one</u> 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 ***<u>likely</u>*** 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 ***<u>known</u>*** 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 is designed with a negatively charged core that specifically attracts the positively charged ammonium groups of rocuronium and vecuronium. Sugammadex sequesters 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 included 209 healthy volunteers and 2,024 patients who received single doses of sugammadex ranging from 0.1 mg/kg to 96 mg/kg. 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 11 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, 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 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 healthy subjects experienced rash, one with pruritus, however, the potential association with sugammadex was unclear as the rashes appeared several hours after infusion. 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. Sensitization would 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 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 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.

D. NDA Resubmission - Complete Response #1 (December 20, 2012)

The Applicant submitted a complete response on December 20, 2012 and as a part of the resubmission, the Applicant provided the results of a repeat-dose clinical study (P06042), as outlined in the Complete Response letter. However, due to concerns that investigators may have been unblinded to treatment assignment, the data were deemed to be of limited utility in defining the frequency of anaphylaxis/hypersensitivity events associated with sugammadex administration. As a result, a Complete Response (CR) letter was issued on September 20, 2013, outlining the same deficiencies as in the first letter. As our ability to interpret the data was limited, and the Applicant has conducted a new study (Study P101), the results of Study P06042 will not be presented in this review (with the exception of the mechanistic studies, some of which were not repeated in the new study). This consultative review will focus on the newly conducted study (P101) submitted in the Applicant's second Complete Response on October 22, 2014 and briefly summarize the sensitivity analysis conducted as part of the most recent Complete Response submitted on June 19, 2015.

i) Mechanistic Study Review

As a part of study P06042, the Applicant 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). A brief description of the results is provided below, as the results are largely objective and therefore, less likely to be influenced by potential un-blinding.

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.

IV. Repeat Dose Data to Evaluate Anaphylaxis and Hypersensitivity Reactions

The focus of this review is the results of Study P101, as presented below. After discussion of the study results, a brief summary of the most recently submitted sensitivity analysis is provided in order to support these results.

A. Study P101; NDA Resubmission-Complete Response #2 (October 22, 2014)

As a part of the resubmission, the Applicant has provided the results of a repeat-dose clinical study (P101), as outlined in the Not Approvable Letter. Once again, DPARP was asked to review and provide feedback on the clinical study 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.

i) Study Overview

Study P101 was 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 age 18-55 years, conducted at 6 trial centers: 4 in the United States and 2 in Belgium. 375 subjects were to be randomized to treatment with 16 mg/kg sugammadex, 4 mg/kg sugammadex, or placebo in a 2:2:1 ratio. Subjects were screened approximately 4 weeks prior to randomization. On Day -1, baseline assessments were performed to confirm eligibility. Randomization was

performed prior to dosing in Period 1 in randomized blocks of 5. Eligible subjects were randomized to receive one of three treatments.

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

Subjects were admitted to the study center the day before each scheduled dose and were discharged from the unit the morning of the day after each dose. There was approximately a 5- week washout period between dosing periods 1, 2 and 3. The duration of the study was approximately 6 months.

The Targeted Hypersensitivity Assessment (THA), outlined in Appendix 3, was the instrument used to identify cases of potential hypersensitivity for adjudication by an external blinded Clinical Adjudication Committee (CAC) composed of experts in hypersensitivity. A physician or an appropriate clinical designate who did not administer study drug or prepare medication was responsible for collecting the THA at 0.5, 4, and 24 hours after dose, or the first time point could be triggered earlier by presence of any AE in Signs and Symptoms of Hypersensitivity (outlined in Appendix 2). Vital signs, adverse events (AEs), concomitant medications, and laboratory tests were recorded throughout the study. Additionally, antibody testing and serum tryptase levels were assessed in patients with hypersensitivity reactions and in a subset of non-reacting patients for comparison.

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:(i) the subject must NOT experience an AE of hypotension, (ii) the signs and symptoms of hypersensitivity must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment, and (iii) 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.

ii) Patient Disposition

Patient disposition for study P101 is summarized in Table 1.

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			
Adverse Events	3 (3.9)	3 (2.0)	5 (3.4)
Lost to Follow Up	2 (2.6)	4 (2.6)	6 (4.1)
Physician Decision	1 (1.3)	0	0
Protocol Violation	1 (1.3)	4 (2.6)	0
Withdrawal by Subject	5 (6.6)	4 (2.6)	3 (2.0)
Hypersensitivity-Related†	1 (1.3)	1 (0.7)	5 (3.4)
Adverse Events	0	1 (0.7)	4 (2.7)
Lost to Follow Up	0	0	1 (0.7)
Withdrawal	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

As seen in Table 1, adverse events were a more common reason for discontinuation among subjects in the sugammadex 16mg/kg group (n=5) compared to the subjects in the sugammadex 4mg/kg (n=3) group. This relationship is even more pronounced among patients experiencing a hypersensitivity event and suggests a possible dose response relationship; (n=4) in the 16mg/kg group compared to (n=1) in the 4 mg/kg group and zero in the placebo group.

Overall, 7 subjects in the study discontinued treatment after experiencing suspected hypersensitivity symptoms: 5 were from the sugammadex 16 mg/kg group, 1 from sugammadex 4 mg/kg, and 1 from the placebo group. Reported reasons for discontinuation varied and included adverse events (n=5), lost to follow up (n=1) and withdrawal (n=1).

The 5 subjects in the sugammadex 16mg/kg group who discontinued the study after experiencing a suspected hypersensitivity event experienced the following symptoms:

- 5020: (anaphylaxis) chills, conjunctival edema, enlarged uvula, nasal congestion, sneezing, urticaria

- 5006: eyelid edema, lacrimation increased, nasal discomfort, ocular hyperemia, sneezing
- 5057: pruritus, urticaria
- 3051: dysgeusia, paresthesia, back pain
- 5061: contact dermatitis, dysgeusia

The subject (5041) in the 4 mg/kg sugammadex group who discontinued the study due to a suspected hypersensitivity reaction experienced headache, nausea, presyncope, and vomiting; the subject in the placebo group (2003) experienced nasopharyngitis.

Of the 11 subjects who were discontinued due to an adverse event, 4 were discontinued after receiving concomitant medication treatment of potential hypersensitivity symptoms. A condition pre-specified in the protocol (Appendix 1) required that subjects who experienced potential hypersensitivity symptoms must have these symptoms resolve spontaneously, without treatment, in order for the subject to proceed to the next dosing occasion. Therefore, the 4 subjects who received concomitant medication treatment of potential hypersensitivity symptoms were discontinued due to the adverse event for which they were treated. Three of the subjects (5020, 5006, 5057) were in the sugammadex 16mg/kg group and one subject (5041) was in the 4mg/kg group with the treatments received listed below.

- 5020: 50mg IV diphenhydramine, 125mg IV methylprednisolone , 25mg IV diphenhydramine
- 5006: 80mg IV diphenhydramine
- 5057: 25 mg IV diphenhydramine, 50 mg IV diphenhydramine
- 5041: 8mg PO ondansetron

iii) Overview of Results

Using a predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (Appendix 2) and the targeted hypersensitivity assessment (Appendix 3), the Applicant identified 137 events in 94 subjects (45, 35, and 14 subjects in the sugammadex16 mg/kg, the sugammadex 4 mg/kg, and placebo groups, respectively) with adverse events potentially consistent with hypersensitivity. The potential cases were referred to the CAC for evaluation. The committee classified 25 subjects as having experienced 43 hypersensitivity events. One subject, 5020, in the 16 mg/kg sugammadex treatment group met NIAID/FAAN Criterion # 1 for anaphylaxis according to the CAC.

DPARP has reviewed the 137 possible hypersensitivity events resulting from the Applicant's search. Each case description was reviewed for symptoms consistent with anaphylaxis. In addition, adverse event 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 outlined in Section II above). Using this method, DPARP identified 1 case of anaphylaxis among the 137 potential hypersensitivity cases in 94 subjects. This case is briefly described below.

iv) Anaphylaxis Case Review

- Subject 5020: A 35 year old white male subject received an initial dose of 16 mg/kg sugammadex. In Period 1, adverse events began immediately after dose administration, starting with mild sneezing and nasal congestion. In rapid succession, the subject experienced mild conjuctival edema, moderate urticaria with surrounding erythema, and moderate swelling of the uvula within 5 minutes of dose administration. The subject also reported mild shivering 30 minutes after receiving the dose. The subject was treated with IV diphenhydramine 3 minutes after the sugammadex dose and IV methylprednisolone 2 minutes later. The AEs resolved within 3 hours of dose administration, with the exception of conjunctival edema that resolved approximately 9 hours after dose administration.

Based on this case review, DPARP identified 1 case of anaphylaxis in healthy subjects in this repeat dose clinical trial. Study P101 consisted of 299 unique healthy volunteer subjects who received sugammadex. As a result, we calculated a frequency of anaphylaxis of 0.33% (1/299) in a healthy volunteer population. It is of note that the case of anaphylaxis occurred on the first dose in the sugammadex 16 mg/kg group.

v) Review of Other Hypersensitivity Cases

The CAC classified 25 subjects as having experienced 43 hypersensitivity events. Fourteen of the 25 subjects were in the 16 mg/kg sugammadex treatment group, 10 subjects were in the 4 mg/kg sugammadex treatment group, and 1 subject was in the placebo group. One subject, 5020, in the 16 mg/kg sugammadex treatment group met NIAID/FAAN Criterion #1 for anaphylaxis and has been described above.

Among the 24 sugammadex-treated subjects with CAC-adjudicated hypersensitivity (one of the 25 total subjects with adjudicated hypersensitivity received placebo), 20 subjects experienced adverse events in the system organ class (SOC) of skin and subcutaneous tissue disorders, with urticaria (n=17) and pruritus (n=14) being reported most often. The next most common SOC was respiratory, thoracic, and mediastinal disorders, which included 9 subjects with adverse events. The most common adverse events in this class were sneezing (n=5), nasal congestion (n=2), throat irritation (n=2), and pharyngeal edema (n=2). There were 7 subjects each with adverse events categorized as gastrointestinal disorders. The most common AEs in gastrointestinal disorders were nausea (n=5) and vomiting (n=2), all of which were considered symptoms and signs of hypersensitivity.

DPARP reviewed the 137 potential hypersensitivity cases in 94 subjects in order to further characterize the types of reactions observed. Out of these 94 subjects, 14

subjects were randomized to the placebo arm, 35 subjects were randomized to sugammadex 4mg/kg, and 45 subjects were randomized to sugammadex 16mg/kg, for a total of 80 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 (45/80, 56.3%) and reacted in ≤ 35 minutes (53/80, 66.3%) on the first dose (49/80, 61.3%). Most of these subjects did not require medical intervention (76/80, 95%) and ultimately completed the study (74/80, 92.5%).

See Table 2 for a summary of the hypersensitivity-related adverse events occurring in ≥ 2% of subjects in any treatment group in study P101.

Table 2. Summary of Hypersensitivity Adverse Events† Occurring in ≥ 2% of Subjects in Any Treatment Group – Study P101

	Placebo N=76	**Sugammadex 4 mg/kg N = 151**	**Sugammadex 16 mg/kg N = 148**
Number of subjects with hypersensitivity adverse event, n (%)	14 (18)	35 (23)	45 (30)
Preferred Term	n (%)		
Abdominal Pain	1 (1.3)	5 (3.3)	1 (0.7)
Diarrhea	1 (1.3)	3(2 .0)	2(1.4)
Erythema†	0 (0.0)	3 (2.0)	6 (4.1)
Eye Disorders†	0	3 (2.0)	4 (2.7)
Nausea	4 (5.3)	16 (10.6)	20 (13.5)
Pruritus	1 (1.3)	11 (7.3)	8 (5.4)
Rhinorrhea	1 (1.3)	6 (4.0)	1 (0.7)
Sneezing	2 (2.6)	2 (1.3)	5 (3.4)
Pre-syncope†	1 (1.3)	5 (3.3)	2 (1.4)
Urticaria	0 (0.0)	6 (4.0)	10 (6.8)
Vomiting	2 (2.6)	5 (3.3)	6 (4.1)

† Predefined and mutually agreed-upon list of possible hypersensitivity signs/symptoms (see Appendix 2), with the exception of erythema, eye disorders and pre-syncope; pre-defined terms were specifically generalized erythema, red and itchy eyes and syncope, respectively.
Source: Table 12-4, p. 116, Clinical Study Report P101, Module 5.3.5.4.

As can be seen in the table above, the most common hypersensitivity adverse events reported in all subjects in study P101 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.

vi) Mechanistic Studies

a) Anti-Sugammadex Antibodies

An exploratory objective of study P101 was to measure levels of anti-sugammadex specific IgG and IgE antibodies in subjects referred to the CAC and in a set of control subjects without hypersensitivity. Measurements were performed pre-dose for each dosing period and at the follow up visit.

The assay was a three-step tiered assay. If an initial screening assay was positive for a subject, the sample was tested in a confirmatory assay, indicating the presence in serum of a sugammadex-reactive substance. If the sample was positive in the confirmatory assay, it was then tested in an isotyping assay for the presence of IgG and IgE. A positive result in the isotyping assay would then demonstrate presence of IgG and/or IgE specific for sugammadex. A negative result indicated that the sugammadex reactive substance was neither IgG nor IgE, or that the concentration was below the detection limit of the isotyping assay.

Of the 25 subjects with adjudicated hypersensitivity, two subjects, 1032 and 5059, were positive for IgG specific for sugammadex at one and three time points, respectively. No subjects had IgE specific for sugammadex. Of the 69 subjects who were referred to the CAC for potential hypersensitivity reactions but whose events were not confirmed as such, no subjects had IgG or IgE specific for sugammadex at baseline and after each dose. There were 281 subjects who were not referred to the CAC, and of these 91 were tested for the presence of anti-sugammadex antibodies (i.e., control subjects). No control subjects had IgG or IgE specific for sugammadex at baseline and after each dose.

Overall, there was no evidence for the generation of anti-sugammadex IgE antibodies from repeated exposure to sugammadex and only two subjects out of the 25 with adjudicated hypersensitivity events were positive for IgG-specific for sugammadex. While, the underlying mechanism for the hypersensitivity reactions is still unclear; the available data do not suggest that sensitization occurs upon repeat exposures or that the risk of hypersensitivity reactions increases with repeat exposure.

b) Tryptase

There were no subjects with adjudicated hypersensitivity that met the predetermined criteria of tryptase levels > 11 ng/mL at either pre-dose or post-dose. The subject with adjudicated anaphylaxis (5020) had a pre-dose tryptase of 4 ng/mL and a post-dose tryptase of 5 ng/mL.

Overall these results suggest that mast cell degranulation as measured by serum tryptase is not significantly involved in the symptoms of hypersensitivity observed in the subjects with adjudicated hypersensitivity to sugammadex.

B. NDA Resubmission – Complete Response #3 (June 19, 2015)

The audit conducted during the routine inspection by the Office of Scientific Investigations (OSI) during the previous review cycle indicated protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P101.

As requested by the Agency in their Complete Response letter dated April 22, 2015, the Applicant performed sensitivity analyses for adjudicated hypersensitivity and adjudicated anaphylaxis based on a subset of subjects who did not have major protocol deviations as well as calendar time intervals for events related to the potential unblinding that occurred during the course of the trial.

The results from both sets of sensitivity analyses, those excluding subjects with protocol deviations, as well as the time interval-related summaries to account for the existence of an unmasked data variable in the statistical platform (CPI), supported the interpretations and conclusions of P101 data as reported in the CSR.

Given that the number of doses administered during the calendar intervals analyzed over time, additional analysis of the total number of suspected hypersensitivity events over the total number of exposures by treatment group and interval was evaluated, as shown in Table 3.

Table 3. Total Number of Suspected Hypersensitivity Events Over Total Number of Exposures by Treatment Group and Interval– Study P101

# of events / # of exposures	**Placebo**	**Sugammadex 4 mg/kg**	**Sugammadex 16 mg/kg**
Interval 1 (Study Start to 3/10/2014)	9/96 (9.4%)	26/190 (13.7%)	33/190 (17.4%)
Interval 2 (3/11/2014 to 4/8/2014)	3/60 (5.0%)	13/120 (10.8%)	17/116 (14.7%)
Interval 3 (4/9/2014 to end of study)	5/53 (9.4%)	12/117 (10.3%)	19/114 (16.7%)
Total	17/209 (8.1%)	51/427 (11.9%)	69/420 (16.4%)

Source: Response to Clinical Information Request August 13, 2015

As seen above, there was no meaningful change in the frequency of suspected hypersensitivity events after the potential unblinding. The results from both sets of sensitivity analyses, those excluding subjects with protocol deviations, as well as the time interval-related summaries to account for the existence of an unmasked data variable in the statistical platform (CPI), support the interpretations and conclusions of

P101 data. In addition, results from the remaining inspections did not reveal any significant concerns regarding data integrity and study conduct. Accordingly, data from study P101were deemed valid for review.

V. Post-Marketing Reports of Hypersensitivity

Sugammadex is approved in more than 75 countries and marketed in more than 50 countries worldwide, with over 12 million doses sold as of April 22, 2015.

The Applicant searched their pharmacovigilance database for cases of serious hypersensitivity and anaphylaxis received in the post-marketing setting from health care providers (HCPs) including non-interventional studies, cumulatively, from market introduction (July 25, 2008) through April 22, 2015. 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. 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. A total of 415 cases were identified, of which 259 represent reports of anaphylaxis and 155 represent reports of serious hypersensitivity.

The Applicant decided to have the 415 cases adjudicated by an independent external Adjudication Committee (AC). The AC reviewed each report for signs and symptoms of anaphylaxis and/or hypersensitivity, using the definition of anaphylaxis according to Sampson[1]. Cases were adjudicated either as anaphylaxis, hypersensitivity, neither, or as containing insufficient information for adjudication. The adjudication results showed that of the 415 cases, 273 were classified as anaphylaxis and 36 were classified as hypersensitivity.

The most commonly described clinical feature in reports of anaphylaxis was dermatologic symptoms including urticaria, rash, erythema, flushing and skin eruption, noted in more than half of the reports (183/273). The next most commonly described clinical feature, reported in 181 patients, was hypotension, noted in the report by either a mention in the narrative or a documented preferred term of blood pressure decreased, hypotension, or circulatory collapse. Of the 273 reports of anaphylaxis, 66 noted the use of additional respiratory support (re-intubation, prolonged intubation, manual or mechanical ventilation) until full recovery. One hundred fifty-seven patients were noted to require vasopressors for circulatory support, including 14 patients who were treated with dopamine. Other vasopressors included epinephrine, norepinephrine, ephedrine and/or phenylephrine. In 23% of all patients (64/273), the need for prolonged hospitalization was indicated by the reporter.

All but 8 of the 36 reports of adjudicated hypersensitivity were manifested by skin reactions such as erythema, rash and urticaria. The 8 cases not manifested by skin

reactions reported symptoms such as laryngospasm, bronchospasm, musculoskeletal stiffness, respiratory arrest, decreased blood pressure, decreased oxygen saturation, tongue edema and angioedema. All responded to standard treatment for anaphylaxis/ hypersensitivity reactions such as adrenaline, antihistamines, bronchodilators, steroids, vasopressors and ventilatory support as required and were readily managed medically, with full recovery and no sequelae.

As there are no generally accepted criteria to adjudicate cases of hypersensitivity, DPARP has not historically attempted to adjudicate these cases. The Applicant's post-marketing summary is presented as a means of providing additional characterization of the types of hypersensitivity reactions that have been observed with use of sugammadex in the controlled clinical studies.

With respect to anaphylaxis, DPARP focused our frequency calculation on the controlled clinical study as outlined in this review. Given the many limitations associated with post-marketing reports (including comorbid conditions, concomitant medications, etc.) and the availability of controlled clinical data to more reliably assess for anaphylaxis; quantification of the frequency of anaphylaxis from the post-marketing database was not conducted.

VI. 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 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 were deemed to be of limited utility in defining the frequency of anaphylaxis associated with sugammadex administration, and a Complete Response letter was issued.

On October 22, 2014, 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. While the resubmission was not approved during the previous review cycle, the most recent submission and inspection results have addressed the deficiencies and the study results have been deemed valid for review.

In Study P101, 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 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.[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.

VII. 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. Blessing-Moore et al. The Joint Task Force on Practice Parameters. J Allergy Clin Immunol 2005. Mar;115(3 Suppl 2):S483-523).

3. Sampson et.al. Symposium on the Definition and Management of Anaphylaxis: Summary report. J Allergy Clin Immunol, March 2005; p:584-591

Appendix 1

Study 101 Protocol
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

Trial Design
This is a randomized, double-blind, placebo-controlled, Sponsor-blind, parallel-group study to evaluate the incidence of hypersensitivity (HS) after repeated single dose administrations of sugammadex in approximately 375 healthy male and female subjects and conducted in conformance with Good Clinical Practices.

Subjects will be screened within approximately 4 weeks of the first admission. On this first admission on Day 1 of Period 1, baseline assessments will be performed to confirm eligibility. Subjects confirmed to be eligible will be randomized on Day 1 of Period 1 to one of the following three treatments:

- Treatment Arm A: Sugammadex 4 mg/kg single intravenous bolus injection in each of 3 periods (N=150)
- Treatment Arm B: Sugammadex 16 mg/kg single intravenous bolus injection in each of 3 periods (N=150)
- Treatment Arm C: Placebo single intravenous bolus injection in each of 3 periods (N=75)

In Treatment Periods 1, 2 and 3, each subject will receive a single intravenous bolus injection of their randomized treatment while confined to the study center. An approximately 5 week washout will be required between treatment periods. Each single dose of trial medication will be administered intravenously as a bolus injection of approximately 10 seconds, to closely match clinical practice.

Adverse events (AEs) and concomitant medications will be recorded throughout the study. AE assessments and the Targeted Hypersensitivity (HS) assessment (Appendix 3) are to be performed by a physician who does NOT administer study drug or prepare medication. All subjects will have Targeted HS Assessments at 0.5, 4, and 24 hours after dose, or the first time point may be triggered earlier by presence of any AE in Signs and Symptoms of Hypersensitivity (Appendix 2) after administration of study drug and prior to the 30 minute time point. The Targeted HS Assessments have been designed to elicit the defined Signs and Symptoms of HS arising within the first 24 hours after administration of study drug. Any subject with an AE identified in any Targeted HS Assessment will be recorded as a case of Potential HS and referred to the blinded external Clinical Adjudication Committee (CAC) for evaluation. Subjects with Potential HS will remain confined to the study center until the investigator considers it safe for the subject to leave the study center. In addition, there will be regular monitoring throughout

the study of recorded AE's by the Sponsor using the current version of the MedDRA SMQ's for hypersensitivity and anaphylactic reaction that may lead to additional referrals to the CAC.

Subjects with signs and symptoms of HS with an AE categorized as 'serious' or rated as severe intensity will be discontinued from the study at any time. Subjects with mild or moderate signs and symptoms of HS may proceed in the study, and will do so according to the algorithm listed below:

A subject with signs and symptoms of HS may discontinue from study treatment at any time. For subjects referred to adjudication, an assessment will be performed in the following sequential manner prior to proceeding to the next dosing period.

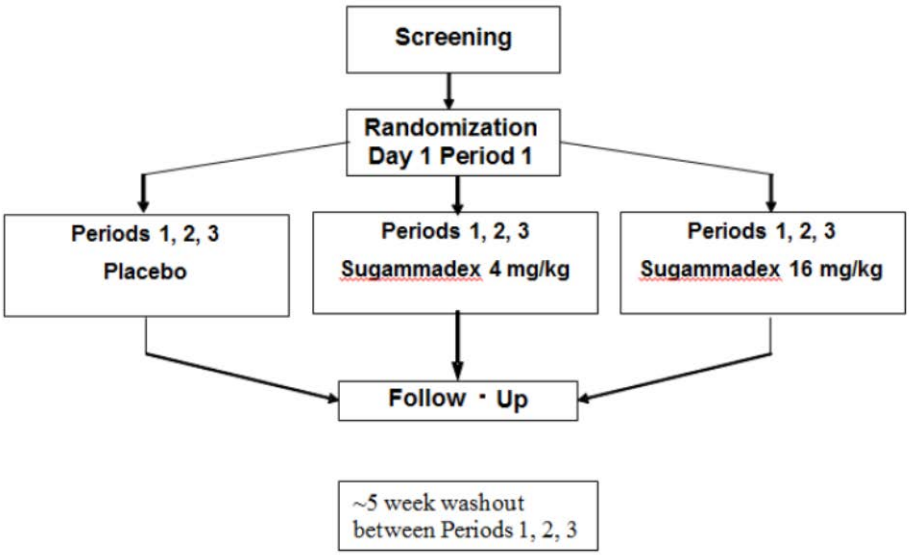
1. If the subject experienced an AE of hypotension as defined in the HS assessment (Appendix 3), the subject should be discontinued from the study.
2. The signs and symptoms of HS must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment.
3. A blinded independent 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 HS for this dosing period, as well as any previous dosing period. This expert may also be a member of the CAC.

Only if item 1 is negative, and requirements 2 and 3 are met, the subject may proceed to the next dosing period.

Each participating investigator will be trained in recognizing HS symptoms and will be instructed on how to act in the event of severe HS symptoms. To ensure subject safety, resuscitative equipment and rescue treatment, including EpiPen ® (epinephrine) 0.3 mg, will be available at each participating study center during the trial. Physicians trained in establishing an airway in acute emergencies will be present in the unit or accessible for support per standard emergency timelines for at least 2 hours after each dose administration.

All subjects, including those who discontinue for any reason, will have a follow-up visit approximately 28 days after the last dose of study drug for IgG/IgE blood sampling and follow-up visit procedures.

Figure 1. Trial Design Schematic



Primary Objectives

- To determine the number and percentage of subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo.
- Estimation: The incidence of subjects with adjudicated hypersensitivity receiving sugammadex will be estimated for both dose groups and compared to 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.

Safety Endpoints

Drug HS is a common medical problem and is often not predictable. Drug HS is a broad term with extremely diverse presentation. These reactions comprise <10–15% of all adverse drug reactions. Specific signs and symptoms are used to recognize HS reaction(s), which usually occur immediately following exposure to a specific drug. HS reactions may also be caused by non-immunological processes, as certain drugs can directly activate mast cells and release inflammatory mediators.

The goal of this study is to assess the potential for HS symptoms upon repeat exposure to sugammadex. The definitions of HS and anaphylaxis are based on the WHO and WAO guidelines.

Hypersensitivity: Hypersensitivity (HS) describes objectively reproducible symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by normal persons.

Anaphylaxis: The term anaphylaxis is an umbrella term for a serious, life-threatening generalized or systemic HS reaction that is rapid in onset. For the purpose of this study, adjudication of potential cases of anaphylaxis is defined by Sampson et al. (Criterion 1)

<u>Sampson Criterion 1 for Anaphylaxis:</u>

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)

- The primary safety endpoint is the number and percentage of subjects with adjudicated symptoms of HS for each dose group of sugammadex and placebo. A Clinical Adjudication

Committee will be used to evaluate all subjects with potential HS signs and symptoms and to determine if the constellation of signs and symptoms can be considered a HS reaction.

- Secondary safety assessments include: [1] 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, [2] the changes over time in frequency and severity of adjudicated HS symptoms for each dose group of sugammadex and placebo and [3] the safety and tolerability of administration of repeated single doses of sugammadex in healthy subjects.
- As exploratory endpoints, anti-sugammadex specific IgG and IgE antibodies in subjects with adjudicated symptoms of HS and in a subset of subjects without adjudicated symptoms of HS will be measured. In addition, mast cell tryptase levels which are a biomarker for degranulation of mast cells in anaphylaxis will be measured for subjects with possible signs and symptoms of HS, and blood samples for potential hypersensitivity research will be collected for all subjects.

Exploratory

Merck will conduct Future Biomedical Research on DNA and blood specimens (leftover blood for hypersensitivity samples) collected during this clinical trial. This research may include genetic analyses (DNA) and/or the measurement of other analytes. Specimens may be used for future assay development.

Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

- understand the study procedures and agree to participate in the study by giving written informed consent, including consent for Future Biomedical Research.
- be male, or non-pregnant and non-breast feeding female 18 to 55 years of age at the pre-trial (screening) visit; further:
    - if female with reproductive potential: subject must demonstrate a serum β-human chorionic gonadotropin (β-hCG) level consistent with the nongravid 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.
    - 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.
    - if surgically sterile female: subject is status post hysterectomy, oophorectomy or tubal ligation.

- have a Body Mass Index (BMI) ≥19 and ≤32 kg/m2. BMI = weight (kg)/height (m)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
- be judged to be in good health based on laboratory safety tests obtained at the screening or prior to administration of the initial dose of trial drug.
- 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
- be willing to comply with the trial restrictions
- must have systolic blood pressure ≥ 110 mm Hg and diastolic blood pressure ≥ 60 mm Hg at screening

Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

- is under the age of legal consent
- 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 has situational depression may be enrolled in the trial at the discretion of the investigator.
- 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.
- has a history of cancer (malignancy)
- 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) or significant intolerability to prescription or non-prescription drugs or food
- is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV
- had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit, 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
- has QTcF interval ≥ 470 msec (for males) or ≥ 480 msec (for females)
- 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.

- has received subcutaneous or sublingual immunotherapy within the past 1 year
- 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
- 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
- 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
- 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
- has a recollection of previously receiving sugammadex, Bridion™, SCH 900616, ORG 25969, or MK-8616
- has a history of chronic urticaria or angioedema
- 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.

Timing of Dose Administration
MK-8616 (sugammadex)/placebo is to be administered by IV bolus over ~10 seconds between approximately 06:00 and 15:00 on treatment days.

Trial Blinding/Masking
A double-blind/masking technique will be used. MK-8616 4 mg/kg, MK-8616 16 mg/kg and placebo will be dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

MK-8616 4 mg/kg, MK-8616 16 mg/kg and placebo will be prepared by the unblended pharmacist or delegate in a syringe masked by a white opaque label to ensure that the contents of the syringe will not be revealed. The individual who administers the study drug is blinded to treatment and will use the masked syringe to inject the saline-lock port or equivalent. No additional butterfly or IV tubing should be employed between the syringe and the saline-lock port or equivalent to prevent any potential coloration of study medication to be perceived. An 18 gauge (or larger) needle will be connected to the saline-lock port or equivalent, will be used for study drug administration and is to be maintained for at least 4 hours after dose administration. *AE assessment and the Targeted HS assessment are to be performed by a physician who does NOT administer study drug or prepare medication.*

Concomitant Medications/Vaccinations (Allowed & Prohibited)
If a subject does not discontinue all prior medications within 14 days or 5 half-lives of starting the trial, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial. Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or allocation) must first be discussed between the investigator and Sponsor Clinical Director prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor Clinical Director can consult. The subject will be allowed to continue in the trial if both the Sponsor Clinical Director and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor Clinical Director.

In addition, the following concomitant medications are permitted:

- Hormonal contraceptives (female subjects)
- Anti-histamines may be used for treatment of seasonal allergies, but cannot be used during a period comprising 5 half-lives before and 2 days after each dosing period.
- Hormone replacement therapy (female subjects)

Use of any of the above medications is to be documented in the CRF.

Rescue Medications & Supportive Care
To ensure subject safety, resuscitative equipment and rescue treatment, including EpiPen® (epinephrine) 0.3 mg, will be available at each participating study center during the trial.
Subjects who require resuscitative treatment will be discontinued from the study for signs/symptoms of HS that are categorized as 'serious'.

Table 1. Visit Procedures

Visit	Screening Visit 1	Visit 2[c, a]			Visit 3[c, a]			Visit 4[c, a]			Visit 5 (F/U)[b]
Period		Period 1[c]			Period 2[c]			Period 3[c]			
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[e]			X[e]			X[e]			X
Body Weight (kg)	X	X[e]			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 [j,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
IgG, IgE blood sampling			X[m]			X[m]			X[m]		X[m]
Tryptase blood sampling			X[n]			X[n]			X[n]		

Visit	Screening Visit 1	Visit 2[c, k]			Visit 3[c, k]			Visit 4[c, k]			Visit 5 (F/U)[b]
Period		Period 1[c]			Period 2[c]			Period 3[c]			
Period Day	Day -28 to -2	-1	1	2	-1	1	2	-1	1	2	
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.

Appendix 2

Hypersensitivity Signs and Symptoms

Generalized urticaria
Localized injection site urticaria
Generalized angioedema
Localized angioedema
Generalized pruritus with skin rash
Generalized pruritus without skin rash
Generalized prickle sensation
Generalized erythema
Red and itchy eyes
Hypotension (reduction > 30% compared to predose baseline or SBP < 90 mm Hg)
Clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following:

- Tachycardia (pulse ≥100)
- Capillary refill time >3 sec
- Reduced central pulse volume
- Decreased or loss of consciousness

Collapse (hypotonia)
Syncope
Incontinence
Bilateral wheeze (bronchospasm)
Stridor
Upper airway swelling (lip, tongue, throat, uvula, or larynx)
Persistent dry cough
Hoarse voice
Difficulty breathing
Sensation of throat closure
Sneezing, rhinorrhea
Respiratory distress - 2 or more of the following:

- Tachypnoea (>30/minute)
- Recession
- Cyanosis
- Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
- Grunting
- Decrease of SPO2 on room air ≥5% (absolute) from baseline
- PEF<70% of baseline

Diarrhea
Abdominal Pain
Nausea
Vomiting
Mast cell tryptase elevation > upper normal limit

Appendix 3

Targeted Hypersensitivity (HS) Assessment

To be performed only by blinded principal investigator or MD designate who has ***NOT*** *been involved in preparation of study drug or in administering study drug by IV bolus. The following assessment is designed to elicit potential Hypersensitivity Signs or Symptoms (Appendix 2). All abnormal findings should be noted. All AE's that have arisen since either the previous HS Assessment or since administration of study drug should be noted, and a corresponding entry should be entered into the AE log for any clinically significant finding, regardless of severity. For AE's that started prior to study drug administration, findings should only be noted if there is a clear change in severity or quality in the nature of the AE. The prompts for elicited adverse events are not intended to be used verbatim, but may be adapted to the appropriate language and understanding of the subject.*

After completion of the Targeted HS Assessment, please note:

- No signs or symptoms present
- Presence of at least one sign or symptom in the HS Signs and Symptoms (Appendix 2)

Dermatologic evaluation

- Ask about pruritus/itching, any prickle sensation (e.g. Do you have any feelings on your skin?)
- Assess for rash (patients should be in a gown that allows for assessment of skin on trunk)
    - presence of generalized urticaria (hives) or localized urticaria, or urticaria at injection site
    - presence of erythema
    - if present, describe characteristics of rash
        - Color
        - Size, shape and number of lesions
        - Arrangement of rash
        - Distribution of rash (facial, truncal, asymmetrical or bilaterally symmetrical, related to injection site) and percent of body surface involved

- Assess for presence of angioedema, generalized or localized

Pulmonary evaluation

- Ask about difficulty breathing (e.g. Has there any change in your breathing?)
- Perform auscultation of lung fields and assess for presence of wheezing or rhonchi
- Assess for presence of tachypnea, stridor, increased use of accessory muscles, recession, grunting, cyanosis or dry cough
- Examine PEF measurements for decrease to <70% of baseline
- Examine SPO2 measurements for decrease ≥5% (absolute) from baseline on room air

HEENT evaluation

- Ask about sensation of tongue swelling, throat swelling, and nose symptoms (e.g. Do you have any symptoms in your mouth, throat or nose?)
- Evaluate for presence of upper airway swelling (lip, tongue or uvula), sneezing, rhinorrhea, and of redness and/or itching of eyes.

GI evaluation

- Ask about nausea, vomiting, abdominal pain, diarrhea

Cardiovascular evaluation

- Assess for hypotension
    - Resting* SBP reduction > 30% compared to predose baseline; OR
    - Resting* SBP < 90 mm Hg.
- Assess for tachycardia
    - Resting* HR ≥ 100 bpm.
- Assess for capillary refill time > 3 seconds,
- Assess for reduced central pulse volume

Neuro Evaluation

- Assess for decreased level of consciousness

- Assess for incidence of incontinence

*Resting for at least 5 minutes quietly.

Narrative: If there is a finding of a Symptom or Sign of Hypersensitivity, a narrative to describe the AE(s) should be provided. This narrative should supplement the information contained in the AE log, providing information about the sequence of events relative to the administration of study drug, and to provide further information about the evolution of AE(s) such as change over time of the AE(s).