CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022225Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 22225
Product Name: BRIDION (sugammadex)

PMR/PMC Description: #3003-1

A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	January 2017
Study/Trial Completion:	May 2021
Final Report Submission:	September 2021
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The submission of the pediatric trial was deferred, because this product is ready for approval for use in adults, and the pediatric trial has not been completed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 3860765

The goal of the clinical trial is to assess the safety, efficacy, and pharmacokinetics of sugammadex when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium in pediatric patients ages birth to 17 years old.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A trial of the safety, efficacy, and pharmacokinetics of sugammadex when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old.

Reference ID: 3860765

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☒ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug
☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 3860765

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3860765

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 22225
Product Name: BRIDION (sugammadex)

PMR/PMC Description: #3003-2
Conduct a postmarketing study to analyze the demographic characteristics, concomitant medication use, and comorbid conditions in patients who did not respond to sugammadex reversal in the development program, in postmarket studies that have been conducted, or as described in cases of non-response/lack of efficacy reported as postmarketing adverse events. The goal of the study is to determine the characteristics and profile of patients who would be expected to be non-responders. The study should also assess the occurrence of hypersensitivity or anaphylaxis, prolonged ventilator support and sedation, and anoxia in these patients.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	October 2016
Study/Trial Completion:	January 2017
Final Report Submission:	May 2017
Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Reference ID: 3860765

A small percentage of patients in the development program required much longer time periods than expected for recovery of full neuromuscular function after sugammadex administration. The Applicant has identified the following reasons for outliers: technical issues, protocol adherence, age, and possible effects of inhalational anesthesia. Concomitant medications, when there is a theoretical risk that compounds with steroidal structures decrease the availability of sugammadex for binding to neuromuscular blocking drugs, should be evaluated, as well as demographic factors and comorbid conditions.

Patients who don't respond to the first dose may get additional doses. Because there is a dose-related risk of anaphylaxis and hypersensitivity reactions, additional doses could increase the risk of such reactions. Other risks associated with non-responders and persistent neuromuscular blockade are the need for continued ventilatory support and sedation, as well as anoxia.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

On November 6, 2105, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss this NDA, the Committee unanimously agreed that the efficacy, safety and overall risk:benefit profile of sugammadex supported approval for the patient population that was studied in the drug development program. However, they noted that it would be important to obtain information in patient populations that did not respond to the administration of sugammadex as expected. Therefore, a postmarketing requirement will be imposed on the Applicant to conduct a study to determine what patient characteristics may predict a prolonged recovery, in which case sugammadex administration should be avoided. One potential risk is prolonged paralysis and administration of anesthesia/sedation with ventilatory support for longer periods in patients who are poor candidates for sugammadex reversal. Another risk is getting additional doses of sugammadex that could increase the risk of hypersensitivity reactions. A third risk is anoxia after administration of high doses of neuromuscular blocker with the expectation that sugammadex would be able to expediently reverse the neuromuscular blockade.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Reference ID: 3860765

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study should include a review of patients in the clinical development program and any postmarket studies, as well as cases of non-response reported as postmarketing adverse events to attempt to determine what patient characteristics may predict a prolonged recovery, in which case sugammadex administration should be avoided.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
analysis of non-response in the clinical development program, postmarket studies, and postmarket spontaneous adverse event reports.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness

Reference ID: 3860765

☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

Reference ID: 3860765

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 22225
Product Name: BRIDION (sugammadex)

PMR/PMC Description: #3003-3
Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in a population of American Society of Anesthesiologists Class 3 and 4 patients. The goal of the trial is characterization of the risks of bradycardia and other cardiac arrhythmias after sugammadex administration in this population that may have more severe outcomes related to cardiac arrhythmias experienced during reversal of neuromuscular blockade. Prespecify the case definition of bradycardia, tachycardia, and the other cardiac arrhythmias of interest.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	March 2017
Study/Trial Completion:	March 2020
Final Report Submission:	August 2020
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☒ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Sugammadex clinical trials revealed serious risks including bradycardia and other cardiac arrhythmias; some cases resulted in cardiac arrest. Patients in the development program have done well despite potentially life-threatening side effects of sugammadex. However, patients with significant comorbidities have largely not been studied and the clinical implications of sugammadex administration in a higher risk population, if they were to experience these adverse events, need better characterization.

Reference ID: 3860765

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

On November 6, 2105, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss this NDA, the Committee unanimously agreed that the efficacy, safety and overall risk/benefit profile of sugammadex supported approval for the patient population that was studied in the drug development program. However, they noted it would be important to obtain safety information in certain patient populations that were not included to a significant extent in the program. Therefore, a postmarketing requirement will be imposed on the Applicant to conduct a clinical trial is to generate data to be able to make a risk-benefit determination regarding sugammadex administration in patients who have less compensatory reserve for recovering from the hemodynamic effects of a sugammadex-related arrhythmia than those studied in the development program, such as patients categorized as being in ASA classification 3 and 4.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3860765

The clinical trial would evaluate the safety of sugammadex administration in high risk patients (ASA classes 3 and 4), in order to assess the outcomes associated with cardiac arrhythmia AEs in the higher risk population.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug

Reference ID: 3860765

☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 3860765

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 22225
Product Name: BRIDION (sugammadex)

PMR/PMC Description: #3003-4
Conduct a postmarketing clinical trial comparing sugammadex to placebo and/or drugs approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in patients with morbid obesity. The goal of the trial is to evaluate the safety of sugammadex (including the serious adverse outcomes of anaphylaxis or hypersensitivity) and to generate data to support dosing recommendations in morbidly obese patients, specifically whether to dose by actual vs. ideal body weight. Prespecify the case definition of morbid obesity that will establish who will be included in the trial.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	March 2017
Study/Trial Completion:	October 2018
Final Report Submission:	March 2019
Other: _____	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

(b) (4)

However, morbidly obese subjects were not well represented in the development program and sugammadex administration (b) (4)

Reference ID: 3860765

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

On November 6, 2105, the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) met to discuss this NDA. The Committee unanimously agreed that the efficacy, safety and overall risk:benefit profile of sugammadex supported approval for the patient population that was studied in the drug development program. However, they noted it would be important to obtain safety information in certain patient populations that were not included to a significant extent in the program. Therefore, a postmarketing requirement will be imposed on the Applicant to conduct a clinical trial to generate data to support dosing recommendations in morbidly obese patients. The potential risk is an unnecessary increased incidence of hypersensitivity adverse events due to the dose-dependent relationship demonstrated for sugammadex-related hypersensitivity reactions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☒ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 3860765

The study would be a clinical trial to evaluate the safety of sugammadex (including the serious adverse outcomes of anaphylaxis or hypersensitivity) and generate data to support dosing recommendations in morbidly obese patients.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☒ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☒ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☒ There is a significant question about the public health risks of an approved drug

Reference ID: 3860765

☒ There is not enough existing information to assess these risks
☒ Information cannot be gained through a different kind of investigation
☒ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☒ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 3860765

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

/s/

DIANA L WALKER
12/15/2015

JUDITH A RACOOSIN
12/15/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date:	November 27, 2015 **Consult Received:** August 20, 2015
From:	Carol H. Kasten, MD, Medical Officer Division of Pediatric and Maternal Health, Maternal Health Team Office of Drug Evaluation IV (ODE IV)
Through:	Tamara Johnson, MD, MS, Team Leader Maternal Health Team Division of Pediatric and Maternal Health, ODE IV Lynne P. Yao, MD, Director Division of Pediatric and Maternal Health, ODE IV
To:	Division of Anesthesia, Analgesia and Addiction Products
Drug:	Bridion (sugammadex), for injection, NDA 22-225
Applicant:	Organon/Merck
Proposed Indication:	Bridion is indicated for the reversal of rocuronium bromide and vecuronium bromide (b) (4) surgery in adults.
Consult Request:	"DAAAP is requesting that PMHS please assist us in reviewing the labeling for the new PLLR content and format."

Documents Reviewed:

- DPMH Consult Review of Bridion (sugammadex), Carol H. Kasten, MD, Primary Author, Dated April 22, 2015; DARRTS Reference ID: 3737009.
- DAAAP Clinical Pharmacology Review of sugammadex NDA 22-225, Lei Zhang, Ph.D., primary author, dated June 23, 2008.

INTRODUCTION

On April 22, 2015 the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) provided the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) with recommendations for the Pregnancy and Lactation subsections of the Bridion (sugammadex) labeling in the Pregnancy and Lactation Labeling Rule (PLLR) format. DAAAP now requests that DPMH - MHT review the August 20, 2015 labeling which the applicant had submitted in this Class 2 Re-submission.

Please see the DPMH-MHT Bridion consult in DARRTS, primary author Carol H. Kasten, M.D., dated April 22, 2015, DARRTS Reference ID: 3737009.

BACKGROUND

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,*"[1] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[2] format to include information about the risks and benefits of using these products during pregnancy and lactation.

Sugammadex Interaction with Hormonal Contraceptives

As noted in the previous DPMH Review, sugammadex has been found to interact with hormonal contraceptives. Following administration of sugammadex, the labeling instructs patients to consider they have missed one dose of their oral contraceptive. Patients using non-oral hormonal contraceptives are advised to use an alternate contraceptive method for 7 days following a bolus dose of sugammadex. In this review cycle, the drug interaction information was updated Specifically, the Agency's pharmacokinetic (PK) modeling data[3] suggested that the systemic hormonal contraceptive exposure may be reduced as much as one third based on area under the curve (AUC) modeling calculations following administration of sugammadex. This decrease is larger than had been assessed previously. No clinical data were included with this application which measured the effect of a bolus injection of sugammadex on systemic levels of progestogen produced by oral or non-oral hormonal contraceptives.

The initial decision was additional data were needed which would be requested in a Post-Marketing Requirement (PMR) to provide clinical PK data investigating the effect of a

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[2] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[3] DAAAP Clinical Pharmacology Review of Sugammadex, NDA 22-225, Lei Zhang, Ph.D., primary author, dated June 23, 2008.

Reference ID: 3852899

bolus injection of sugammadex on hormonal contraceptive levels. Further discussion determined that the sugammadex labeling should be revised to reflect the available data rather than requiring a PMR. Specifically, the labeling instructions should indicate that a woman of reproductive potential should use an alternative method of contraception for one month following a dose of sugammadex. If the applicant does not agree with this labeling change, they will be required to produce clinical PK data measuring the effect of a bolus injection of sugammadex on hormonal contraceptive levels.

Aprepitant Labeling for Hormonal Contraceptive Interaction

There is precendence for the labeling language being considered. The drug aprepitant (Emend®, NDA 22-023 (IV), 21-549 (oral)) contains the following language under (7) Drug Interactions, 7.1 Effect of Aprepitant on the Pharmacokinetics of Other Drugs:

Hormonal Contraceptives	
Clinical Impact	Decreased hormonal exposure during administration of and for 28 days after administration of the last dose of EMEND *[see Clinical Pharmacology (12.3)].*
Intervention	Alternative or back-up methods of contraception should be used during treatment with EMEND and for 1 month following the last dose of EMEND
Examples	birth control pills, skin patches, implants, and certain IUDs

In (17) Patient Counseling Instructions section of the Emend labeling, the following is included:

> **17 PATIENT COUNSELING INFORMATION**
>
> Drug Interactions
>
> Hormonal Contraceptives: Advise patients that administration of EMEND may reduce the efficacy of hormonal contraceptives. Instruct patients to use alternative or back-up methods of contraception during treatment with EMEND and for 1 month following the last dose of EMEND.

DPMH-MHT respects the Division's decision to change the sugammadex labeling to recommend an alternative contraceptive method be used for one month following sugammadex administration; however, the recommendation from the Division of Bone, Reproductive and Urology Products (DBRUP) is that use of alternative non-hormonal contraceptives for seven days should be sufficient to reduce the effect of a dose of sugammadex. DPMH agrees with the DBRUP recommendation.

LABELING RECOMMENDATIONS

Since completion of the DPMH-MHT Bridion consult review on April 22, 2015, no new nonclinical data has been submitted by the applicant; nor have there been any new clinical submissions or scientific publications containing safety data that should be added to the Pregnancy or Lactation labeling subsections. However, in light of the new information indicating sugammadex may reduce hormonal contraceptives' efficacy more than previous thought, DPMH-MHT has modified its previous labeling recommendations. Changes were added to (8.3) Females and Males of Reproductive Potential and (17) Patient Counseling Instructions.

DPMH labeling recommendations are below and reflect discussion with DAAAP. Final labeling will be negotiated with the applicant and may not fully reflect changes recommended here.

BRIDION (sugammadex) Injection, for intravenous use
HIGHLIGHTS
----------DRUG INTERACTIONS----------

- Hormonal contraceptives: [redacted] using hormonal contraceptives [redacted] use an additional non-hormonal [redacted] for the next 7 days following BRIDION administration. (7.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

7 DRUG INTERACTIONS
7.1 Interactions Potentially Affecting the [redacted] of BRIDION
7.3 Interactions Potentially Affecting the Efficacy of [redacted]

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on BRIDION use in pregnant women to inform any drug-associated risks. In animal reproduction studies, there was no evidence of teratogenicity [redacted] to rats and rabbits during organogenesis at exposures up to 6 and 8 times, respectively, the maximum recommended human dose (MRHD) of 16 mg/kg. However, there was an increase in the incidence of incomplete ossification of the sternebra and reduced fetal body weights in the rabbit study. In a pre- and postnatal development study, sugammadex treatment resulted in an [redacted] increase in [redacted] which correlated with [redacted]. [redacted] The background risk of major birth defects and miscarriage for the indicated population are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryofetal development study in rats, pregnant animals were administered sugammadex intravenously at 0, 20, 100, and 500 mg/kg (0.2, 1.2, and 6.2-times the

MRHD of 16 mg/kg/day, respectively, based on AUC comparison) during fetal organogenesis (Gestational Day 6 - 17). No treatment-related maternal and embryofetal changes were observed.

In an embryofetal study in rabbits, pregnant New Zealand white rabbits were administered intravenous sugammadex at 0, 20, 65, 200 mg/kg (0.6, 2.4, and 8.2 times the MRHD, respectively, based on AUC comparison) during the period of organogenesis (Gestational Day 6-18). Fetal body weight decrease (5, 10, and 14%) was observed in the offspring in the presence of maternal toxicity (body weight and food consumption decrease). In addition, skeletal examination showed increased percentage of incomplete ossification of 1st to 4th sternebra and 6th sternebra, and unossified 1st metacarpal at 200 mg/kg. There was no evidence of teratogenicity at any dose.

In a prenatal and postnatal development study, pregnant rats (22/group) were administered sugammadex intravenously at 0, 30, 120, and 500 mg/kg (0.3, 1.3, 5.8 times the MRHD, respectively, based on AUC comparison) from Gestational Day (GD) 6 to Postnatal Day (PND) 21 (corresponding to the beginning of organogenesis through parturition and subsequent pup weaning). Increased postnatal mortality at ≥ 120 mg/kg on PND 1-4 were observed, which correlates with an increase in pups cannibalized by the Dam. The reason for the cannibalization is not known; however, an effect of sugammadex on steroidal hormones and/or pheromones cannot be ruled out. In addition, there were no drug-related effects on parturition in rats during evaluations for prenatal or postnatal development.

8.2 Lactation

Risk Summary

No data are available regarding the presence of sugammadex in human milk, the effects of sugammadex on the breast fed infant, or the effects of sugammadex on milk production. However, sugammadex is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRIDION and any potential adverse effects on the breastfed infant from BRIDION or from the underlying maternal condition.

Data

In a milk excretion study in rat dams following single intravenous dose of 20 mg/kg sugammadex on Postnatal Day 9, the maximum level was achieved at about 30 minutes after dosing with a ratio of milk to plasma level approximately 1:1. The oral exposure via milk did not induce effects on survival, body weight and physical or the behavioral developmental parameters monitored in rats in the prenatal and postnatal development studies *[see Use in Specific Populations (8.1)]*.

8.3 Females and Males of Reproductive Potential

Contraception

Upon administration of BRIDION, the efficacy of hormonal contraceptives may be reduced for up to 7 days. Advise females of reproductive potential using hormonal

contraceptives to use an additional non-hormonal contraceptive for the next 7 days following BRIDION administration *[see Drug Interactions (7.3)]*.

17 PATIENT COUNSELING INSTRUCTIONS

- Advise females of reproductive potential using hormonal contraceptives that BRIDION may reduce the contraceptive effect. Instruct females to use an additional non-hormonal method of contraception for the next 7 days following BRIDION administration *[see Drug Interactions (7.3)*.

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/s/

CAROL H KASTEN
11/27/2015

LYNNE P YAO
11/28/2015

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) CONSULTATION

Date:	November 23, 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 sodium for injection (Org 25969, SCH 900616, MK-8616)

General Information

NDA#:	22-225
Applicant:	Merck & Co., Inc., (on behalf of Organon USA, Inc., a subsidiary of Merck)
Drug Product:	Sugammadex sodium for injection (Org 25969, SCH 900616, MK-8616)
Request From:	Diana Walker, Regulatory Project Manager, DAAAP
Date of Request:	June 25, 2015
Date Received:	June 25, 2015
Materials Reviewed:	NDA 22-225 Complete Response (Sensitivity Analysis) June 19, 2015, Complete Response October 22, 2014, Complete Response December 20, 2012, DPARP Medical Officer Consultations dated May 2008, June 2008, November 2008, April 2009, September 2009, and December 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 safety 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 (P101) 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 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.

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 ***likely*** allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to ***known*** allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to identify cases consistent with anaphylaxis. For the evaluation of new molecular entities, DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling Criterion #1 above, in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. In addition, any cases reported by investigators or other healthcare professionals as "anaphylaxis" or "anaphylactoid" are accepted as cases of anaphylaxis, even if the case report does not detail more specific signs and symptoms.

III. Background and Regulatory History

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex 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, representing 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 as described below.

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 effects 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 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 (third) 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 provided the results of a repeat-dose clinical study (P101). DPARP was asked to review and provide feedback on the clinical study to evaluate the risk of hypersensitivity reactions with repeat exposure to sugammadex. The proposed study design, duration, interval of exposure, and patient number were 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

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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:

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- 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. Using this method, DPARP identified 1 case of anaphylaxis among the 137 potential hypersensitivity cases in 94 subjects. This case was also identified by the Applicant. 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, moderate swelling of the uvula and a reduction in peak expiratory flow by 26% 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.

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	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	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.

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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 Applicant has conducted an adequate investigation into the possible mechanisms of hypersensitivity and anaphylaxis. Importantly, 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 ([redacted] (b) (4)) supported the interpretations and conclusions of P101 data as reported by the Applicant.

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 ((b) (4) 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. There were 4 deaths reported in patients with complex medical conditions and multiple comorbidities.

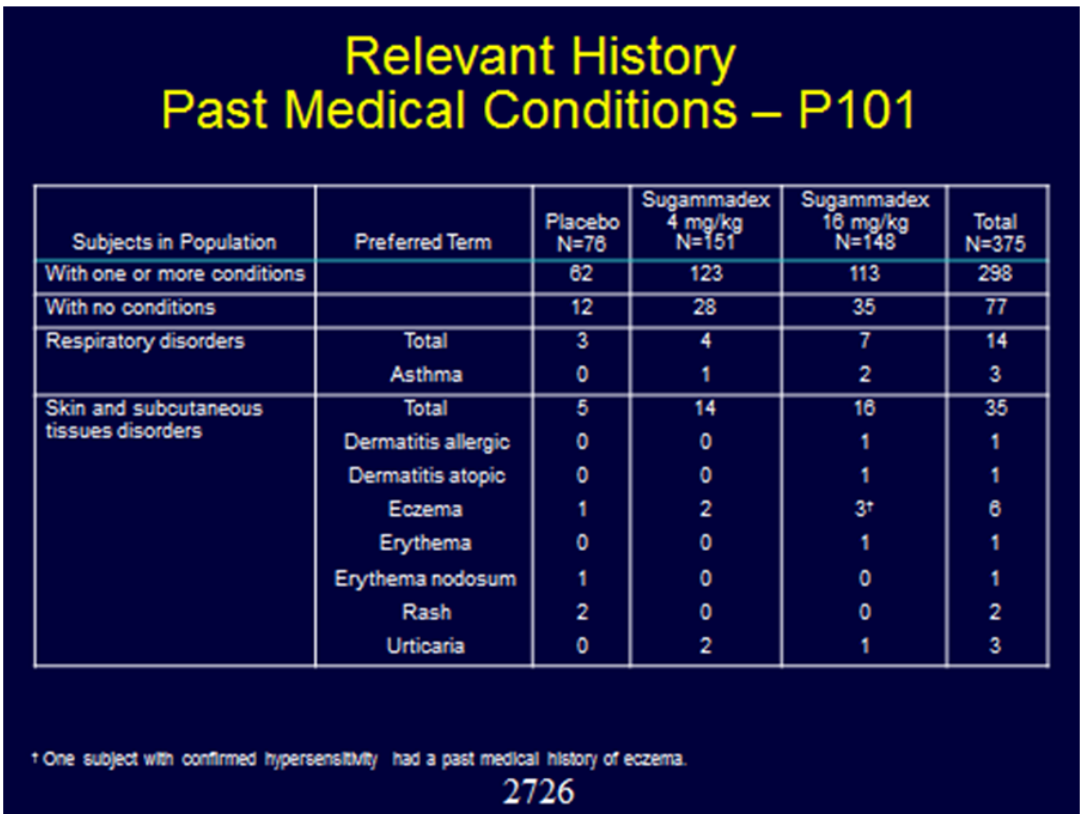
All but 8 of the 36 reports of adjudicated hypersensitivity were manifested by skin reactions such as erythema, rash and urticaria. The 8 cases not manifested by skin reactions reported symptoms such as laryngospasm, bronchospasm, musculoskeletal stiffness, respiratory arrest, decreased blood pressure, 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. Advisory Committee

This application was presented to the ALSDAC on November 6, 2015. The Applicant provided clarification regarding the frequency of hypersensitivity events in patients with other medical conditions, and specifically atopic disease (as seen in the slide below).



The Applicant stated that as the hypersensitivity reactions in P101 do not appear to be immune mediated, a history of an atopic condition would not be expected to be a risk factor for a hypersensitivity reaction to sugammadex. The Applicant displayed slide 2726 (above), which showed that there were a few subjects in study P101 who had a history of atopic conditions, such as asthma and various skin conditions (deemed "relevant medical history"). This information was further clarified in post-meeting comments to the Agency, using the summary table provided below:

Table 4. Number of adjudicated cases of hypersensitivity (HS) by relevant medical history and treatment group

	Placebo N=76	Sugammadex 4mg/kg N=151	Sugammadex 16mg/kg N=149	Total N=375
HS Cases in those with relevant medical history	0/4 (0%)	0/5 (0%)	1/9 (11.1%)	1/18 (5.6%)
HS Cases in those without relevant medical history	1/72 (1.4%)	10/146 (6.8%)	13/139 (9.4%)	24/357 (6.7%)

HS: hypersensitivity
Source: provided by the Applicant on November 13, 2015.

The Applicant stated that there were 18 of 375 subjects (4.8%) in P101 that had one of the conditions identified on Slide 2726 as seen in Table 4. Of the subjects with a history of one of the conditions identified on Slide 2726, only one of nine subjects (11.1%) in the 16 mg/kg treatment group had adjudicated hypersensitivity event, as compared to 13 of 139 subjects (9.4%) without relevant medical history. No subjects in the placebo or 4 mg/kg treatment groups with relevant medical history had adjudicated hypersensitivity. The Applicant stated that given the small numbers, it is not possible to draw definitive conclusions, but there is no evidence to indicate that these conditions are risk factors for hypersensitivity reactions to sugammadex.

Voting and Comments

After the data was presented by the Agency and the Applicant, the committee was asked if the Applicant presented sufficient information to characterize the risk of hypersensitivity/ anaphylaxis. The majority of the committee voted "Yes", agreeing that the Applicant presented sufficient information to characterize the risk of hypersensitivity/anaphylaxis (13 "Yes", 1 "No"). However, the committee expressed concerns regarding the risk of hypersensitivity in vulnerable populations such as pediatric, obstetric, obese, and elderly patients and suggested further studies in these vulnerable populations. The committee member who voted "No" also stated that there is a lack of information available to identify patients most at risk for experiencing anaphylactic or hypersensitivity events and was apprehensive that StudyP101 was conducted only in healthy volunteers.

The committee was also asked to discuss if there were issues that were not addressed by the data that warrant additional studies and if these studies should be conducted prior to or post approval. The committee suggested a large post approval single or multicenter trial evaluating electronic medical records in patients who may be at higher risk for reactions and poor outcomes, such as patients with asthma, allergic disease and elderly patients with multiple comorbidities. Members also suggested conducting further studies to elucidate the underlying mechanism for the hypersensitivity events.

Finally, the committee was asked if the efficacy, safety and overall risk-benefit profile of sugammadex support the approval of the application, and the committee unanimously voted "Yes" (14 "Yes", 0 "No"). The committee agreed that while additional data regarding the identification of patients at higher risk for experiencing reactions, the outcomes in vulnerable subpopulations and the identification of a potential mechanism related to the events would be beneficial, they agreed that the Applicant provided sufficient information to characterize the anaphylactic and hypersensitivity events to support approval. The committee felt that the risk of anaphylaxis associated with sugammadex administration would be sufficiently mitigated by the predominant use of the lower (4mg/kg) dose and its use in an operating room setting with the personnel and equipment required to treat these events.

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

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 and the Applicant has adequately investigated potential mechanisms of hypersensitivity.

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. As sugammadex will be used in a highly monitored clinical setting, with health care providers who are well-trained to address potential anaphylaxis and hypersensitivity, DPARP agrees that the risk of anaphylaxis and hypersensitivity can be addressed through labeling.

The advisory committee suggested various post-marketing studies to identify the population(s) most at risk for experiencing anaphylactic and hypersensitivity events, to describe the outcomes in vulnerable subpopulations, and to further elucidate the underlying mechanism related to these events. While we acknowledge the committee's concerns, DPARP concludes that the Applicant has performed sufficient analyses and mechanistic studies to address the anaphylaxis and hypersensitivity safety signal. . No individual patient or population risk factors were identified in this dedicated, repeat dose hypersensitivity study (P101). While it is true that Study P101 was conducted in a healthy volunteer population, this provides the most reliable information in an unconfounded manner. While we cannot use these data to determine the exact risk estimates and outcomes in patient populations with varying levels of illness/comorbidities, the data we have can help to inform this risk. Anaphylaxis is by definition, a severe life threatening event; and therefore an appropriate assessment of the risks and benefits of sugammadex administration must be considered when treating patients with multiple comorbidities. While the underlying mechanism remains uncertain, requiring additional mechanistic studies in the context of numerous studies with predominantly negative results is of limited utility. Accordingly, DPARP does not recommend any additional post marketing studies to evaluate anaphylaxis and hypersensitivity at this time.

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.

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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.
1. The signs and symptoms of HS must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment.

2. 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.

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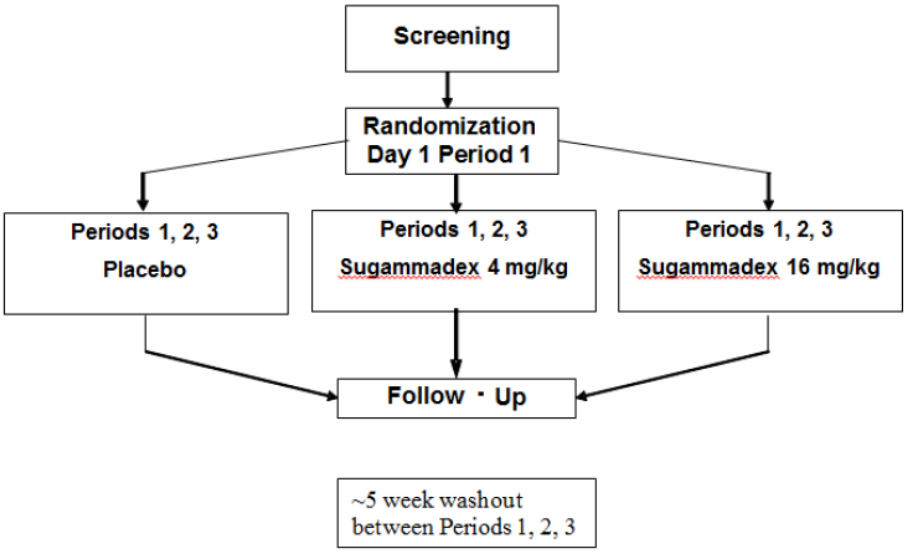
Figure 1. Trial Design Schematic



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.

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- 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)

Sampson Criterion 1 for Anaphylaxis:

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.

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- 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

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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.

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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

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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'.

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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[a]			Period 2[a]			Period 3[a]			
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[j]	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]		

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Visit	Screening Visit 1	Visit 2[c, s]			Visit 3[c, s]			Visit 4[c, s]			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.

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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 pre-dose 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:

- Tachypnea (>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

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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).

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/s/

ERIKA N TORJUSEN
11/23/2015

BANU A KARIMI SHAH
11/23/2015

BADRUL A CHOWDHURY
11/23/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 18, 2015

To: Diana Walker
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Koung Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Shenee' Toombs, Regulatory Review Officer - OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 22225
Bridion (sugammadex) Injection
Professional Labeling Review

As requested in DAAAP's consult dated July 10, 2015, OPDP has reviewed the substantially complete prescribing information for Bridion (sugammadex) Injection. The substantially complete prescribing information was provided to OPDP on Novmeber 5, 2015, via email by Diana Walker with the filename "\\fdsfs01\ODE2\DAAAP\NDA and sNDA\NDA 022225 (sugammadex Organon-Merck)\4th Cycle\Labeling".

OPDP has completed the review of the substantially complete prescribing information and have added our comments to the attached document.

We have no comments on the carton/container labeling submitted in the January 20, 2015 submission at this time.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Koung.Lee@fda.hhs.gov.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3848779

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

/s/

KOUNG U LEE
11/18/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 17, 2015

TO: Rigoberto A. Roca, M.D., Deputy Director
Sharon H. Hertz, M.D., Director
Diana Walker, Ph.D., Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22225

APPLICANT: Organon USA Inc. (Merck & Co., Inc.)

DRUG: Sugammadex injection (Org 25969/SCH 900616/MK-8616)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard, but this submission is in response to a CR action letter, so the review timeline is 6 months.

INDICATIONS: Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium

CONSULTATION REQUEST DATE: March 19, 2015* (in anticipation for resubmission)
CLINICAL INSPECTION SUMMARY GOAL DATE: November 21, 2015
DIVISION ACTION GOAL DATE (original): December 18, 2015
DIVISION ACTION GOAL DATE (revised): November 21, 2015
PDUFA DATE: December 18, 2015

I. BACKGROUND

Merck, Sharp & Dohme Corp. (Merck), a subsidiary of Merck & Co., Inc. submitted a third resubmission on behalf of Organon USA Inc., which is also a subsidiary of Merck & Co., Inc., seeking approval for sugammadex with the indication "reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium."

This resubmission is in response to the Complete Response (CR) letter received from the FDA on April 22, 2015. (Initial NDA submission was in 2007, which resulted in a "Not Approvable" letter; second submission (December 19, 2012) resulted in a CR letter September 20, 2013). The routine inspections from the December 19, 2012 resubmission indicated that there were protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P06042, including accidental unblinding at several sites. These major protocol deviations were also not reported in the final clinical study report (CSR). This resulted in an inspection of Merck September 16-27, 2013 and a resulting Untitled Letter September 5, 2014. In order to address the deficiencies identified in Study P06042 as a result of inspection findings, Merck conducted Study P101, a hypersensitivity trial similar in overall design to Study P06042.

Inspections from the third submission (October 22, 2014) found that Merck'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 prior to database lock. The FDA inspectors were not able to confirm the attestations of the statisticians and programmers (that they had not viewed the unblinded data) 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 any of the staff involved as they all were no longer working for Merck. The two site inspections conducted during the third review cycle had not shown any evidence of knowledge of allocation due to the potential for (accidental) unblinding of the statisticians.

This fourth submission (June 19, 2015) includes requested sensitivity analyses (as a Statistical Report) and case-by-case documentation for changes to the adverse event and hypersensitivity case reports agreed upon during the June 11, 2015 End of Review meeting.

In order to address the concerns raised regarding data reliability as a result of potential unblinding, it was decided that the remaining four sites participating in Study P101 should be inspected.

Study P101 entitled "*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*" was conducted at six trial centers: four in the United States and two in Belgium. The study began January 7, 2014 and completed July 1, 2014. There were 382 subjects screened and 375 healthy subjects were randomized to one of three parallel arms assigned to treatment with three successive single doses five weeks apart in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex or placebo. The primary safety endpoint was the number and percentage of subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo. Database lock was July 6, 2014.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 22225 in accordance with Compliance Program 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	**P101 # of Subjects Randomized and Dosed**	**Inspection Date**	**Classification**
Luc M.A.B. Van Bortel Site 001	40 subjects	06/08 – 06/11/2015	No Action Indicated (NAI)*
Magdalena Petkova Site 002	80 subjects	06/01– 06/05/2015	Voluntary Action Indicated (VAI)*
Dennis Swearingen Site 004	60 subjects	06/08 – 06/11/2015	No Action Indicated (NAI)
George J. Atiee Site 006	62 subjects	05/18 – 5/22/2015	No Action Indicated (NAI)

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. **Luc M.A.B. Van Bortel**
(b) (4)

   a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 42 randomized subjects' records were reviewed. Six screen failure records were also reviewed.

   b. **General observations/commentary:** There were 102 subjects screened and 42 subjects randomized into the study. Three subjects were withdrawn from the study; two never received investigational product. The first subject signed the informed consent on January 16, 2014. The Independent Ethics Committee (IEC) used for this study was (b) (4).

   The site records were legible and well organized. All data points in the source documents matched the provided line listings. Furthermore, the source documents contained the necessary identification points regarding staff members performing work on the study.

   The study blind appeared to remain intact for the duration of the study. Observations for Targeted Hypersensitivity Assessment and other adverse events were performed by delegated study staff that had no other role in the study. There was no evidence of under reporting of queried or spontaneous AEs.

   The communication file for the study was reviewed. There were no communications noted that suggested any knowledge of the allocation of the subjects. Particular attention was given during the time of sponsor staff potential unblinding March 11, 2014 through April 7, 2014.

   The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

   c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Magdalena Petkova (b) (4)

[redacted]

a. What was inspected: The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, investigator agreement, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 82 randomized subjects' records were reviewed. Twelve screen failure records were also reviewed.

b. General observations/commentary: A total of 142 persons were screened for study participation; there were 83 randomization numbers assigned; randomization number 2029 was never used; 82 persons were randomized, however, only 80 persons were dosed with study drug. Seven subjects were discontinued. The Independent Ethics Committee used for the study was [redacted] (b) (4). The first subject received study drug on 02/03/2014.

Each subject had a General Entry Form which documented the date of first drug administration and the activities around that administration, including the time, who did the activity, other procedures done, who did those procedures, timing of the procedures, and who quality controlled (rechecked) the activities.

As per the protocol and site procedures, the person dosing the subjects should not evaluate the subjects or have any other trial responsibility. Nurses [redacted] (b) (6) and [redacted] (b) (6) were designated as drug administrators only. However, [redacted] (b) (6) took vital signs of subjects 2001 – 2010 and later administered study drug to subjects 2063 – 2072. These protocol deviations were not reported on the protocol deviations line listing sent to FDA in the initial application submission of major protocol deviations. These deviations were subsequently submitted in the efficacy information amendment of June 17, 2015 in response to the 483 items found at the previous sponsor inspection. More deviations subsequently reported late by the sponsor were that subjects 2032 – 2042 had pre-dose activities done by [redacted] (b) (6) and were dosed by [redacted] (b) (6)

The communication file in the electronic site trial master file was also reviewed. There were no communications noted that suggested any knowledge of the allocation of the subjects. Particular attention was given during the time of sponsor staff potential unblinding March 11, 2014 through April 7, 2014.The blind appeared to remain intact for the duration of the study.

At the conclusion of the inspection, a 3-item Form FDA-483, Inspectional Observations, was issued. It was noted that the protocol was not followed as there were episodes where the drug administrators also participated in study-related procedures:

a. On 3 February 2014, Subjects 2001 - 2010 had study related vital signs taken by staff (b) (6). On 24 February, 2014, staff (b) (6) dosed Subjects 2063 - 2072.
OSI comment: As noted above, these deviations had been reported late by the sponsor.

b. Subject 2003 was dosed by study nurse (b) (6) 3 February 2014. (b) (6) also was involved with post-study questioning regarding AEs and procedures at visit discharge 17 March 2014.

c. Subject 2034 had pre-dose blood for laboratory safety done by (b) (6) on 12 February 2014. Subject was dosed by (b) (6) 13 February 2014.
OSI comment: As noted above, these deviations had been reported late by the sponsor.

d. Subject 2035 had pre-dose activities performed on 12 February, 2014 by (b) (6) and was dosed by (b) (6) on 13 February 2014.
OSI comment: As noted above, these deviations had been reported late by the sponsor.

e. Subject 2045 had pre-dose safety labs collected by (b) (6) on 30 January, 2014 and had catheter placed by (b) (6) on 17 February 2014.

Most of the adverse events were appropriately reported to the sponsor. However, there were a few abnormal laboratory tests that were not reported as adverse events. It was also noted that there is no assessment of causality for any adverse event noted in the subject files or AE logs. An Adverse Event Report was generated for each group dosed and sent to the sponsor. In this report, relationship is marked as a "yes" or 'no". There are no corresponding source records to support the assessment.
OSI comment: The PI stated that she did the assessment when she generated the AE Report.

The PI was cited for inadequate documentation of case reports and data pertinent to the study. The subject files contained templated worksheets but no progress notes to document what was written in the forms, how adverse events were assessed, why conclusions were made, why changes to the forms were made, etc. There was very poor oversight of the templated documents that were used in the trial. There was inaccurate information inserted into the templated worksheets, which had to be manually corrected as they were used. Review of the Targeted Hypersensitivity Assessment (THA) worksheets was very confusing as wrong worksheets were used for the assessments. Sometimes the assessors realized the error, would then cross out the header of the worksheet and put the correct header. At other times, the error was not noticed and the document was found in the assessments for that period but

had the wrong header. Documents were also found in subjects' files that did not have the subject ID number.
OSI comment: Although there was sloppiness at the site, the data in the line listings could be confirmed.

The PI was cited for failure to obtain informed consent. Subject 2070 (Screening Number 106) had screening procedures performed on 27 January, 2014 and received study drug in Period 1 on 24 February, 2014. The subject did not sign the informed consent form until 26 March, 2014.
OSI comment: This was an isolated incident.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Dennis Swearingen, M.D.
(b) (4)

a. What was inspected: The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All 61 subject files were reviewed.

b. General observations/commentary: Dr. Swearingen was not available during the inspection. The sub-investigator (b) (4) and other clinic staff were present. There were 161 subjects screened and 61 subjects enrolled into the study (but one was dropped prior to randomization). The first subject signed the informed consent 01/07/2014. The institutional review board of record was (b) (4). Subject documents were translated in Spanish and used as needed.

The study site enrolled subjects in cohorts of 10 subjects. Records were organized and legible. Each subject had a unique barcode ID that was scanned in prior to conducting visit procedures. It was verified that the dosing and assessing of subjects was conducted by different individuals. No discrepancies were noted between the source documents and data listings. All adverse reactions reported by subjects at protocol-specified time points were captured in the hypersensitivity assessment forms. There was no documentation of any discussion of allocation by the site and sponsor staff. A sponsor audit had

occurred at the site March 24–26, 2014.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. **George J. Atiee, M.D.**
(b) (4)

a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, recruitment materials, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Fifty-five subject records were reviewed.

b. **General observations/commentary:** There were 160 subjects screened, 62 subjects enrolled into the study and 53 subjects who completed the study. The IRB used for the study was (b) (4). The first study subject signed the ICF on 1/16/2014.

All records were in order, although there were a lot of write-overs, footnotes and corrections. Dosing for all subjects was carried out utilizing a single nurse administering study medication as specified by the protocol. The nurse administering the study medication did not subsequently assess subjects for adverse events, including targeted hypersensitivity assessments, as required by the protocol. There was no evidence of unblinding. All protocol deviations were reported. There were no drug accountability issues. There were no discrepancies noted with source documents versus the line listings.

The correspondence between the site and sponsor was maintained in a storage box, roughly in chronological order. Review of this correspondence did not reveal any evidence of a change in study procedures at the site during or following the period of potential unblinding (March 11- April 7, 2015) of statisticians at the sponsor site.

It was reported that the PI stratified the subjects by gender, which was not per

protocol. However, the sponsor was present for the randomization of the first treatment group. The Sponsor's Clinical Director was present and did not indicate to the site any concern or objections with the conduct of randomization/stratification of subjects.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA resubmission consisted of all four remaining clinical sites of the six sites participating in Study P101: two domestic and two foreign clinical sites.

Observations noted above for all four sites are based on the review of the Establishment Inspection Reports. One site, Dr. Petkova, was issued a Form FDA-483 citing inspectional observations and classification is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.

Drs. Van Bortel, Swearingen and Atiee were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites are considered reliable based on the available information.

The study blind appeared to remain intact for the duration of the study at all four sites despite the potential unblinding of sponsor statisticians between March 11 and April 7, 2014. There was no evidence found that suggested any knowledge of the allocation of the subjects.

In general, based on the inspections of the four clinical sites, the inspectional findings of these sites support validity of data as reported by the Sponsor under this NDA.

{See appended electronic signature page}

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11/18/2015

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 21 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 22225
Product Name and Strength:	Bridion (Sugammadex) Injection 500 mg/5 mL and 200 mg/2 mL
Submission Date:	June 19, 2015
Applicant/Sponsor Name:	Organon
OSE RCM #:	2015-1452
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

Organon re-submitted container labels, carton labeling, and prescribing information after receiving a Complete Response letter dated April 22, 2015. The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels, carton labeling, and prescribing information (Appendix A) to determine if they are acceptable from a medication error perspective. We previously reviewed the labels and labeling in OSE Review# 2014-2252-1 and determined they were acceptable from a medication error perspective.[1]

2 CONCLUSIONS

The proposed container labels and carton labeling are acceptable from a medication error perspective.

[1] Schlick J. Label and Labeling Review for Bridion (NDA 022225) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 23. 4 p. OSE RCM No.: 2014-2252-1.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES H SCHLICK
07/21/2015

BRENDA V BORDERS-HEMPHILL
07/22/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Pharmacovigilance Review

Date:	4/28/15
Reviewer:	Martin Pollock, PharmD, Safety Evaluator Division of Pharmacovigalance-2 (DPV-2)
Team Leader:	Sara Camilli, PharmD, Safety Evaluator Team Leader DPV-2
Division Director:	S. Christopher Jones PharmD, MS, MPH, Deputy Director DPV-2
Product Name:	Bridion (Sugammadex)
Subject:	All events
Application Type/Number:	NDA 22-225
Applicant/Sponsor:	Merck
OSE RCM #:	2014-2378

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Reference ID: 3742280

EXECUTIVE SUMMARY

In support of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) review of NDA 22225 for Bridion (sugammadex), DAAAP consulted DPV-2 to review the FDA's Adverse Event Reporting System (FAERS) database for select adverse event reports that may further inform the safety of the product. Bridion is not currently an FDA approved drug, but it is approved in several other countries. DPV-2 found 31 FAERS cases for sugammadex that were not part of a Merck postmarket adverse event report evaluation, which was submitted in support of the Bridion NDA. The Merck evaluation described 886 postmarket reports of AEs associated with sugammadex. The 31 new FAERS cases reported 75 MedDRA Preferred Terms (PTs); about half were labeled and half were unlabeled (per Bridion's proposed labeling). There were 11 PTs reported two or more times; the most frequently reported event was cardiac arrest (n=4, labeled). There was a single fatal case of cardiac arrest for which sugammadex could have contributed. Overall, these findings represent a small number of cases and should be considered in context with the other reports (n=886) submitted by Merck.

Based on our review of this small dataset, we do not offer any labeling recommendations.

1 INTRODUCTION

1.1 BACKGROUND

Sugammadex is a modified cyclodextrin that selectively binds aminosteroidal neuromuscular blockers. Merck initially submitted a NDA for sugammadex (trade name Bridion; NDA 22225) in 2007 for the indication of neuromuscular blockade reversal of rocuronium or vecuronium. DAAAP issued a not approvable (NA) letter in 2008. Merck replied to the NA letter in 2012; DAAAP found the response to be inadequate and issued a complete response (CR) in 2013. Merck has received approval for sugammadex in 75 other countries (European Union was first in 2008), with actual marketing in 41 countries.[1] Merck's 2014 response to the 2013 CR provided a postmarket safety update consisting of 886 (1798 MedDRA Preferred Term (PT) mentions) foreign cases received from 2008 to April 21, 2014.[2]

DAAAP has asked DPV-2 to provide summary information (event type, outcomes, and time period) for all sugammadex FAERS reports that were not included in Merck's submission of 886 reports.

1.2 PRODUCT LABELING

Safety-related information from the sponsor's proposed sugammadex labeling is located in Appendix 7.1.

[1]Silber, C, (Merck Safety Director); Sugammadex Periodic Update Report (European Union): 2/1/12-1/31/13; approved by Merck on 3/27/13.
[2]NDA 22-225: Sugammadex injection (Org 25969/SCH 900616/MK-8616); Response to Complete Response Letter: Clinical Overview; received by FDA on 10/22/14.

Reference ID: 3742280

2 METHODS

2.1 CASE DEFINITION

We included cases that had a temporal relationship between the event(s) and sugammadex administration[3]

Cases were excluded if any of the following were evident:

- Lack of temporal relationship between the event(s) and sugammadex administration
- Event(s) clearly attributed to
  - ♦ underlying disease
  - ♦ other drug therapy
- Substantial missing information that prevents assessment

2.2 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	12/4/14
Time period of search	1/1/69-11/4/14
Product Terms (as ingredient)	Sugammadex, Sugammadex Sodium
Product role	Suspect or concomitant [+]
* See Appendix 7.2 for a description of the FAERS database. [+] DPV-2's usual strategy is to search only for the drug role as *suspect*. However, to be more comprehensive, we expanded this search to *any* drug.	

.

3 RESULTS

The FAERS search retrieved 191 (non-deduplicated) expedited reports; one was domestic[4] and the remaining were foreign reports. The product role of sugammadex was suspect (n=146) and concomitant (n=45).

The reports were submitted by 21 different manufacturers; Merck was the most common (Table 2).

[3]Some events like cardiac, respiratory, and hypersensitvity events can be expected to occur within less than an hour after an offending *i.v.* drug like sugammadex. Other events like liver renal, and, metabolic changes, could take longer (e.g. days) to appear.
[4]Patient was enrolled in a sugammadex clinical study.

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Table 2. FAERS Sugammadex Reports (n=191): Submitting Manufacturer

Index	Mfr	N	Index	Mfr	N
1	Merck	119	11	Actavis	1
2	Schering Plough	15	12	Actavis South Atlantic	1
3	Astrazeneca	13	13	Boehringer Ingelheim	1
4	Baxter	10	14	JHP	1
5	Abbvie	9	15	Mallinckrodt	1
6	Abbott	5	16	Novartis	1
7	Sandoz	3	17	Organon	1
8	Glaxosmithkline	2	18	Roxane	1
9	Mylan	2	19	Shire	1
10	Roche	2	20	Vertex	1
			21	Watson	1

We stratified the191 report dataset into four subsets based on the manufacturer sender, manufacturer received date and a third factor that enumerated submission overlap between FAERS and Merck's NDA postmarketing (n=886) submission (Table 3).

Table 3. Sugammadex FAERS Reports (n=191) Subsets

Subset number	Sender Mfr*	Mfr received date†	in FAERS	in Merck's NDA post marketing submission(n=886)	N
1	Merck‡	<=4/21/14	Yes	Yes	108
2	Merck‡	<=4/21/14	Yes	No	14
3	Merck	>4/21/14	Yes	No	13
4	Other than Merck	No restriction	Yes	No	56

*Mfr=manufacturer

†When a time period is a parameter, DPV-2 usually searches FAERS for FDA-received date. We assume the sponsor's 4/21/14 data lock date to mean when these reports were received by Merck. Therefore, we used "Initial manufacturer received date" in our FAERS analysis to eliminate any undercounting that could have resulted from using FDA-received date.

‡Organon was the original sponsor for sugammadex. Schering-Plough acquired Organon in 2007. Schering-Plough received sugammadex approval in the European Union on 7/29/08. Schering-Plough merged with Merck in 2009. Therefore, some of these "Merck" reports were sent to FDA by Organon or Schering-Plough.

We do not know why subset #2 was not included in Merck's submission. To inform DAAAP about these "missing" 14 cases that we would expect to be part of Merck's n=886 data set, DPV-2 sent DAAAP these cases as 'preliminary information' on February 5, 2015.

Datasets #2[5], #3 and #4 (n=83 combined) are the FAERS reports which were not in Merck's submission. We established a case series of 31[6] after individual review of the 83 reports (Table 4).

[5]Although we have already sent DAAAP 14 (Dataset #2) of these 83 reports, we include them in this case series.

[6]Drug role (Table 1) for sugammadex was suspect (n=21) and concomitant (n=10). Sender (Table 2) was Merck for 12 cases. FDA received year: 2008 (n=1), 2012 (n=10), 2013 (n=7), 2014 (n=13).

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Table 4. Sugammadex FAERS Reports (n=83; Dataset #2, #3 and #4): Case Selection	
Report status	**N**
Initial number of reports	83
Duplicates	7
Exclusions (as per Section 2.1)	45
Included for case series	31

The 31 cases were coded with 75 MedDRA Preferred Terms (PTs) mapped to 17 different System Organ Classes (SOCs). The four most common SOCs representing more than half (53%) of all PTs were Cardiac, Injury and Poisoning, Respiratory and Nervous (Table 5).

Table 5. Sugammadex FAERS Case Series (n=31): Event (Preferred Term) count by SOC					
Index	SOC	N	Index	SOC	N
1	Card	19	10	Vasc	3
2	Inj&P	8	11	Blood	2
3	Resp	7	12	Skin	2
4	Nerv	6	13	Genrl	2
5	Inv	5	14	Gastr	2
6	Psych	5	15	Surg	2
7	Renal	4	16	Eye	1
8	Immun	3	17	Metab	1
9	Musc	3			

Table 6 shows the labeling status[7] (per Appendix 7.1) for all of the reported PTs (n=75). The 75 PTs were split in approximately equal amounts of labeled versus unlabeled.

Table 6. Sugammadex FAERS Case Series (n=31): Labeling Status for PT Mentions (n=75)		
Label status	Labeled*	Unlabeled
N	40	35[†]
Percentage	53.3	46.7
* Explicit or Implicit[7] The 35 unlabeled PT mentions came from 19 cases.		

Table 7 shows the labeling status for PTs with two or more mentions. Cardiac events are the most commonly reported AEs. Most (9/11) all of these PTs are labeled (n=8) or not relevant for sugammadex (n=1[8]) and are therefore not unexpected.

[7]Some PTs are *explicitly* unlabeled. However, the proposed package insert mentions events that are similar to the unlabeled PTs and therefore can be considered to be *implicitly* labeled. Comments are provided for these PTs are considered *implicitly* labeled.
'Toxicity to various agents' referred to rocuronium, not sugammadex.
[8]Toxicity to various agents' referred to rocuronium, not sugammadex.

Reference ID: 3742280

Table 7. Sugammadex FAERS Case Series (n=31); Labeling Status for PTs with Count >=2					
SOC	PT	N	Labeled: yes or no	If labeled: explicit or implicit	Comments
Card	Cardiac arrest	4	Yes	Explicit	
Card	Ventricular fibrillation	2	No		
Card	Bradycardia	2	Yes	Explicit	
Card	Atrioventricular block second degree	2	No		
Inj&P	Toxicity to various agents	2	No		Referred to rocuronium
Inj&P	Post procedural haemorrhage	2	Yes	Explicit	
Musc	(b) (4)	2	Yes	Explicit	
Nerv	Depressed level of consciousness	2	Yes	Implicit	Labeled for depressed respiratory function
Resp	Respiratory arrest	2	Yes	Implicit	Labeled for depressed respiratory function
Resp	Hypoventilation	2	Yes	Implicit	Labeled for depressed respiratory function
Surg	Endotracheal intubation	2	Yes	Implicit	Labeled for neuromuscular (NM) blockade recurrence following extubation; prolonged NM blockade

Overall, most (n=33; 94%) of the 35 unlabeled events (Table 6) have only 1 mention*; ventricular fibrillation and toxicity to various agents* each have 2 mentions. The labeling status of the remaining PTs (all with a count of 1 each) are listed in Appendix 7.3.

There was one fatality among the 31 cases:

> FAERS Case# 10568428: 72-year-old male patient with cancer of duodenal papilla and asymptomatic cerebral infarction (left parietal lobe), depression, arteriosclerosis and a medical history of liver disorder underwent a pylorus-preserving pancreaticoduodenectomy. He was given sugammadex (2.3 mg/kg at 1600 hrs) for rocuronium reversal. His blood pressure (BP) increased; he was given nicardipine and flumazenil (0.25 mg).[9] Anesthesia was completed at 1640 hrs. The patient entered the ICU at 1646 hrs with hypertension (147/100 mm Hg). At 1700 hrs, he lost (BP 199/95 mm Hg) and regained consciousness. At 1715 hrs, he had bradycardia and loss of palpable carotid artery pulse (pulseless electrical activity); CPR was performed. He experienced ventricular fibrillation at 1727 hrs and a depressed ST wave. Despite treatment with adrenalin and defibrillation, he had a cardiac arrest at 1751 hrs and died at 1900 hrs.
>
> Postmortem computed tomogram (CT) revealed severe coronary artery sclerosis. Acute myocardial infarction (AMI) was mentioned as the cause of death; an autopsy was not performed. The reporting physician also 'felt that cardiac arrest was related to sugammadex sodium (BRIDION) and rocuronium bromide (ESLAX) and considered that nicardipine hydrochloride was the other causative factor.' There were 14 other (in addition to sugammadex and rocuronium) medications given during the procedure.[10] We do not know the time intervals between the administration of these other medications and sugammadex.

[9]There was no benzodiazepine administration mentioned (for which flumazenil is indicated as a reversal agent).
[10]Flomoxef (cephalosporin), ephedrine, phenylephrine, aprotinin, factor XII, fibrinogen, thrombin, albumin, fentanyl, remifentantil, propofol, mepivacaine, sevoflurane and lidocaine.

Reference ID: 3742280

This case was coded for the MedDRA PTs: acute myocardial infarction, bradycardia, cardiac arrest, electrocardiogram ST segment depression, hypertension, hypotension, pulseless electrical activity and ventricular fibrillation.

Reviewer comment: *Sugammadex may have contributed to the initial cardiovascular insult, from which the patient did not recover. However, this case was confounded by pre-existing cardiovascular pathology and multiple concomitant medications.*

A line listing of FAERS Case ID, version and manufacturer control number, subset (Table 3) and sugammadex drug role for the 31 cases is in Appendix 7.4

4 DISCUSSION

We found 31 FAERS cases for sugammadex that were not part of Merck's 886 postmarket report submission for the Bridion NDA. In all of these cases, based upon temporality (Section 2.1), sugammadex may have contributed to the events. The most common events were cardiac (e.g., cardiac arrest, bradycardia) or respiratory (e.g., respiratory arrest), which are listed in the sponsor's proposed labeling. Our case series (n=31) is less than 5% of all spontaneous postmarket adverse event reports for sugammadex; the large majority of the reports (n=886) were previously submitted to DAAAP by Merck. Therefore, this small case series must be considered in the context of all the available postmarketing data.

The single patient (72-year-old male) who died from a cardiac arrest, first experienced hypertension (unlabeled) and then depressive cardiac events of bradycardia and arrest; he also experienced an arrhythmia (ventricular fibrillation). The initial insult (hypertension) appeared to occur a short time (i.e., some number of minutes) after sugammadex administration. However, before sugammadex, the patient received more than a dozen other perioperative drugs. Some of these drugs could have been contributory, depending on how close they were administered to the time sugammadex was given. Unfortunately, the timing of these concomitant drugs is unknown. The post-mortem finding of coronary arteriosclerosis also could have been a contributory factor. Despite all of these factors, we believe sugammadex could have played a role.

There were 35 unlabeled event mentions included in 19 cases. With the exception of ventricular tachycardia in a fatal case, all of the other 34 PT mentions were from non-fatal cases. About a quarter (9/35; 26%) of the unlabeled PT mentions (representing 4 cases) are cardiovascular. Ventricular fibrillation (n=2) was the most common (Table 7). Other cardiac events (single mention) included ventricular flutter, supraventricular tachycardia, electrocardiogram ST segment depression and hypertension (Appendix 7.3). These types of cardiac events can be life threatening. These nine unlabeled cardiovascular events and the 26 other unlabeled events must be considered in the context of the 886 other reports submitted by Merck.

Reference ID: 3742280

5 CONCLUSION

DPV-2 found 31 FAERS cases for sugammadex that were not part of Merck's 886 postmarket report submission for NDA 22225. The 31 cases were coded with 75 PTs; about half were considered labeled and the other half unlabeled (per Bridion's proposed labeling). There were 11 PTs reported twice or more; the most frequently reported event was cardiac arrest (n=4, labeled). There was a single fatal case of cardiac arrest for which sugammadex could have contributed. Overall, these findings represent a small number of cases and must be considered in context with the other reports (n=886) submitted by Merck.

6 RECOMMENDATIONS

Based on review of these 31 FAERS cases, we do not offer any labeling recommendations. We recommend DAAAP consider our FAERS findings in the context of the larger (n=886) postmarket dataset provided by Merck.

1 Page of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

7.2 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 SUGAMMADEX FAERS CASES (N=31): PTS (COUNT OF 1 EACH) AND LABEL STATUS;[11] (THIS IS A CONTINUATION OF TABLE 7, SECTION 3)

SOC	PT	N	Label status: yes no	If labeled 'yes': explicit or implicit	Comments
Blood	Ovarian haemorrhage	1	Yes	Implicit	Labeled for bleeding and increased bleeding time (lab parameter)
Blood	(b) (4) test abnormal	1	Yes	Explicit	
Card	Acute myocardial infarction	1	No		
Card	Atrioventricular block	1	Yes	Implicit	Labeled for cardiac arrest
Card	Coronary artery occlusion	1	No		
Card	Cyanosis	1	Yes	Implicit	Labeled for depressed respiratory function
Card	Myocardial ischaemia	1	No		
Card	Pulseless electrical activity	1	Yes	Implicit	Labeled for cardiac arrest
Card	Supraventricular tachycardia	1	No		
Card	Tachycardia	1	Yes	Explicit	
Card	Ventricular flutter	1	No		
Eye	Eye pain	1	No		
Gastr	Nausea	1	No		
Gastr	Tongue oedema	1	Yes	Explicit	
Genrl	Chills	1	No		
Genrl	Drug interaction	1	No		Not clear which (of several) drugs interacted
Immun	Anaphylactic reaction	1	Yes	Explicit	
Immun	Drug hypersensitivity	1	Yes	Explicit	
Immun	Hypersensitivity	1	Yes	Explicit	
Inj&P	Delayed recovery from anaesthesia	1	Yes	Explicit	
Inj&P	Overdose	1	No		Referred to rocuronium
Inj&P	Recurrence of neuromuscular blockade	1	Yes	Explicit	
Inj&P	Subcutaneous haematoma	1	Yes	Implicit	Labeled for bleeding and increased bleeding time (lab parameter)
Inv	Blood pressure increased	1	Yes	Explicit	
Inv	C-reactive protein increased	1	No		
Inv	Electrocardiogram st segment depression	1	No		
Inv	Hepatic enzyme abnormal	1	No		
Inv	Urine output decreased	1	No		

[11] Some PTs are *explicitly* unlabeled. However, the proposed package insert mentions events that are similar to the unlabeled PTs and therefore can be considered to be *implicitly* labeled. When PTs are listed individually, unlabeled events that are implicitly labeled will have an explanation.

Reference ID: 3742280

SOC	PT	N	Label status: yes no	If labeled 'yes': explicit or implicit	Comments
Metab	Diabetes insipidus	1	No		
Musc	Rhabdomyolysis	1	No		
Nerv	Aphasia	1	No		
Nerv	Dyskinesia	1	No		
Nerv	Hypoxic-ischaemic encephalopathy	1	Yes	Implicit	Labeled for depressed respiratory function
Nerv	Tremor	1	No		
Psych	Anxiety	1	No		
Psych	Delirium	1	No		
Psych	Hallucination	1	No		
Psych	Polydipsia psychogenic	1	No		
Psych	Psychotic behaviour	1	No		
Renal	Chromaturia	1	No		
Renal	Hyposthenuria	1	No		
Renal	Polyuria	1	No		
Renal	Urine analysis abnormal	1	No		
Resp	Haemoptysis	1	No		
Resp	Laryngeal oedema	1	Yes	Implicit	Labeled for swelling of pharynx, bronchospasm pulmonary obstructive events
Resp	Laryngospasm	1	Yes	Implicit	Labeled for swelling of pharynx, bronchospasm pulmonary obstructive events
Skin	Angioedema	1	Yes	Implicit	Labeled for swelling of tongue, swelling of pharynx, urticaria
Skin	Rash	1	Yes	Explicit	
Vasc	Hypertension	1	No		
Vasc	Hypotension	1	Yes	Explicit	
Vasc	Shock	1	No		

7.4 SUGAMMADEX FAERS CASES (N=31): CASE ID, VERSION, MANUFACTURER CONTROL NUMBER, SUBSET AND SUGAMMADEX DRUG ROLE

Index	Case ID	Version #	Manufacturer control number	Subset[12]	Sugammadex Drug Role[13]
1	10300184	3	JP-BAXTER-2014BAX023620	Subset #4	Suspect
2	10309434	2	JP-009507513-1406JPN003458	Subset #3	Suspect
3	10342793	1	FR-ASTRAZENECA-2014SE53065	Subset #4	Suspect
4	10405874	4	KR-009507513-1408KOR013024	Subset #3	Suspect
5	10446411	4	KR-009507513-1409KOR000531	Subset #3	Suspect
6	10451574	2	KR-009507513-1409KOR002154	Subset #3	Suspect
7	10468691	3	JP-009507513-1409JPN010099	Subset #3	Suspect
8	10479013	1	JP-BAXTER-2014BAX056854	Subset #4	Suspect
9	10506172	2	JP-009507513-1410JPN002814	Subset #3	Suspect
10	10560623	1	JP-MALLINCKRODT-T201403919	Subset #4	Concomitant
11	10568428	2	JP-009507513-1410JPN003063	Subset #3	Suspect
12	10596589	1	TR-ACTAVIS-2014-24790	Subset #4	Suspect
13	6795900	2	2008-182751-NL	Subset #2	Suspect
14	8396703	2	JP-ASTRAZENECA-2012SE05100	Subset #4	Suspect
15	8441930	1	AU-ROCHE-1044540	Subset #4	Suspect
16	8444612	2	JP-ASTRAZENECA-2012SE07535	Subset #4	Suspect
17	8547580	1	JP-ASTRAZENECA-2012SE10651	Subset #4	Concomitant
18	8676940	4	DE-009507513-2012SP006053	Subset #2	Suspect
19	8883862	1	JP-WATSON-2012-17750	Subset #4	Suspect
20	8888701	1	US-009507513-1209USA007137	Subset #2	Suspect
21	8898057	1	DE-MERCK-2012SP013883	Subset #2	Suspect
22	8941787	1	JP-ASTRAZENECA-2012SE73564	Subset #4	Concomitant
23	8941887	1	JP-ASTRAZENECA-2012SE48490	Subset #4	Concomitant
24	9099930	1	JP-ASTRAZENECA-2012SE80427	Subset #4	Suspect
25	9189642	2	JP-MYLANLABS-2013S1006157	Subset #4	Concomitant
26	9346099	2	JP-BAXTER-2013BAX017296	Subset #4	Concomitant
27	9375376	2	JP-009507513-1306JPN001597	Subset #2	Concomitant
28	9664104	1	JP-ABBVIE-13P-087-1164667-00	Subset #4	Concomitant
29	9542899	1	CH-ASTRAZENECA-2013SE69765	Subset #4	Suspect
30	9784036	2	JP-ABBVIE-13P-087-1182394-00	Subset #4	Concomitant
31	9996866	4	JP-BAXTER-2014BAX011166	Subset #4	Concomitant

[12]See Table 3 in Section 3: RESULTS.
[13]As coded in FAERS.

Reference ID: 3742280

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/s/

MARTIN L POLLOCK
04/28/2015

SARA L CAMILLI
04/28/2015

STEVEN C JONES
04/28/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Review

Date:	April 22, 2015 **Consult Received:** January 12, 2015
From:	Carol H. Kasten, MD, Medical Officer Division of Pediatric and Maternal Health, Office of Drug Evaluation IV (ODE IV)
Through:	Tamara Johnson, MD, MS, Acting Team Leader Division of Pediatric and Maternal Health, ODE IV Lynne P. Yao, MD, Acting Director Division of Pediatric and Maternal Health, ODE IV
To:	Division of Anesthesia, Analgesia and Addiction Products
Drug:	Bridion (Sugammadex), NDA 22225
Applicant Proposed Indication:	Bridion is a selective relaxant binding agent indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium
Subject:	Labeling Review
Applicant:	Organon USA, Inc.
Consult Request:	"DAAAP is requesting that PMHS please assist us in review the labeling for the new PLLR format."

INTRODUCTION

Organon USA, Inc., re-submitted this New Molecular Entity (NME) NDA for Bridion (sugammadex) with the proposed indication for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium to the Agency on October 30, 2014. The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for Pregnancy (Section 8.1) and Lactation (Section 8.2) for sugammadex in the Pregnancy and Lactation Labeling Rule (PLLR) format.

BACKGROUND

Brief Regulatory History

The sugammadex regulatory history is extensive. This DPMH-MHT review is part of the current Class 2 resubmission dated October 30, 2014. Significant events and their dates for the sugammadex NDA are summarized here:

October 31, 2007	Original Submission
February 27, 2008	Major Amendment
July 30, 2008	Not Approved
December 12, 2012	Complete Response
March 1, 2013	Major Amendment
January 3, 2013	Resubmission – Class 2
September 20, 2013	Complete Response
October 30, 2014	Resubmission – Class 2

Clinical Pharmacology

Sugammadex is an NME in a new class of drugs, the modified δ cyclodextrins. Gamma cyclodextrins are cyclic oligosaccharide carbohydrates formed by the bacterial degradation of starches.[1] Sugammadex was specifically developed to reverse the nondepolarizing neuromuscular blocking agents (NMBA) such as rocuronium or vecuronium.[2] The ring structure of sugammadex confers its ability to form a complex with rocuronium or vecuronium. The NMBA is 'encapsulated' by sugammadex which thereby reverses the block at the neuromuscular junction. This is a novel mechanism to reverse NMBAs, independent of acetylcholinesterase, and appears to be a stable 1:1 conformation with one sugammadex molecule encapsulating one rocuronium (or vecuronium) molecule.[3,4]

Following intravenous injection, sugammadex is not metabolized and is excreted unchanged in the urine. If administered in a patient treated with rocuronium or

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[1] Shields M, Giovanneli M, *et al*. Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block. Br J Anaesth 2006; 96: 36–43. doi:10.1093/bja/aei314.

[2] Sacan O, White P, *et al*. Sugammadex Reversal of Rocuronium-Induced Neuromuscular Blockade: A Comparison with Neostigmine–Glycopyrrolate and Edrophonium–Atropine. Anesth Analg 2007;104:569 – 74).

[3] Clinical pharmacology online©, www.clinicalpharmacology-ip.com Elsevier. Gold Standard. Revision date: October 29, 2008. Accessed March 7, 2015.

[4] See Sacan, *et al.*

vecuronium, the drug is excreted as a sugammadex-rocuronium (or vecuronium) complex. Ninety percent of sugammadex is excreted within 24 hours of intravenous administration, 96% of the dose is excreted in urine. [5] Sugammadex has been found to interact with hormonal contraceptives and the labeling instructs patients to consider they have missed one dose of their oral contraceptive. Patients using non-oral hormonal contraceptives are advised to use an alternate contraceptive method for 7 days following a bolus dose of sugammadex.[6]

Drugs currently used in the U.S. to reverse an NMBA are a combination of an acetylcholinesterase inhibitors and a muscarinic antagonist (ex. neostigmine and glycopyrrolate, edrophonium and atropine). The onset of action of this drug combination is slow and is accompanied by adverse effects such as tachycardia, bradycardia, dry mouth, nausea and vomiting.[7] The applicant's intent is to provide an alternative to an acetylcholinesterase inhibitor-muscarinic antagonist.

Sugammadex is not expected to be used repeatedly during a woman's pregnancy; however, pregnant women may be exposed to sugammadex because they are at risk of serious medical problems which may require surgery just as non-pregnant adults.[8] Intestinal obstruction may occur in pregnancy, particularly in women with a previous history of abdominal or pelvic surgery. There are many other surgical emergencies which may require use of general anesthesia during pregnancy, and reversal of neuromuscular blockade with sugammadex could be used.

Nonclinical Data

The animal data indicates that no congenital malformations were found in embryo-fetal studies of rats and rabbits following sugammadex exposure at doses that were six to eight times higher the maximum recommended human dose. The applicant also found that sugammadex was transferred across the placenta, albeit at very limited levels following a single dose in rats (dose not stated). In repeated dose, pre- and postnatal studies in rats, some transfer of sugammadex to fetal tissues was reported. Renal excretion into the amniotic fluid was also noted although no fetal malformations were demonstrated (dose not stated). In single dose, juvenile and adult rat studies ^{14}C-labeled sugammadex was clearly demonstrated to be deposited in bone with significantly higher amounts in juvenile rats compared to adult. The levels were considered very low and extensive bone studies demonstrated no deposition of drug in the epiphyses. For further details on the nonclinical studies, refer to the Pharmacology Toxicology review by Z. Alex Xu, PhD, DABT, dated December 20, 2012, DARRTS Reference ID: 3362422.

[5] Bridion (sugammadex) proposed labeling
[6] Bridion (sugammadex) proposed labeling
[7] See Sacan, *et al.*
[8] Augustin G, Majerovic M. Non-obstetrical acute abdomen during pregnancy. Eur J Obstet Gynec Reprode Biol.2007;131: 4–12.

DATABASE AND LITERATURE REVIEW

The Reprotox[9] review only discussed sugammadex in conjunction with rocuronium. No data on sugammadex use in pregnancy in humans or animals were described. The TERIS[10] review noted that no epidemiological studies of prenatal exposure to sugammadex have been reported and the animal teratology studies by the applicant have not been published. There was no review of sugammadex available in LactMed.[11]

Although Sugammadex is an NME in the U.S., the drug has been approved in Europe since 2008. A search of PubMed found several references using the search terms sugammadex, pregnancy and English; however, none of the publications described use of sugammadex during human organogenesis in the first trimester. All of the publications described outcomes of immediate postpartum use of sugammadex to reverse the neuromuscular blockade from rocuronium (or vecuronium) following completion of the cesarean delivery. Nothing can be inferred from these references regarding the risk of teratogenesis or harm to the fetus or pregnant mother following exposure to sugammadex.

Use of Sugammadex in the Immediate Postpartum Period

There are two case series publications among the references found in PubMed which describe use of sugammadex immediately postpartum. Williamson, *et al*. reviewed a case series of 17 pregnant women for whom sugammadex was used to reverse rocuronium at the completion of the cesarean delivery.[12] Rocuronium was rapidly reversed with sugammadex in each woman with few difficulties. In two instances, the delivery was emergent due to fetomaternal compromise and another two patients were anesthetized for an emergency forceps delivery. The median Apgar scores at one minute for the 17 infants was 5.5 (range 1-9) and at five minutes the Apgar score was 9 (range 5-10). Following delivery, three of the infants were admitted to the neonatal unit, although none required assisted ventilation and no additional adverse events were reported for these neonates. The infants' mothers all recovered well with no evidence of re-curarization.[13]

Pühringer, *et al*. presented a case series of seven pregnant women who were given rocuronium as part of the general anesthesia for their cesarean delivery.[14] The

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[9] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed March 8, 2015.

[10] TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Review date January, 2013. Accessed March 8, http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/

[11] LACTMED®: The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women. LactMed Record Number: 990; Last Revision Date: 20130907

[12] Williamson R, Mallaiah S, Barclay P. Rocuronium and sugammadex for rapid sequence induction of obstetric general anaesthesia. Acta Anaesthesiol Scand 2011; 55: 694–699. PMID: 21480829.

[13] See Williamson *et al*.

rocuronium was rapidly reversed by sugammadex without adverse events. McGuigan, *et al.* commented on the case series and emphasized that there is insufficient data on the placental transfer of sugammadex to the fetus and its safety.[15] These references describe the safe use of sugammadex in postpartum women; however, no publications were found on the use of sugammadex in pregnant women whose fetuses were exposed and subsequently followed for any possible adverse outcomes after birth.

DISCUSSION

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,"[16] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[17] format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pregnancy and Lactation Labeling

No publications could be found on the postnatal outcomes of sugammadex exposure in pregnant women nor are any such data provided in this re-submitted application. No congenital malformations were found in embryo-fetal studies of rats and rabbits following sugammadex exposure. The nonclinical data submitted did demonstrate that a very limited amount of a single dose of sugammadex crossed the placenta although no accumulation was reported. Based on the animal data, sugammadex appears to pose a very low risk of teratogenicity.

Publications on use of sugammadex in the immediate postpartum period to reverse neuromuscular blockade following a cesarean delivery were consistent and suggested that the risk to the mother post-partum may be low.

There are no data on the presence or absence of sugammadex in human milk; nor are there any data on whether sugammadex may be absorbed from the gastrointestinal tract if it is present in human milk. Inasmuch as 90% of sugammadex is excreted from the maternal circulation in the first 24 hours after administration, the exposure risk to the breastfed infant will likely be of brief duration. However, because no data are available,

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[14] Pühringer F, Kristen P, Rex C. Sugammadex reversal of rocuronium-induced neuromuscular block in Caesarean section patients: a series of seven cases. Br J Anaesth. 2010 Nov;105(5):657-60. PMID: 20736231.

[15] McGuigan P, Shields M, McCourt K. Role of rocuronium and sugammadex in rapid sequence induction in pregnancy. Br J Anaesth. 2011 Mar;106(3):418-9. PMID: 21317233.

[16] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

[17] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

it remains unknown the degree to which the drug is transferred to breast milk. Because the period of exposure is not chronic and the time available for the drug to be transferred to breastmilk brief, DPMH recommends that the following regulatory statement appear in the lactation section of labeling, "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRIDION and any potential adverse effects on the breastfed infant from BRIDION or from the underlying maternal condition."

Effect of Sugammadex on Effectiveness of Hormonal Contraceptives
DPMH makes note of the reduction in hormonal contraceptive effectiveness caused by sugammadex and recommends that the Division of Bone, Reproductive and Urology Products (DBRUP) be consulted for a review of these data.

CONCLUSIONS

- The effect of sugammadex administered during pregnancy has not been studied to identify potential risks to the fetus or the pregnant woman. The effect on the neonate following maternal exposure near term remains unstudied and is, therefore, unknown.
- The risk of sugammadex exposure to a breastfed infant is likely to be low.
- DPMH recommends that DBRUP be consulted to review the effects of sugammadex on hormonal contraceptives.

RECOMMENDATIONS

DPMH-MHT attended meetings with DAAAP in February and March, 2015 and provided our specific labeling recommendations at the March 12, 2015, labeling meeting.

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for BRIDION in PLLR format.

FULL PRESCRIBING INFORMATION: CONTENTS*

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on BRIDION use in pregnant women to inform any drug-associated risks. In animal reproduction studies, there was no evidence of (b) (4) (b) (4) during organogenesis at (b) (4) exposures up to 6 and 8 times, respectively, the maximum recommended human dose (MRHD) of 16 mg/kg. In a pre- and postnatal development study, sugammadex treatment resulted in an (b) (4) (b) (4)

(b) (4) The background risk of major birth defects and miscarriage for the indicated population are unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

Data

Animal Data

In an embryofetal development study in rats, pregnant animals (b) (4) intravenous sugammadex at 0, 20, 100, and 500 mg/kg (0.2, 1.0, and (b) (4) times the MRDH of 16 mg/kg/day by AUC, respectively) during (b) (4) organogenesis (Gestational Day 6 - 17). No treatment-related maternal and embryofetal changes were observed.

(b) (4) pregnant New Zealand white rabbits were administered intravenous sugammadex at 0, 20, 65, 200 mg/kg (0.6, 2.4, and (b) (4) times the MRHD by AUC, respectively) during organogenesis (Gestational Day 6-18). A (b) (4)

In a prenatal and postnatal development study, pregnant rats (b) (4) were administered sugammadex at 0, 30, 120, and 500 mg/kg from Gestational Day (GD) 6 to Postnatal Day (PND) 21 (corresponding to the beginning of organogenesis through parturition and subsequent pup weaning). (b) (4) postnatal loss (b) (4) PND 1-4 (b) (4) pups cannibalized by the Dam. The reason for the cannibalization is not known; (b) (4) an effect of sugammadex on steroidal hormones and/or pheromones cannot be ruled out. (b) (4) (b) (4)

8.2 Lactation

Risk Summary

No data are available regarding the presence of sugammadex in human milk, the effects of sugammadex on the breast fed infant, or the effects of sugammadex on milk production. However, sugammadex is present in rat milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRIDION and any potential adverse effects on the breastfed infant from BRIDION or from the underlying maternal condition.

Data

The maximum level (b) (4) at about 30 minutes after (b) (4) milk to plasma level approximately 1:1 at this time point.

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

/s/

CAROL H KASTEN
04/22/2015

TAMARA N JOHNSON
04/22/2015

LYNNE P YAO
04/22/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 24, 2015

TO: Arthur Simone, M.D., Ph.D., Medical Officer
Erika Torjusen, M.D., Medical Officer
Rigoberto A. Roca, M.D., Deputy Director
Sharon H. Hertz, M.D., Acting Director
Diana Walker, Ph.D., Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22225

APPLICANT: Organon USA Inc. (Merck & Co., Inc.)

DRUG: Sugammadex injection (Org 25969/SCH 900616/MK-8616)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard, but this submission is in response to a CR action letter, so the review timeline is 6 months.

INDICATIONS: Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium

CONSULTATION REQUEST DATE: November 19, 2014
CLINICAL INSPECTION SUMMARY GOAL DATE: March 29, 2015
DIVISION ACTION GOAL DATE: April 22, 2015
PDUFA DATE: April 22, 2015

I. BACKGROUND

Merck, Sharp & Dohme Corp. (Merck), a subsidiary of Merck & Co., Inc. submitted a second resubmission on behalf of Organon USA Inc., which is also a subsidiary of Merck & Co., Inc., seeking approval for sugammadex with the indication "reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium."

This resubmission is in response to the Complete Response (CR) letter received from the FDA on September 20, 2013. (Initial submission was in 2007, which resulted in a "Not Approvable" letter). The routine inspections from the previous submission indicated that there were protocol deviations and other findings that could impact the validity, reliability, and integrity of the data from Study P06042, including accidental unblinding at several sites. These major protocol deviations were also not reported in the final clinical study report (CSR). This resulted in an inspection of Merck September 16-27, 2013 and a resulting Untitled Letter September 5, 2014. In order to address the deficiencies identified in Study P06042, Merck conducted Study P101, a hypersensitivity trial similar in overall design to Study P06042.

Study P101 entitled "*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*" was conducted at six trial centers: four in the United States and two in Belgium. The study began January 7, 2014 and completed July 1, 2014. There were 382 subjects screened and 375 healthy subjects were randomized to one of three parallel arms assigned to treatment with three successive single doses five weeks apart in a 2:2:1 ratio: 4 mg/kg sugammadex, 16 mg/kg sugammadex or placebo. The primary safety endpoint was the number and percentage of subjects with adjudicated symptoms of hypersensitivity for each dose group of sugammadex and placebo. Database lock was July 6, 2014.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 22225 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with this assignment.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol P101 Number of Subjects Randomized	Inspection Date	Preliminary Classification
Michael R Gartner, M.D. Site 003	56	1/05-09/2015	Voluntary Action Indicated (VAI)
Martha Hernandez-Illas, M.D. Site 005	79	1/12-16/2015	No Action Indicated (NAI)
Merck (Sponsor)	375 total	1/28-2/23/2015	Pending

Key to Classifications

NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Michael R. Gartner, M.D.

(b) (4)

a. What was inspected: The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, recruitment materials, randomization, subject discontinuations, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, subject source documents including ECGs and laboratory testing, drug accountability, concomitant medication records, and adverse event reports. Twenty-five (25) subject records were reviewed.

b. General observations/commentary: There were 198 subjects screened, 56 subjects randomized and 50 subjects who completed the study. The first subject was screened January 15, 2014 and the last subject completed September 18, 2014. The IRB of record was (b) (4). The protocol was reviewed and approved by the IRB on 12/19/2013.

Of note, (b) (4). is a contract research organization (CRO) which has the capability to perform early stage clinical research and bioanalytical laboratory activities. (b) (4) took ownership of the site in (b) (4). Prior to this

date, the site was owned by (b) (4). The corporate headquarters of (b) (4) is located at this site.

Subjects were scheduled to dose in groups (i.e. Group 2, 4, 6, 8, 10 and 12); three dosing periods were conducted per group. File folders and three-ring binders were used to organize source documentation for the study. File folders were subject specific containing initial medical history, ICF and ECG and laboratory results. Six binders were treatment group specific containing up to ten subjects' information organized by event (e.g. adverse events, dosing, Targeted Hypersensitivity Assessments [THAs] and concomitant medications).

The site uses (b) (4), an electronic based computer system, to capture subject visit data directly from the subject using a scanner and bar code. Adverse events, concomitant medications, study medication infused, blood draws and meals consumed are all captured using this system. Data captured on the initial screening forms was entered into (b) (4) by trained staff. There were no discrepancies between source documents and (b) (4) data from the review of subject records.

Concomitant medications found within the source documentation for Subject 3055 were not reported on the data listing. Subject 3055 was admitted to the hospital for appendicitis. Hospital records were requested by the site; however, records received were incomplete. Two Note-to-Files were completed for Subject 3055 at the site pertaining to incomplete hospital and medication records and how concomitant medications were reported by the firm. There were no other discrepancies.

It was noted that, per protocol Section 5.1.2, in order to be eligible for participation in the trial, females with reproductive potential had to agree to use (and/or have their partner use) two acceptable methods of birth control. The methods of birth control were not solicited and documented for each subject. The site explained that the subjects signed the informed consent with this agreement and, thus, the site used signing of the informed consent as verifying this inclusion criterion. It was stressed that for future studies the site should document in the records what two forms of birth control are being used.

There were no discrepancies between AE source documentation compared to that of the data listing. All Targeted Hypersensitivity Assessments (THAs) with an abnormal finding contained a narrative completed by the Investigator. All events recorded on THAs were reported in the AE logs and reported on the data listing.

Per several sections of the protocol (e.g., Section 5.2.3 and Section 7.1.2.10) it states, "... AE assessment and the Targeted HS assessment are to be performed by a physician who does NOT administer study drug or prepare medication." A protocol deviation was reported regarding subject dosing and assessment across

groups on the following dates:

01/24/2014:
Group 2, Period 1: 3001 to 3010 dosed by site staff member (b) (6)
Group 4, Period 1: 3016, 3017, 3020 assessed by site staff member (b) (6)

02/11/2014:
Group 4, Period 1: 3011 to 3020 dosed by site staff member (b) (6)
Group 6, Period 1: 3021, 3024, 3030 assessed by site staff member (b) (6)

However, it was noted at the site that the staff contacted the Sponsor (i.e. Merck) on 01/20/2014 requesting clarification on whether or not an individual dosing one group could assess another group in which the individual did not dose. The Sponsor's Medical Monitor initially informed the site they were allowed to have an individual who performed dosing for one group perform other study roles for another group in which they did not have the role of dosing. Email correspondence beginning 02/11/2014 and a memo dated 02/28/2014 confirm this approval. The Sponsor (i.e. Merck) conducted a monitoring visit at the site 04/14-18/2014 and noted the protocol deviation. This was reported to upper management.

Based on Sponsor internal discussions, as well as the desire to maintain a consistent approach across the sites, Site 003 was informed that staff should not switch roles, not even between cohorts of subjects. On 05/14/2014, a Note-to-File was created by the site identifying two blinded individuals who had no involvement with the study and who would dose for the remainder of the study. This protocol deviation was reported in the Clinical Study Report and to the IRB. The FDA field investigator found no instances during this deviation of staff conducting dosing and assessment procedures for the same subject.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

OBSERVATION 1
An investigation was not conducted in accordance with the investigational plan. Specifically, the PI failed to ensure the study drug (sugammadex) was dosed appropriately per the investigational plan for two subjects. On 02/14/2012, two subjects were dropped and replaced with two alternates (Subject 3031 and Subject 3033). The following day, the study drug was prepared by the pharmacist and the weights of the dropped subjects were used in error for preparation calculation of the two alternates.

- Subject 3033 had been randomized to the highest dose level (16 mg/kg). This subject was overdosed, receiving 169% of the expected dosage by weight (27 mg/kg) at the first dosing. This subject experienced sensation of warmth in the face, throat and genitals (up to 90 minutes after dose)

and an occipital headache for 44 hours post-dosing. These were initially considered non-serious adverse events. The subject then received the second and third dose. One month after the third dose, it was discovered that the subject was overdosed with the first dosing.

- Subject 3031 had been randomized to the lowest dose level (4 mg/kg). This subject was under-dosed for all doses, receiving only 65% of the expected dosage by weight (2.7 mg/kg). This subject had no AEs at all during the course of the study and had no signs/symptoms of hypersensitivity at the scheduled assessments.

On 05/29/2014, the Sponsor (i.e. Merck) conducted a query of the data and questioned the study drug administration for the two subjects; the site was contacted. On 06/06/2014, a deviation summary was prepared by the site which confirmed two subjects were given wrong doses resulting in deviations of more than 10% from the planned doses for the two subjects. The protocol required that any AE determined to be drug related associated with overdose be considered an SAE and Subject 3033 was reported accordingly on May 29, 2014. The subject was also prematurely unblinded when the overdose was discussed with the site and Sponsor staff; the unblinded pharmacist was on the call and mentioned the treatment group. This accidental unblinding was also reported as a protocol deviation.

It was determined that employee error occurred with the subject overdosing as the pharmacist had not followed the documented pharmacy drug preparation procedure. All pharmacy drug preparation records for this study were reviewed; no other discrepancies were noted

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Protocol violation occurred when six subjects interacted with a study staff person who dosed and also assessed subjects; however, there was no evidence seen by the FDA field investigator of staff dosing and assessing the same subject. More so, the deviation was caught and corrected. Therefore, data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Martha Hernandez-Illas, M.D.
Medical Director
Miami Research Associates
MRA Clinical Research Phase 1 Unit
6280 Sunset Drive, Suite 600
South Miami, Florida 33143

a. What was inspected: The inspection focused on informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial

disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Records of 24 subjects were reviewed.

b. General observations/commentary: There were 197 subjects screened, 79 subjects randomized and 58 subjects who completed the study. The IRB of record was (b) (4). Approval of the protocol occurred 12/19/2013 and the first subject signed the informed consent 1/8/2014. The last follow-up for any study subject was 5/29/2014. The clinical laboratory used to process blood samples throughout the study was (b) (4).

The center is a clinical research Phase 1 unit. All original paper records were maintained on site inside binders located in a locked room. Subject records were clearly labeled and organized. All the data collected in the paper forms or original case report forms (CRFs) was transcribed manually to the Sponsor through an electronic data capture system.

Each subject file contained information that documented that each subject existed and met the study's inclusion criteria before enrollment in the study. There was no evidence that the Principal Investigator did not maintain oversight during the conduct of the study. There was no evidence of under-reporting of adverse events and the primary endpoint was verifiable.

Protocol deviations were documented as Note to Files in the regulatory binder. All were submitted to the Sponsor and IRB in a timely manner.

- There was a randomization error when one subject was randomized twice and received two randomization numbers (5021 and 5049). Screening subject L-B/0005-00052 was randomized with number 5021 on January 28, 2014. During pre-dose procedures the subject presented with an elevated heart rate and did not receive the study drug. On February 5, 2014 the subject was admitted to the unit after approval from the Sponsor but the unblinded pharmacist was not notified that this subject was previously randomized and was re-randomized with another number (5049). This event is a deviation from protocol Section 7.1.1.7 which states, "A single subject cannot be assigned more than 1 randomization number." The site completed a Note to File for this event to document the occurrence of a major deviation. The quality assurance department of the site alerted the Sponsor the day of the error and revised the Pre-dose Communication Form to include a comments column for coordinators to enter any information that the unblinded pharmacist needs to be aware of prior to randomizing subjects.

- Subject 5008 presented potential hypersensitivity symptoms on 1/23/2014 but was not referred to the Clinical Adjudication Committee

(CAC) prior to proceeding to the next dosing period (2/27/2014) as required in Protocol Section 7.1.2. The site did report the event as a hypersensitivity event when it occurred but the Sponsor did not consider it a hypersensitivity event at that time and did not refer it to the CAC. Later, the Sponsor documented in a memo that they considered the event as a hypersensitivity sign/symptom and prompted the site to document it 4/23/2014. This was because the Sponsor established a (b) (4) Department that conducted hypersensitivity reviews beginning March 2014 and concluded that the event of "feeling hot in face" could be interpreted as flushing and considered it to be a potential sign/symptom of hypersensitivity. The Sponsor notified the site of this decision through an email sent to Dr. Hernandez on 4/17/2014.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

3. Merck and Co., Inc.
126 East Lincoln Avenue
PO Box 2000
Mailstop RY34-B188
Rahway, NJ 07065

a. What was inspected: The inspection consisted of reviewing the organizational structure and responsibilities, contracts with contract research organizations (CROs) and vendors, training (clinical trial staff and monitors), test article integrity and accountability, Certificate of Analyses, monitoring processes and monitoring reports, adequacy of monitoring and corrective actions taken by the Sponsor, capturing and reporting of protocol deviations, financial disclosures, SOPs, processes of the Adjudication Committee, registration of the study on ClinicalTrials.gov, protocol writing, the clinical study report writing, FDA 1572 (Statement of Investigator), selection of clinical sites, safety/adverse event reporting, data collection and handling and protocol deviations related to key safety and efficacy endpoints.

b. General observations/commentary: Merck Sharp & Dohme **(**MSD) has four locations in New Jersey. The current inspection was conducted in Rahway, New Jersey. The study drug (sugammadex) was manufactured at the Merck, Sharpe and Dome facility in the Netherlands, packaged in Pennsylvania, and shipped to clinical sites in Belgium and the United States. (b) (4)

(b) (4)

The clinical sites were selected by Merck (b) (4). Furthermore, (b) (4) (Site 003/ Lincoln, NE and Site 004/Tempe, AZ) (b) (4). No site was terminated during the conduct of the study. The training records (i.e. protocol, hypersensitivity assessment, (b) (4) case report forms and GCP) including the Principal Investigators (PIs), Sub Investigators (SIs), Clinical Research Coordinators (CRCs) and other site staff and their curriculum vitaes were reviewed and appeared adequate.

The computer systems/servers used during the trial included, but were not limited to, the following:

- (b) (4)

The subjects' clinical data is entered into (b) (4) from the clinical site. Cleaned data is transferred and stored from (b) (4) to Merck's (b) (4) (b) (4) Pre-specified Statistical Analysis System (SAS) datasets are extracted from the (b) (4) and stored in a protocol-specific secure folder on Merck's (b) (4) system. In (b) (4) the SAS analysis programs and the associated SAS datasets are executed to create tables, listings and figures.

A potential unblinding issue was reported in the Clinical Study Report (Section 10.3, *Subjects Whose Treatment Was Prematurely Unblinded*).

"During routine analysis and reporting (A&R) activities, staff from the Sponsor's Department of Biostatistics and Research Decision Sciences (BARDS) with access to study clinical trial data sets in the statistical (b) (4) had the potential to view an unblinded exposure domain variable in both the test and production area of the (b) (4) between 11-Mar-2014 and 02-Apr-2014. The variable in question is the "Calculated Dose Prepared" study medication. This variable was not blinded in the (b) (4) data extracted into (b) (4) by BARDS between 11-Mar to 13-Mar-2014. In the A&R process, these extracted datasets are converted to enriched analyses datasets. The potential unblinding issue was discovered on 02-Apr-2014 and corrective actions were taken immediately. The variable was blinded within the (b) (4) as of 04-Apr-2014 and all unblinded datasets were deleted from the (b) (4) system on or before 07-Apr-2014. BARDS confirmed that no person who had access to (b) (4) and the file that contained potential unblinding information (variable EXIVDOSE in dataset EX) before 08-Apr-2014 was actually unblinded to the treatment assignment for any subject".

The potential unblinding was thoroughly explored during the inspection and it was determined that Merck'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 prior to database lock.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

OBSERVATION 1

Failure to permit FDA to have access to, review, and copy records or reports related to a clinical investigation.

1. Merck failed to make available the underlying raw data from the clinical investigation for FDA's audit and maintain audit trails for the deletion of data sets in the statistical (b) (4) system.

While preparing reports, eleven (11) staff from the Department of Biostatistics and Research Decision Sciences (BARDS) with access to study clinical trial datasets in the statistical (b) (4) had access to an unblinded exposure domain variable in both the test and production area of the (b) (4) between March 11, 2014 and April 2, 2014. The variable "Calculated Dose Prepared" (EXIVDOSE) was not blinded in the (b) (4) data extracted into (b) (4) by BARDS from March 11-13, 2014. Knowledge of the value of EXIVDOSE for an individual subject would indicate the

treatment/dose group (i.e., placebo, 4 mg/kg sugammadex, or 16 mg/kg sugammadex) to which the subject had been randomized (assuming the pharmacist was correctly following the allocation schedule).

The extent of the records exposed is as follows:

Total Subject Records in Final EX SAS data set:

Total	Period 1	Period 2	Period 3
1056	375	347	334

Total Subject Records with dose given prior to April 1 (Date of EX SAS data set extract):

Total	Period 1	Period 2	Period 3
688	375	313	0

Although the "unblinding" of this variable alone would not result in knowing the actual dose received, using the unblinded information in conjunction with the available unblinded variable "EXNUMDOS" (which is the total volume of solution actually injected in the subject, in mL) and the subject's weight would allow an observer to become "unblinded" to the actual dose administered in mg/kg. The potential unblinding issue was discovered on April 2, 2014. Although BARDS staff who were potentially unblinded each signed an attestation that they were not actually unblinded to the study treatment and corrective actions were taken, all unblinded EXIVDOSE datasets were deleted from the (b) (4) local computers and shared drives where the datasets resided on or before April 7, 2014. More so, the (b) (4) does not have a fully automated folder-level audit trail. Therefore, audit trails for deletion of datasets were also not available during this inspection to determine who actually accessed the unblinded data and the actual extent of the unblinding. Currently, Merck continues to utilize the (b) (4) which does not include a fully automated folder-level audit trail.

OSI Reviewer Comment: While Merck acknowledged that there was an inadvertent error in the study that could have potentially led to unblinding of their personnel at the subject-level, they identified the issue, did a root-cause analysis, took corrective actions, and believe they prevented actual unblinding from occurring. Corrective actions included deletion of the potentially unblinding EX SAS datasets contained in (b) (4) review of the (b) (4) database for any other studies containing the EXIVDOSE field, addition of the EXIVDOSE field to the list of fields to be blinded in (b) (4) by default and updating of the (b) (4) system to align with the updated default list, and inclusion of a rule in the Global Data Management guide to ensure blinding is applied when one (b) (4) field is mapped to multiple (b) (4) fields.

Merck is also intending to undertake additional longer term preventative actions to be completed by July 31, 2015. A cross-functional team from the

Global Data Management and Standards (GDMS) group and BARDS has been commissioned to review existing processes, identify potential gaps, and strengthen the blinding specifications and implementation. This Merck team will assess each blinding process to identify steps where inadvertent unblinding may occur and develop training on the importance of blinding, on the processes to implement blinding and what to do if inadvertent unblinding occurs.
Merck stressed that of the 11 staff that had access to the unblinded datasets, only one statistician admitted that she viewed the unblinded variable EXIVDOSE. Merck reported that this statistician did not have interactions with the sites, was not involved with production of adjudication packages, and did not participate in medical monitoring.

Regarding the deleted datasets, Merck stated that the decision to delete the EX SAS dataset containing the potentially unblinding EXIVDOSE field was driven by a desire to expeditiously limit potential unblinding and there appeared to the team involved to be no preferable alternative.

Regarding the lack of a directory-level automated audit trail in the (b) (4) *system, Merck agreed that none exists. However, they stressed that it is 21 CFR Part 11compliant, has unique accounts and passwords with controlled access. The SAS datasets in the* (b) (4) *system are "Read Only" files. Nevertheless, in the event of a suspected inadvertent unblinding in the future, the unblinded SAS datasets will be moved to a secure storage area external to* (b) (4) (b) (4)

Merck stated that audit trails do exist for (b) (4) *extractions including requester, data/time, protocol specifics, type of request and target environment.*

This observation is of significant concern. Nothing could correct the activities that had already occurred which led to the potential unblinding. In addition, during the inspection, FDA staff was not able to confirm the attestations of the statisticians and programmers 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. Furthermore, this incident was not reported as a protocol deviation immediately to the FDA and, in addition, was not reported as a protocol deviation in the CSR.

Observation 1b: Merck failed to provide the FDA with adequate descriptions and analyses of any other data or information relevant to the evaluation of the safety and effectiveness of the drug product obtained.

Specifically, Section 9.8.2.5.3 of the Clinical Study Report (CSR) states "The number and percentage of subjects screened, randomized, **the primary reasons for screening failure**, and the primary reason for discontinuation are

displayed". Although the reason for screening failure was captured for the first subject at each site, Merck failed to capture additional information on case report forms for any subsequent subjects who screen failed. Only source records at the sites contain the reasons for screening failure for all subsequent subjects. The CSR is not accurate because Merck failed to capture all data for screen failure and, therefore, such information was not available for inspection.

OSI Reviewer Comment: Merck acknowledged the CSR did not contain the primary reasons for screening failures and the CSR did not accurately reflect information that was collected during the trial. This was due to standard language being inserted into the CSR because of human error. No corrective action was conducted. However, a reminder will be communicated by April 30, 2015 to CSR authors about the importance of ensuring that the language in the CSR appropriately reflects the information that was collected during the trial.

OBSERVATION 2
Failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan.

Merck failed to conduct the study according to the protocol.

1. According to Sections 5.2.3, 7.1.1.8 and 7.1.2.10 of the protocol, adverse event (AE) and the Targeted Hypersensitivity (HS) assessments are to be performed by a physician/investigator who does NOT administer or prepare the study drug. Furthermore, the training slides titled "Prestudy meeting, 21 Nov 2013" under "Drug Administration" and at each dosing states "Specially dedicated investigator and nurse for drug administration (not involved in AE and HS assessment)." However, the Principal Investigator at Site 003 was granted permission by Merck to allow site staff who dosed subjects to also assess AEs. A total of six subjects at Site 003 had AE assessments performed by staff members who had previously performed dosing in other subjects.

    - The site staff member who dosed Subjects 3001 to 3010 during Treatment Period 1 (Group 2) also participated in the assessment of AEs for Subjects 3016, 3017 and 3020 during Treatment Period 1 (Group 4).

    - The site staff member who dosed Subjects 3011 to 3020 during Treatment Period 1 (Group 4) also participated in the assessment of AEs for Subjects 3021, 3024 and 3030 during Treatment Period 1 (Group 6).

    OSI Reviewer Comment: Merck acknowledged that this permission was granted by the Merck Medical Monitor for Study P101, although study documents indicate that this same monitor in an earlier communication to another site had clearly stated that the staff dosing subjects should not be involved in assessment of AEs or other

study procedures. Specifically, in a letter addressed to Dr. Bortel (Site 001) prior to study start-up, dated December 23, 2013, Merck's Medical Monitor stated "The individual initially conducting the Targeted HS Assessment, as well as the investigator evaluating the results of the initial Targeted HS Assessment conduct must not administer study drug or prepare medication. Furthermore, the individual who administers study drug is to be blinded to treatment and should not be involved in the conduct of the study (assessment of AEs and performance of other study procedures such as vital sign measurements)". This is consistent with the protocol training materials reviewed during the inspection. However, approximately one month later, on January 20, 2014, Merck's Medical Monitor allowed Dr. Gartner (Site 003) to have a staff person that administered study drug assess AEs and perform other study procedures if the subjects were not one and the same. Then, on February 12, 2014, based upon further internal discussions within Merck, this decision was subsequently reversed and Dr. Gartner was told that the dosing individual could not perform any other task for the remainder of the study. Merck stressed that at no point during the conduct of the study did a site staff member administer study drug to a subject and act as an assessor for AEs for that same subject.

These events were documented as protocol deviations in the CSR. To prevent further occurrences, Merck has implemented an operational and feasibility assessment at protocol review forums to help identify potential compliance risk areas in complex trial conduct. This forum meets weekly and includes representatives from clinical and cross functional areas, including protocol writers.

2. The protocol did not specify for stratification of subjects by sex; however at one site (Site 006), subjects in each cohort were assigned allocation numbers according to sex, with males receiving the lowest numbers and females receiving the highest numbers in each cohort.

OSI Reviewer Comment: *The protocol specified that randomization would be stratified according to site only (Section 5.4, Stratification). Merck acknowledged that the protocol did not specify for stratification of subjects by sex and that Site 006 applied site specific gender stratification. This was not realized until enrollment was completed. Site 006 had stratified subjects by sex in order to make it easier for the staff to place cohorts of the same sex in the same rooms. Merck's Medical Monitor stated that the site usually did Phase 1 studies and was using a procedure often used in early development studies. Merck is revising the standard site protocol training materials to include a review of the randomization process. An assessment of compliance of the randomization process will be incorporated into the Site Monitoring Plan template for early development studies.*

3. The clinical study teams from Merck and clinical site 003 were unblinded to the treatment group assignment for Subject 3033 prior to database lock.

OSI Reviewer Comment: *Merck acknowledged that Site 003 and the clinical study teams were unblinded to Subject 3033 treatment prior to database lock during the reporting of an overdose for this subject. The unblinded pharmacist and site project manager gave sufficient details of the dosing error to inadvertently unblind the Early Clinical Scientist, who unblinded the Clinical Director and co-Early Clinical Scientist. At a subsequent teleconference call, the unblinded pharmacist provided details of the pharmacy error and unblinded all study team members on the call. Although site and Sponsor unblinded job roles were available for the study, these roles were not utilized in reporting the overdose. Of note, at the time of unblinding, the subject had completed dosing. After the overdose occurred, the remaining medical review required was completed by blinded study personnel. This accidental unblinding was reported in the CSR.*

No preventive actions have occurred at the Sponsor site to prevent a reoccurrence but many are planned, including re-examining the approach to defining studies requiring designated unblinded roles and responsibilities of those roles as well as management of overdose reported in blinded trial design. The SIV training slides are to be updated to include an explanation of the designed unblinded roles and corresponding contacts for each study as applicable. Activities are to be completed by July 31, 2015.

4. Section 7.1.2.10 of the protocol requires "Targeted Hypersensitivity 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/Symptoms of HS prior to the 0.5 hour time point." However, in early April 2014, Merck contacted the sites and requested that phone calls be made to subjects that had potential signs/symptoms of hypersensitivity during dosing confinement to determine if the subjects experienced any additional adverse events from the time of discharge from that period through at least seven days post-dose. Merck did not make a formal change to the protocol nor generate a Protocol Clarification Letter as outlined in the Sponsor's Protocol Change/Clarification Impact Guide with respect to the calling of subjects after discharge.

OSI Reviewer Comment: Merck acknowledges the activity; the team did not consider a protocol amendment. Merck will assess and modify the decision process for initiating protocol amendments and will retrain on the utilization of Protocol Clarification Letters or protocol amendments by the Early Clinical Development Clinical Directors, Clinical Scientists and Scientists by June 30, 2015.

5. The protocol (Section 7.1.2.5) and CSR (Section 9.5.1.4.2) state "The predose Peak Expiratory Flow (PEF) for each period will be taken in triplicate and the best effort will be used as the baseline value…At the other PEF scheduled timepoints, single measurements are to be taken, with two additional measurements allowed within 5 minutes for out of range results or if decrease to <70% of baseline. The best effort of the three measurements will then be documented as the value for the timepoint". However, Section 2 of the Study Operations and Laboratory Manual (Versions 3

and 4) states "The expected value for a normal healthy subject is ≥ 80% of the predicted average PEF values. If the best effort of the triplicate screening PEF values is < 80% of the predicted value in the table below, the subject may be retrained on peak flow meter use and a repeat set of triplicate PEF assessments performed. In addition, for each period, a repeat set of predose PEF assessments may be performed at investigator discretion..., with the best effort of the 6 PEF values serving as the baseline for that period, if performed. The best effort PEF value taken predose in each period will be considered the baseline for that period."

Clinical sites were informed by Merck that, assuming subjects were still within the screening window, those excluded solely because of their screening PEF values could be brought back for a repeat set of triplicate PEF measurements. Those subjects rescreened are noted in the table below:

Site No.	Subject Screening Number (Allocation Number, if applicable)	Status of subjects who were excluded due to screening PEF values that were < 80% of the expected value for a normal healthy subject
2	200020	Subject returned for repeat triplicate measurements of PEF and was an alternate subject for Group 1 but was not enrolled in the study as the group was fully enrolled.
2	200046	Subject returned for repeat triplicate measurements of PEF which were out of the normal range. The subject was excluded per investigator discretion under exclusion criterion 15 that there "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."
5	500121 (Subject 5061)	Subject returned for a repeat triplicate PEF measurement and was enrolled in the study
5	500147 (Subject 5070)	Subject returned for a repeat triplicate PEF measurement and was enrolled in the study.
6	600131 (Subject 6060)	Subject returned for a repeat triplicate PEF measurement and was enrolled in the study.

Merck did not make a formal change to the protocol nor generate a Protocol Clarification Letter as outlined in the Sponsor's Protocol Change/Clarification Impact Guide with respect to the repeat set of triplicate PEF measurements.

OSI Reviewer Comment: Merck acknowledged that there was a discrepancy between the protocol, which had no PEF inclusion or exclusion criterion, and the Study Operations Manual, which defined what was considered normal and requested repeated PEF measurements for low values. Merck acknowledged that a protocol amendment should have been submitted.

The first error by Merck was the fact that no lower limit PEF was used for screening, even though healthy subjects were to be enrolled. Merck stated that the sites erred in assuming that the wording in the Study Operations Manual "The expected value for a normal healthy subject is ≥ 80% of the predicted average PEF values" (along with a

chart of the values) meant that any screening subject below those values would be excluded. That is a very valid assumption.

6. Section 7.1.1.7 of the protocol states "All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number." However, the following subjects were assigned with more than one randomization number:

    - Site 005: Subject 5021 was randomized on January 28, 2014 and re-randomized on February 6, 2014 as 5049. This was reported as a deviation in the CSR.

    - Site 004: Subject 4017 had dose drawn and was given a randomization number but was not dosed. An alternate person was included in the randomization as Subject 4017 and a new dose was calculated and provided.

OSI Reviewer Comment: *Merck acknowledged the observation. The sites failed to adhere to the protocol requirement for randomization number assignment. Standard protocol training will be revised to include a review of the protocol randomization process. An assessment of compliance of the randomization process will be incorporated into the Site Monitoring Plan template. Activities will be completed by June 30, 2015.*

b. Merck failed to ensure proper monitoring and failed to ensure adequate and accurate monitoring reports. Specifically,

    1. The Study Monitoring Plan (Appendix 3: "ESD Data Monitoring & SDV Plan"), Versions 1 and 2, requires 100% source data verification by the Clinical Research Associate (CRA), with a few exceptions noted. After database lock on September 17, 2014, it was discovered at Site 004 that changes made prior to database lock in (b) (4) source records were not updated in the (b) (4) Electronic Data Capture (EDC) System. A subsequent audit showed seven additional source record changes had been made regarding adverse events and concomitant meds that were not updated in the (b) (4) EDC, including one adverse event. The final spreadsheet of all discrepancies (including the previous seven) totaled 169. For example,

        - Subject 4020 medical history source records list a spinal surgery report; however, this was not captured in the case report form.
        - Subject 4007 lab dated February 24, 2014 states ALT 9 but case report form has 17. Also, AST lab source states 17 but case report form states 11.

- Subject 4057 had abnormal source screening urinalysis on February 11, 2014 but the case report form listed the urinalysis as normal.
- Subject 4060 had a clinically significant abnormal source screening urinalysis on June 11, 2014 but the case report form listed the urinalysis as not clinically significant.
- Subject 4018 had Targeted HS Assessment in Period 1 on January 29, 2014 with source note of burning sensation mid-chest during IV administration that was not captured in the case report form.
- Subject 4018 had Targeted HS Assessment in Period 2 on April 2, 2014 with source note of nausea, sneezing episode, and itchiness of eyes that were not captured in the case report form.
- Subject 4034 had repeat PEFs for Periods 2 and 3 but the original values were not captured in the case report forms.

OSI Reviewer Comment: Merck acknowledged the findings but felt that they had done proper monitoring. Discrepancies were due to human error. Merck will reinforce with all monitors the importance of ensuring that the case report forms accurately reflect the data in the source documents. This activity will be completed by April 30, 2015.

2. In reviewing the monitoring visit reports for the study, the information in the reports is not consistent with the dates of the reports. Furthermore, the information in the reports is not consistent within the report itself. For example,

   - The Site Initiation Visit report for Site 005 dated January 7, 2014 and approved and finalized on January 23, 2014 has site enrollment tracking showing 197 subjects were screened and 80 subjects were randomized. There are also "Action Items" of dosed subjects within the report.

   - The Monitoring Visit report for Site 005 on January 20-23, 2014, approved and finalized on February 6, 2014 has no subjects at the beginning of the report manually entered by the CRA for screening, randomization, etc. However, in the body of the report, there is discussion by the CRA of subjects randomized and dosed.

   - The Monitoring Visit report for Site 005 on February 3-6, 2014, approved and finalized on February 20, 2014 has no subjects at the beginning of the report manually entered by the CRA for screening, randomization, etc. However, in the body of the report, there is discussion of subjects randomized and dosed. Also, the Site Visit Tool (SVT) indicates 68 subjects were screened, but the body of the report indicates 168 subjects were screened. The SVT says 0 subjects were randomized but the body of the report says 57 subjects were randomized.

OSI Reviewer Comment: Merck acknowledged that the information in the Monitoring Reports was not consistent. Human error and wrong version uploaded into the Trial

Master File led to these inconsistencies. Enrollment tracking in the future will be done in one section only. The automated Subject Visit Tracking Feed to the Visit Report will be disabled and removed. Reinforcement of the process will be done for all CRAs and Clinical Research Managers by October 31, 2015.

c. **Assessment of data integrity:** Merck'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 prior to database lock. We were not able to confirm the attestations of the statisticians and programmers 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 potential unblinding of all subjects prior to database lock could impact the validity and reliability of the submitted data to determine the primary safety and efficacy analyses, although the two site inspections conducted have not shown any evidence of bias as a result of the observation.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of two domestic clinical sites as well as the Sponsor.

Observations noted above for Drs. Gartner and Hernandez-Illas, and the Sponsor Merck are based on the preliminary reviews of the Establishment Inspection Reports.

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

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

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

{See appended electronic signature page}

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/s/

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03/24/2015

JANICE K POHLMAN
03/25/2015

KASSA AYALEW
03/25/2015

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Memorandum

Date:	March 20, 2015
From:	Erika Torjusen, MD, MHS, Medical Officer (DPARP)
Through:	Banu Karimi-Shah, MD, Medical Team Leader (DPARP)
Through:	Badrul Chowdhury, MD, PhD, Division Director (DPARP)
To:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Subject:	Sugammadex Complete Response

Summary

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) was consulted on October 27, 2014 to review a newly completed repeat-dose study that was conducted by the Sponsor to address the safety concern of anaphylaxis with sugammadex sodium for injection. A full review of the complete response, including a history of previous DPARP consultations, is attached to this memorandum. The results of the review were to be presented at an advisory committee meeting on March 18, 2015. However, just prior to the advisory committee meeting, concerning inspection findings came to light. Based upon the findings from the sponsor (Merck) investigation, it was noted that 11 staff from the Department of Biostatistics and Research Decision Sciences (BARDS) with access to study clinical trial data sets in the statistical (b) (4) ((b) (4) had access to an un-blinded exposure domain variable in both the test and production area of the (b) (4) between March 11, 2014 and April 2, 2014. The potential un-blinding issue was discovered on April 2, 2014 and all of the BARDS staff who were potentially un-blinded signed an attestation that they were not actually un-blinded to the study treatment and corrective actions were taken by the sponsor. However, the Agency was limited in its investigation regarding the impact of the potential un-blinding because all un-blinded datasets were deleted from the (b) (4) system on or before April 7, 2014. In addition, the (b) (4) did not have a fully automated folder-level audit trail. Therefore, FDA investigators were not able to review an audit trail to determine who actually accessed the un-blinded data and evaluate the extent of the un-blinding. The Agency also inspected two United States study sites and it was determined that, at Site 3, study staff who were administering the study drug were also assessing adverse events (although not on the same patients). This protocol violation as well as the potential statistician un-blinding were briefly, but incompletely, mentioned in section 10.3 of the CSR. Due to concerns regarding poor study conduct, and questions regarding the integrity of the repeat-dose study data, the advisory committee meeting was postponed so that the Agency could inspect the other four study sites and determine the validity of the P101 study results.

The review of study P101 and presentation of the study results are in the attached consult based on the information provided in this submission; these may be subject to change pending the outcome of the new site inspections. DPARP understands that DAAAP plans to take a Complete Response action on this application, and to request inspection of the 4 remaining study sites. Currently, conclusions that can be drawn from the submitted data are pending the results of the inspections.

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) CONSULTATION

Date:	February 19, 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 sodium for injection (Org 25969, SCH 900616, MK-8616)

General Information

NDA#:	22-225
Applicant:	Merck & Co., Inc., (on behalf of Organon USA, Inc., a subsidiary of Merck)
Drug Product:	Sugammadex sodium for injection (Org 25969, SCH 900616, MK-8616)
Request From:	Diana Walker, Regulatory Project Manager, DAAAP
Date of Request:	October 27, 2014
Date Received:	October 27, 2014
Materials Reviewed:	NDA 22-225 Resubmission October 22, 2014, Resubmission December 20, 2012, DPARP Medical Officer Consultations dated May 2008, Jun. 2008, Nov. 2008, April 2009, Sept. 2009, Dec. 2010

I. Introduction

This Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) medical officer review evaluates the safety concern of anaphylaxis with sugammadex sodium (MK-8616) for injection, which is being proposed for marketing in the US as a selective relaxant binding agent indicated for 1) the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium (dose 4 mg/kg), and 2) the immediate reversal of neuromuscular blockade after administration of rocuronium (dose 16 mg/kg). The original new drug application (NDA) was submitted to the Agency on October 31, 2007, by Organon USA, Inc. During the first review cycle, the application was deemed Not Approvable, citing among the clinical deficiencies the evaluation of anaphylaxis, as will be further outlined in the body of this consultative review. The Applicant submitted a Complete Response on December 20, 2012, having conducted a repeat-dose hypersensitivity study to evaluate the risk of anaphylaxis with sugammadex; however, this submission was also deemed Not Approvable as concerns related to potential unblinding of investigators to treatment assignment limited the utility of the data. The Applicant has conducted and submitted a new repeat-dose hypersensitivity study, which will be the focus of this consultative review.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) has requested consultation from DPARP on multiple occasions to evaluate the anaphylaxis signal with sugammadex (as listed in the table above). The following review covers the regulatory history of sugammadex by summarizing the prior reviews completed by DPARP, as well as data from a new repeat-dose clinical study presented by the Applicant to address the deficiencies with respect to the evaluation of anaphylaxis, as cited in the Not-Approvable Letter, dated July 31,

Reference ID: 3719384

2008. The presence of anaphylaxis in both the original controlled development program and this newly submitted repeat-dose clinical trial data will be the primary emphasis of this review. Sugammadex was approved in the European Union (EU) in July 2008, and has been commercially available since September 2008. From product launch through April 21, 2014, approximately (b) (4) 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.

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 ***known*** allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to identify cases consistent with anaphylaxis. For the evaluation of new molecular entities, DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling Criterion #1 above, in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. In addition, any cases reported by investigators or other healthcare professionals as "anaphylaxis" or "anaphylactoid" are accepted as cases of anaphylaxis, even if the case report does not detail more specific signs and symptoms.

III. Background and Regulatory History

Sugammadex is a new molecular entity, a gamma-cyclodextrin, that is an octasodium salt with a ring-like structure resulting in a lipophilic core and a hydrophilic outer surface. Sugammadex 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 Not Approvable 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 Not Approvable letter. As our ability to interpret the data was limited, and the Applicant has conducted a new study, 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 submitted in the Applicant's most recent complete response on October 22, 2014.

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.) 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.

A) Study P101

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

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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

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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.

vi) 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 $\leq$ 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 $\geq$ 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.

vii) 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.

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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) Post-Marketing Reports of Hypersensitivity

Sugammadex is approved in more than 75 countries and marketed in more than 50 countries worldwide, with a total of (b) (4) vials sold as of April 21, 2014.

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 21, 2014. 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 318 cases were identified, of which 201 represent reports of anaphylaxis and 117 represent reports of serious hypersensitivity.

The Applicant decided to have the 318 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 318 cases, 133 were classified as anaphylaxis and 47 were classified as hypersensitivity.

The most common clinical feature identified in the adjudicated anaphylaxis reports was signs or symptoms of hypotension, noted in 80% (106/133) of the cases. Among the adjudicated serious hypersensitivity cases 89% (42/47) demonstrated skin reactions such as erythema, rash, and urticaria. In the reports where outcome was provided, all describe the patient as having recovered and responded to standard treatment for anaphylaxis/hypersensitivity reactions such as adrenaline, antihistamines, bronchodilators, steroids, vasopressors, and enhanced ventilatory support.

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.

V. Summary and Discussion

Sugammadex sodium is a modified gamma-cyclodextrin being proposed for the indications of 1) the routine reversal of neuromuscular blockade induced by rocuronium or vecuronium (dose 4 mg/kg), and 2) the immediate reversal of neuromuscular blockade after administration of rocuronium (dose 16 mg/kg).

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

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

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

Using a predefined 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.

VI. References

1. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NJ, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006; 117:391-7

2. 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.
1. The signs and symptoms of HS must be non-serious and rated as mild to moderate in intensity and return to baseline without treatment.
2. 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)

Sampson Criterion 1 for Anaphylaxis:

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 $\geq$ 470 msec (for males) or $\geq$ 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,s]			Visit 3[c,s]			Visit 4[c,s]			Visit 5 (F/U)[h]
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[a]			X[a]			X[a]			X
Body Weight (kg)	X	X[e]			X[e]			X[e]			
Body Height and Body Mass Index (BMI)	X										
Administration of trial medication[r]			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, s]			Visit 3[c, s]			Visit 4[c, s]			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 pre-dose 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:

- Tachypnea (>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).

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/s/

ERIKA N TORJUSEN
03/20/2015

BANU A KARIMI SHAH
03/20/2015

BADRUL A CHOWDHURY
03/20/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 17, 2015

To: Diana Walker, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 022225
OPDP labeling comments for Sugammadex injection

OPDP acknowledges receipt of your November 7, 2014, consult request for the proposed Package Insert, and Carton/Container Labeling for Sugammadex injection. Reference is made to the March 13, 2015 email response from DAAAP, confirming that a Complete Response (CR) letter would be issued. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAAAP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
03/17/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 23, 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 22225
Product Name and Strength:	Bridion (Sugammadex) Injection 500 mg/5 mL and 200 mg/2 mL
Submission Date:	January 20, 2015
Applicant/Sponsor Name:	Merck
OSE RCM #:	2014-2252-1
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations we made after the proposed proprietary name, Bridion, was found conditionally acceptable.[1] We asked Merck to resubmit the container labels and carton labeling with the proposed proprietary name, Bridion, for our review.

[1] Schlick J. Proprietary Name Review for Bridion (NDA 022225) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 DEC 19. 42 p. OSE RCM No.: 2014-40699.

Reference ID: 3691422

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

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Reference ID: 3691422

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/s/

JAMES H SCHLICK
01/23/2015

BRENDA V BORDERS-HEMPHILL
01/23/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 05, 2015
Requesting Office or Division:	Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 22225
Product Name and Strength:	Bridion (Sugammadex Sodium) Injection
Submission Date:	October 22, 2014
Applicant/Sponsor Name:	Merck
OSE RCM #:	2014-2252
DMEPA Primary Reviewer:	James Schlick, RPh, MBA
DMEPA Acting Team Leader:	Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels, carton labeling, and insert labeling (Appendix A) to determine if it is acceptable from a medication error perspective. Merck received a Complete Response to the Application on September 20, 2013. They resubmitted their Application on October 22, 2014 with revised labels and labeling in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSIONS

The revised container labels and carton labeling do not include the proprietary name, Bridion. We provide a recommendation in Section 3 to address this.

[1] Borders-Hemphill, V. Label and Labeling Review for Bridion (NDA 022225). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 SEPT 12. 10 p. OSE RCM No.: 2013-115.

Reference ID: 3681994

3 RECOMMENDATION TO MERCK

A. Add the proprietary name, Bridion, to the container labels and carton labeling, and resubmit them for review.

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/s/

JAMES H SCHLICK
01/05/2015

BRENDA V BORDERS-HEMPHILL
01/05/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	September 12, 2013
Reviewer:	Vicky Borders-Hemphill, Pharm.D Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name(s):	(b) (4) (Sugammadex Sodium) Injection
Strength(s):	200 mg/2 mL and 500 mg/5 mL
Application Type/Number:	NDA 22225
Applicant/Sponsor:	Merck Sharp & Dohme Corp.
OSE RCM #:	2013-115

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container labels and carton and professional labeling for [redacted] (Sugammadex Sodium) injection, 200 mg/2 mL and 500 mg/5 mL, NDA 22225, for areas that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the December 21, 2012, insert labeling submission.

- Sponsor: Merck Sharp & Dohme Corp
- Active Ingredient: sugammadex sodium
- Established name: sugammadex [redacted] injection
- Indication of Use: [redacted] reversal of [redacted] neuromuscular blockade induced by rocuronium or vecuronium [redacted]
- Route of Administration: intravenous
- Dosage Form: solution (clear colorless to slightly yellow)
- Strength: 100 mg/mL
- Dose and Frequency:
  - Routine reversal – 2 mg/kg to 4 mg/kg single bolus injection intravenously rapidly ([redacted] 10 seconds) following administration of rocuronium or vecuronium-induced blockade
  - Immediate reversal – 16 mg/kg single bolus injection intravenously rapidly [redacted] 10 seconds) at 3 minutes following administration of rocuronium
- How Supplied: 2 mL and 5 mL vial (500 mg/5 mL, 200 mg/2 mL in Box of 10 vials)
- Storage: 25°C (77°F), with excursions permitted to 15 to 30°C (59-86°F) [see USP Controlled Room Temperature. [redacted] protect from light
- RLD: NME
- Container Closure System: vial with peel-off label to be placed on dosing syringe (not provided)

2 METHODS AND MATERIALS REVIEWED

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Proposed Container Labels (Appendix B)
- Proposed Carton Labeling (Appendix C)
- Proposed Package Insert Labeling

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 3372347

3 CONCLUSIONS

DMEPA concludes that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of these products. We request the recommendations for the container labels in Section 4 be communicated to the Applicant prior to approval.

4 RECOMMENDATIONS

DMEPA provides the following recommendations and requests these recommendations be forwarded to the Applicant and implemented prior to approval of the application:

A. All Container Labels and Carton Labeling

1. Ensure that the term "TRADEMARK" is replaced by the proprietary name and revise it from appearing in all capital letters to appear in title case to improve readability (e.g., Trademark).
2. Increase the size of the established name so that it is at least ½ the size of the proprietary name as set forth in 21 CFR 201.10(g)(2) which states that the established name should be displayed with size and prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features.

B. All Container labels (peel-off and vial)

1. Relocate the word "injection" to appear on the same line as "(suggamadex (b) (4))" to provide additional space for recommended label.
2. To provide further distinction between the two vial sizes, remove the proprietary and established name statements from the colored box. Only the strength statement should appear in the box which uses a distinct color for each vial size.
3. (b) (4)

C. Peel-off Container Labels

1. Relocate the concentration strength statement (100 mg/mL) to appear directly beneath the established name so that it appears in the primary viewing plane of the principal display panel. In its current location, the vial must be rotated to read the strength.
2. (b) (4)
3. Add the following directly beneath the concentration statement (100 mg/mL): "Total dose:____mL" so that the total dosage volume

contained in the dosing syringe may be transcribed on the peel off section of the label by the healthcare professional.

4. Revise the route of administration on the label to read "For Intravenous Use Only" and place this statement in bolded font as the last line on the peel-off section of the label.
5. The peel-off section of the container label should appear in line order as follows:

   Proprietary name

   Suggamadex (b) (4) injection

   100 mg/mL

   Total dose: ____mL

   For Intravenous Use Only

D. Vial Container Labels

1. Relocate the strength statement [e.g. 200 mg/ 2mL (100 mg/mL)] to appear directly beneath the established name and dosage form so that it appears in the primary viewing plane of the principal display panel. In its current location, the vial must be rotated to read the strength.
2. Revise the route of administration on the vial label to read "For Intravenous Use Only".
3. Revise the net quantity statement to read "2 mL single dose vial" or "5 mL single dose vial" as appropriate, if space permits.
4. Relocate the "Rx only" statement to the bottom one-third of the label below the peel-off section as this distracts from important information on the principal display panel.
5. Remove the statement (b) (4) as this contributes to clutter and distracts from important information on the principal display panel.
6. The vial container label may appear in line order as follows:

   2 mL single dose vial or 5 mL single dose vial and NDC #

   Proprietary name

   Suggamadex (b) (4) injection

   200 mg/2 mL or 500 mg/5 mL

   (100 mg/mL) (100 mg/mL)

   For Intravenous Use Only

   Rx Only

   Storage: 25°C (77°F)

Protect from Light

Manufacturer statement

E. Carton Labeling

1. Ensure that the carton labeling uses a distinct trade dress color uniquely designated for each vial size on the corners and edges of the principal display, side, and back panels to further differentiate between the two vial sizes and help to minimize selection errors.

If you have further questions or need clarifications, please contact Vaishali Jarral, project manager, at 301-796-4248.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 3372347

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/s/

BRENDA V BORDERS-HEMPHILL
09/13/2013

JAMIE C WILKINS PARKER
09/13/2013

CAROL A HOLQUIST
09/13/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY CLINICAL INSPECTION SUMMARY

DATE: August 27, 2013

TO: Arthur Simone, M.D., Medical Reviewer
Christopher Breder, M.D., Ph.D., Clinical Team Leader
Diana Walker, Senior Regulatory Project Manager
Bob A. Rappaport, M.D., Division Director
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D for
Kassa Ayalew, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections

NDA: 22225

APPLICANT: Organon (Merck)

DRUG: Sugammadex for injection (MK-8616, SCH 900616, Org 25969)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard, six month review timeline for resubmission in response to a CR letter (subsequent 3 month extension due to a major amendment)

INDICATIONS: Routine reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

CONSULTATION REQUEST DATE: January 31, 2013
CLINICAL INSPECTION SUMMARY GOAL DATE: August 27, 2013
DIVISION ACTION GOAL DATE: September 10, 2013
PDUFA DATE: September 20, 2013

I. BACKGROUND

Merck, Sharp & Dohme Corp. (on behalf of Organon USA, Inc., a subsidiary of Merck) is seeking approval of sugammadex solution for injection 100 mg/mL for reversal of neuromuscular blockade by the agent rocuronium in general anesthesia. This is a resubmission to provide Merck's response to the Not Approvable letter received from the FDA on July 31, 2008. The application was deemed Not Approvable because sugammadex sodium drug development program did not adequately characterize the hypersensitivity reactions noted during clinical trials with sugammadex sodium, particularly with regard to the safety of repeat exposure to the drug. The effects of sugammadex on coagulation were not evaluated in any subject in the clinical development program.

The application is based on the results of two multicenter, randomized, double-blind trials:

- P07038: A Randomized, Controlled, Parallel-Group, Double-Blind, Trial of Sugammadex or Usual Care (Neostigmine or Spontaneous Recovery) for Reversal of Rocuronium- or Vecuronium-Induced Neuromuscular Blockade in Patients Receiving Thromboprophylaxis and Undergoing Hip Fracture Surgery or Joint (Hip/Knee) Replacement

- 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 studies were originally sponsored by Schering-Plough Research Institute (SPRI). Organon was acquired by Schering-Plough in 2007; Schering-Plough merged with Merck in 2009. Sugammadex is now owned and sold by Merck. Schering-Plough submitted an NDA for sugammadex in 2008 and received a Complete Response (CR) letter in August 2008.

The P07038 study began on Oct 30, 2011 and was completed on September 26, 2012. There was enrollment at 22 sites located in Austria, Belgium, and Germany. The primary objective was to assess the effect of reversal of rocuronium- or vecuronium-induced neuromuscular blockade (NMB) with 4 mg/kg sugammadex compared with reversal according to usual care (neostigmine or spontaneous reversal) on the incidence of adjudicated events of bleeding with

onset within 24 hours in subjects receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip/knee) replacement. In total, 1198 subjects were randomized in this trial, and 1184 subjects were treated, 596 subjects with sugammadex and 588 subjects with usual care.

For study P7038, one site in Austria was chosen due to high enrollment and no previous history of inspection.

The P6042 study began on August 24, 2009 and was completed on April 13, 2010. This was a non-IND Phase 1 clinical study conducted in Germany, the Netherlands and the United Kingdom. There was one site in the United States that was conducted under IND. The primary objective of this study was to determine the number and percentage of subjects with adjudicated signs/symptoms of hypersensitivity for each dose of sugammadex (4 mg/kg and 16 mg/kg intravenous and placebo bolus injection on Days 8, 36, and 78). A total of 480 subjects received the single-blind placebo dose on Day 1, and 448 of these subjects were assigned to randomized treatment (148 subjects in the sugammadex 4 mg/kg group, 150 subjects in the sugammadex 16 mg/kg group, and 150 subjects in the placebo group).

For study P6042, one domestic US site was initially chosen for inspection:

Lawrence Galitz, M.D.
(b) (4)

This site was chosen based on the large number of subjects enrolled (129 subjects). The site also underwent a For-Cause inspection in December 2011 based on two complaints. The final classification of that inspection was a downgrade to Voluntary Action Indicated (VAI).

During the planning of the inspection, it was discovered that the site is no longer in existence. The site was initially owned by the contract research organisation (CRO) (b) (4) . The inspection was to begin in March 2013 at a satellite location owned by (b) (4) but that site suddenly closed and the files were not available for inspection. (b) (4) . The sponsor has continued to work towards release of the site records for inspection.

An alternative site in the United Kingdom was chosen for inspection. At the conclusion of the inspection, the data from this site were considered unreliable (discussed further below).

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 22225 in accordance with Compliance Program 7348.811. General instructions were also provided with the assignments.

In consultation with the review division, it was decided to arrange to inspect the final two sites in the PO6042 study, Dr. Yelka Koster in Utrecht, Netherlands and Dr. Doris Neuenhofer in

Monchengladbach, Germany, and the sponsor.

II. RESULTS (by Site)

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Final Classification
Dr. Walter Klimscha Vienna, Austria Site #302	Protocol: P07038 158 Subjects	May 27-31 2013	Preliminary NAI
Dr. Ulrike Lorch Surrey, United Kingdom Site #02	Protocol: P06042 127 Subjects	June 10-21, 2013	Preliminary OAI
Dr. Lawrence Galitz Miami, Florida Site #01	Protocol: P06042 129 Subjects	Pending	Pending
Dr. Yelka Koster* Utrecht, Netherlands Site #03	Protocol: P06042 111 Subjects	Pending	Pending
Dr. Doris Neuenhofer Monchengladbach, Germany Site #04	Protocol: P06042 81 Subjects	Pending	Pending

* (b) (4). This inspection will be conducted at the (b) (4).

Key to Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Dr. Walter Klimscha

Langobardenstrasse 122
Abteilung fur Anasthesiologie und Intensivmedizin
Wien A-1220 Austria

a. What was inspected: A total of 70 subject records were reviewed. Also available were the subjects' medical records. Reviewed were case report forms, laboratory results, ECG results, anesthesiology records, concomitant medication logs, and adverse event logs. Regulatory records containing laboratory accreditations, medical personnel qualifications, and laboratory reference ranges were reviewed. Records containing all communications with the Ethics Committee were reviewed. All signed consent forms were reviewed. All financial disclosure forms were reviewed. Drug accountability records were reviewed.

b. General observations/commentary: The first subject was screened on 12/4/2011 and randomized on 12/5/2011. The study was officially closed at the site on 9/26/2012. The site screened 163 subjects, enrolled/randomized 158 subjects; 155 subjects completed the study. One subject withdrew consent prior to investigational medicinal product (IMP) administration (Subject 100888); one subject was removed due to an adverse event prior to IMP administration (Subject 100895); one subject withdrew due to administrative reasons prior to IMP administration (Subject 100520). Overall, the records were adequate and well organized. No deficiencies were noted with respect to the informed consent process. The study file records showed timely review and approval by delegated staff personnel. The regulatory records contained the appropriate information. Subject 100020 did not meet inclusion/exclusion criteria for thrombocytes and was enrolled due to oversight. This deviation had been previously documented by the sponsor. There were four subjects (100874, 100371, 100304, and 200100) randomized prior to completion of all Visit 1 study-specific procedures. Central blood samples were collected after randomization; however, local blood samples were collected and reviewed prior to randomization. Contraceptive use was not recorded in the files**.** There was no evidence of under-reporting of adverse events. There was no indication that any of the subjects or Blinded Safety Assessors were unblinded.

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. (b) (4)

a. **What was inspected:** Approximately 34 subject charts and case report forms (CRFs) were reviewed during the current inspection. All nine CRFs of subjects receiving hypersensitivity adjudication were reviewed. All consent forms were reviewed. Financial disclosures were reviewed. Drug accountability records were reviewed.

b. **General observations/commentary:** Approximately 616 subjects were screened, 127 were randomized, and 115 completed the study. The study records were unorganized and difficult to maneuver efficiently. Binders were overflowing with open clamps and papers without adequate identification. There were a significant number of instances where hand-written information was covered by firm identification stickers, obstructing the ability to view the original information. Several objectionable conditions were observed. The inspection resulted in a Form FDA 483-Inspectional Observations. The inspectional results were communicated to OSI on July 12, 2013. Of critical

significance was the observation that protocol specific blinding procedures were not followed.

Observation 1
An investigation was not conducted according to the investigational plan.
Protocol P06042, section 7.4.1.4, "Management of Blinding of Study Treatments," requires, in part that, "*This study will be performed as a double-blind study. The syringes used for the intravenous administration of trial medication(s) will be blinded to ensure that the light color difference between sugammadex and placebo will not be revealed. Moreover, the investigator who evaluates the adverse events will not be involved in dosing of the subjects*."

On multiple occasions, a dosing investigator evaluated adverse events, potentially affecting six (6) cohorts (approximately 53 randomized subjects).

OSI Comment: A Note to File signed by the PI on 25 June 2010 was found by the FDA inspector which acknowledged that the protocol had not been followed. A transparent colored foil was placed on the syringe and the PI assumed that that was enough for blinding. The sub-investigator was dosing the study product and also evaluating the subjects for adverse events. This continued for approximately 8 weeks. On October 20, 2009, Dr. Pavlovic notified sponsor personnel that he noticed increased viscosity between the IMP (saline, 4 mg sugammadex, and 16 mg sugammadex) upon manual administration. It was at this point that the practice of a single sub-investigator administering the medication and evaluating for adverse events was discovered and this practice ceased. In the review of 34 case report forms during the FDA inspection, several subjects were observed to have been impacted by being dosed by a sub-investigator who attended an adverse event for the same subject (e.g., Subjects 007, 206, 213, and 230).

The incident was not reported as a protocol deviation in the clinical study report nor was there any discussion of the issue. There is a footnote on the document showing evidence that the sponsor considered the breach a protocol deviation. It has also been confirmed that the Data and Safety Monitoring Board overseeing the study was not made aware of this breach.

The PI acknowledged during the inspection that the protocol had not been followed as she did not think it was necessary, and it was also impractical to have separation of the duties of drug administration and adverse event evaluation since the syringes were covered.

Observation 2
Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent.

The firm's case report form (CRF) template associated with Protocol PO6042 Appendix IV "Signs and Symptoms of Hypersensitivity" did not contain all of the

elements of Appendix IV, including the "Gastrointestinal" section, which elicited subject information associated with "Diarrhea, Abdominal Pain, Nausea, and Vomiting".

OSI Comment: The site had a practice of migrating sponsor information to its own templates. The site used its own case report form template, "Signs and Symptoms of Hypersensitivity", which did not contain all the elements of the protocol's such as the "Gastrointestinal" section, which elicited subject information associated with "Diarrhea, Abdominal Pain, Nausea, and Vomiting". The incorrect version was used from the study's start until on or about October 1, 2009, affecting at least 8 randomized study subjects and all screening subjects having achieved Visit 2 (Day 1) by that date. Furthermore, all subjects were affected by missing information required by the sponsor to be on the form after October 13, 2010 concerning laboratory mast cell tryptase elevation.

These protocol deviations were not reported to the FDA.

Other issues found during the inspection included no signed informed consent for screened Subject 2427, no signed Pharmacogenetic informed consent for screened Subject 2055, and three separate instances of duplicated screening numbers were observed (S02004, S02128, S02185).

c. Assessment of data integrity: The full Establishment Inspection Report (EIR) was submitted for review. The audit indicates serious deviations/findings that would impact the validity and reliability of the submitted data. Due to the PI's decision not to follow the blinding procedures outlined in the protocol, there was significant unblinding at the site. Data from this inspection are considered not reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA included one planned foreign site inspection of Dr. Klimscha's site for Study PO7038. There were only minor deviations noted and overall the inspection was considered satisfactory and the data are considered reliable. The planned domestic site inspection of Dr. Galitz's site for Study PO6042 has not been possible because of the inability to inspect the files. In an attempt to adjust inspectional coverage, an alternative site, Dr. Lorch in the United Kingdom, was chosen. Data from that inspection are considered not reliable.

Because of the above issues, in consultation with the review team, the three remaining sites for Study P06042 (Drs. Galitz, Koster, and Neuenhofer) and the sponsor will be inspected.

Observations noted above for Drs. Klimscha and Lorch are based on the review of the Establishment Inspection Reports, 483 Observations, and communications with the FDA field investigators. A final clinical inspection summary will be generated once the additional inspections have been completed.

{See appended electronic signature page}

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Janice Pohlman, M.D., M.P.H.
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Susan D. Thompson, M.D. (covering for Kassa Ayalew, M.D., M.P.H.)
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/s/

CYNTHIA F KLEPPINGER
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JANICE K POHLMAN
08/27/2013

SUSAN D THOMPSON
08/27/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Provision of Pharmacovigilance Data

Date:	8/20/13
Reviewer:	Martin Pollock, Pharm.D., Division of Pharmacovigilance II
(Acting) Team Leader:	Martin Pollock, Pharm D., DPV II
Product Name:	Sugammadex
Subject:	All events
Application Type/Number:	NDA 22225
Applicant/Sponsor:	Merck
OSE RCM #:	2013-1425

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1 INTRODUCTION

DAAAP is reviewing sugammadex (NDA (22225; Merck), a cyclodextrin selective for reversal of neuromuscular blockade from rocuronium or vecuronium. As of March, 2013, sugammadex is marketed in 75 foreign countries; first approval was in European Union in 2008.[1]

On 6/17/13, DAAAP asked the sponsor to "Send a copy of all of the postmarketing reports/CIOMS forms that you have received." The sponsor provided DAAAP the CIOMS forms[2] (data locked to 5/31/13) on 6/21/13. The sponsor's submission of sugammadex reports safety reports to FDA is voluntary because to date, sugammadex has no U.S. approval. Therefore, the sponsor's CIOMS submission is considered to be more complete than what is in FAERS.

Considering the above limitation and as per DAAAP's request, DPV-II provides summarized crude counts of all sugammadex FAERS reports.

2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.[3]

Table 1. FAERS Search Strategy	
Date of search	7/26/13
Time period of search	1969 to 6/29/13
Product Terms	Sugammadex (as active ingredient)

3 DATA

DPV-II retrieved 88 cases (not de-duplicated) from FAERS. We provide the data as:

1) Standard Reports:
   a) All Preferred Terms (PTs) ranked
   b) All PTs by System Organ Class (SOC)
   c) All cases by year/quarter[4] and outcome

2) Line Listing of cases

We send these data files in a separate email.

---

[1] Sugammadex periodic safety update report for period 2/1/12 to 3/31/13. Issued 3 /27/13 by Merck Sharp & Dohme, Whitehouse Station, N.J.

[2] CIOMS=Council for International Organizations of Medical Science. CIOMS forms are similar to FDA's MedWatch form 3500 and are used to report postmarket adverse events in foreign countries.

[3] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

[4] Based upon FDA received date.

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/s/

MARTIN L POLLOCK
08/20/2013

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22225
Brand Name	Bridion (proposed)
Generic Name	Sugammadex sodium
Sponsor	Organon
Indication	Routine Reversal of Shallow or Profound NMB induced by revuronium or vecuronium, and immediate reversal NMB at 3 minutes after administration of rocuronium
Dosage Form	IV
Drug Class	Supramolecular family of cyclodextrins (CDs)
Therapeutic Dosing Regimen	4 mg/kg sugammadex with sevoflurane or propofol
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	Single dose: 96 mg/kg
Submission Number and Date	SDN 051, 20 Dec 2012
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 Overall Summary of Findings

No significant QTc prolongation effect of sugammadex was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/sugammadex were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

In this randomized, blinded, four-treatment parallel study, 132 healthy subjects received sugammadex with propofol or sevoflurane, or placebo with propofol or sevoflurane. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Sugammadex (FDA Analysis)

Treatment	Time (min)	ΔΔQTcF (ms)	90% CI (ms)
Propofol/Sugammadex	120	2.7	(-3.1, 8.5)
Sevoflurane/Sugammadex	30	2.0	(-1.6, 5.7)

Reference ID: 3279233

There was no significant concentration-QT relationship observed for the studied sugammadex dose of 4 mg/kg. In addition, there was no supratherapeutic dose evaluated in this study, and the evaluated dose is not sufficient to address the high exposure scenario (e.g., elderly subject with moderate renal impairment treated with 16 mg/kg for immediate reversal), which would result in an 8.8-fold increase in AUC compared to sugammedex 4 mg/kg. However; a previous submission evaluated a supratherapeutic dose of sugammedex 32 mg/kg, and the mean QT prolongation was less 10 ms. The combination of the previous study results where an appropriate supratherapeutic dose was evaluated and the current study results, which demonstrate no significant concentration-QT relationship support that substantial QT prolongation under the high exposure scenario is unlikely with the proposed maintenance regimens.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

(b) (4)

2.2 QT-IRT'S PROPOSED LABEL

(b) (4) Cardiac Electrophysiology

At a dose 2 times the maximum recommended dose, sugammadex does not prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Sugammadex is a modified gamma cyclodextrin that binds neuromuscular blocking agents rocuronium and vecuronium.

3.2 MARKET APPROVAL STATUS

As of 2009, Sugammadex was marketed in 31 countries.

3.3 PRECLINICAL INFORMATION

Sugammadex blocks hERG and lengthens the cardiac action potential, but this effect is described as occurring only at exposure large compared to what is experienced in the clinic. Other ion channel activity is not described in the NDA Nonclinical Overview.

3.4 PREVIOUS CLINICAL EXPERIENCE

Around 2000 subjects had been exposed to sugammadex in the studies supporting the original NDA. Not that the perioperative setting is particularly easy to interpret, but cardiovascular adverse events do not seen to have been common.

Reference ID: 3279233

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of sugammadex's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under NDA 22225. The sponsor submitted the study report P06315-19.4.116 for sugammadex, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

"A study to investigate the potential for QT/QTc prolongation after administration of SCH 900616 (sugammadex) in combination with propofol or sevoflurane in healthy volunteers (protocol no. P06315)"

4.2.2 Protocol Number

P06315

4.2.3 Study Dates

6 April 2010 – 1 December 2010

4.2.4 Objectives

"Primary Objective:

- To evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers.

Secondary Objective:

- To evaluate the safety and tolerability of the different treatment groups.

Other Objectives:

- To evaluate the effect of propofol and sevoflurane on the QT/QTc interval.
- To compare QT, RR, PR interval, QRS duration, heart rate, morphological abnormalities and tachyarrhythmias between sugammadex and placebo in combination with propofol or sevoflurane."

Source: Sponsor's study report, page 3.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, 2-factorial, blinded, parallel design with one dosing occasion.

4.2.5.2 Controls

The sponsor used a negative placebo control.

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4.2.5.3 Blinding

All sugammadex treatments were administered double-blinded, and propofol or sevoflurane were administered single-blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were four treatment arms:

"Treatment 1: Maintenance anesthesia with sevoflurane, followed by single IV administration of placebo (NaCl 0.9%) at approximately t = 20 minutes;
Treatment 2: Maintenance anesthesia with sevoflurane, followed by single IV administration of 4 mg/kg sugammadex at approximately t = 20 minutes;
Treatment 3: Maintenance anesthesia with propofol, followed by single IV administration of placebo (NaCl 0.9%) at approximately t = 20 minutes;
Treatment 4: Maintenance anesthesia with propofol, followed by single IV administration of 4 mg/kg sugammadex at approximately t = 20 minutes."
Source: Sponsor's study report, page 4.

4.2.6.2 Sponsor's Justification for Doses

The 4 mg/kg dose of sugammadex is administered to reverse a profound rocuronium and vecuronium induced neuromuscular block, and is considered to be the most frequently administered dose to be used in future clinical practice. This study used commonly used doses of propofol and sevoflurane and a single dose of 4 mg/kg sugammadex, to match clinical practice: Anesthesia was to be induced via a propofol IV TCI, with propofol 2–6 µg/mL. TCI was also to be used for maintenance anesthesia of propofol (IV) with target 4 µg/mL; sevoflurane 1.5 MAC, adjusted for age, for maintenance of volatile anesthesia.
Source: Sponsor's study report, page 51-52.

Reviewer's Comment: The sponsor did not include a supratherapeutic dose in this study. The worst case scenario for increased exposure would be an elderly subject with moderate renal impairment treated with 16 mg/kg for immediate reversal (not recommended for use in subjects with severe renal impairment), which would result in ~8.8 increase in AUC compared to sugammedex 4 mg/kg. A supratherapeutic dose to address this scenario (i.e..35 mg/kg or more) was not included in this study, but a higher dose of 32 mg/kg was evaluated in study report 19.4.109. As there was no observed differences in C_{max} due to renal impairment, the 32-mg/kg dose evaluated in 19.4.109 is also sufficient to address the high exposure scenario with regard to C_{max}.

4.2.6.3 Instructions with Regard to Meals

All subjects were to abstain from food for 8 hours and from water for at least 4 hours prior to anesthesia. No food was to be allowed for at least 4 hours post-dose and until the subject had recovered from anesthesia.

Reviewer's Comment: The instructions with regards to meals were acceptable.

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4.2.6.4 ECG and PK Assessments

Triplicate ECGs were extracted at 1 hour pre-dose propofol induction, pre-dose sevoflurane/propofol maintenance anesthesia, pre-dose sugammadex/placebo, 2, 5, 15 and 30 minutes and 2 hours after administration of sugammadex/placebo. Blood samples for sugammadex were collected pre-anesthesia (0 hour) 2, 5, 15 and 30 minutes and 2 hours after the administration of sugammadex/placebo.

Reviewer's Comment: The timing of ECG and PK samples is adequate to capture C_{max}; however, the sampling was limited to 120 minutes post-dose and does not depict the full concentration time-course PK time course.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

4.2.7 ECG Collection

Twelve-lead Holter monitoring was used to obtain digital ECGs.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 132 subjects were randomized; all completed study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

"QTc intervals were analyzed by timepoint using an ANCOVA model on change from pre-dose sugammadex/placebo baseline with factors anesthetic (propofol or sevoflurane), treatment (sugammadex or placebo), gender, site and baseline measurement (pre-dose sugammadex/placebo) as covariate to estimate the contrast between sugammadex and placebo in change of QTcF. The time-matched difference in change from pre-dose sugammadex/placebo (=baseline) in the QTc interval between sugammadex and placebo, and corresponding 95% one sided confidence interval was calculated for each post-sugammadex/placebo timepoint measured in the interval of interest (2, 5, 15 and 30 minutes after sugammadex/placebo administration). If for all assessments the one-sided 95% confidence interval excluded a 10 msec prolongation, it would be concluded that sugammadex when combined with propofol or sevoflurane maintenance treatment does not clinically prolong the QTc interval.

As a key sensitivity analysis, the interaction between type of maintenance anesthetic (propofol or sevoflurane) and sugammadex/placebo treatment was tested. If at least for one of the timepoints the interaction term between the factor for anesthetic and sugammadex was statistically significant at the 0.05 level, the contrasts of sugammadex versus placebo would be computed from separate ANCOVAs on the propofol arm and the sevoflurane arm. If for both anesthetics separately the one-sided 95% confidence intervals of QTcF excluded a prolongation of 10 msec, it would also be concluded that sugammadex when combined with propofol and/or sevoflurane maintenance treatment does not prolong the QTc interval to a level of clinical relevance."

Source: Sponsor's report, page 6.

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The sponsor found that sugammadex does not prolong the QT interval.

"The primary analysis revealed that sugammadex 4 mg/kg is 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 IMP), the estimated differences between sugammadex and placebo in change of QTcF from pre-IMP baseline and corresponding upper one-sided 95% confidence limits were clearly below the margin of 10 ms for each type of maintenance anesthetic separately as well as combined over both anesthetic arms."
Source: Sponsor's report, page 7.

Table 2: Sponsor's estimated mean QTcF difference between sugammadex and placebo and corresponding upper limit of the one-sided 95% CI (estimates from ANCOVA) for time-matched change from baseline - Combining both Maintenance Anesthetic Arms - Full Analysis Set

	Difference between sugammadex and placebo (msec)	
Time point	Estimate	Upper limit one-sided 95% CI
2 min Post IMP Dose	0.5666	1.9894
5 min Post IMP Dose	-0.5690	1.0670
15 min Post IMP Dose	-0.7216	1.2293
30 min Post IMP Dose	-2.3841	-0.08957

Source: Sponsor's study report, page 7.

Reviewer's Comments: The sponsor's conclusions agree with the FDA analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

The sponsor did not administer a positive control treatment.

4.2.8.2.3 Categorical Analysis

"During maintenance anesthesia with propofol, incidental QTcF values between 450 and 480 ms were reported, with similar incidences for sugammadex and placebo, 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 incidentally QTcF values between 480-500 msec or exceeding 500 msec were observed. The incidence of the finding "Electrocardiogram QT prolonged" was higher in the sevoflurane maintenance arm than in the propofol maintenance arm, but there was no notable difference between sugammadex and placebo in frequency of "Electrocardiogram QT prolonged" or other reported ECG findings."
Source: Sponsor's report, page 7.

4.2.8.2.4 Additional Analyses

"In the absence of QTc interaction between sugammadex and (type of) maintenance anesthetic (propofol/sevoflurane), mean QTcF increases exceeding the level of regulatory relevance were observed during maintenance anesthesia with both propofol and sevoflurane. The mean QTcF prolongations compared to preanesthesia 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.
On top of these relatively large QTcF prolongations induced by anesthetic treatment, the effect of sugammadex on QTcF compared to placebo was negligible. Results on Bazetts QTc were similar to the primary analysis on QTcF."
Source: Sponsor's report, page 7.

4.2.8.3 Safety Analysis

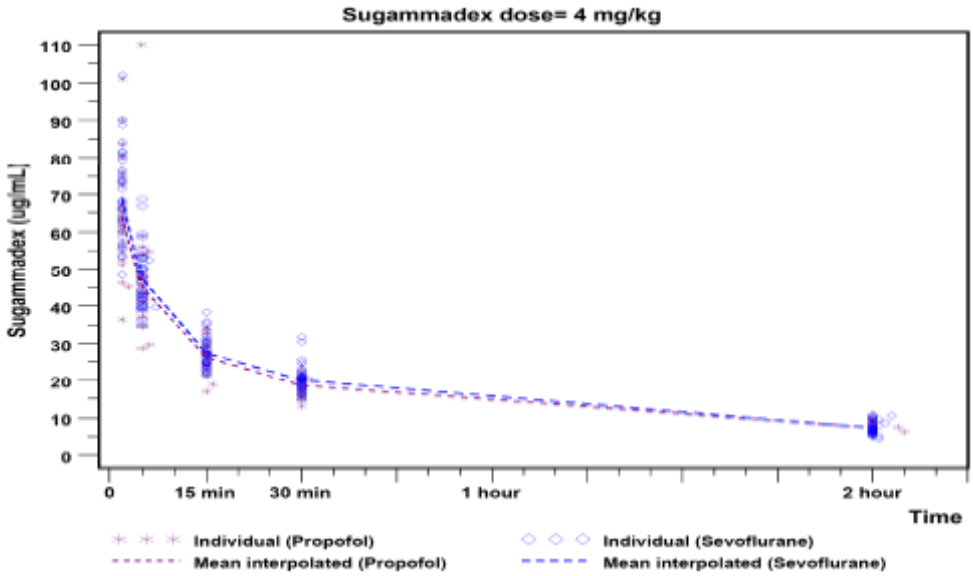
There were few cardiovascular adverse events, none portending arrhythmia.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK sampling of sugammadex (pre-dose, and 2, 5, 15, 30, and 120 minutes post dose) was insufficient to characterize sugammadex pharmacokinetics. The mean sugammadex concentration time course plots including individual observed concentrations are shown in Figure 1 below.

Figure 1: Geometric mean and scatter plots for sugammadex concentration versus time



Sponsor's TQT study-report, pg 82

The plasma PK parameters based on the sampling scheme until 2 hours after dosing are summarized in Table 3 below. A supratherapeutic dose was not evaluated as part of the

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study. Analysis was performed using only a therapeutic dose of 4 mg/kg, which is considered to be the most frequently administered dose to be used in clinical practice.

Table 3: Summary of the plasma PK parameters of sugammadex

		Propofol (n=31)	Sevoflurane (n=33)	Overall (n=64)
tmax (min)	Median	2	2	2
	Minimum-Maximum	2 - 5	2 - 2	2 - 5
Cmax (ug/mL)	Mean	65.5	68.9	67.2
	CV (%)	22.9	17.2	20.1
AUC0-2hours (µg·min/mL)	Mean	2160	2272	2217
	CV (%)	13.7	15.6	14.8

Mean = geometric mean and CV(%) = geometric CV(%).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB and QTcF). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcB and QTcF distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcB and QTcF versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 4, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 4: Comparison of QTcB and QTcF Using the Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P-value
Propofol/Placebo	-0.1083	-0.0308	0.0000
Propofol/Sugammadex	-0.1085	-0.0282	0.0000
Sevoflurane/Placebo	-0.1378	-0.0552	0.0000
Sevoflurane/Sugammadex	-0.1021	-0.0227	0.0000
All	-0.1112	-0.0312	0.0000

We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

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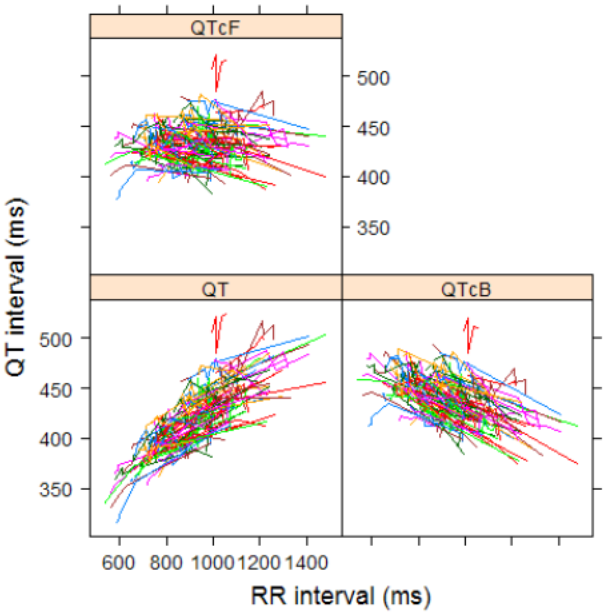
Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcB		QTcF	
	N	MSSS	N	MSSS
Propofol/Placebo	32	0.0187	32	0.0059
Propofol/Sugammadex	31	0.0127	31	0.0030
Sevoflurane/Placebo	34	0.0850	34	0.0553
Sevoflurane/Sugammadex	34	0.0847	34	0.0662
All	131	0.0516	131	0.0337

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 Statistical Assessments

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Sugammadex

The statistical reviewer used mixed model to analyze the ΔQTcF effect. The model includes treatment and sex as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 6 and Table 7.

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Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group A: Propofol/Sugammadex x 1 day

	ΔQTcF: propofol/ Sugammadex (ms)			ΔQTcF: placebo (ms)			ΔΔQTcF (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	31	-0.6	0.9	66	0.4	0.6	31	-1.0	(-3.1, 1.1)
5	31	0.3	1.0	66	2.3	0.7	31	-2.1	(-4.5, 0.4)
15	31	0.8	1.2	66	3.9	0.9	31	-3.1	(-6.1, -0.2)
30	31	0.2	1.6	66	7.8	1.1	31	-7.6	(-11.3, -4.0)
120	27	-9.9	2.5	62	-12.6	1.6	27	2.7	(-3.1, 8.5)

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group B: Sevoflurane/Sugammadex x 1 day

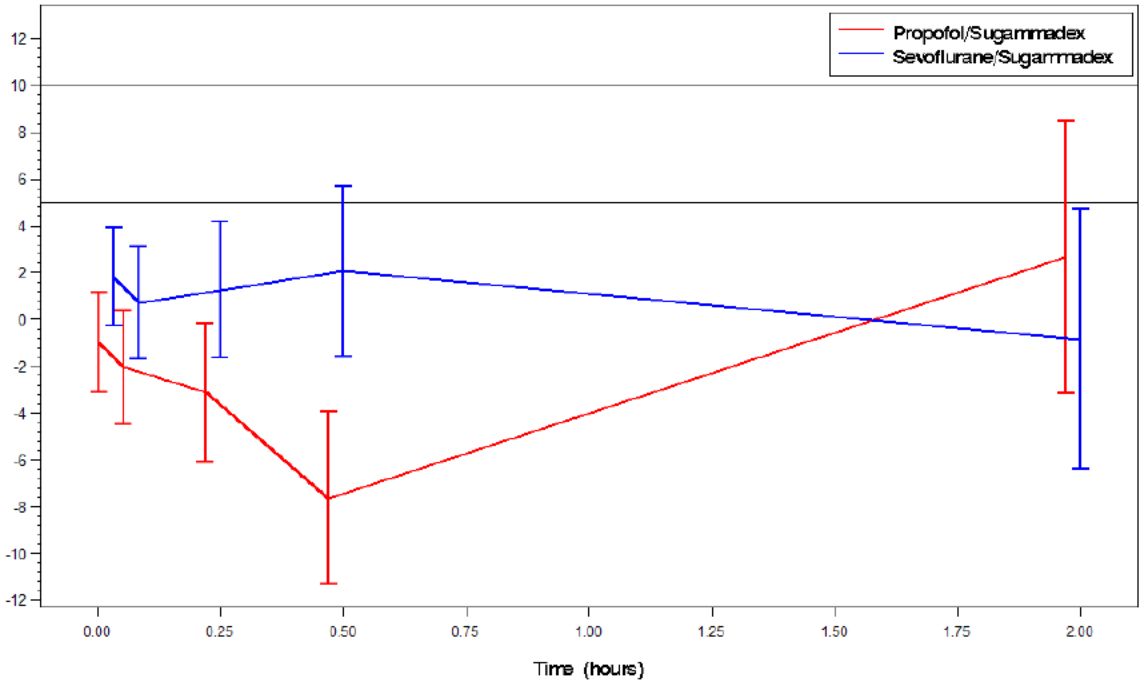
	ΔQTcF: sevoflurane/ Sugammadex (ms)			ΔQTcF: placebo (ms)			ΔΔQTcF (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	34	2.2	0.9	66	0.4	0.6	34	1.8	(-0.3, 3.9)
5	34	3.1	1.0	66	2.3	0.7	34	0.7	(-1.7, 3.1)
15	34	5.2	1.2	66	3.9	0.9	34	1.2	(-1.7, 4.2)
30	34	9.9	1.5	66	7.8	1.1	34	2.0	(-1.6, 5.7)
120	32	-13.4	2.3	62	-12.6	1.6	32	-0.8	(-6.4, 4.7)

The largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/sugammadex and placebo were 8.5 ms and 5.7 ms, respectively.

5.2.1.2 Graph of ΔΔQTcF over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Timecourse



All CIs are unadjusted.

5.2.1.3 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and ≥ 500 ms. There are 2 (5.8%) and 1 (2.9%) subjects who experienced QTcF greater than 480 ms in sevoflurane/placebo and sevoflurane/sugammadex, respectively. There were no subjects whose change from baseline (ΔQTcF) was above 30 ms.

Table 8: Categorical Analysis for QTcF

Treatment Group	N	Value <= 450 ms	450 ms < Value <= 480 ms	480 ms < Value <= 500 ms	Value > 500 ms
Propofol/Placebo	32	26 (81.3%)	6 (18.8%)	0 (0.0%)	0 (0.0%)
Propofol/Sugammadex	31	25 (80.6%)	6 (19.4%)	0 (0.0%)	0 (0.0%)
Sevoflurane/Placebo	34	18 (52.9%)	14 (41.2%)	1 (2.9%)	1 (2.9%)
Sevoflurane/Sugammadex	34	16 (47.1%)	17 (50.0%)	1 (2.9%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 9 and Table 10. The largest upper limits of 90% CI for the HR mean differences between propofol/sugammadex and placebo and sevoflurane/sugammadex and placebo are 3.6 bmp and 8.0 bpm, respectively.

Table 9: Analysis Results of ΔHR and ΔΔHR for Treatment Group A: Propofol/Sugammadex x 1 day

	ΔHR: propofol/ Sugammadex (bpm)			ΔHR: placebo (bpm)			ΔΔHR (bpm)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	31	0.1	0.5	66	-0.3	0.3	31	0.4	(-0.7, 1.5)
5	31	0.0	0.6	66	-0.5	0.4	31	0.5	(-1.0, 2.0)
15	31	0.4	0.9	66	-0.3	0.7	31	0.7	(-1.6, 2.9)
30	31	1.1	1.1	66	0.1	0.8	31	0.9	(-1.7, 3.6)
120	27	-14.5	1.4	62	-12.8	0.9	27	-1.7	(-5.0, 1.7)

Table 10: Analysis Results of ΔHR and ΔΔHR for Treatment Group B: Sevoflurane/Sugammadex x 1 day

	ΔHR: sevoflurane/ Sugammadex (bpm)			ΔHR: placebo (bpm)			ΔΔHR (bpm)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	34	-0.9	0.4	66	-0.3	0.3	34	-0.6	(-1.6, 0.5)
5	34	-1.3	0.6	66	-0.5	0.4	34	-0.8	(-2.3, 0.7)
15	34	-1.9	0.9	66	-0.3	0.7	34	-1.6	(-3.8, 0.6)
30	34	-1.0	1.1	66	0.1	0.8	34	-1.1	(-3.7, 1.4)
120	32	-8.0	1.3	62	-12.8	0.9	32	4.8	(1.6, 8.0)

Table 11 lists the number of subjects as well as the number of observations whose HR values are < 100 bmp and ≥ 100 bpm. There are 2 (6.3%), 3 (9.7%), and 1 (2.9%) subjects who experienced HR greater than 100 bpm in propofol/placebo, propofol/sugammadex, and sevoflurane/placebo, respectively.

Table 11: Categorical Analysis for HR

Treatment Group	N	HR < 100 bpm	HR >= 100 bpm
Propofol/Placebo	32	30 (93.8%)	2 (6.3%)
Propofol/Sugammadex	31	28 (90.3%)	3 (9.7%)
Sevoflurane/Placebo	34	33 (97.1%)	1 (2.9%)
Sevoflurane/Sugammadex	34	34 (100%)	0 (0.0%)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. The largest

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upper limits of 90% CI for the PR mean differences between propofol/sugammadex and placebo and sevoflurane/sugammadex and placebo are 4.5 ms and 6.9 ms, respectively.

Table 12: Analysis Results of ΔPR and ΔΔPR for Treatment Group A: Propofol/Sugammadex X 1 day

	ΔPR: propofol/ Sugammadex (ms)			ΔPR: placebo (ms)			ΔΔPR (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	31	0.5	0.6	66	-0.6	0.4	31	1.1	(-0.4, 2.6)
5	31	-0.6	0.9	66	-0.8	0.6	31	0.2	(-2.0, 2.3)
15	31	-0.8	1.3	66	-1.1	0.9	31	0.3	(-2.7, 3.3)
30	31	-1.0	1.5	66	-1.9	1.0	31	0.9	(-2.6, 4.5)
120	27	2.0	2.8	62	7.7	1.8	27	-5.7	(-12.3, 0.9)

Table 13: Analysis Results of ΔPR and ΔΔPR for Treatment Group B: Sevoflurane/Sugammadex X 1 day

	ΔPR: sevoflurane/ Sugammadex (ms)			ΔPR: placebo (ms)			ΔΔPR (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	34	-0.4	0.6	66	-0.6	0.4	34	0.3	(-1.2, 1.7)
5	34	-0.2	0.9	66	-0.8	0.6	34	0.5	(-1.5, 2.6)
15	34	-1.5	1.2	66	-1.1	0.9	34	-0.5	(-3.4, 2.4)
30	34	-3.1	1.4	66	-1.9	1.0	34	-1.2	(-4.7, 2.2)
120	32	8.3	2.6	62	7.7	1.8	32	0.7	(-5.5, 6.9)

Table 14 lists the number of subjects as well as the number of observations whose PR values are < 200 ms and ≥ 200 ms. There are 2 (6.3%), 1 (3.2%), 1 (2/9%), and 1 (2.9%) subjects who experienced HR greater than 100 bpm in propofol/placebo, propofol/sugammadex, sevoflurane/placebo, and sevoflurane/sugammadex, respectively.

Table 14: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR >= 200 ms
Propofol/Placebo	32	30 (93.8%)	2 (6.3%)
Propofol/Sugammadex	31	30 (96.8%)	1 (3.2%)
Sevoflurane/Placebo	34	33 (97.1%)	1 (2.9%)
Sevoflurane/Sugammadex	34	33 (97.1%)	1 (2.9%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 15 and

Table **16**. The largest upper limits of 90% CI for the QRS mean differences between propofol/sugammadex and placebo and sevoflurane/sugammadex and placebo are 1.8 ms and 1.7 ms, respectively.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group A: Propofol/Sugammadex x 1 day

	ΔQRS: propofol/ Sugammadex (ms)			ΔQRS: placebo (ms)			ΔΔQRS (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	31	0.1	0.4	66	-0.1	0.3	31	0.2	(-0.7, 1.0)
5	31	0.5	0.4	66	0.1	0.2	31	0.4	(-0.4, 1.3)
15	31	0.1	0.4	66	0.2	0.3	31	-0.1	(-1.1, 0.9)
30	31	0.4	0.5	66	-0.3	0.3	31	0.6	(-0.5, 1.8)
120	27	-1.5	0.8	62	-0.3	0.6	27	-1.2	(-3.2, 0.8)

Table 16: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group B: Sevoflurane/Sugammadex X 1 day

	ΔQRS: sevoflurane/ Sugammadex (ms)			ΔQRS: placebo (ms)			ΔΔQRS (ms)		
Time (min)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
2	34	-0.1	0.3	66	-0.1	0.3	34	0.0	(-0.8, 0.8)
5	34	-0.1	0.3	66	0.1	0.2	34	-0.2	(-1.0, 0.6)
15	34	0.3	0.4	66	0.2	0.3	34	0.1	(-0.9, 1.0)
30	34	-0.5	0.5	66	-0.3	0.3	34	-0.2	(-1.3, 0.9)
120	32	-0.5	0.8	62	-0.3	0.6	32	-0.2	(-2.0, 1.7)

Table 17 lists the number of subjects as well as the number of observations whose QRS values are < 110 ms and ≥ 110 ms. There is 1 (3.2%) subject who experienced QRS greater than 110 ms in propofol/sugammadex.

Table 17: Categorical Analysis for QRS

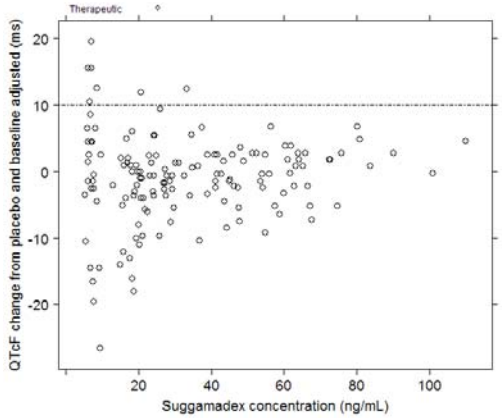
Treatment Group	N	QRS < 110 ms	QRS >= 110 ms
Propofol/Placebo	32	32 (100%)	0 (0.0%)
Propofol/Sugammadex	31	30 (96.8%)	1 (3.2%)
Sevoflurane/Placebo	34	34 (100%)	0 (0.0%)
Sevoflurane/Sugammadex	34	34 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

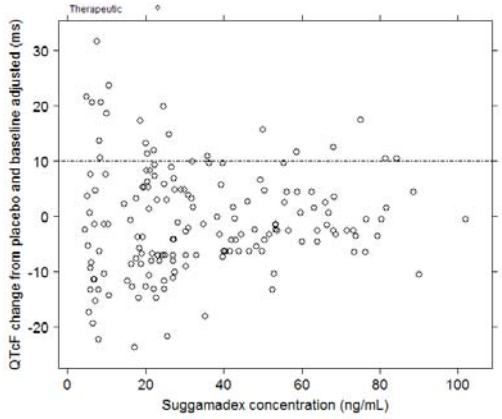
The relationship between ΔΔQTcF and sugammadex concentrations is visualized in Figure 4 (propofol maintenance, top), (sevoflurane maintenance, middle), and (combined analysis, bottom) with no evident exposure-response relationship. The previous IRT QT review identified a significant concentration-QT relationship; however that study included sugammadex doses up to 32 mg/kg. The narrower dose range included in this study (e.g., only 4 mg/kg) may have limited identification of a concentration-QT relationship for sugammadex in the current analysis.

Figure 4: ΔΔQTcF vs. Sugammadex concentration

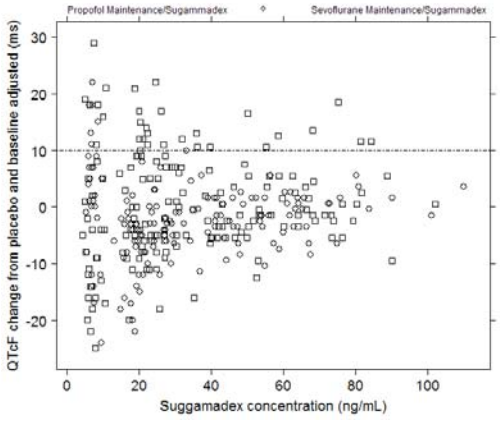
Propofol Maintenance



Sevoflurance Maintenance



Combined Datasets



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study are acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on PR or QRS.

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	Routine reversal: A dose of 4.0 mg/kg Bridion™ is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade. A dose of 2.0 mg/kg Bridion™ is only recommended, if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade. Immediate reversal: If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg Bridion™ is recommended.	
Maximum tolerated dose	Bridion™ was evaluated upto 96 mg/kg (highest dose tested)	
Principal adverse events	Bridion™ was safe and well tolerated at doses up to 96 mg/kg. The most common adverse reactions (incidence>5%) observed after treatment with Bridion ™ in clinical trials were anesthetic complications (8.0%) and dysgeusia (12.6%). Dysgeusia was only reported in healthy volunteers, especially at higher doses (mostly > 32 mg/kg Bridion ™).	
Maximum dose tested	Single Dose	96 mg/kg
	Multiple Dose	Not applicable
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} (i.e. C_0): 1168 µg/mL (CV 21.1%) Mean AUC_{0-inf}:71273 µg*min/mL (CV 16.2%)
	Multiple Dose	Not applicable
Range of linear PK	Overall, across trials and across dose groups, ranging from 0.1 to 96 mg/kg, similar values of CL of Bridion ™ were observed. Therefore, overall the data indicated dose linearity with respect to exposure to Bridion ™.	
Accumulation at steady state	Not applicable	
Metabolites	Metabolism of Bridion ™ is at most very limited and the compound is predominantly, if not exclusively, eliminated via renal excretion of the unchanged product.	
Absorption	Absolute/Relative Bioavailability	IV formulation

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	t_{max}	2 min (first sample taken after bolus IV administration)
Distribution	V_{ss}	V_{ss} of Bridion ™ was found to be approximately 12 to 15 L
	% bound	Bridion ™ does not bind to plasma proteins or erythrocytes
Elimination	Route	Renal excretion
	Terminal $t_{½}$	For the terminal elimination half-life of Bridion ™ in plasma, a relatively wide range of mean values from 66 to 260 min was observed within and across trials.
	CL	The observed CL of Bridion ™ was similar across trials, with mean values ranging from 97 to 138 mL/min.
Intrinsic Factors	Age	Using PK modeling: in a typical subject aged 81 years, CL was decreased by 51% compared to a typical subject of 49 years and by 32% compared to a typical subject of 68 years. Differences in volumes of distribution between the age groups were small. Renal function decreases with age and CL of Bridion ™ in elderly was dependent on CL_{CR} according to the equation: $CL = 87\ mL.min^{-1} + 0.61*(CL_{CR} - 105.4)$. This means that a 10% reduction of CL_{CR} (compared to 105 $mL.min^{-1}$) causes a 7.4% reduction in CL of Bridion ™.
	Sex	The PK of Bridion ™ is similar in female and male subjects.
	Race	No major differences in PK of Bridion ™ were observed between Japanese and Caucasian subjects. CL was 9% lower and V_{ss} was 12% lower in the Japanese compared to the Caucasian subjects. After body weight normalization (wn-) CL and V_{ss} were similar in both ethnic groups. The population PK data set contained too few subjects from other races to allow for separate evaluation of these race effects on the PK of Bridion ™.
	Hepatic & Renal Impairment	*Severe renal impairment* In severely renal impaired patients CL of Bridion™

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		was reduced approximately 16-fold compared to normal patients. V_{ss} of Bridion ™ was increased 25 % compared to normal patients. This resulted in a prolonged and 17-fold higher exposure to Bridion ™ in renal impaired patients. However, during the first 60 minutes post administration of Bridion ™ there was little difference in plasma levels between the two groups (thus neither in C_{max}). As there is currently no efficient dialysis method available, it is strongly recommended not to use Bridion ™ in severely renal impaired patients. *Mild and moderate renal impairment* Based on PK modeling for the elderly/renal impaired population three typical subjects with body weight 75 kg were simulated: • An elderly subject with borderline severe/moderate renal impairment (CLcr=30 mL/min) is predicted to have a 55% lower clearance compared to the typical adult. • An elderly subject with borderline moderate/mild renal impairment (CLcr=50 mL/min) is predicted to have a 41% lower clearance compared to the typical adult. • An elderly subject with borderline mild renal impairment (CLcr=80 mL/min) is predicted to have a 21% lower clearance compared to the typical adult.
		Hepatic impairment No trial in hepatically impaired subjects has been performed, as Bridion ™ is almost exclusively excreted via the renal route and therefore no major effects on Bridion ™ PK of severe hepatic impairment are expected.
Extrinsic Factors	Drug interactions	No drug interaction studies have been performed , but drug interaction potential was assessed based on a strategy using the in vitro determination of the binding affinity and clinical considerations. Based on this strategy, it has been concluded that a clinically relevant interaction cannot be ruled out for toremifene, flucloxacillin, fusidic acid and hormonal contraceptives. However, there are no indications, from preclinical or clinical studies, that these interactions occur. As there is no further information available to assess these potential

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		interactions, these drugs will be listed in the labeling.
	Food Effects	Not applicable (IV formulation)
Expected High Clinical Exposure Scenario	Since Bridion ™ not recommended to be used in severely renal impaired patients, an elderly subject with moderate renal impaired function was considered to represent the worst case scenario (as sex and race do no play major roles). For an elderly subject with borderline severe/moderate renal impairment, the clearance is predicted to be 55% lower as compared to for a typical adult. This means total exposure to Bridion ™ is increased by a factor 2.2. Therefore, an increase in total exposure to Bridion ™ of a factor two is considered to be the worst case scenario in clinical practice as compared to the 'normal' situation of an adult subject. A supratherapeutic dose of 32 mg/kg Bridion ™ provides an 8-fold margin for routine reversal, since for routine reversal doses upto 4 mg/kg Bridion ™ are recommended. For immediate reversal, following administration of rocuronium, a dose of 16.0 mg/kg Bridion ™ is recommended, and the two-fold margin provided by the supratherapeutic dose of 32 mg/kg is considered to be sufficient. For the evaluation of the applied supra-therapeutic dose of 32 mg/kg Bridion ™, it is also important to note that, during the first 60 minutes post administration of Bridion ™ there is little difference in plasma levels of Bridion ™ between severely renal impaired and control subjects (thus neither in C_{max}).	

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6.2 TABLE OF STUDY ASSESSMENTS

Protocol No. P06315

Day Relative to Dose of Study Drug	Screening Days -21 to -2	-1	1	2	FU 7[a]
Explain Study and Obtain Informed Consent(s)	X				
Review inclusion/exclusion Criteria	X	X			
Demographic Profile	X				
Physical Exam	X				X
Medical History	X				
Body Height (cm) and Weight (kg)	X	X[b]			
Body Mass Index (BMI, kg/m^2)	X				
Elbow Breadth Measurement	X				
HIV/HBsAg/HCV	X				
Drug/Alcohol Screen	X	X			
Pregnancy Test	X	X			
FSH and estradiol (postmenopausal females only)	X				
Routine Clinical Laboratory Tests[c]	X	X			X
SPO_2			X[d]		
Screening Number Assignment	X				
Randomization Number Assignment (Part 1 only)			X		
Record AEs and Concomitant Meds	X	X	X	X	X
Provide Subject Identification Card (see 9.1.3)			X		
ECG (12-Lead) Safety	X	X[f]		X[f]	X
ECG (12-Lead) Central lab		X (4 hours)	X[g]		
Vital Signs (BP, Pulse Rate, Oral Temp.)	X	X[f]		X[f]	X
Propofol/Sevoflurane Administration			X		
Sugammadex/Placebo Administration (Part 1)			X		
Neostigmine-glycopyrrolate Administration (Part 2)			X		
Pharmacokinetic Blood Samples[h]			X		
Sampling for hypersensitivity research[e]			X	X	X
Recording of TCI and MAC values[i]			X		
Sample for Pharmacogenetic Analysis[j]			X		
Subject Confinement		X	X	X	
Outpatient Visits	X				X

a) Follow up was performed +/- 2 days of the 7th day after the administration of trial medication.

b) Weight only, used for calculation of amount of sugammadex administration.

c) Complete Blood Count (CBC) and differential, chemistry panel, and urinalysis collected at least 4 hours without food, including aPTT and PT (INR).

d) Only during anesthesia and until recovery from anesthesia.

e) Blood samples for optional hypersensitivity research (Part 1 only) were collected as follows:

1. anti-sugammadex antibodies: predose. In case of the occurrence of suspected hypersensitivity symptoms additional samples were taken at 24 hours post dosing and at FU;

2. tryptase: predose, FU. In case of the occurrence of suspected hypersensitivity symptoms additional samples were taken at 1, 3, and 24 hours post dosing;

3. additional hypersensitivity research: predose. In case of the occurrence of suspected hypersensitivity symptoms additional samples were taken at 1, 3, 24 hours post dosing and at FU.

f) Obtained prior to dosing on Day -1 and prior to discharge on Day 2. The "ECG (12-Lead) Safety" assessment on Day -1 should have been performed at distinct timepoints from the "ECG (12-Lead) Central lab", to avoid interference of ECG equipment.

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Day Relative to Dose of Study Drug	Screening Days -21 to -2	-1	1	2	FU 7[a]

g) ECG monitoring using a 12-lead digital ECG Holter monitor was started approximately 2 hrs. prior to anesthesia induction and continued until 6 hrs. post- anesthesia induction. Triplicate ECGs were extracted at 1 hour pre-dose propofol induction, pre-dose sevoflurane/propofol maintenance anesthesia, pre-dose sugammadex/placebo (Part 1) and neostigmine-glycopyrrolate (Part 2), 2, 5, 15 and 30 minutes and 2 hours after administration of sugammadex/placebo (Part 1), 1, 2, 3, 5, 15 and 30 minutes and 2 hours after administration of neostigmine-glycopyrrolate (Part 2).

h) Blood samples for sugammadex (Part 1 only) were collected pre-anesthesia (0 hour) 2, 5, 15 and 30 minutes and 2 hours after the administration of sugammadex/placebo.

i) Part 1: TCI and MAC values must have been recorded pre-dose sevoflurane/propofol maintenance anesthesia, pre-dose sugammadex/placebo, 2, 5, 15 and 30 minutes after the administration of sugammadex/placebo. Part 2: TCI values must have been recorded pre-dose propofol maintenance anesthesia, pre-dose neostigmine-glycopyrrolate, 1, 2, 3, 5, 15 and 30 minutes after the administration of neostigmine-glycopyrrolate.

j) Informed consent for pharmacogenetic samples must have been obtained before the DNA sample. DNA sample for analysis should have been 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 was obtained.

Reference ID: 3279233

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/s/

JANICE B BRODSKY
03/20/2013

QIANYU DANG
03/20/2013

JEFFRY FLORIAN
03/20/2013

KEVIN M KRUDYS
03/21/2013

NORMAN L STOCKBRIDGE
03/21/2013

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 16, 2009

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Allison Meyer
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products

Subject: QT-IRT Consult to NDA 22-225

This memo responds to your consult to us dated March 31, 2009 regarding cardiac safety of sugammadex sponsored by Organon. The QT-IRT received and reviewed the following materials:

- Your consult
- Type C meeting package submitted by the sponsor
- Meta-analysis of QTcF data in patients in the sugammadex clinical trials submitted by the sponsor
- Reviews by the QT-IRT of the TQT studies

QT-IRT Comments for DAARP

1. The TQT study provides accurate quantification of the QT effect. There is significant confounding due to co-morbidities and concomitant medications in the patient population. The sponsor's explanation regarding QTcF outliers in the patient population appears reasonable.
2. With respect to the other serious cardiac AEs, again 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 sponsor's explanation of the incidence being representative of the post-surgical population appears reasonable.

BACKGROUND

In a Approvable letter of July 31,2008 under Additional Comments and requests, DAARP recommended "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."

On December 1, 2008, an End of Review meeting was held to discuss the issues outlined in the Not Approvable letter.

The division had recommended the expanded ECG evaluation although two thorough QTc trials (19.4.109 and 19.4.105) have been conducted as per ICH E14 guideline. These trials not only studied the effect of therapeutic (4 mg/kg) and supra-therapeutic (32 mg/kg) doses of sugammadex alone on QTc, but also the rocuronium/sugammadex and vecuronium/sugammadex complex at the request of the Agency. Both thorough QTc trials were negative according to the ICH-E14 criteria. The division was concerned about a three-fold greater incidence of QTc prolongation in sugammadex-treated subjects than in placebo-treated subjects that rose to the level of a serious adverse event (SAE), 3% versus 1%, respectively. In addition to QTc prolongation, other serious cardiac adverse events occurred more frequently in sugammadex-treated subjects than in either placebo- or neostigmine-treated subjects It was noted that none of these cardiac adverse events occurred in a manner that appeared to be dose related and most occurred while subjects were being monitored as part of their anesthetic care, i.e., intra-operatively or in the Post Anesthesia Care Unit, where the monitoring and readily available treatments would favor a positive outcome.

SPONSOR'S PROPOSAL

QTCF Data in the Patient Population:

> "The descriptive statistics of the changes from baseline of QTcF values by study and assessment have been presented in Table 5.

“

Table 5 **Descriptive statistics of QTcF change from baseline by trial and assessment. All Subjects Treated group.**

Trial /Assessment		Placebo						Sugammadex					
		N	Mean	SD	Min	Med	Max	N	Mean	SD	Min	Med	Max
P194202	2 min.	7	-0.1	7.3	-11	2	9	83	6.2	14.5	-23	7	42
	30 min.	9	-1.7	9.8	-11	-5	17	86	10.1	17.0	-32	10	54
P194204	2 min.							37	4.9	15.4	-24	3	31
	30 min.							36	8.5	16.1	-18	9	44
P194205	2 min.	5	9.4	19.3	-13	12	35	30	4.7	15.1	-25	7	43
	30 min.	5	13.2	25.9	-15	20	49	29	13.5	18.1	-29	14	59
P194206	2 min.	15	-1.8	20.8	-54	3	25	153	-0.2	16.7	-66	-1	71
	30 min.	15	7.3	12.3	-15	7	28	154	6.2	18.3	-43	6	61
	Post-anesthetic	16	4.7	25.3	-40	5	55	152	7.9	19.4	-68	7	104
P194210	2 min.							41	11.9	18.2	-27	12	60
	30 min.							38	20.7	20.4	-15	17	78
P194306	2 min.	5	1.4	12.8	-19	4	15	19	5.3	14.1	-29	5	30
	30 min.	6	4.8	15.6	-22	10	19	19	10.7	16.3	-21	14	40
P194309	2 min.	36	0.4	16.6	-30	1	70	65	-4.9	19.4	-66	-4	43
	5 min.	37	-1.8	18.2	-29	-3	77	72	1.2	24.4	-51	2	115
	10 min.	35	0.0	13.2	-30	2	32	69	-4.9	21.7	-66	-1	44
	30 min.	37	1.8	20.0	-27	0	91	70	-4.9	23.5	-93	0	62
	Endpoint	38	1.3	19.9	-27	0	91	72	-6.0	25.6	-95	0	62
	Post-anesthetic	38	-5.8	24.7	-63	-5	56	74	0.6	21.2	-42	0	63

Notes: SD: standard deviation; Min: minimum, Med: median; Max: maximum

“It should be noted that there is a clear difference between QTcF baseline values taken before or after administration of NMBA; the P194309 study, taking a baseline after NMBA tends to have lower mean changes from baseline than the other studies, where the baseline was taken before NMBA. In addition the P194210 study features relatively large changes from baseline. In this trial for half of the patients anesthesia was maintained with sevoflurane instead of propofol (which was typically used in the other protocols).

“Prolonged post-treatment QTcF values have been summarized by criterion in Table 6. From this Table it can be concluded that for all three criteria (QTcF>450, 480 and 500 ms) the frequency of patients with an outlying value on sugammadex were smaller than for placebo, both overall as well as limiting the analysis to placebo-controlled trials.

Table 6 Patients (n, %) with a prolonged post-treatment QTcF value by criterion and trial. All Subjects Treated group

Criterion/ Protocol		Placebo			Sugammadex		
		Total	n	%	Total	n	%
QTcF>450 ms	P194202	10	0	0.0%	87	5	5.7%
	P194204				36	6	16.7%
	P194205	5	0	0.0%	32	3	9.4%
	P194206	16	4	25.0%	157	30	19.1%
	P194210				42	19	45.2%
	P194306	6	1	16.7%	22	1	4.5%
	P194309	40	15	37.5%	76	24	31.6%
	Total	77	20	26.0%	452	88	19.5%
	Plac-Cont	77	20	26.0%	374	63	16.8%
QTcF>480 ms	P194202	10	0	0.0%	87	0	0.0%
	P194204				36	0	0.0%
	P194205	5	0	0.0%	32	1	3.1%
	P194206	16	0	0.0%	157	10	6.4%
	P194210				42	5	11.9%
	P194306	6	0	0.0%	22	0	0.0%
	P194309	40	5	12.5%	76	8	10.5%
	Total	77	5	6.5%	452	24	5.3%
	Plac-Cont	77	5	6.5%	374	19	5.1%
QTcF>500 ms	P194202	10	0	0.0%	87	0	0.0%
	P194204				36	0	0.0%
	P194205	5	0	0.0%	32	0	0.0%
	P194206	16	0	0.0%	157	4	2.5%
	P194210				42	1	2.4%
	P194306	6	0	0.0%	22	0	0.0%
	P194309	40	4	10.0%	76	4	5.3%
	Total	77	4	5.2%	452	9	2.0%
	Plac-Cont	77	4	5.2%	374	8	2.1%

Criterion/ Protocol		Placebo			Sugammadex		
		Total	n	%	Total	n	%
QTcF change > 30 ms	P194202	9	0	0.0%	87	12	13.8%
	P194204				36	5	13.9%
	P194205	5	1	20.0%	31	3	9.7%
	P194206	16	2	12.5%	157	23	14.6%
	P194210				41	11	26.8%
	P194306	6	0	0.0%	20	3	15.0%
	P194309	40	2	5.0%	76	15	19.7%
	Total	76	5	6.6%	448	72	16.1%
	Plac-Cont	76	5	6.6%	371	56	15.1%
QTcF change > 60 ms	P194202	9	0	0.0%	87	0	0.0%
	P194204				36	0	0.0%
	P194205	5	0	0.0%	31	0	0.0%
	P194206	16	0	0.0%	157	1	0.6%
	P194210				41	2	4.9%
	P194306	6	0	0.0%	20	0	0.0%
	P194309	40	1	2.5%	76	3	3.9%
	Total	76	1	1.3%	448	6	1.3%
	Plac-Cont	76	1	1.3%	371	4	1.1%
Any criterion	P194202	9	0	0.0%	87	14	16.1%
(QTcF > 450 ms OR	P194204				36	8	22.2%
QTcF change >30 ms)	P194205	5	1	20.0%	31	5	16.1%
	P194206	16	5	31.3%	157	41	26.1%
	P194210				41	19	46.3%
	P194306	6	1	16.7%	20	3	15.0%
	P194309	40	13	32.5%	76	33	43.4%
	Total	76	20	26.3%	448	123	27.5%
	Plac-Cont	76	20	26.3%	371	96	25.9%
Maximum criterion	P194202	9	0	0.0%	87	0	0.0%
(QTcF > 500 ms OR	P194204				36	0	0.0%
QTcF change >60 ms)	P194205	5	0	0.0%	31	0	0.0%
	P194206	16	0	0.0%	157	4	2.5%
	P194210				41	3	7.3%
	P194306	6	0	0.0%	20	0	0.0%
	P194309	40	3	7.5%	76	5	6.6%
	Total	76	3	3.9%	448	12	2.7%
	Plac-Cont	76	3	3.9%	371	9	2.4%

Note: Plac-Cont: totals for placebo-controlled trials

"The analysis on categorical analysis revealed a higher percentage of subjects with QTcF changes exceeding 30 ms after sugammadex (15.1%) than after placebo (6.6%) in placebo controlled trials which was statistically significant (p=0.047 using conditional logistic regression controlling for trial and adjusting for sex and age). However, for the criterion of QTcF changes exceeding 60 ms the incidences for the sugammadex and placebo groups were similar (1.3% vs. 1.1%, respectively, p=0.96).

"For the P194210 trial the incidence of QTcF prolongations was somewhat increased as compared to the other trials, both for prolonged QTcF values as well as outlying changes

from baseline. This finding can be explained when considering that in the P194210 trial for 21 patients anesthesia was maintained using sevoflurane, for which outlying QTcF values were more frequently observed (Table 7 - see the clinical trial report for details)."

Reviewer's Comment: The sponsor's explanation is reasonable. Moreover, the QT effect is best quantified and characterized in the TQT study.

Response to other serious cardiac events:

- The incidence of subjects with at least one (S)AE in the SOC Cardiac disorders is comparable for sugammadex, neostigmine and placebo.
- The incidence of individual AEs, including AF, is overall low, does not show a dose response relation and is comparable for sugammadex, neostigmine and placebo.
- The occurrence of serious cardiac events were sporadic and occurred in the sugammadex group as well as placebo group. These events are known to occur in isolated cases during and following non-cardiac surgery as reported in a number of publications[7, 8]
- Given the low overall incidence and group size differences there is no evidence that an incidence difference exists.
- For the most serious cases there are clearly identifiable circumstances that provide a very good explanation for the clinical findings.

Comparison to placebo

As shown in Table 2, bradycardia, extra systoles, cardiac arrest, palpitations, ventricular tachycardia and electrocardiogram QT corrected interval prolonged (see section above) were reported with a higher incidence for sugammadex. Tachycardia, acute myocardial infarction, angina pectoris, atrial fibrillation and sinoatrial block were reported with a higher incidence for placebo (isolated single reports except for AF). With the exception of electrocardiogram QT corrected interval prolonged (sugammadex group) and ventricular extra-systoles (placebo group). The sponsor reports that the incidence of all events was below 2% regardless of treatment group and very broadly com-parable to the incidence of such events during and following non-cardiac surgery as reported in published studies.

Reviewers' Comments: except for bradycardia (8) all the others were isolated events.

Table 2 Number (%) of subjects with AEs; Cardiac events in pooled Phase 1-3 trials with placebo group.

SOC Cardiac disorders Preferred Term	Rocuronium or vecuronium + Org 25969 (N=640) n (%)	 Placebo (N=140) n (%)
At least one AE	*15 (2.3)*	*7 (5.0)*
Bradycardia	8 (1.3)	0 (0.0)
Tachycardia	2 (0.3)	1 (0.7)
Extrasystoles	2 (0.3)	0 (0.0)
Cardiac arrest	1 (0.2)	0 (0.0)
Palpitations	1 (0.2)	0 (0.0)
Ventricular tachycardia	1 (0.2)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	3 (2.1)
Acute myocardial infarction	0 (0.0)	1 (0.7)
Angina pectoris	0 (0.0)	1 (0.7)
Atrial fibrillation	0 (0.0)	2 (1.4)
Sinoatrial block	0 (0.0)	1 (0.7)
Soc Investigations		
Electrocardiogram QT corrected interval prolonged	16 (2.5)	2 (1.4)

Source: CTD 2.7.4 Table 32

Table 3 Number (%) of subjects with SAEs; in pooled Phase 1-3 trials with placebo group

SOC Cardiac disorders Preferred Term	Rocuronium or vecuronium + Org 25969 (N=640) n (%)	 Placebo (N=140) n (%)
At least one SAE	2 (0.3)	1 (0.7)
Cardiac arrest	1 (0.2)	0 (0.0)
Ventricular tachycardia	1 (0.2)	0 (0.0)
Acute myocardial infarction	0 (0.0)	1 (0.7)
Soc Investigations		
Electrocardiogram QT corrected interval prolonged	16 (2.5)	2 (1.4)

Source: CTD 2.7.4 Table 55

Trials, 19.4.301 and 19.4.302, compared sugammadex to neostigmine. Table 4 shows that the incidence of subjects with at least one adverse event in the MedDRA System Organ Class (SOC) Cardiac disorders was similar in both groups. Single events occurred in no more than 2 subjects in either group.

Table 4 Number (%) of subjects with AEs; Cardiac events in Phase 3 controlled trials 19.4.301 and 19.4.302

SOC Cardiac disorders Preferred Term	Rocuronium or vecuronium + Org 25969 (N=179) n (%)	 Neostigmine (N=167) n (%)
At least one AE	*5 (2.8)*	*5 (3.0)*
Sinus tachycardia	2 (1.1)	0 (0.0)
Tachycardia	2 (1.1)	0 (0.0)
Angina pectoris	1 (0.6)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	2 (1.2)
Atrial fibrillation	0 (0.0)	1 (0.6)
Cardiac failure	0 (0.0)	1 (0.6)
Cardiomegaly	0 (0.0)	1 (0.6)
Palpitations	0 (0.0)	1 (0.6)
Ventricular extrasystoles	0 (0.0)	1 (0.6)
Soc Investigations		
Electrocardiogram T wave abnormal	0 (0.0)	1 (0.6)

Source: CTD 2.7.4 Table 35

Pooled Phase 1 – 3 data

As Table 5 through Table 8 show there is no indication for a relation between dosage and the incidence of cardiac (serious) adverse events, regardless of data set.

Table 8 Number (%) of subjects with AEs; Cardiac events in pooled Phase 1-3 and Phase 1 data sets together.

SOC Cardiac disorders Preferred Term	n (%) of subjects (exposures) Rocuronium, vecuronium or pancuromium + Org 25969 ($mg.kg^{-1}$) 0 (Placebo) (N=336)	<2 (N=311)	2 (N=612)	3 (N=9)	4 (N=735)	6 (N=28)	8 (N=154)	12 (N=39)	16 (N=127)	20 (N=4)	32 (N=326)	64 (N=12)	96 (N=12)	Total Org 25969 (N=2369)
At least one AE	*9 (2.7)*	*7 (2.3)*	*22 (3.6)*	*0 (0.0)*	*16 (2.2)*	*2 (7.1)*	*4 (2.6)*	*0 (0.0)*	*2 (1.6)*	*0 (0.0)*	*6 (1.8)*	*0 (0.0)*	*0 (0.0)*	*59 (2.5)*
Tachycardia	1 (0.3)	1 (0.3)	6 (1.0)	0 (0.0)	6 (0.8)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	15 (0.6)
Bradycardia	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)	1 (0.1)	1 (3.6)	3 (1.9)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.5)
Palpitations	1 (0.3)	1 (0.3)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.5)	0 (0.0)	0 (0.0)	9 (0.4)
Atrial fibrillation	2 (0.6)	1 (0.3)	7 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.3)
Sinus tachycardia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.2)
Angina Pectoris	1 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Arrhythmia	0 (0.0)	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Extrasystoles	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Ventricular extrasystoles	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)
Ventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.1)
Cardiogenic shock	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Myocardial infarction	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

SOC Cardiac disorders Preferred Term	n (%) of subjects (exposures) Rocuronium, vecuronium or pancuromium + Org 25969 (mg.kg^{-1}) 0 (Placebo) (N=336)	<2 (N=311)	2 (N=612)	3 (N=9)	4 (N=735)	6 (N=28)	8 (N=154)	12 (N=39)	16 (N=127)	20 (N=4)	32 (N=326)	64 (N=12)	96 (N=12)	Total Org 25969 (N=2369)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Electromechanical dissociation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Wolf-Parkinson-White syndrome	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Atrioventricular block second degree	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)
Bundle branch block right	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Supra ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)
Acute myocardial infarction	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinoatrial block	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block first degree	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: CTD 2.7.4 Table 36 and Table 75

Sponsor's Conclusion:
The clinical findings with respect to cardiac events, including QTc prolongation, are representative for the surgical population that was studied and do not indicate that sugammadex would negatively impact cardiac safety.

Reviewer's Comments:

On review of the CSR's, the sponsor reports no clinically relevant changes in the PR interval, QRS duration in both TQT studies (194.105 and 194.109). The sponsor's proposition that the other serious cardiac events are representative of the surgical population appears reasonable.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

Suchitra Balakrishnan
7/16/2009 04:03:50 PM
MEDICAL OFFICER

Norman Stockbridge
7/16/2009 04:39:17 PM
MEDICAL OFFICER

ADRA Rev #1 of Action Package for NDA 22-225, (b) (4) ~~Bridion~~ (suggamadex sodium) Injection

Reviewer: Lee Ripper, ODE II
Date received: 7-14-08
Date of review: 7-30-08
Date original NDA received: 10-31-07
UF goal date: 7-31-07

Proposed Indication: Routine reversal of neuromuscular blockage induced by rocuronium or vecuronium; immediate reversal of neuromuscular blockage at 3 minutes after administration of rocuronium
Action type: NA
RPM: Allison Meyer
Drug Classification: 1P
505(b) application

Debarment Certification: AC
Financial Disclosure: AC
Safety Update: Submission dated 2-27-08; rev'd by Art Simone, MOR pp 17, 82, 95
REMS: N/A
Clinical Inspection Summary: 3/28/08: Audits were performed of Organon, Roseland NJ and 4 investigator sites. Protocol violations were noted at one site; "division should evaluate the impact, if any, that the inability to verify data for the aforementioned subjects has on the acceptability of the efficacy data."
DMEDP Review of Proprietary Name: (b) (4) found not objectionable 5/23/08
DMEDP Review of Carton and Container Labels: 5/23/08 name review includes comments on labels.
DRISK Review of PPI: N/A
DDMAC Review: 4/29/08 labeling review
SEALD Review of PLR: None
CSS: None
EA: Claim of CE acceptable, CMC Rv#1, page 131
EER: AC 7/24/08
PSC Mtg: N/A
CDTL Review: 7/18/08
DD Review:
OD Review:

CMC review by Blair Fraser, approval from CMC, 7/21/08
P/T section to Paul Brown, CM 7/18/08 with comments

Outstanding items:
1. DD review
2. OD review
3. Second SGE anaphylaxis consult (not requried before action)
4. Action Package Checklist

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/s/

Leah Ripper

7/30/2008 05:49:58 PM

CSO

MAYO CLINIC

Fax

Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905

To: Dr. Sally Seymour	Date: July 23, 2008
Company: FDA	Fax: 301-796-9728
No. of Pages (including cover sheet): 3	Phone: 301-796-1290
Delivery Instructions: ☐ Routine ☒ Urgent	
From: James T. C. Li, M.D., Ph.D.	Fax: (507) 284-0902
	Phone: (507) 284-4966

Message:

This faxed information is intended only for the use of the individual or entity to which it is addressed and contains information that is **confidential**. Furthermore, this information may be protected by Federal law relating to confidentiality (42 CFR Part 2) prohibiting any further disclosure. If the reader of this message is not the intended recipient or the employee or agent responsible for delivering this message to the intended recipient, you are hereby notified that any review, dissemination, distribution, or copying of the communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and destroy the original message. Thank you.

Consultation on hypersensitivity to sugammadex
James T. Li MD
July 22, 2008
Confidential

Case 106101008 meets the Sampson (2006) criteria for "anaphylaxis highly likely" based on criterion 2 (acute onset, flushing with [persistent] gastrointestinal symptoms). The elevated tryptase demonstrates mast cell involvement and the positive skin tests suggest IgE mediated sensitization. It is not possible to determine whether sugammadex was a "likely allergen" for this subject. In my opinion, this event was most likely an anaphylactic event.

Case 105101030 meets the Sampson criteria for "anaphylaxis highly likely" based on criteria 1 (rapid onset, flushing, difficulty breathing). The time course of events suggests an escalating severity of reactions.

Case 105101028 does not seem to meet Sampson criteria for "anaphylaxis highly likely" (rapid onset and flushing), but no dyspnea, hypotension or gastrointestinal symptoms. Palpitations and tachycardia (without hypotension) are not criteria for anaphylaxis. A room air oxygen saturation of 96% does not meet criteria for "hypoxemia".

The other reactions in "healthy" subjects (109101073, 115101008 and 105101001) are cases of rapid onset, with symptoms of nausea/burning, pruritus/urticaria, and sneezing/nasal congestion. These cases are suggestive of immediate drug reactions (although not anaphylaxis).

Taking cases 106101008 and 105101030 as "highly likely" cases of anaphylaxis, the anaphylaxis rate in healthy volunteers is about 1%. None of the cases seemed life-threatening. The rate in the overall exposed population can be estimated at 0.1% if only these 2 cases are included.

In my opinion, there is significant uncertainty, and some risk of drug reactions with widespread use of sugammadex. Further, if immune-mediated drug sensitization is the mechanism of reaction (so far unproven), then repeated use of sugammadex might increase the number of sensitized individuals, leading to an even higher rate of reactions. The observation of skin test sensitization in some exposed subjects supports this concern.

One of the challenges is extrapolating the observed experience of 209 healthy volunteers, and around 2000 exposed individuals, to a much larger anticipated patient population. On one hand, the anaphylaxis rate in patients with widespread use might be 0.1% or less. On the other hand, the anaphylaxis rate could substantially exceed 1%, with even higher rates for non-anaphylactic drug reactions.

The skin prick and intradermal tests are inconclusive. The skin test results suggest that unexposed individuals do not show (spurious) skin test reactions, and that exposed individuals (whether symptomatic or not) show a higher rate of positive skin tests. As

stated above, this suggests that sensitization to sugammadex might develop with exposure. Obviously a much larger series of cases and controls are needed to draw any significant conclusions.

Likewise, the basophil histamine release studies are inconclusive. The predictive value and clinical relevance of this test, especially for drug allergy, have not been established. So the negative results are not particularly reassuring.

There's much that the medical community doesn't know about adverse reactions to drugs. IgE mediated hypersensitivity (and anaphylaxis) is only one of a wide variety of possible mechanisms. For example prior exposure to an allergen might (at first glance) seem to be a prerequisite for future reactions; but the evidence to support this notion in a clinical setting is sparse. Similarly, it's well known that individuals with negative skin tests to a drug can develop serious systemic reactions. The clinical utility of the basophil histamine release assay in drug allergy is unknown, and probably limited.

Investigation of possible (immunologic and non-immunologic) mechanisms of reactions to sugammadex would be of interest, but might in the end be unrevealing. The high clinical utility of skin tests in penicillin allergy seems to be the exception rather than the rule. Nevertheless, study of the rate of skin test sensitization to sugammadex after exposure might be of interest. In vitro IgE (and perhaps IgG) antibody tests to sugammadex might shed some light on sensitization. Certainly, measurement of serum tryptase at the time of reaction may be very informative. Deliberate challenge or rechallenge of sensitized individuals (or individuals who have experienced a systemic reaction) could be conducted in specialized centers. Basophil histamine release studies might help determine whether basophil or mast cell activation is involved.

In summary, there are at least 2 cases of possible anaphylactic reactions to sugammadex, and some skin test evidence suggesting that sensitization can occur. Given the anticipated widespread use of sugammadex, caution regarding the potential for frequent drug reactions is reasonable. Tracking of subjects receiving multiple doses of sugammadex, monitoring skin test (or invitro) sensitization of exposed (and re-exposed) subjects, and more extensive use of serum tryptase are reasonable approaches.

One final thought. Post-marketing study of reactions to suggammadex will likely be rather difficult, given the heterogeneity of patients, polypharmacy, and multiplicity of symptoms in the perioperative period.

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/s/

Allison Meyer
7/29/2008 09:47:01 AM
CSO
consult on behalf of:James Li, MD, PhD FAAAAI
Professor of
Medicine
Chair of Division of Allergic Diseases
Mayo Clinic College
of Medicine

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-225 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Bridion
Established Name: sugammadex sodium
Strengths: 100 mg/mL

Applicant: Organon USA Inc.
Agent for Applicant (if applicable):

Date of Application: 10/30/07
Date of Receipt: 10/31/07
Date clock started after UN:
Date of Filing Meeting: 12/4/07
Filing Date: 12/30/07
Action Goal Date (optional): 4/30/08 User Fee Goal Date: 4/30/08

Indication(s) requested: (b) (4)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P ☒
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☒ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☒ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 5 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 68,029

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) May 3, 2005 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 10/30/06 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 9/2/05 NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12/4/07

NDA #: 22-225

DRUG NAMES: Bridion

APPLICANT: Organon USA Inc.

BACKGROUND: This NDA is an NME priority review [redacted] (b) (4). Advisory committee will occur March 11, 2008.

ATTENDEES: Bob Rappaport, Dionne Price, Tom Permutt, Lex Schultheis, Adam Wasserman, Alex Xu, Danae Christodoulou, Lei Zhang, Rigoberto Roca, Rob Shibuya, Kathryn Gaines, Jason Woo, Mary Purucker, Allison Meyer, Art Simone

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Rob Shibuya/Art Simone
CDTL/Secondary Medical:	Mary Purucker
Statistical:	Tom Permutt
Pharmacology:	Alex Xu
Statistical Pharmacology:	
Chemistry:	Alan Schroeder
Environmental Assessment (if needed):	
Biopharmaceutical:	Lei Zhang
Microbiology, sterility:	Vinnie Pawar
Microbiology, clinical (for antimicrobial products only):	
DSI:	Sherbet Samuels
OPS:	
Regulatory Project Management:	Allison Meyer/Parinda Jani
Other Consults:	QT, OSE (Tradename, Label), DDMAC, Renal, Allergy

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known March 11, 2008 NO ☐

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☒

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☒ NO ☐
  If yes, was microbiology consulted for validation of sterilization? YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional): formatting issues with the PLR will be identified, along with a microbiology request, CMC request, pharmacology request and biopharmaceutic requests

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Allison Meyer
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  *If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

Allison Meyer
7/14/2008 10:57:52 AM
CSO

Parinda Jani
7/14/2008 12:03:32 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: April 29, 2008

To: Allison Meyer – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Bridion (sugammadex (b) (4)) Injection
NDA 22-225

DDMAC has reviewed the proposed product labeling (PI) (version dated 4/29/08) and proposed carton and container labeling (version dated 2/19/08) for Bridion (sugammadex (b) (4) Injection (Bridion) submitted for consult on April 29, 2008. We offer the following comments.

Highlights

Indications and Usage

1. Is (b) (4) considered a pharmacological class? If not, we recommend revising. According to the Description section of the proposed PI, Bridion is a modified gamma cyclodextrin.

Warnings and Precautions

1. As proposed this section omits certain risk information about Bridion therapy. Therefore, is it appropriate to include more risk information from sections 5.4-5.11?

Full Prescribing Information

Contents

1. For consistency with the Indications and Usage section of the proposed PI, we recommend (b) (4)

Adverse Reactions

(b) (4)

Recurrence of neuromuscular blockade (b) (4)

1. (b) (4)

   Would it be possible to provide the incidence for placebo-treated patients? Also, would it be possible to provide context for (b) (4)?

(b) (4)

1. (b) (4)

   Would it be possible to provide context for (b) (4)?

Drug Interactions

1. (b) (4)

   This claim is promotional in tone and minimizes the risks of Bridion therapy. Therefore, we recommend deleting.

Interference with Laboratory Tests

1. (b) (4)

   As proposed, this claim minimizes the risks of Bridion therapy. Therefore, we recommend deleting the underlined text.

Description

1. "BRIDION™ contain (b) (4) of the mono OH-derivative of sugammadex."

   Would it be possible to provide context for (b) (4)?

Clinical Pharmacology

Pharmacodynamics

1. "BRIDION™ contain (b) (4) of the mono OH-derivative of sugammadex."

   Would it be possible to provide context for (b) (4)?

2. (b) (4)

   Is this claim clinically relevant for the prescriber to know? If this is not critical information, we recommend deleting as it is promotional in tone.

Pharmacokinetics

1. (b) (4)

   (b) (4) are promotional in tone. Therefore, we recommend deleting as context is provided later in the sentence (b) (4) (b) (4)

Clinical Trials

1. This section of the proposed PI describes (b) (4) studies. Were these studies appropriately designed to be considered substantial evidence to include in labeling and to support superiority claims in promotion? If not, we recommend deleting.

(b) (4)

1. (b) (4)

   (b) (4) is promotional in tone. Therefore, we recommend deleting.

2. (b) (4)

   As proposed, this claim minimizes the risks of Bridion therapy. Therefore, we recommend deleting the underlined text.

[redacted] *QT/QTc Study*

1. [redacted] is promotional in tone. Therefore, we recommend deleting.

Carton and Container Labeling

1. [redacted]

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

/s/

Michelle Safarik
4/29/2008 04:05:30 PM
DDMAC REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

DATE: April 3, 2008

FROM: Fred Hyman, D.D.S. M.P.H, Dental Officer, DDDP

THROUGH: John Kelsey, D.D.S., M.B.A., Dental Team Leader, DDDP

THROUGH: Susan Walker, M.D., Division Director, DDDP

cc: Julie Beitz, M.D., Office Director, ODE III
Bronwyn Collier, ADRA, ODE III
Margo Owens, Supervisory PM, DDDP

TO: Allison Meyer, Project Manager
Division of Anesthetics, Analgesics and Rheumatology Products

SUBJECT: Request for Information about Adverse Effect of Sugammadex, an Anesthetic Reversal Agent, on Tooth Development

DDDDP Consult #1066
Received Date: February 8, 2008
Requested Completion Date: March 8, 2008

Purpose of Consult

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) is currently reviewing NDA 22-225, Sugammadex (Org 25969), a substituted gamma-cyclodextrin. The drug is intended to reverse the anesthesia associated with neuromuscular blocking agents including rocuronium and vecuronium.

One safety concern that is currently under review in DAARP is the incorporation of Sugammadex into bones and developing teeth that arises from the drug's strong affinity for hydroxyapatite. DAARP has consulted the dental team within DDDP to respond to questions about the potential effects on tooth formation, particularly in children whose teeth have not yet fully mineralized and could be markedly impacted by incorporation of this drug into the developing structures.

To date, the only clinical trials that have been conducted under this IND were in adults. In those trials, no dental considerations were under investigation. However, the sponsor submitted results of several studies in both juvenile and adult rats to measure the effect on bones and teeth. These studies are under review by the toxicology group in DAARP, and in this consult they request assistance with interpreting the dental outcomes.

Please note that it is not the intent of this consult to provide recommendations for regulatory action of this drug. DDDP is providing thorough answers to the questions posed in the consult in a way that reflects the expertise of a clinical reviewer who is familiar with dental drugs and procedures. However, since the indication of this drug is to reverse the anesthesia associated with neuromuscular blocking agents, any risk/benefit or other regulatory decisions regarding potential dental adverse events will need to be in accordance with the policies of the DAARP. DDDP was not involved with this drug during its IND development, and has not provided any input towards designing either the clinical trials or the pharm/tox studies to help determine any dental adverse events.

Request from Division of Anesthesia, Analgesia, and Rheumatology Products

Following is the verbatim request from DAARP to DDDP:

1. Has the Sponsor adequately addressed the issue of Org 25969 deposition in teeth through conduct of nonclinical toxicology studies? Are there other in vitro/in vivo studies you believe would be appropriate?
2. Do the dental findings in the juvenile rat represent a risk for pediatric subjects/patients?
3. If the findings represent risk in pediatric patients, is the safety margin adequate to allow pediatric trials to go forward? Does the single-dose use of the product mitigate concern?
4. Is there an age above which pediatric patients would not be at excess risk for dental deposition of Org 25969?
5. Has the Sponsor adequately addressed concerns with prenatal exposure and effects on the dentition of the fetus? If not, does the data rise to the level of a warning & precaution or a pregnancy contraindication?

Response

Summary

The consensus of literature reveals that exposure to a substance which impacts the hydroxyapatite formation in children under the age of 8 has the potential to disrupt enamel formation in those teeth. The rat studies that were conducted and submitted to the Agency by the sponsor show that no discernable adverse effects on fully developed teeth were uncovered; some untoward cosmetic effects were observed on developing teeth, but only after three weeks of daily use of a high (120 $mg \cdot kg^{-1}/day^{-1}$) dose. A change in the growth of the rats' teeth was noted after three weeks of a very high (500 $mg \cdot kg^{-1}/day^{-1}$) dose of Sugammadex. Due to these known outcomes, caution should be exercised in future clinical trials planned for a human pediatric population. In particular, pediatric studies should be restricted to surgical procedures in which only a single use of Sugammadex is anticipated until more information about the safety margin is determined. One possibility for gathering safety data on young children is to have the sponsor design a trial that includes a follow-up period during which teeth that are shed either naturally or extracted for orthodontic or other reasons can be collected and studied histologically. Another possibility of establishing safety with multiple dosing is experimentation in a species of animal that more closely mimics human dentition than the rat.

Based upon the results of the animal studies and knowledge of dental development, there is not a concern from a dental perspective about the effect of Sugammadex on fully mineralized human teeth, as in adults, and children ages 8 and older. In addition, data from rat studies strongly suggest a safety margin that is sufficiently great to begin conduct of clinical trials on children of any age for a single use of Sugammadex. However, early trials should exclude children who are scheduled for multiple surgeries, which would necessitate repeated use of the drug.

Specific Consultative Questions:

In the following section of this review, each question from DAARP will be restated, along with DDDP's response and support for the response. Questions 1 and 2 will be answered together as there is much overlap in responding to these. For the same reason, questions 3 and 4 will also be answered with one response. Prior to answering these questions, differences between growth and development of rat teeth and human teeth will be briefly described here. The use of the rat data to draw conclusions about the effect on human dentition requires an understanding of these distinctions.

The most relevant qualities that rats possess and humans do not are: 1) rats have only one set of teeth in their lives, unlike humans who have both a primary and permanent set; 2) rats have only molars and incisors; and 3) rat incisors continue to grow and lay down new enamel throughout life. (Because the rat incisors, which are sharp and very pointed, are continuously worn down through chewing, these teeth grow an average of five inches per year.)

Enamel formation of human permanent teeth, other than third molars, occurs from the time of birth until approximately five years of age. Once human teeth have been fully mineralized, they do not have the ability to produce more enamel. Therefore, in the rat,

the incisors are a good model for developing human teeth; the rat molars, which have only an extremely limited ability to continue growth[1], are a good model for permanent human teeth, as in individuals over the age of 7. Evaluation of the effects of Sugammadex on rat incisors simulates the effect on developing human teeth, whereas the effects of Sugammadex on rat molars more closely simulates fully mineralized human teeth.

1. *Has the Sponsor adequately addressed the issue of Org 25969 deposition in teeth through conduct of nonclinical toxicology studies? Are there other in vitro/in vivo studies you believe would be appropriate?*
2. *Do the dental findings in the juvenile rat represent a risk for pediatric subjects/patients?*

Response:

The Sponsor has conducted extensive nonclinical research using various doses of Org 25969 (Sugammadex) in various age groups of rats. These rat studies provide support for safety in adults, whose teeth are already fully mineralized, and to which Sugammadex cannot bind. In addition, clinical trials of Sugammadex, which to date have been conducted only in adults, have not demonstrated adverse effects to the teeth (although a dental examination was not specifically performed as a part of the clinical trial protocol).

Rat studies have confirmed that Sugammadex does interfere with mineralization of developing teeth as are found in children under the age of 8. (*Note: further details about the identification of age limits for potential concerns of mineralization interference are provided in the response to question 4, later in this review.*) However, the extremely high doses and chronicity of exposure required to produce detectable adverse effects on the developing enamel provides a margin of safety for its labeled use in humans under the age of 8. It is beyond the scope of this clinical review to comment about whether the exact safety margin calculated via the rat studies is sufficient to conclude that there will be no adverse events experienced in children under 8. The clinical review staff of DAARP in conjunction with its toxicology support staff will make that decision. Nonetheless, the results that the sponsor has submitted show an approximately 50 X margin of safety between the dosing needed to demonstrate adverse events on the teeth in juvenile rats; if these numbers are accurate, the study should be safe to proceed with one dose planned in the clinical trial. However, the safety margin drops if multiple dosing of the drug is planned; i.e., if a child needs multiple surgical procedures which will result in many doses of the drug over a short period of time.

In several of the rat studies, Sugammadex was radioactively labeled and its incorporation into various bones as well as teeth was measured. As a reference point for comparison of rat exposure to human exposure, the human exposure as proposed for labeling ranges from 4 – 16 mg/kg, given as one dose. In one of the rat studies that used a single dose of Sugammadex at a level of 8 mg/kg, it was demonstrated that the radioactivity measured

[1] The rat molars grow rapidly for the first four months of life, and then "continue to grow and wear away, but at such as slow rate as to be almost indiscernible" (Ref: Shour and Massler)

in the incisors peaked at one week and began to decrease after 3 weeks until it returned to a level of 0 at day 84. At all time points, the levels in the incisors were less than in any of bones measured. The disappearance of the drug from the incisors is explained by the continued growth and attrition of these teeth. Another rat study in which rats were given a single dose of 30, 120, or 400 mg/kg shows that the amount absorbed increases somewhat with increasing dosing levels, but it not a linear increase. The extent of binding per gram in the teeth increases with the dose, but this increase is subproportional linear to the dose. In another study, rocuronium was given before Sugammadex (as it will be used clinically); the binding to the teeth in young rats is diminished by a third to a half when this is the case.

In terms of clinical effect on the teeth, results showed that a large single dose of 2000 mg/kg in adult rats showed no change in tooth color or anatomy. In juvenile rat studies of chronic high exposure, the group with the highest dose (500 mg/kg/day) developed pearly white discoloration in the incisors after the third week of daily exposure. The molars showed no discoloration. The incisors also showed overgrowth, which implies an increased resistance to incisor wearing (increased tooth strength). Nonetheless, one cannot conclude that this is a desirable change in the enamel (as would the addition of fluoride) without more studies. Histologically, a disruption of the enamel layer of the incisors was noted in half the animals at the 120 mg/kg/day and almost all at the 500 mg/kg/day groups. In the molars, no enamel disruption was noted in the 120 mg/kg group, but it was noted in approximately half the 500 mg/kg group. It must also be pointed out here that if the rat molars were fully mineralized at eruption as in human dentition, there should not be any enamel disruption, even at the 500 mg/kg/day group; the small but present amount of mineralization that occurs in the rat molars of very young rats explains the incorporation of some drug with very high exposure; one would not expect any incorporation of Sugammadex in erupted human teeth. Of great reassurance, however, is that even with this extremely high exposure, no clinical adverse effects on rat molar teeth, including either discoloration or loss of strength or function was observed. Even in the developing incisors, no discoloration was observed until after three weeks of a dosing that is greater than 30 times the highest planned human dose.

Another useful comparison to Sugammadex's potential effects on developing enamel is the effect of ingested fluoride on teeth. Both Sugammadex and fluoride have strong affinity for the hydroxyapatite molecule. In the case of fluoride, the binding forms a new molecule, fluorapatite. An ideal amount of fluoride as obtained from fluoridated drinking water incorporates enough fluorapatite into the developing enamel to make the teeth more resistant to acid dissolution from bacterial plaque by-products. However, chronic exposure to above optimal levels results in white or brown spots on the teeth, as does high exposure to Sugammadex. With excessive fluoride exposure to developing human teeth, neither compromised strength nor function accompanies the white discoloration. In support of this not being considered an adverse event of significance, the Surgeon General's Report on Oral Health (2000) classifies dental fluorosis as a cosmetic effect rather than a pathological one.

The preponderance of evidence from the rat studies in addition to the clinical trial data in humans, supports safety from a dental perspective in adults. For the effect of Sugammadex on developing teeth, in vitro testing or testing on rats would not provide further data. Studies on extracted human teeth could provide further information about the incorporation of Sugammadex, but only on teeth that were exposed to drug while developing. One possibility, for example, is that the protocol could include a follow-up portion in which young children who receive Sugammadex and later require extraction for orthodontic purposes, would contribute these teeth for histological study. Additional animal data could be useful in a species such as primates whose teeth are anatomically extremely similar to humans.

Questions 3 and 4 will be answered together as these responses overlap.

3. *If the findings represent risk in pediatric patients, is the safety margin adequate to allow pediatric trials to go forward? Does the single-dose use of the product mitigate concern?*

4. *Is there an age above which pediatric patients would not be at excess risk for dental deposition of Org 25969?*

Response:
Based upon the completed animal studies, there is no evidence of a risk for adverse events occurring in teeth of children over the age of 7, the age at which the enamel of all permanent dentition has been mineralized. (See the appendix at the end of this review for a table and explanation of human tooth mineralization) For developing teeth such as those found in children under age 8, the rat studies have shown a signal that the potential exists for incorporation into the developing enamel with high exposure on a chronic basis. Therefore, if the clinical and toxicology staff from DAARP believe the safety margin is adequate to begin trials in children under 8, they should consider at which multiple dosing the safety margin shrinks to one that is generally not accepted in their Division for initiating trials. For initial pediatric trials, it may be prudent to exclude enrollment of pediatric subjects under the age of 8 who will need multiple surgeries and would be exposed to multiple doses of Sugammadex.

5. *Has the Sponsor adequately addressed concerns with prenatal exposure and effects on the dentition of the fetus? If not, does the data rise to the level of a warning & precaution or a pregnancy contraindication?*

Response:
The sponsor conducted placental transmission studies in rats and concluded that Sugammadex does not readily pass the placenta (Maximally, 0.096% of Sugammadex transferred to the fetus. Further, postnatal development of rats exposed in utero to drug showed no abnormalities in the bone or teeth. With such a low level of transmission through the placenta and any lack of evidence for an affect on the developing bones, no dental adverse events on the fetus from exposure to the mother is expected, and no further study is warranted. Since rats do not develop primary teeth, this model does not

specifically support the lack of any effect on primary dental development in humans. However, given the lack of placental transfer and what is known about human tooth growth and development, permanent teeth would not be affected as their mineralization does not begin until after birth. Any cosmetic effect such as white spots on human primary dentition, which does begin mineralization in utero, would be shed with the primary teeth, which occurs between ages 5 through 11.

Appendix
Tooth development is highly variable in terms of ages of tooth mineralization and eruption. The table included at the end of this appendix gives the range in which individual teeth in the mouth begin and complete mineralization. During that period, any drug that has an affinity for enamel has the potential to be incorporated into the developing teeth. Since the human body does not have the ability to form new enamel after mineralization of teeth is complete, any incorporation of foreign components into enamel is permanent.

The American Dental Association as well as the Food and Drug Administration have been consistent through published literature that products with the potential to affect tooth development should be avoided in children whose teeth are still mineralizing. (Sources: ADA Guide to Dental Therapeutics; 2003; American Dental Association's Fluoridation Facts; 2005; Federal Register 52479: Volume 60, No 194 October 6, 1995 – *Anticaries Drug Products for Over-the-Counter Human Use*; Class Labeling for Tetracycline, Warnings Section) In the tetracycline class of drugs, the Agency recommends exclusion of use for children under the age of 8. For fluoride containing drugs, the recommended exclusionary age is children under the age of 6.

The difference in age cutoffs between fluoride and tetracycline are due to several factors, which are explained in the language that appears in the FR as cited at the end of this appendix. The primary reason that fluoride has a lower age than the tetracyclines is that fluoride achieves its anticaries effect through topical activity on the teeth; ingestion of fluoride is inadvertent. Prior to the age of 6, children have not yet developed sufficient swallowing skills to prevent inadvertently swallowing of significant amounts of topical fluoride. In addition, fluoride is extremely effective as a topical cavity preventing agent in children for which there is no substitute, whereas other antibiotics can often be used in place of tetracycline. Finally, tetracyclines have an exclusionary warning for women in the last period of pregnancy because tetracycline crosses the placenta, whereas fluoride does not.

The dental concerns about Sugammadex more closely match those with tetracycline than fluoride. Sugammedex's IV delivery system ensures distribution to the bones and teeth, and it has no benefit to the teeth to offset the risk of impaired dental development. Until further safety is established, including the specific margins of safety, the potential for adverse dental effects accompanying the administration of Sugammadex to children under the age of 8 cannot be ruled out.

Class Labeling for Tetracycline:

> "The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of eight years) may cause permanent discoloration of the teeth (yellow-gray brown). This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group, or in pregnant or nursing women, unless the potential benefits are considered to outweigh the potential risks."

Anticaries Drug Products for Over-the-counter Human Use: Federal Register 52479: Volume 60, No 194. October 6, 1995

> "As discussed in the tentative final monograph (50 FR 39854 at 39864), developing teeth of children under 6 years of age may show objectionable dental fluorosis from repeated ingestion of excessive amounts of fluoride. However, epidemiological and clinical findings indicate that the formative state of the teeth of children 6 years of age and older (excepting third molars) is too advanced to be affected by the amount and frequency of use of fluoride dentifrices."

Table: Age of Human Tooth Development

Permanent Tooth Development		
	First evidence of calcification	Completion of enamel development:
Incisors:	3-4 months	4-5 years
Canine:	4-5 months	6-7 years
First premolars:	1 ½ to 1 ¾ years	5 – 6 years
Second premolars:	2- 2 ½ years	6-7 years
First molars:	birth	3-4 years (maxillary) 2 ½ - 3 years (mandibular)
Second molars	: 2 ½ - 3 years	7 - 8 years
Third molars:	7 – 9 years (max) 8 – 10 years (mandibular)	12 – 16 years
Primary Tooth Development		
Primary teeth begin to calcify at 13 to 16 weeks in utero and the calcification is completed by birth for the primary incisors and within 6 months for the primary molars.		

Table Source: Balog and Fehrenbach, Illustrated Dental Embryology, Histology, and Anatomy, Saunders Philadelphia, 1997.

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/s/

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Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review

NDA	NDA 22225
Brand Name	Bridion™
Generic Name	Suggamadex, Org 25969
Sponsor	Organon
Indication	Routine Reversal of Shallow or Profound NMB induced by revuronium or vecuronium, and immediate reversal NMB at 3 minutes after administration of rocuronium
Dosage Form	Intravenous
Drug Class	Supramolecular family of cyclodextrins (CDs)
Therapeutic Dose	(b) (4) • A dose of 4.0 mg/kg Bridion is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade. • A dose of 2.0 mg/kg Bridion is only recommended, if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade. (b) (4) If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg Bridion is recommended.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	96 mg/kg
Application Submission Date	31 Oct 2007
Review Classification	Priority NDA
Date Consult Received	8 Nov 2007
Clinical Division	DAARP / HFD 170
PDUFA Date	April 30 2008

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant effect of Bridion (Suggamadex, Org25969) was detected in the 'thorough QT' study' conducted under Protocol 19.4.109. The largest upper limit of the two-sided 90% CI for the mean difference between Org 25969 (4 mg/kg and 32 mg/kg doses) alone and in combination of 32 mg/kg Org 25969 with rocuronium (1.2 mg/kg), vecuronium (0.1 mg/kg) and placebo was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

The thorough QT study was a randomized, double-blind, placebo-controlled, six-period, cross-over study to investigate the effect of intravenous single doses of Org 25969/rocuronium, Org 25969/vecuronium and Org 25969 alone on the QTc interval and an open label active control part consisting of a single intravenous dose of moxifloxacin in healthy volunteers (N=80).

The overall findings are summarized in the following table.

FDA Analysis: The Point Estimates and the 90% CIs for Various Treatment Arms (Protocol 19.4.109)

Treatment	Time, h	ΔΔQTcI, ms	90%CI, ms
4 mg/kg Org 25969	23:30	2.1	0.1, 4.1
32 mg/kg Org 25969	0:05	2.9	1.1, 4.7
32 mg/kg Org 25969+0.1 mg/kg vecuronium	0:05	4.5	2.7, 6.2
32 mg/kg Org 25969 + 1.2 mg/kg rocuronium	23:30	2.9	1.1, 4.8
Moxifloxacin 400mg	1:00	20.8	18.5, 23.1*

* If a Bonferroni adjustment is applied, the largest lower bound will be 17.0 ms.

Concentration dependent increases in the QTcI interval were observed. Overall, the mean QT prolongation with Org 25969 with and without rocuronium, vecuronium is less than the regulatory threshold of 10 ms.

1.2 RESPONSES TO QUESTIONS POSED BY REVIEW DIVISION

1.2.1 Does Org 25969 cause QT prolongation?

Yes, there is a concentration-dependent increase in QTcI. However, the mean increase in QTcI for the supratherapeutic dose (32 mg/kg) is below 10 ms, the regulatory threshold for concern. This dose gives 2-fold higher peak concentrations than the dose recommended for immediate reversal, 16 mg/kg, and 6-fold higher peak concentrations of the doses recommended for routine reversal.

1.2.2 Does the thorough QT study report show that Org 25969 does not cause QT prolongation?

See our response to the previous question (1.2.1).

1.2.3 Were the studies conducted sufficient to assess the effect of Org 25969 on the QT interval?

Yes, the Study 19.4.109 was conducted satisfactorily. A single IV infusion over 60 minutes of 400 mg moxfloxacin was used as the positive control. The maximum mean increase occurred at the end of infusion and was 21 ms (90% CI: 19 to 23 ms). The time-course of the mean changes in the QTcI is expected based on the pharmacokinetic profile of IV moxifloxacin.

The sponsor conducted a second TQT study under Protocol 19.4.105. No significant effect of Org 25969 was detected in that study according to the sponsor's analysis. We did not repeat the analysis for that study because the same Org25969 doses were assessed.

2 PROPOSED LABEL

The sponsor proposed (b) (4) of the package insert.

(b) (4)

Reviewer's Comments: The suggested labeling is acceptable. (b) (4)

3 BACKGROUND

Org 25969 is a modified γ cyclodextrin (CD) and a Selective Relaxant Binding Agent (SRBA); preclinical data have shown that this compound can reverse a profound aminosteroid-induced NMB. Upon complexation with the NMBAs rocuronium or vecuronium bromide, Org 25969 prevents the binding of the NMBAs to the nicotinic receptors in the neuromuscular junction and, hence, results in reversal of NMB in vivo. The Sponsor believes that the mechanism of action of Org 25969 does not result in stimulation of the cholinergic nervous system, thereby avoiding the undesired autonomic nervous system side effects associated with neostigmine and other similar drugs.

3.1 MARKET APPROVAL STATUS

Org 25979 is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: Non Clinical Summary

In hERG-1 cDNA transfected HEK-293 cells, Org 25969 at $1.5x10^{-3}$M produced a noticeable inhibition of HERG tail current. However, Org 25969 failed to produce more

than 70% inhibition of HERG tail current. In these conditions, no IC50 value (i.e. the concentration that induced 50% inhibition of HERG tail current) could be determined.

Under the same experimental conditions, E-4031 at 100 nM induced 88% inhibition of HERG tail current, supporting the validity of the method used.

Taken together, these results suggest that Org 25969 produced a slight inhibition of HERG tail current in stably transfected HEK-293 cells, with a maximum effect of 22 ± 2% obtained at $1.5x10^{-3}$M.

Org 25969 at concentrations of $1.5x10^{-4}$ and $1.5x10^{-3}$ M (= 300 and 3000 µg/mL) induced dose-dependent increases in Action Potential Duration (APD). No reverse-use dependency or early after depolarization is observed.

Org 48302 (related CD) at concentrations of $1.5x10^{-4}$ and $1.5x10^{-3}$ M (= 287 and 2870 µg/mL) induced dose-dependent increases in APD. A minimal to almost no reverse-use dependency and no early after depolarization is observed for this related CD. The effect observed at $1.5x10^{-4}$ M is considered of no biologically relevance given its magnitude, thus $1.5x10^{-4}$ M (300 µg/mL) is considered to be the No Observed Effect Concentration for Org 25969 and Org 48302.

Both reference CDs, hydroxypropyl-ß-cyclodextrin and γ cyclodextrin, at 1.5 mM (1309 and 1297 µg/mL), caused a slight increase in APD, mainly observed in APD_{90}. No effect was reported at 0.015 and 0.15 mM. Neither early nor delayed after-depolarization was observed with the two compounds whatever the concentration.

In all experiments, the method-control (cisapride at 3 X10-7 M) induced its typical electrophysiological effects i.e. an increase in action potential duration under the same conditions, showing the validity of the method used.

In anaesthetized dogs, a dose of 1.8 $mg \cdot kg^{-1}$ rocuronium bromide followed after 2 min by administration of 25 $mg \cdot kg^{-1}$ or 250 $mg \cdot kg^{-1}$ Org 25969 resulted in no other drug related effects on hemodynamics and electrocardiographic parameters other than observed with 1.8 $mg \cdot kg^{-1}$ rocuronium bromide alone (minimal and short lasting increase in heart rate and coronary blood flow and a concomitant slight decrease in coronary vascular resistance). A slight and transient increase in corrected QT was observed at the end of a 5 min perfusion period of 250 $mg \cdot kg^{-1}$ Org 25969 after rocuronium bromide administration.

Reviewers comment: The test substance is positive in the assays performed, albeit at a high concentration in vitro (concentration-related increase in APD90 in canine Purkinje fibers and small but consistent (22%) inhibition in hERG tail current - clear effects in both assays were seen at 1.5 mM, which the sponsor said was the highest soluble concentration).

In vivo, test substance induced a transient QT prolongation in anesthetized dogs at a dose that is 10 times the pharmacologically active dose in dogs. The dose (250 mg/kg corrected for body surface area to 125 mg/kg) that prolonged QT in dogs is also 10 times the proposed therapeutic human dose (12.5 mg/kg). So, overall the test substance was positive non-clinically.

These findings are interesting given the molecular weight, structure and hydrophilicity. It is possible that the test substance is binding to a structure on the extra-cellular surface

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Integrated Summary of Safety

The safety data presented in this ISS come from 32 completed clinical trials (nine Phase 1 trials, 12 Phase 2 trials, and 11 Phase 3 trials). There have been a total of 2369 exposures to Org 25969 (in 2054 unique subjects) in Phase 1, Phase 2, and Phase 3 clinical trials. The pooled Phase 1-3 dataset includes 1926 subjects (1845 unique subjects) who received Org 25969 and an NMBA, and 140 unique subjects who received placebo and an NMBA.

Overall, 76.3% of all subjects exposed to any dose of Org 25969 plus an NMBA (either rocuronium, vecuronium, or pancuronium) experienced at least one AE. No dose response was apparent for the overall incidence of AEs. The most frequent (i.e., ≥ 5.0% incidence) AEs (according to PT) in the Total Org 25969 group included procedural pain (40.8%), nausea (23.2%), vomiting (10.5%), pyrexia (7.4%), headache (7.2%), and constipation (5.3%).

Two subjects died after exposure to Org 25969 and one died after exposure to placebo. In each case the subject's death occurred after the trial was completed (42 days post-surgery due to MI/cardiogenic shock and 18 days post-surgery due to a PE). Each death was judged to be unrelated to treatment with the trial medication by both the investigator and the sponsor.

Individual SAEs (by PT) most often occurred in only one subject in a treatment group. Those that occurred in more than one subject per group included electrocardiogram QT corrected (2.5% [16 subjects] Org 25969, 1.4% [2 subjects] placebo) and small intestinal perforation (0.3% [2 subjects] Org 25969, and no placebo subject).

Due to the relatively low number of SAEs, it is difficult to judge if the incidence of SAEs was influenced by the type of NMBA administered. All SAEs of electrocardiogram QT corrected interval prolonged (in both treatment groups) occurred only in subjects who received rocuronium. However, ECG data were not collected in three of the four trials in which subjects received the trial medication plus vecuronium as an NMBA (19.4.207, 19.4.208A, and 19.4.208B).

A 61 year old male subject was scheduled for panendoscopy, due to a tumor in the paranasal sinus. As part of the anaesthetic procedure the subject received Org 25969. 12 minutes later the subject experienced a severe oculocardiac reflex, due to pressure on the eye bulbus during the surgery and presented with Asystole (Cardiac arrest) for 1 minute.

Reviewer's Comment: QTc prolongation with Org 25969 combined with NMBAs (dose 2 to 32mg/kg) was not associated with clinically significant events (death, syncope seizure or significant ventricular arrhythmias).

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Org 25969's clinical pharmacology.

4 SPONSOR'S SUBMISSION

The sponsor submitted two TQT study reports: one each for Protocol 19.4.105 and 19.4.109. Electronic data sets for each report were also submitted. Digital ECGs were submitted to the ECG Warehouse.

The QT-IRT primarily focused on the results of Protocol 19.4.109 because this study assessed the effects of administering Org 25969 alone and in combination with the neuromuscular blockers rocuronium and vecuronium. This study was specifically requested by the Division to meet the requirements for an NDA submission.

The study results for Protocol 19.4.105 are briefing described in section 4.1.

4.1 PROTOCOL 19.4.105

This study was a single center, randomized, placebo-controlled five-period crossover study. In total 62 subjects were randomized (including two replaced subjects) to ten treatment sequences. All subjects received at least one dose of moxifloxacin 400 mg by IV infusion, 4 mg/kg Org 25969, 32 mg/kg Org 25969 and placebo. In total 31 females and 31 males were treated, in the age of 22 to 65 years. All subjects were Caucasian.

No QTcI prolongation was observed in subjects treated with therapeutic (4 mg/kg) and supratherapeutic (32 mg/kg) Org 25969 dosages. The sponsor's results for the primary endpoint are summarized in Table 1. These results are comparable to the results presented in the second TQT study for the same dosage strengths of Org 25969.

Table 1. Largest Time-Matched Mean QTcI Difference to Placebo with Corresponding One-Sided 95% Upper CI

	Treatment group	
	4 $mg.kg^{-1}$ Org 25969	32 $mg.\ kg^{-1}$ Org 25969
Time after dosing	1.5 hrs	2 min
Largest time-matched mean QTcI difference to placebo (msec)	1.8	2.8
one-sided 95% upper confidence limit (msec)	4.3	5.3

Data taken from Appendix F, Analysis 6.7.3-B.1

Source: Sponsor's Table 14, page 85 of the CSR for Protocol 19.4.105.

4.2 TQT STUDY REVIEW FOR PROTOCOL 19.4.109

4.2.1 Title

Protocol 19.4.109: Randomized, double-blind, placebo-controlled, six-period, cross-over study to investigate the effect of intravenous single doses of Org 25969/rocuronium, Org 25969/vecuronium and Org 25969 alone on the QTc interval and an open label active control part consisting of a single intravenous dose of moxifloxacin in healthy volunteers.

4.2.2 Study Dates

November 2006 to April 2007

4.2.3 Objectives

Primary objectives:

- To investigate if i.v. single dose treatment with 32 $mg.kg^{-1}$ Org 25969 and 1.2 $mg.kg^{-1}$ rocuronium does not clinically significantly prolong the QTc interval as compared to placebo.

- To investigate if i.v. single dose treatment with 32 mg.kg-1 Org 25969 and 0.1 $mg.kg^{-1}$ vecuronium does not clinically significantly prolong the QTc interval as compared to placebo.
- To investigate if i.v. single dose treatment with 32 $mg.kg^{-1}$ Org 25969 does not clinically significantly prolong the QTc interval as compared to placebo.
- To investigate if i.v. single dose treatment with 4 $mg.kg^{-1}$ Org 25969 does not clinically significantly prolong the QTc interval as compared to placebo.
- To establish assay sensitivity by demonstrating QT/QTc interval prolongation as compared to placebo after single dose i.v. treatment with 400 mg moxifloxacin.

Secondary objectives:

- To relate the plasma concentrations of Org 25969, vecuronium and rocuronium with the QTc intervals.
- To investigate safety and tolerability of the various treatments.

4.2.4 Study Description

4.2.4.1 Design

This was a single center, randomized, double-blind, placebo-controlled, six-period cross-over trial in healthy volunteers. The trial was open-label for moxifloxacin and double-blind for Org 25969 alone, Org 25969 in combination with rocuronium/vecuronium and placebo.

The period between administrations of Treatments A-F (Day 1) from one period to the next period was to be four days.

4.2.4.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.4.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were to be randomized according to a Latin Square of the Williams design to treatment sequences of treatments, and the treatments were to be randomized to the letters A-F. At the baseline days prior to each cross-over period, subjects were to receive a single i.v. injection of placebo.

Open label treatment (Treatment B):

- Single i.v. infusion of 400 mg of moxifloxacin over 60 min.

Double-blind treatments (Treatments A, C, D, E and F):

- Single i.v. injection of 32 $mg.kg^{-1}$ Org 25969 and 1.2 $mg.kg^{-1}$ rocuronium (Esmeron®)

- Single i.v. injection of 32 mg.kg^{-1} Org 25969 and 0.1 mg.kg^{-1} vecuronium (Norcuron®)

- Single i.v. injection of 4 mg.kg^{-1} Org 25969

- Single i.v. injection of 32 mg.kg^{-1} Org 25969

- Single i.v. injection of placebo (NaCl 0.9%)

4.2.5.2 Sponsor's Justification for Doses

Since Bridion is not recommended to be used in severely renal impaired patients, an elderly subject with moderate renal impaired function was considered to represent the worst case scenario (as sex and race do no play major roles). For an elderly subject with borderline severe/moderate renal impairment, the clearance is predicted to be 55% lower as compared to a typical adult. This means total exposure to Bridion is increased by a factor 2.2. Therefore, an increase in total exposure to Bridion of a factor two is considered to be the worst case scenario in clinical practice as compared to the 'normal' situation of an adult subject.

A supratherapeutic dose of 32 mg/kg Bridion provides an 8-fold margin for routine reversal, since for routine reversal doses up to 4 mg/kg Bridion are recommended. For immediate reversal, following administration of rocuronium, a dose of 16.0 mg/kg Bridion is recommended, and the two-fold margin provided by the supratherapeutic dose of 32 mg/kg is considered to be sufficient. For the evaluation of the applied supra-therapeutic dose of 32 mg/kg Bridion, it is also important to note that, during the first 60 minutes post administration of Bridion there is little difference in plasma levels of Bridion between severely renal impaired and control subjects (thus neither in C_{max}).

Reviewer's comment: The reviewer finds the supratherapeutic dose of 32 mg/kg acceptable as well as doses of rocuronium and vecuronium.

4.2.5.3 Instructions with Regard to Meals

Trial medication was to be administered after an overnight fasting period but at least four hours before lunch. Water was not allowed in the morning. Water (room temperature) could be allowed as desired from one hour after drug administration.

4.2.5.4 ECG and PK Assessments

Table 2: Sampling Schedule

Study Day	**-1**	**1**
Intervention	No treatment (Baseline)	Single dose
12-Lead ECGs	Record ECGs[1]	Record ECGs[1]
PK Samples for drug	None collected	Collected[2]

[1]ECGs were to be evaluated, consisting of triplicate ECGs at the following time points: 2, 5, 15 and 30 minutes and 1, 1½, 2, 3, 5, 8, 12, 16, 23½ hours after the placebo dose (timepoints were calculated from start of dosing).

[3]PK samples samples were to be taken in the double-blind part only at –5, 3, 6, 16 and 31 minutes and 1:01, 5:05 and 12:05 hours post dose. For moxifloxacin no PK samples were to be taken.

Reviewer's comment: The timing of ECG and PK samples is adequate.

4.2.5.5 Baseline

The sponsor used time-matched baseline (Day -1, non-treatment) for its QT assessment.

4.2.6 ECG Collection

Continuous 12-lead ECGs were to be obtained digitally using Mortara H12+24 hour recorders, which were to obtain ECGs on Day -1 and on Day 1 of each treatment period at the pre-specified time points. The continuous ECG recordings were stored on Mortara´s high fidelity compact cards, to be transferred to the central ECG laboratory. Subjects were to be supine for at least 10 minutes prior to the scheduled ECG assessments. At each assessment day the placed electrodes were to be marked in their location such that the placement position remained constant throughout the trial.

All ECGs were to be taken in triplicate. Within a two-minutes window, between one minute before and one minute after the target time point, three interval durations with good quality and stability of heart rhythm were be selected by the cardiologist. If the ECG signal was not accurate during this pre-defined two-minutes time window, it was to be shifted in time until an adequate evaluation of three interval durations within a two-minutes window could be determined (for the two-minutes assessment this two-minutes window was fixed). The QT intervals were to be evaluated manually. For evaluation of T-offset the tangent method was to be used. RR, PR, QRS and QT were to be measured in three consecutive complexes in triplicate per scheduled time point in lead II. Lead V2 was to be used if the signal of lead II was not evaluable.

The ECG reading and blinding was to be guaranteed by the specialized ECG laboratory by using a limited number of certified cardiologists who were to be blinded to time, treatment and subject number. One cardiologist was to read all ECG recordings from a subject.

Safety ECGs were obtained as specified by the subject flow sheet (appendix 6.2).

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

In total 84 subjects with a normal screening ECG and BMI between 18-30 kg/m^2 were randomized at this site, of which 83 (41 males, 42 females) subjects were treated. One randomized subject withdrew informed consent and discontinued the trial before any investigational product (IP) was administered. This subject and three other subjects, who discontinued the trial, were replaced. Their replacements were not randomized again but received the same treatment sequence as the randomized discontinued subjects. 80 subjects completed the trial.

In total four subjects discontinued prematurely from the trial. Subject 101021 (A/F/B/E/C/D) was randomized and withdrew informed consent before administration of

IP. Subject 101073 (D/C/E/B/F/A) discontinued due to AEs of hypersensitivity, burning sensation, nausea, sensation of heaviness, agitation, abdominal pain and infusion site rash during Period 3 (32.0 mg.kg-1 Org 25969). Subjects 101055 (C/B/D/A/E/F) and 101058 (F/E/A/D/B/C) withdrew their informed consent (not AE related), on Day -1 in Period 4 after administration of 4.0 mg.kg-1 Org 25969 and in Period 5 after administration of moxifloxacin, respectively.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The **primary variable** was the time-matched QTcI change from baseline (Day -1*)* at time point t (i.e. t = 2, 5, 15, 30 minutes, 1, 1½, 2, 3, 5, 8, 12, 16, 23½ hours). The **primary endpoint** was the largest time-matched mean difference in QTcI change as compared to placebo across timepoints on Day 1. The **primary analysis** was based on the largest time-matched mean difference in QTcI change as compared to placebo across timepoints on Day 1. The primary analysis was performed for the PP group.

Per time point t, the **primary variable** was analyzed using an ANCOVA model with the following factors:

- fixed factors: gender, treatment and period;
- random factor: subject;
- covariable: baseline QTc interval at timepoint t.

For each time point t, the treatment differences from placebo and their corresponding two-sided 90% confidence intervals were estimated from this model.

Assay sensitivity was established if for the moxifloxacin group the lower limit of the two-sided (1-α) confidence interval for the largest time-matched mean difference between moxifloxacin and placebo exceeded 0 ms. Bonferroni adjustment was applied to adjust the α-level for confirmation of assay sensitivity due to multiple testing of 13 timepoints of assessment i.e., an α of 5%/13= 0.385% was applied.

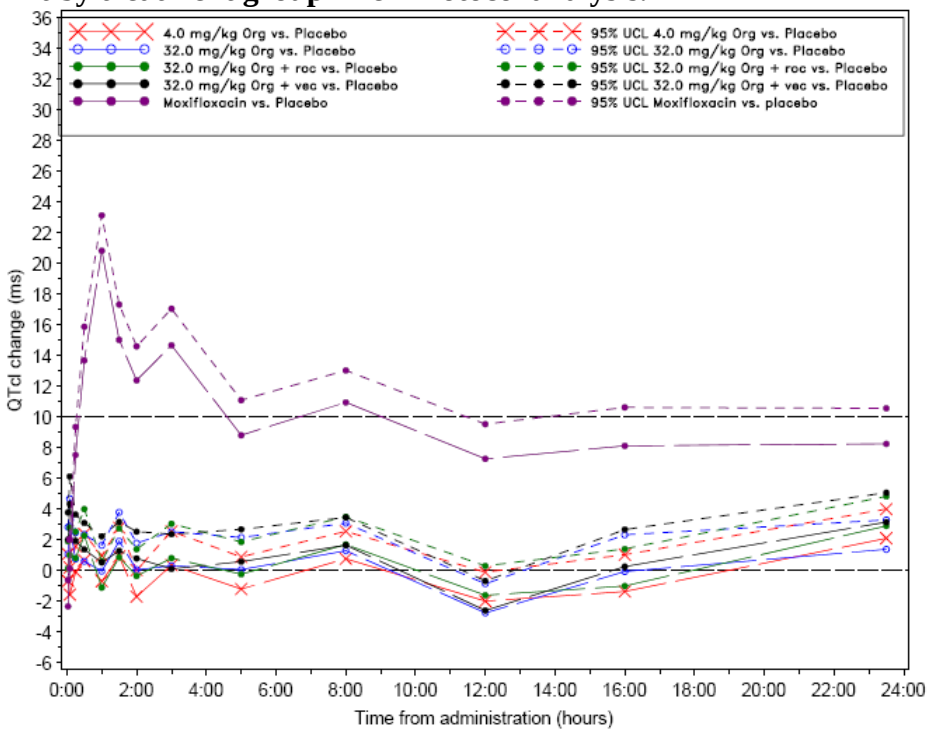
The sponsor's analysis, according to the criteria of the ICH E14 guideline, demonstrates that the thorough QTc trial with Org 25969 alone and Org 25969 combination treatments was negative.

Table 3 Largest time-matched difference to placebo for the time-matched QTcI change with corresponding one-sided 95% upper confidence limit by treatment group (estimates from ANCOVA) - Per Protocol analysis (N=83)

	Treatment group				
	4 $mg.kg^{-1}$ Org 25969	32 $mg.kg^{-1}$ Org 25969	32 $mg.kg^{-1}$ Org 25969/roc	32 $mg.kg^{-1}$ Org 25969/vec	Moxifloxacin
Time after dosing	23.5 hrs	5 min	23.5 hrs	5 min	1 hr
Largest difference to placebo for the time-matched QTcI change (ms)	2.1	2.9	2.9	4.3	20.8
One-sided 95% upper confidence limit (ms)	4.0	4.7	4.8	6.1	23.1

Source: Sponsor's Table 14, Section 8.6.7.3 Primary QTc outcome, Study report 194109.pdf

Figure 1. Primary analysis: estimated time-matched mean difference to placebo for the time-matched QTcI change with corresponding one-sided 95% upper confidence limit by treatment group - Per Protocol analysis.



Source: Sponsor's Figure 1, Section 8.6.7.3 Primary QTc outcome, Study report 194109.pdf

The following table presents the results of analysis (mixed model ANCOVA) on QTcF (Fridericia) and QTcB (Bazett). The results on QTcF and QTcB confirmed the robustness of results of the primary analysis.

Table 4. Largest time-matched difference to placebo for the time-matched QTcF and QTcB change with corresponding one-sided 95% upper confidence limit by treatment group (estimates from ANCOVA) - Per Protocol analysis (N=83).

QTc interval		Treatment group				
		4 mg.kg^{-1} Org 25969	32 mg.kg^{-1} Org 25969	32 mg.kg^{-1} Org 25969/roc	32 mg.kg^{-1} Org 25969/vec	Moxifloxacin
QTcF	Time after dosing	23.5 hrs	5 min	30 min	5 min	1 hr
	Largest time-matched QTcI difference to placebo (ms)	1.5	3.1	3.0	4.3	22.4
	one-sided 95% upper confidence limit (ms)	3.5	4.9	4.8	6.1	24.8
QTcB	Time after dosing	23.5 hrs	1.5 hrs	30 min	5 min	1 hr
	Largest time-matched QTcI difference to placebo (ms)	1.9	3.9	4.7	4.4	27.1
	one-sided 95% upper confidence limit (ms)	4.5	6.3	7.0	6.7	30.1

Source: Sponsor's Table 21, Section 8.6.7.4 Secondary QTc evaluations: continuous variables, Study report 194109.pdf

The sponsor reached the following conclusions:

The subjects included in this thorough QT/QTc trial were prone to develop QTc prolongation, because assay sensitivity was clearly demonstrated after moxifloxacin treatment. In the presence of assay sensitivity, the therapeutic (4 mg.kg-1 Org 25969) and supra-therapeutic doses (32 mg.kg-1 Org 25969 alone and in combination with rocuronium or vecuronium) did not lead to QTc interval prolongations of regulatory concern (i.e., < 10 ms). Therefore, this thorough QT/QTc trial with Org 25969 alone and in combination with rocuronium or vecuronium was **negative** according to the criteria of the ICH E14 guideline.

4.2.7.2.2 Categorical Analysis

The following table shows the categorical comparison of absolute QTcI (QTcIPP) intervals, frequency, percentage, cumulative frequency and cumulative percentage per−protocol analysis (Sponsor's Table 6.7.5−B.1).

Table 5. Sponsor's categorical analysis based on QTcI using per-protocol patients' ECG data.

Table 6.7.5-B.1 Categorical comparison of absolute QTCIPP intervals, frequency, percentage, cumulative frequency and cumulative percentage
Per-Protocol analysis

			Gender											
			Female				Male				Total			
Treatment group	Relative timepoint	Category a)	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.
placebo	2 min.	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	5 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	15 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	30 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	1 hr	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	1.5 hrs	0	41	100.0	41	100.0	39	100.0	39	100.0	80	100.0	80	100.0
	2 hrs	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	3 hrs	0	41	100.0	41	100.0	40	100.0	40	100.0	81	100.0	81	100.0
	5 hrs	0	41	100.0	41	100.0	40	100.0	40	100.0	81	100.0	81	100.0
	8 hrs	0	41	100.0	41	100.0	40	100.0	40	100.0	81	100.0	81	100.0
	12 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	16 hrs	0	39	100.0	39	100.0	41	100.0	41	100.0	80	100.0	80	100.0
	23.5 hrs	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
4.0 mg/kg Org 25969	2 min.	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	5 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	15 min.	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	30 min.	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	1 hr	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	1.5 hrs	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	2 hrs	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	3 hrs	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	5 hrs	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	8 hrs	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	12 hrs	0	42	100.0	42	100.0	41	100.0	41	100.0	83	100.0	83	100.0
	16 hrs	0	40	97.6	40	97.6	40	100.0	40	100.0	80	98.8	80	98.8
		1	1	2.4	41	100.0					1	1.2	81	100.0
	23.5 hrs	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
32.0 mg/kg Org 25969	2 min.	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	5 min.	0	39	100.0	39	100.0	41	100.0	41	100.0	80	100.0	80	100.0
	15 min.	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	30 min.	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	1 hr	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	1.5 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	2 hrs	0	39	97.5	39	97.5	41	100.0	41	100.0	80	98.8	80	98.8

			Female				Male				Total			
Treatment group	Relative timepoint	Category a)	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.
32.0 mg/kg Org 25969	2 hrs	1	1	2.5	40	100.0					1	1.2	81	100.0
	3 hrs	0	39	97.5	39	97.5	41	100.0	41	100.0	80	98.8	80	98.8
		1	1	2.5	40	100.0					1	1.2	81	100.0
	5 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	8 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	12 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	16 hrs	0	39	97.5	39	97.5	41	100.0	41	100.0	80	98.8	80	98.8
		1	1	2.5	40	100.0					1	1.2	81	100.0
	23.5 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
32.0 mg/kg Org 25969 + rocuronium	2 min.	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	5 min.	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	15 min.	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	30 min.	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	1 hr	0	37	100.0	37	100.0	40	100.0	40	100.0	77	100.0	77	100.0
	1.5 hrs	0	39	100.0	39	100.0	39	100.0	39	100.0	78	100.0	78	100.0
	2 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	3 hrs	0	38	100.0	38	100.0	40	100.0	40	100.0	78	100.0	78	100.0
	5 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	8 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	12 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	16 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0
	23.5 hrs	0	38	100.0	38	100.0	40	100.0	40	100.0	78	100.0	78	100.0
32.0 mg/kg Org 25969 + vecuronium	2 min.	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	5 min.	0	40	100.0	40	100.0	38	100.0	38	100.0	78	100.0	78	100.0
	15 min.	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	30 min.	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	1 hr	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	1.5 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	2 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	3 hrs	0	40	100.0	40	100.0	37	100.0	37	100.0	77	100.0	77	100.0
	5 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	8 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
	12 hrs	0	39	100.0	39	100.0	39	100.0	39	100.0	78	100.0	78	100.0
	16 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0

			Gender											
			Female				Male				Total			
Treatment group	Relative timepoint	Category a)	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.	Freq.	Pct.	Cum. freq.	Cum. pct.
32.0 mg/kg Org 25969 + vecuronium	23.5 hrs	0	40	100.0	40	100.0	39	100.0	39	100.0	79	100.0	79	100.0
moxifloxacin	2 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	5 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	15 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	30 min.	0	41	100.0	41	100.0	41	100.0	41	100.0	82	100.0	82	100.0
	1 hr	0	35	87.5	35	87.5	40	100.0	40	100.0	75	93.8	75	93.8
		1	5	12.5	40	100.0					5	6.3	80	100.0
	1.5 hrs	0	38	95.0	38	95.0	40	100.0	40	100.0	78	97.5	78	97.5
		1	2	5.0	40	100.0					2	2.5	80	100.0
	2 hrs	0	38	92.7	38	92.7	40	100.0	40	100.0	78	96.3	78	96.3
		1	3	7.3	41	100.0					3	3.7	81	100.0
	3 hrs	0	37	94.9	37	94.9	40	100.0	40	100.0	77	97.5	77	97.5
		1	2	5.1	39	100.0					2	2.5	79	100.0
	5 hrs	0	38	97.4	38	97.4	41	100.0	41	100.0	79	98.8	79	98.8
		1	1	2.6	39	100.0					1	1.3	80	100.0
	8 hrs	0	40	100.0	40	100.0	40	100.0	40	100.0	80	100.0	80	100.0
	12 hrs	0	41	100.0	41	100.0	40	100.0	40	100.0	81	100.0	81	100.0
	16 hrs	0	40	100.0	40	100.0	41	100.0	41	100.0	81	100.0	81	100.0
	23.5 hrs	0	39	100.0	39	100.0	40	100.0	40	100.0	79	100.0	79	100.0

a) 0 = QTCIPP <= 450 msec
1 = 450 msec < QTCIPP <= 480 msec
2 = 480 msec < QTCIPP <= 500 msec
3 = QTCIPP > 500 msec

4.2.7.3 Safety Analysis

None of the subjects died or experienced a Serious Procedure related event (SPE) after administration of IP.

Two subjects experienced an SAE. Subject 101064 (B/A/C/F/D/E) experienced an SAE in Period 1, one hour after moxifloxacin administration. Subject 101173 (D/C/E/B/F/A) experienced an SAE in Period 3, two minutes after extravascular injection of 32.0 $mg.kg^{-1}$ Org 25969. For both subjects a QTc prolongation, change of mean QTcB from baseline > 60 ms, was observed. For Subject 101064 the QTcB change was 61 ms and for Subject 101173 the QTcB change was 62 ms. According to the investigator the SAE for Subject 101064 was not related to IP and the SAE for Subject 101173 was possibly related to IP. Both SAEs were considered mild and the subjects recovered without treatment.

One subject discontinued due to an AE as described earlier.

Two AEs (dizziness and eyelid ptosis) of severe intensity were reported for Subject 101088 (C/B/D/A/E/F), after administration of 32.0$mg.kg^{-1}$ Org 25969/rocuronium on Day1 in Period 4. The duration of these AEs were 20 seconds each.

One subject experienced a ventricular tachycardia with palpitations after administration of 32.0$mg.kg^{-1}$ Org 25969. The subject recovered and no action was taken.

The highest percentage of subjects who experienced one or more AEs was observed after administration of 32.0$mg.kg^{-1}$ Org 25969/rocuronium (51.9%). The most frequently reported AEs were dysgeusia, parosmia, headache, nausea and dizziness.

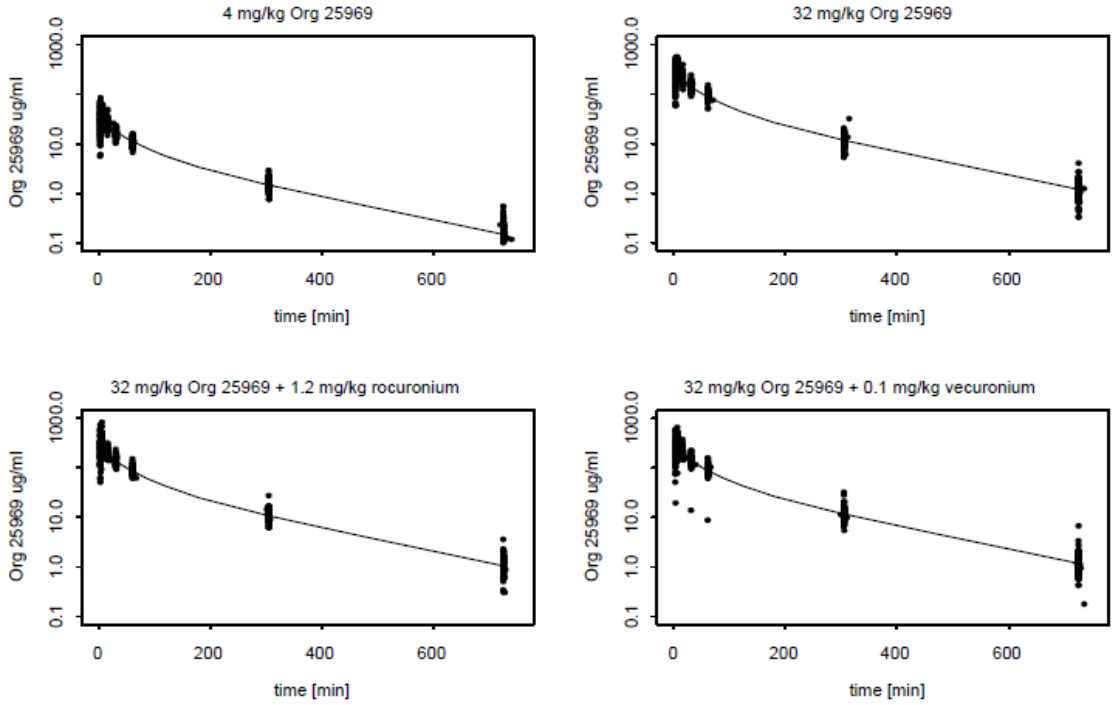
4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

Figure 2 shows the time course of Org 25969 concentrations after 4mg/kg Org 25969, 32 mg/kg Org 25969, 32 mg/kg Org 25969+1.2 mg/kg rocuronium, 32 mg/kg Org

25969+0.1 mg/kg vecuronium. A three compartment model was used to analyze the concentrations of Org 25969. The estimates of the pharmacokinetic parameters are shown in **Table 6**.

Figure 2. Observed Org 25969 plasma concentrations per treatments and simulated PK profile for a subject with body weight 70.9 kg



Source: Figure 4 from sponsor's report on Page Number 111.

Table 6. Summary of pharmacokinetic parameters for Org 25969.

Parameter	units	population estimate	SE	CV%	IIV%
CL	L/min	0.114	0.002	1.55 %	12.2 %
effect body weight		·(1+0.00355·(BW-70.9)	0.00110	31.0 %	
effect rocuronium administration		· exp(0.0366)	0.00602	16.5 %	
Vc	L	5.840	0.207	3.54 %	25.3 %
Q2	L/min	0.193	0.016	8.29 %	
V2	L	3.03	0.242	8.0 %	23.9%
effect body weight		·(1+0.0186·(BW-70.9)	0.00434	23.3 %	
Q3	L/min	0.044	0.004	8.91 %	
V3	L	4.92	0.302	6.1 %	6.3%
effect body weight		·(1+0.00546·(BW-70.9)	0.00123	22.5 %	
Residual error		CV (%)			
σ_1 (proportional)		19.7 %			

Data was taken from Appendix BI-4, Table 4.2.
SE=standard error, CV%=coefficient of variation (100*SE/pop.estimate), IIV (ω^2)=interindividual variability expressed as a variance, IIV%=(100·√(IIV)). The CV of the proportional part of the residual error was 100·√ σ_1.

Source: Table 24 from sponsor's report on Page Number 110

The median clearance Org 25969 was predicted to be 0.114 L/min (median body weight 70.9 kg) and ranged from 0.106 to 0.129 L/min (body weight 51.4 – 107 kg). After co-

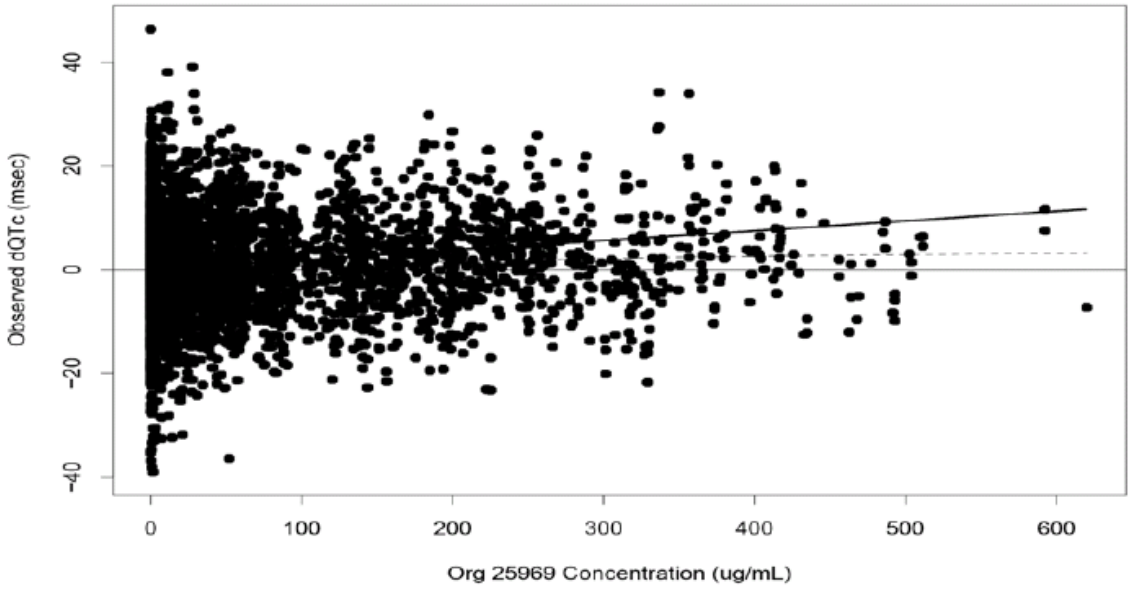
administration of rocuronium the median clearance of Org 25969 was predicted to be 3.7% higher (0.118 L/min). The first peripheral volume of distribution was predicted to be 3.03 L and ranged from 1.93 to 5.06 L (body weight 51.4 – 107 kg). The second peripheral volume of distribution was predicted to be 4.92 L and ranged from 4.40 to 5.89 L (body weight 51.4 – 107 kg).

4.2.7.4.2 Exposure-Response Analysis

The PK-PD analysis using circadian rhythm models for baseline was performed on individual correction (QTcI). Graphical analyses showed that QTcI was superior to both Fredericia (QTcF) and Bazett correction (QTcB) and similar to population correction (QTcN) for removing the dependence of QTc on heart rate.

Figure 3 shows the relationship between observed and mean dQTc versus Org 25969 concentrations. The estimate of the slope is 0.0188 (SD 0.00932) per ug/mL.

Figure 3. Observed and mean predicted dQTc vs. Org 25969 concentrations.



Source: Figure 6 from sponsor's report on Page 120.

Based on the PK-PD model the sponsor predicted the mean QTc prolongation at Cmax after 4 mg/kg Org 25969, 8 mg/kg Org 25969, 32 mg/kg Org 25969 + 1.2 mg/kg rocuronium, 32 mg/kg + 0.1 mg/kg vecuronium. The upper 90% confidence interval is less than 10 ms as shown in Table 7.

Table 7. Predicted drug effect of Org 25969 (dQTc) at mean Cmax.

Dose Org 25969	co-administered drug	Mean C_{max} (ng/mL)	dQTc (ms)	90% confidence limit (ms)
4 mg.kg^{-1}	--	42	0.79	0.69 – 0.89
32 mg.kg^{-1}	--	319	6.00	5.26 – 6.74
32 mg.kg^{-1}	1.2 mg.kg^{-1} rocuronium	332	6.24	5.47 – 7.01
32 mg.kg^{-1}	0.1 mg.kg^{-1} vecuronium	317	5.96	5.22 – 6.69

Source: Table 30 from sponsor's report on Page 122

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

The statistical reviewer's evaluation is based on the sponsor's data and in accordance with the ICH E14 guideline. The QT data files used in the statistical evaluation were **ECGT.XPT**. This data file has been converted to a SAS data set, restructured and renamed as **ECGTANA1a** for the statistical evaluation.

5.1.1 Descriptions of Subjects

In this study, there were 42 (51%) females and 41 (49%) males. Most of them were whites (n=79, 95%). The subjects were 19 to 55 years of age with an average of 34 years.

5.1.2 Analysis of QTcI

The statistical analyses based on QTcI (variable QTcIPP) were performed using ANCOVA including: fixed effects of TREATMENT, PERIOD and SEX; random effect of SUBJECT; and covariate of QTcIPP_BASELINE. Key findings are demonstrated in the following tables and graphs.

Table 8. Analysis of QTcI difference between 4 mg/kg Org 25969 and placebo at all time points.

Time	(Treatment Difference) LS-Mean	Std Err	DF	T-Value	P-Value	Alpha	Lower CL	Upper CL
0:02	-0.59	1.02	72	-0.58	0.5635	0.1	-2.29	1.11
0:05	-1.51	1.07	74	-1.41	0.1615	0.1	-3.29	0.27
0:15	-0.20	1.07	69	-0.18	0.8541	0.1	-1.98	1.58
0:30	0.74	1.20	71	0.61	0.5423	0.1	-1.27	2.74
1:00	-0.75	0.87	73	-0.86	0.3915	0.1	-2.21	0.70
1:30	0.71	1.10	70	0.65	0.5193	0.1	-1.12	2.54
2:00	-2.31	1.24	73	-1.86	0.0670	0.1	-4.38	-0.24
3:00	0.32	1.47	73	0.22	0.8290	0.1	-2.12	2.76
5:00	-1.30	1.32	70	-0.98	0.3282	0.1	-3.50	0.90
8:00	0.79	0.97	71	0.81	0.4217	0.1	-0.84	2.41
12:00	-2.06	1.22	73	-1.69	0.0952	0.1	-4.09	-0.03
16:00	-1.41	1.47	69	-0.96	0.3421	0.1	-3.86	1.05
23:30	**2.10**	**1.20**	**73**	**1.75**	**0.0851**	**0.1**	**0.10**	**4.10**

The largest upper limit of the 90% confidence intervals for the QTcI mean difference between 4 MG/KG ORG 25969 and placebo after baseline adjustment is 4.10 (at hour 23:30), below the 10 ms threshold.

Figure 5. 90% confidence intervals for mean QTcI differences between 4 mg/kg Org 25969 and placebo.

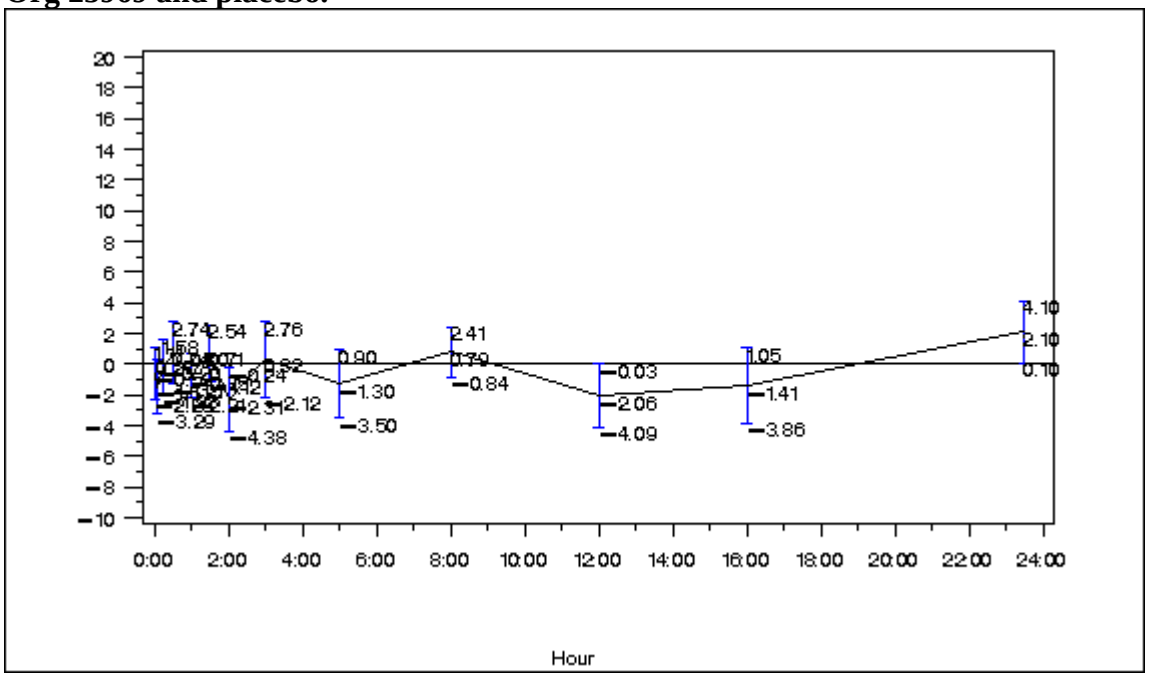


Table 9. Analysis of QTcI difference between 32 mg/kg Org 25969 and placebo at all time points.

Time	(Treatment Difference) LS-Mean	Std Err	DF	T-Value	P-Value	Alpha	Lower CL	Upper CL
0:02	1.48	1.07	73	1.38	0.1719	0.1	-0.31	3.27
0:05	**2.91**	**1.10**	**73**	**2.66**	**0.0097**	**0.1**	**1.09**	**4.74**
0:15	0.12	1.11	67	0.11	0.9153	0.1	-1.74	1.97
0:30	0.37	1.27	69	0.29	0.7739	0.1	-1.75	2.48
1:00	-0.27	1.04	74	-0.26	0.7952	0.1	-2.00	1.46
1:30	1.54	1.22	72	1.27	0.2087	0.1	-0.48	3.57
2:00	-0.87	1.21	75	-0.72	0.4745	0.1	-2.88	1.14
3:00	0.29	1.48	73	0.20	0.8436	0.1	-2.17	2.75
5:00	0.03	1.31	71	0.02	0.9808	0.1	-2.15	2.22
8:00	1.24	1.07	70	1.15	0.2525	0.1	-0.55	3.02
12:00	-2.79	1.17	72	-2.39	0.0194	0.1	-4.74	-0.85
16:00	-0.24	1.55	71	-0.15	0.8793	0.1	-2.81	2.34
23:30	1.36	1.21	72	1.13	0.2638	0.1	-0.65	3.38

The largest upper limit of the 90% confidence intervals for the QTcI mean difference between 32 MG/KG ORG 25969 and placebo after baseline adjustment is 4.74 (at hour 0:05), below the 10 ms threshold.

Figure 6. 90% confidence intervals for mean QTcI differences between 32 mg/kg Org 25969 and placebo.

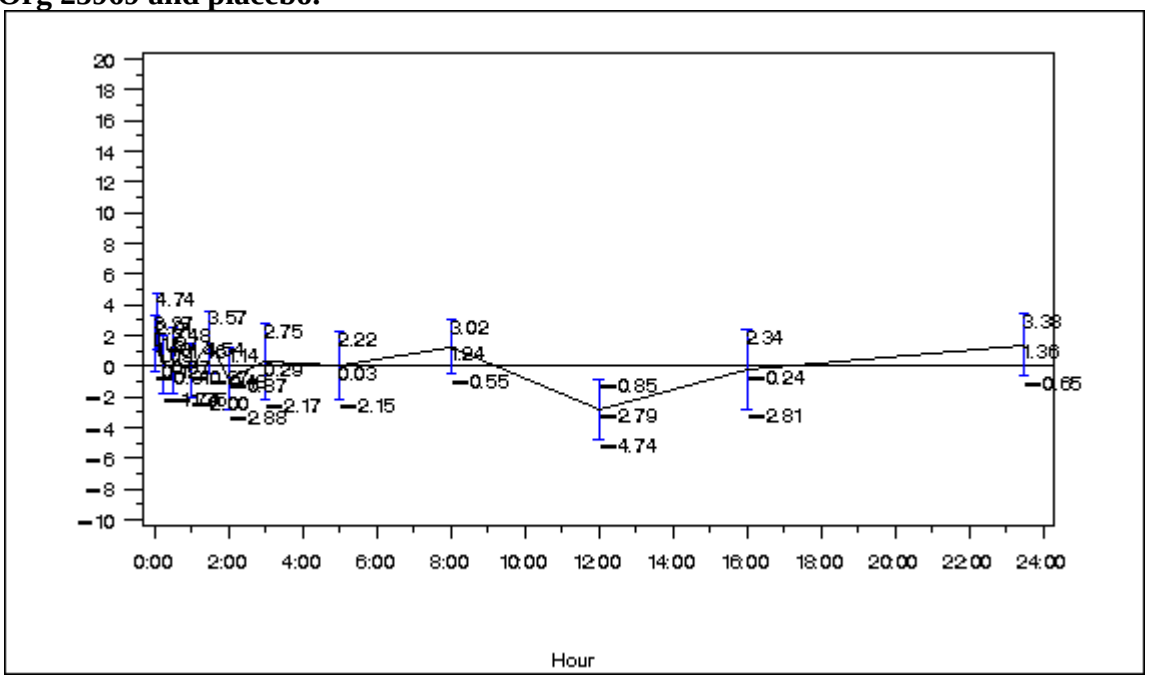


Table 10. Analysis of QTcI difference between 32 mg/kg Org 25969 AND 0.1 mg/kg Vecuronium and placebo at all time points.

Time	(Treatment Difference) LS-Mean	Std Err	DF	T-Value	P-Value	Alpha	Lower CL	Upper CL
0:02	2.08	0.97	74	2.14	0.0355	0.1	0.46	3.70
0:05	**4.46**	**1.06**	**74**	**4.22**	**<.0001**	**0.1**	**2.70**	**6.22**
0:15	2.04	1.06	69	1.92	0.0590	0.1	0.27	3.81
0:30	1.35	1.10	73	1.23	0.2223	0.1	-0.48	3.17
1:00	0.55	1.11	73	0.49	0.6257	0.1	-1.31	2.40
1:30	0.85	1.15	73	0.74	0.4644	0.1	-1.07	2.77
2:00	0.77	1.25	75	0.62	0.5387	0.1	-1.31	2.85
3:00	0.24	1.31	70	0.18	0.8572	0.1	-1.95	2.42
5:00	0.54	1.05	72	0.51	0.6099	0.1	-1.21	2.28
8:00	1.46	1.11	71	1.31	0.1942	0.1	-0.40	3.31
12:00	-2.82	1.21	73	-2.33	0.0226	0.1	-4.84	-0.80
16:00	0.21	1.59	72	0.13	0.8949	0.1	-2.44	2.86
23:30	3.08	1.17	74	2.63	0.0104	0.1	1.13	5.04

The largest upper limit of the 90% confidence intervals for the QTcI mean difference between 32 mg/kg Org 25969 AND 0.1 mg/kg vecuronium and placebo after baseline adjustment is 6.22 ms (at hour 0:05), below the 10 ms threshold.

Figure 7. 90% confidence intervals for mean QTcI differences between 32 mg/kg Org 25969 AND 0.1 mg/kg Vecuronium and placebo.

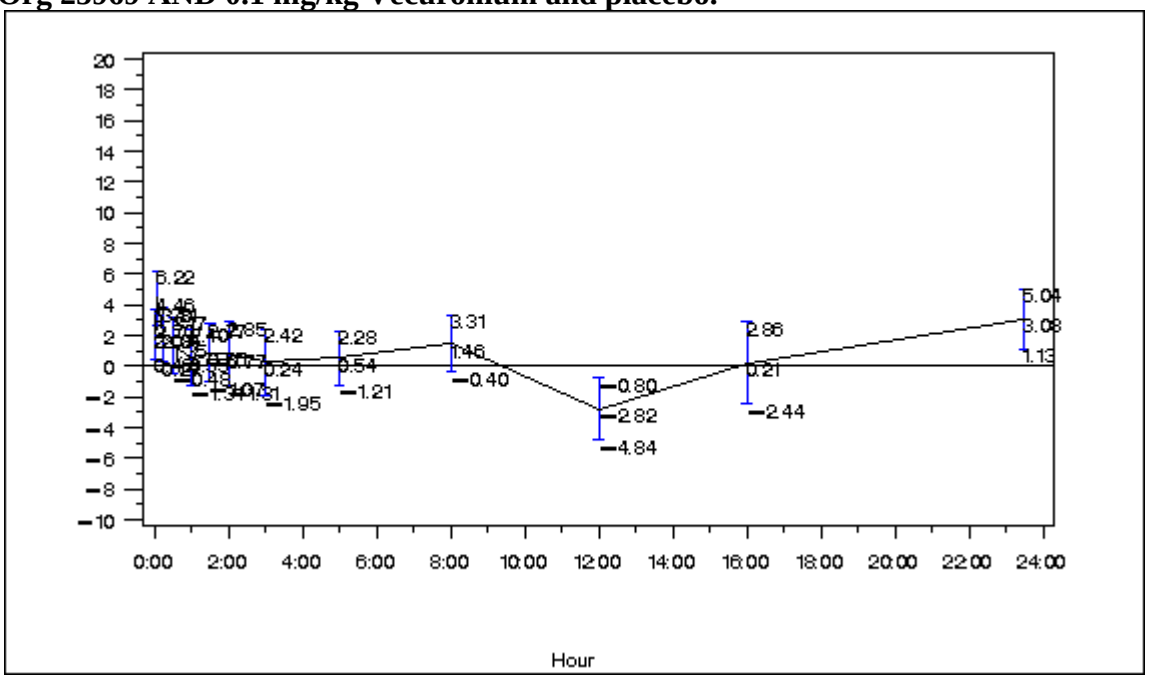
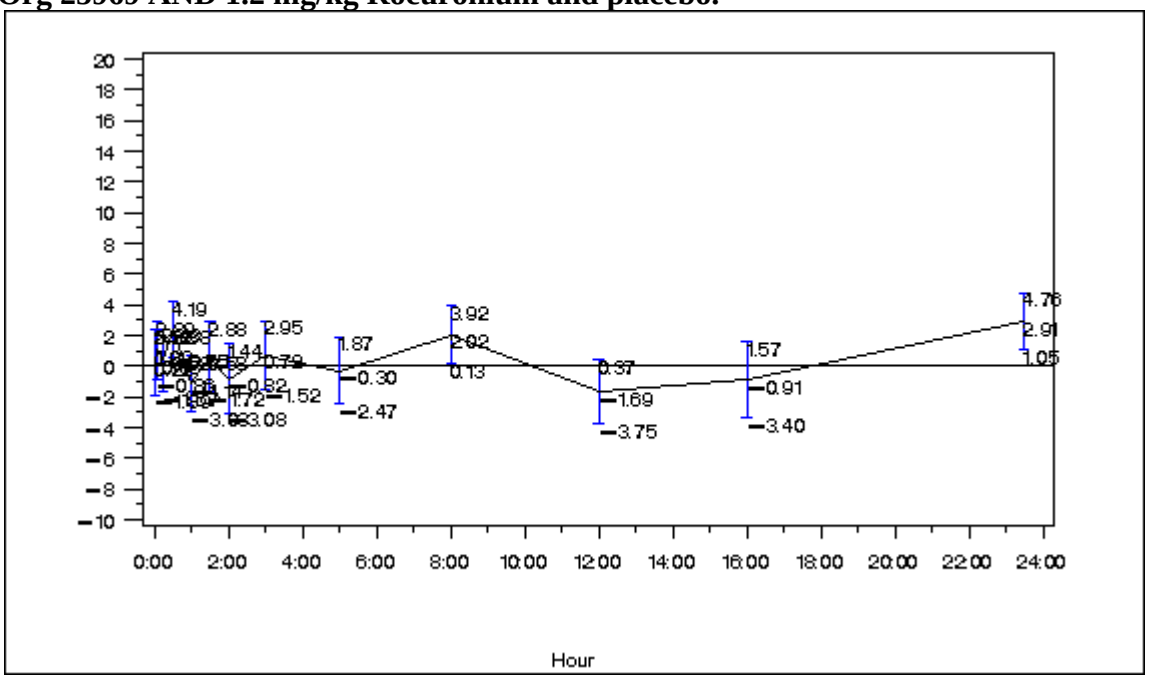


Table 11. Analysis of QTcI difference between 32 mg/kg Org 25969 AND 1.2 mg/kg Rocuronium and placebo at all time points

Time	(Treatment Difference) LS-Mean	Std Err	DF	T-Value	P-Value	Alpha	Lower CL	Upper CL
0:02	0.22	1.26	73	0.17	0.8649	0.1	-1.89	2.32
0:05	1.02	1.13	73	0.90	0.3692	0.1	-0.86	2.89
0:15	0.38	1.23	67	0.31	0.7565	0.1	-1.67	2.43
0:30	2.38	1.08	72	2.20	0.0311	0.1	0.58	4.19
1:00	-1.14	1.13	71	-1.01	0.3173	0.1	-3.03	0.75
1:30	0.58	1.38	72	0.42	0.6760	0.1	-1.72	2.88
2:00	-0.82	1.36	73	-0.60	0.5476	0.1	-3.08	1.44
3:00	0.72	1.34	72	0.53	0.5950	0.1	-1.52	2.95
5:00	-0.30	1.30	71	-0.23	0.8202	0.1	-2.47	1.87
8:00	2.02	1.14	71	1.78	0.0793	0.1	0.13	3.92
12:00	-1.69	1.24	72	-1.37	0.1754	0.1	-3.75	0.37
16:00	-0.91	1.49	71	-0.61	0.5411	0.1	-3.40	1.57
23:30	**2.91**	**1.12**	**73**	**2.60**	**0.0111**	**0.1**	**1.05**	**4.76**

The largest upper limit of the 90% confidence intervals for the QTcI mean difference between 32 mg/kg Org 25969 and 1.2 mg/kg rocuronium and placebo after baseline adjustment is 4.76 ms (at hour 23:30), below the 10 ms threshold.

Figure 8. 90% confidence intervals for mean QTcI differences between 32 mg/kg Org 25969 AND 1.2 mg/kg Rocuronium and placebo.



5.1.3 Assay Sensitivity Analysis: Moxifloxacin and Placebo Compared

The assay sensitivity results are presented in the following table.

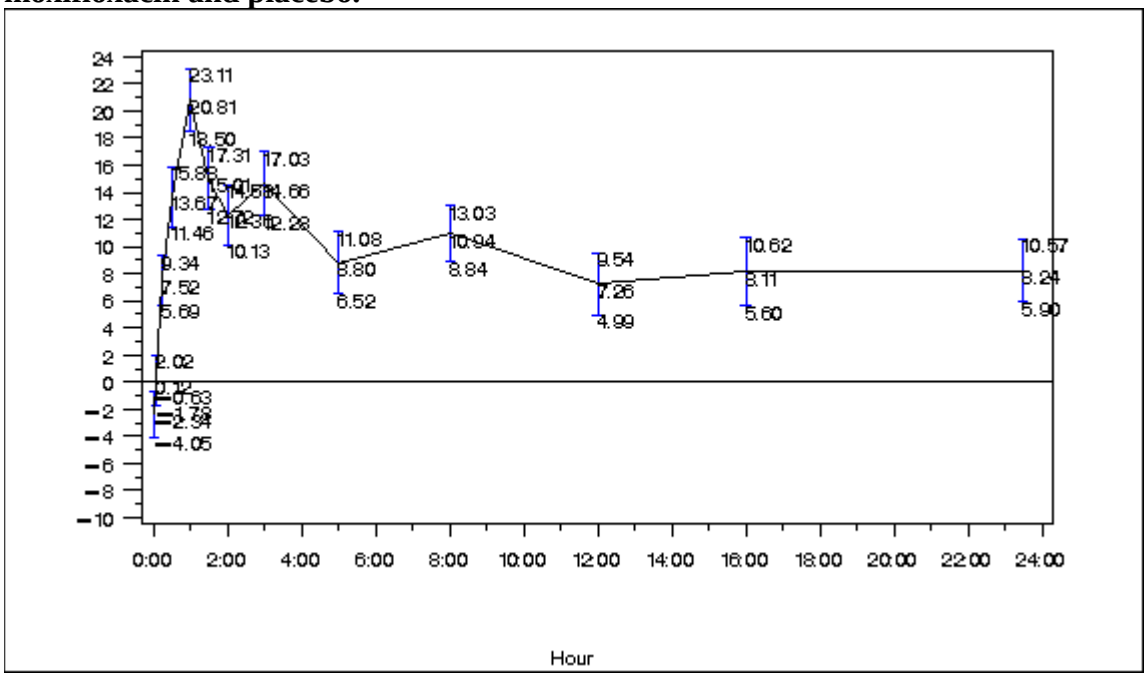
Table 12. Analysis of QTcI difference between moxifloxacin and placebo at all time points*

Time	(Treatment Difference) LS-Mean	Std Err	DF	T-Value	P-Value	Alpha	Lower CL	Upper CL
0:02	-2.34	1.03	71	-2.28	0.0259	0.1	-4.05	-0.63
0:05	0.12	1.14	72	0.11	0.9140	0.1	-1.78	2.02
0:15	7.52	1.09	67	6.87	<.0001	0.1	5.69	9.34
0:30	13.67	1.32	69	10.32	<.0001	0.1	11.46	15.88
1:00	**20.81**	**1.38**	**71**	**15.05**	**<.0001**	**0.1**	**18.50**	**23.11**
1:30	15.01	1.38	70	10.90	<.0001	0.1	12.72	17.31
2:00	12.36	1.34	73	9.25	<.0001	0.1	10.13	14.58
3:00	14.66	1.42	70	10.29	<.0001	0.1	12.28	17.03
5:00	8.80	1.37	70	6.44	<.0001	0.1	6.52	11.08
8:00	10.94	1.26	69	8.70	<.0001	0.1	8.84	13.03
12:00	7.26	1.36	70	5.32	<.0001	0.1	4.99	9.54
16:00	8.11	1.50	68	5.39	<.0001	0.1	5.60	10.62
23:30	8.24	1.40	68	5.89	<.0001	0.1	5.90	10.57

*: The multiple-time-point adjustment is not considered. If a Bonferroni adjustment is applied, the largest lower bound will be 17.01 ms.

The largest lower bound of the 90% confidence intervals for the QTcI mean difference between moxifloxacin 400-mg and placebo after baseline adjustment is **18.50** ms (at hour 1:00), above the 5 ms threshold.

Figure 9. 90% confidence intervals for mean QTcI differences between moxifloxacin and placebo.



5.1.4 Categorical Analysis

The categorical analysis based on individually QTcI observations is shown in Table 13. The categorical analysis based on the changes from baseline in QTcI is shown in Table 14.

Table 13. Categorical analysis of QTcI based on individual observations.

Treatment		No Obs	No QTcI>450	% QTcI>450	No QTcI>480	% QTcI>480	No QTcI>500	% QTcI>500
Baseline	**Placebo org 25969**	3195	6	0.2	1	0.0	0	0.0
	4 mg/kg org 25969	3234	2	0.1	0	0.0	0	0.0
	32 mg/kg org 25969	3192	2	0.1	0	0.0	0	0.0
	32 mg/kg org 25969 and 0.1 mg/kg norcuron	3153	8	0.3	0	0.0	0	0.0
	32 mg/kg org 25969 and 1.2 mg/kg esmeron	3198	5	0.2	0	0.0	0	0.0
	Moxifloxacin	3195	0	0.0	0	0.0	0	0.0
Post-dosing	**Placebo org 25969**	3198	2	0.1	0	0.0	0	0.0

Treatment		No Obs	No QTcI>450	% QTcI>450	No QTcI>480	% QTcI>480	No QTcI>500	% QTcI>500
	4 mg/kg org 25969	3237	3	0.1	0	0.0	0	0.0
	32 mg/kg org 25969	3180	10	0.3	1	0.0	1	0.0
	32 mg/kg org 25969 and 0.1 mg/kg norcuron	3159	4	0.1	0	0.0	0	0.0
	32 mg/kg org 25969 and 1.2 mg/kg esmeron	3159	4	0.1	0	0.0	0	0.0
	Moxifloxacin	3198	37	1.2	0	0.0	0	0.0

Table 14. Categorical analysis of QTcI_CHG (QTcIPP change from baseline) based on individual observations.

Treatment	No Obs	No QTcI_CHG>30	% QTcI_CHG>30	No QTcI_CHG>60	% QTcI_CHG>60
Placebo org 25969	3195	20	0.6	0	0.0
4 mg/kg org 25969	3234	15	0.5	2	0.1
32 mg/kg org 25969	3174	15	0.5	1	0.0
32 mg/kg org 25969 and 0.1 mg/kg norcuron	3150	22	0.7	0	0.0
32 mg/kg org 25969 and 1.2 mg/kg esmeron	3159	22	0.7	1	0.0
Moxifloxacin	3195	202	6.3	2	0.1

5.1.5 Summary of Statistical Reviewer's Findings

Table 15 summarizes the statistical findings for this report.

Table 15. Summary of statistical findings based on QTcI.

4 mg/kg Org 25969 vs. Placebo	**32 mg/kg Org 25969 vs. Placebo**	**moxifloxacin 400**
Largest upper CL: LS mean diff = 2.1 ms, CI=(0.1, 4.1), Hour=23:30 Max Upper CL<10ms	Largest upper CL: LS mean diff = 2.91 ms, CI=(1.09, 4.74), Hour=0:05 Max Upper CL<10ms	Largest lower 90% CL: LS mean diff = 20.81 ms, CI=(18.5, 23.11), Hour=1:00 (unadjusted for comparisons at multiple time points) If a Bonferroni adjustment is applied, the largest lower bound will be 17.01 ms
32 mg/kg Org 25969 AND 0.1 mg/kg norcuron vs. Placebo	**32 mg/kg Org 25969 AND 1.2 mg/kg esmeron vs. Placebo**	
Largest upper CL: LS mean diff = 4.46 ms, CI=(2.7, 6.22), Hour=0:05 Max Upper CL<10ms	Largest upper CL: LS mean diff = 2.91 ms, CI=(1.05, 4.76), Hour=23:30 Max Upper CL<10ms	

Based on the statistical analyses summarized, above, the statistical reviewer concludes:

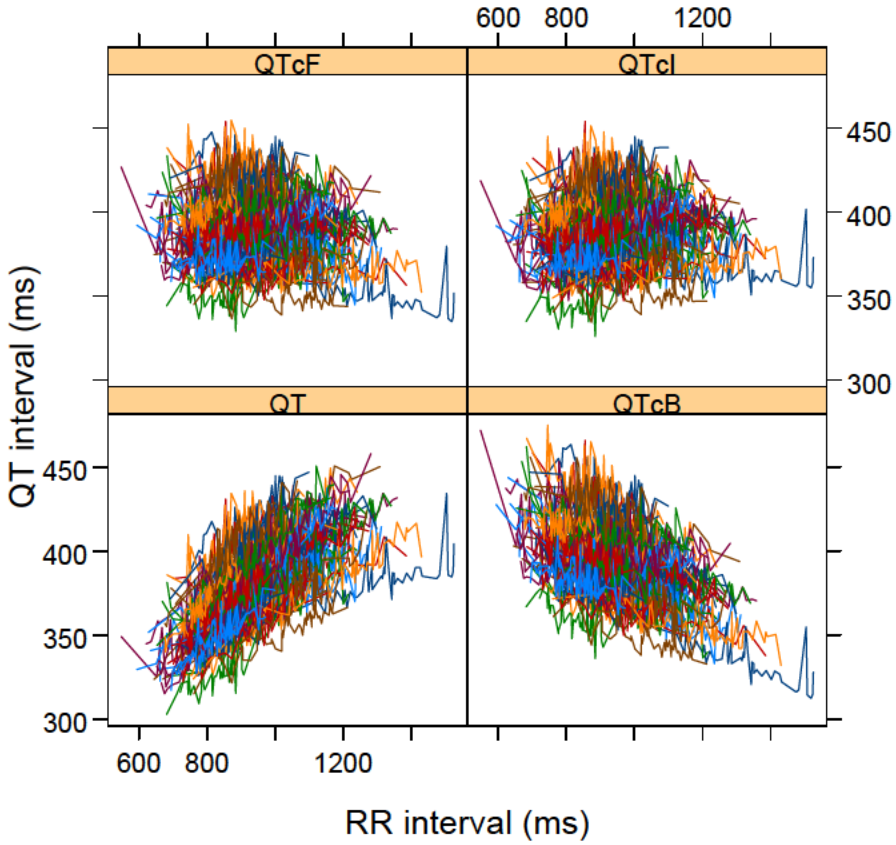
- 4 and 32 mg/kg Org 25969, 32 mg/kg Org 25969+0.1 mg/kg norcuron, and 32 mg/kg Org 25969+1.2 mg/kg esmeron do not appear to prolong QTcI.
- Statistical evaluation based on QTcF reached consistent results.
- The assay sensitivity is established.

5.2 Clinical Pharmacology Assessments

The sponsor conducted extensive analysis to understand the effects of Org 25969 on QTc prolongation. The reviewer briefly summarized the change from baseline and placebo corrected QTcF observed in the studies and its relationship to plasma concentrations of Org 25969.

Figure 10 shows that the individual correction method is reasonable.

Figure 10. Relationship between QT, QTcF, QTcB and QTcI versus RR.



Concentration-QT relationship in the presence of Org 25969 alone

Figure 11 shows that the mean (90% CI) time matched changes from baseline and placebo adjusted QTcF together with the mean (90% CI) Org 25969 concentration time profiles after 4 mg/kg, 32 mg/kg Org 25969. Moxifloxaxin was given as intravenous infusion of 400 mg for 60 minutes which explains the larger effect than usually is reported.

Figure 11. Mean (90% CI) time matched changes from baseline and placebo adjusted QTcF and concentration-time profiles after 4 mg/kg Org 25969, 32 mg/kg Org 25969 and Moxifloxacin.

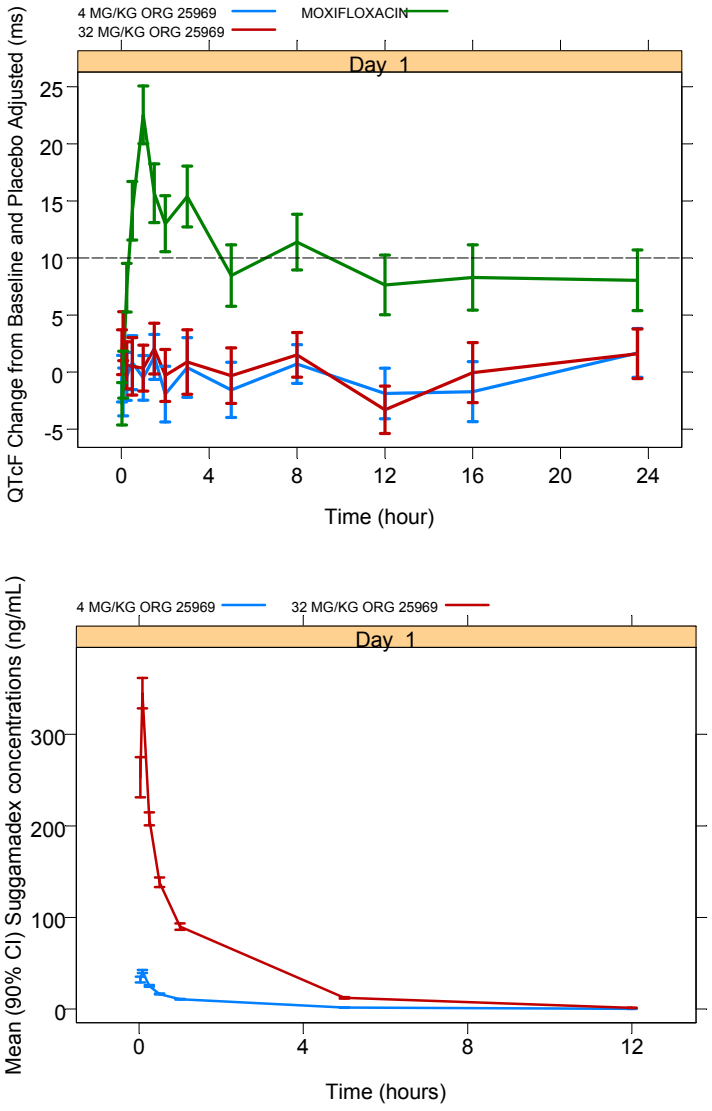
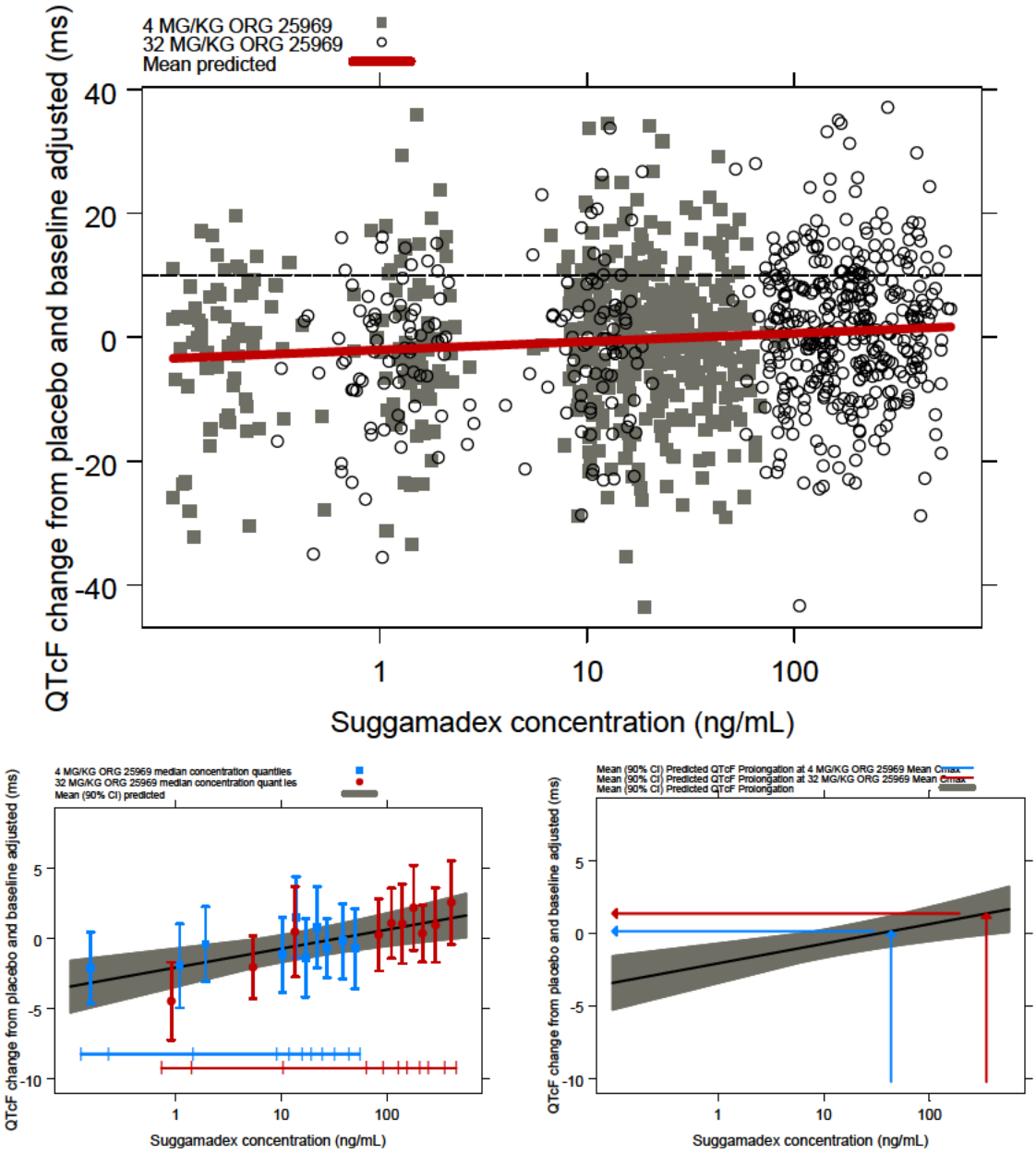


Figure 12 shows the relationship between Org 25969 concentrations and change from baseline and placebo adjusted QTcF (ms). A significant exposure-response relationship was identified for Org 25969. The ΔΔQTcF is well below 10 ms and consistent with E14 analysis.

Figure 12. (Top) Observed baseline and placebo adjusted QTcF (ΔΔQTcF) versus Org 25969 concentrations on a log-scale. (Bottom Left) Median concentration quantile with corresponding observed mean (90% CI) ΔΔQTcF. (Bottom Right) ΔΔQTcF predictions at mean Cmax following 4 and 32 mg/kg Org 25969.



Concentration-QT relationship in the presence of rocuronium and Org 25969

Figure 13 shows that the mean (90% CI) time matched changes from baseline and placebo adjusted QTcF together with the mean (90% CI) Org 25969 concentration time profiles after 32 mg/kg Org 25969 + 0.1 mg/kg Vecuronium and 32 mg/kg Org 25969 + 1.2 mg/kg Esmeron.

Figure 13. Mean (90% CI) time matched changes from baseline and placebo adjusted QTcF and concentration-time profiles after 32 mg/kg Org 25969+0.1 mg/kg Vecuronium and 32 mg/kg Org 25969 + 1.2 mg/kg Rocuronium and Moxifloxacin.

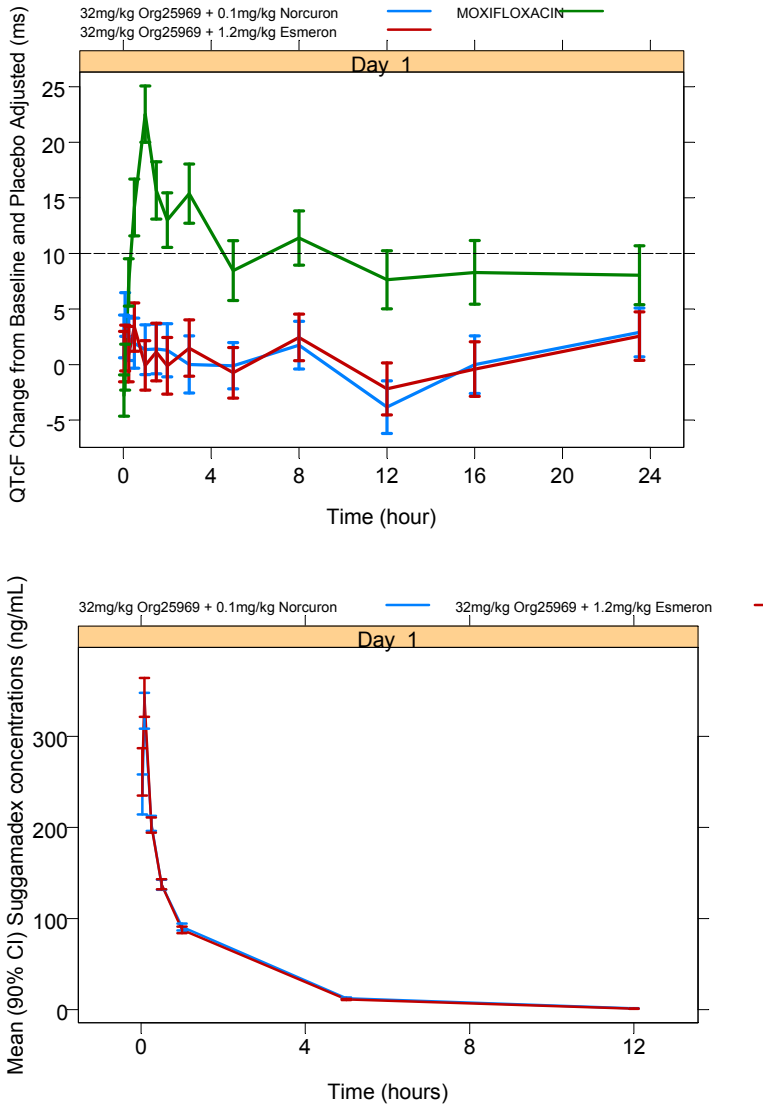
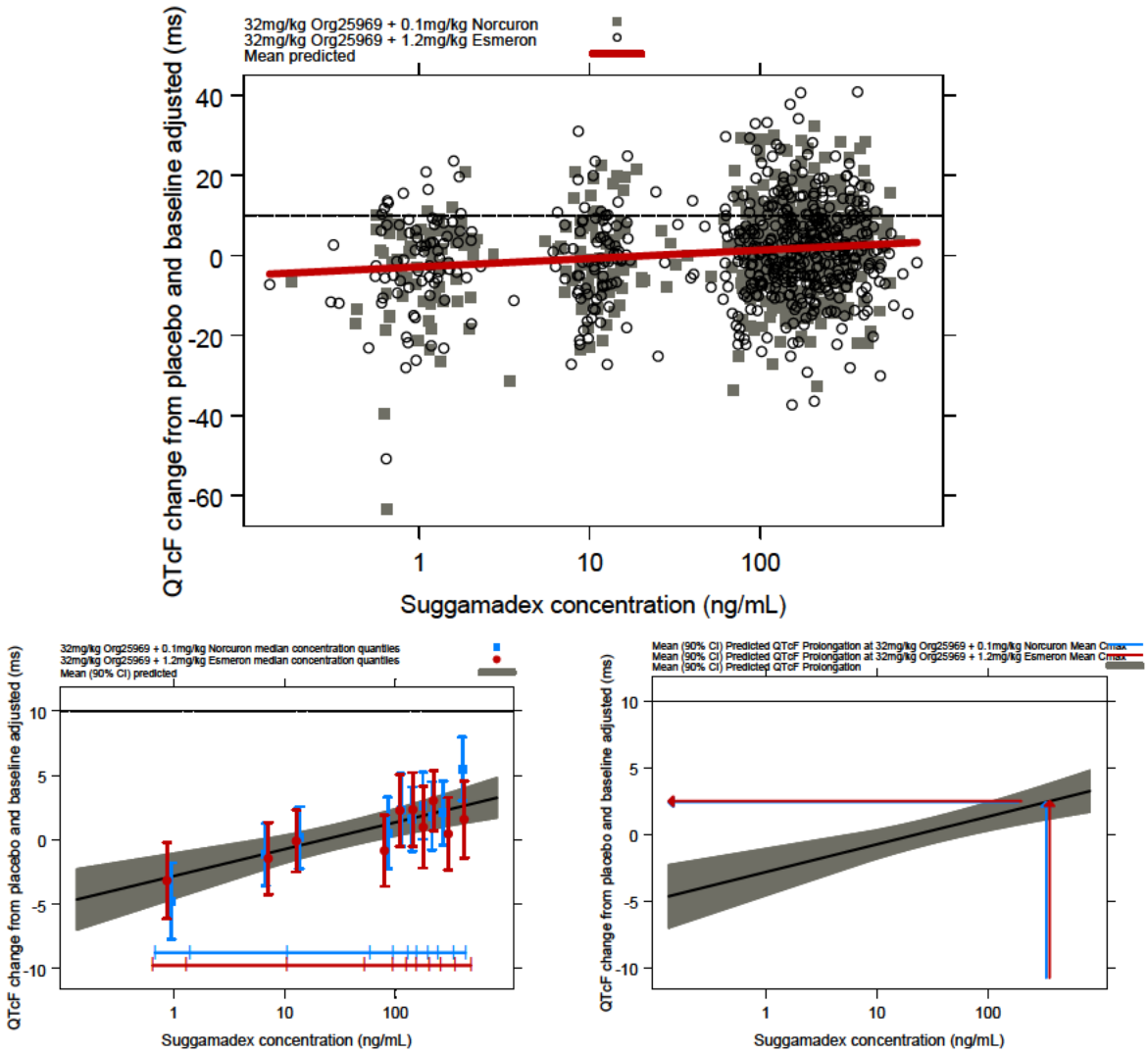


Figure 14 shows the relationship between Org 25969 concentrations together with norcuron and esmeron and change from baseline and placebo adjusted QTcF. A significant exposure-response relationship was also identified for Org 25969 together with norcuron and esmeron. The ΔΔQTcF is well below 10 ms and consistent with E14 analysis.

Figure 14. (Top) Observed baseline and placebo adjusted QTcF (ΔΔQTcF) versus Org 25969 concentrations on a log-scale. (Bottom Left) Median concentration quantile with corresponding observed mean (90% CI) ΔΔQTcF. (Bottom Right) ΔΔQTcF predictions at mean Cmax following 32 mg/kg Org 25969+0.1 mg/kg and 32 mg/kg Org 25969 + 1.2 mg/kg Rocuronium.



5.3 Clinical Assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. death, syncope, significant ventricular arrhythmia and seizures) occurred in this study. As described earlier 1 subject on study drug experienced QTcB prolongation of over 60ms not associated with any clinical events. Another subject experienced ventricular tachycardia which resolved.

ECG assessments-waveforms submitted to the ECG warehouse were reviewed. ECG acquisition and interpretation appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	Routine reversal: A dose of 4.0 mg/kg Bridion™ is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade. A dose of 2.0 mg/kg Bridion™ is only recommended, if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium or vecuronium induced blockade. Immediate reversal: If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg Bridion™ is recommended.	
Maximum tolerated dose	Bridion™ was evaluated upto 96 mg/kg (highest dose tested)	
Principal adverse events	Bridion™ was safe and well tolerated at doses up to 96 mg/kg. The most common adverse reactions (incidence>5%) observed after treatment with Bridion ™ in clinical trials were anesthetic complications (8.0%) and dysgeusia (12.6%). Dysgeusia was only reported in healthy volunteers, especially at higher doses (mostly > 32 mg/kg Bridion ™).	
Maximum dose tested	Single Dose	96 mg/kg
	Multiple Dose	Not applicable
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean C_{max} (i.e. C_0): 1168 µg/mL (CV 21.1%) Mean $AUC_{0\text{-}inf}$: 71273 µg*min/mL (CV 16.2%)
	Multiple Dose	Not applicable
Range of linear PK	Overall, across trials and across dose groups, ranging from 0.1 to 96 mg/kg, similar values of CL of Bridion ™ were observed. Therefore, overall the data indicated dose linearity with respect to exposure to Bridion ™.	
Accumulation at steady state	Not applicable	
Metabolites	Metabolism of Bridion ™ is at most very limited and the compound is predominantly, if not exclusively, eliminated via renal excretion of the unchanged product.	
Absorption	Absolute/Relative Bioavailability	IV formulation

	t_{max}	2 min (first sample taken after bolus IV administration)
Distribution	V_{ss}	V_{ss} of Bridion ™ was found to be approximately 12 to 15 L
	% bound	Bridion ™ does not bind to plasma proteins or erythrocytes
Elimination	Route	Renal excretion
	Terminal $t_{½}$	For the terminal elimination half-life of Bridion ™ in plasma, a relatively wide range of mean values from 66 to 260 min was observed within and across trials.
	CL	The observed CL of Bridion ™ was similar across trials, with mean values ranging from 97 to 138 mL/min.
Intrinsic Factors	Age	Using PK modeling: in a typical subject aged 81 years, CL was decreased by 51% compared to a typical subject of 49 years and by 32% compared to a typical subject of 68 years. Differences in volumes of distribution between the age groups were small. Renal function decreases with age and CL of Bridion ™ in elderly was dependent on CL_{CR} according to the equation: $CL = 87\ mL.min^{-1} + 0.61*(CL_{CR} - 105.4)$. This means that a 10% reduction of CL_{CR} (compared to 105 $mL.min^{-1}$) causes a 7.4% reduction in CL of Bridion ™.
	Sex	The PK of Bridion ™ is similar in female and male subjects.
	Race	No major differences in PK of Bridion ™ were observed between Japanese and Caucasian subjects. CL was 9% lower and V_{ss} was 12% lower in the Japanese compared to the Caucasian subjects. After body weight normalization (wn-) CL and V_{ss} were similar in both ethnic groups. The population PK data set contained too few subjects from other races to allow for separate evaluation of these race effects on the PK of Bridion ™.
	Hepatic & Renal Impairment	*Severe renal impairment* In severely renal impaired patients CL of Bridion™

		was reduced approximately 16-fold compared to normal patients. V_{ss} of Bridion ™ was increased 25 % compared to normal patients. This resulted in a prolonged and 17-fold higher exposure to Bridion ™ in renal impaired patients. However, during the first 60 minutes post administration of Bridion ™ there was little difference in plasma levels between the two groups (thus neither in C_{max}). As there is currently no efficient dialysis method available, it is strongly recommended not to use Bridion ™ in severely renal impaired patients. *Mild and moderate renal impairment* Based on PK modeling for the elderly/renal impaired population three typical subjects with body weight 75 kg were simulated: • An elderly subject with borderline severe/moderate renal impairment (CLcr=30 mL/min) is predicted to have a 55% lower clearance compared to the typical adult. • An elderly subject with borderline moderate/mild renal impairment (CLcr=50 mL/min) is predicted to have a 41% lower clearance compared to the typical adult. • An elderly subject with borderline mild renal impairment (CLcr=80 mL/min) is predicted to have a 21% lower clearance compared to the typical adult.
		Hepatic impairment No trial in hepatically impaired subjects has been performed, as Bridion ™ is almost exclusively excreted via the renal route and therefore no major effects on Bridion ™ PK of severe hepatic impairment are expected.
Extrinsic Factors	Drug interactions	No drug interaction studies have been performed , but drug interaction potential was assessed based on a strategy using the in vitro determination of the binding affinity and clinical considerations. Based on this strategy, it has been concluded that a clinically relevant interaction cannot be ruled out for toremifene, flucloxacillin, fusidic acid and hormonal contraceptives. However, there are no indications, from preclinical or clinical studies, that these interactions occur. As there is no further information available to assess these potential

		interactions, these drugs will be listed in the labeling.
	Food Effects	Not applicable (IV formulation)
Expected High Clinical Exposure Scenario	Since Bridion ™ not recommended to be used in severely renal impaired patients, an elderly subject with moderate renal impaired function was considered to represent the worst case scenario (as sex and race do no play major roles). For an elderly subject with borderline severe/moderate renal impairment, the clearance is predicted to be 55% lower as compared to for a typical adult. This means total exposure to Bridion ™ is increased by a factor 2.2. Therefore, an increase in total exposure to Bridion ™ of a factor two is considered to be the worst case scenario in clinical practice as compared to the 'normal' situation of an adult subject. A supratherapeutic dose of 32 mg/kg Bridion ™ provides an 8-fold margin for routine reversal, since for routine reversal doses upto 4 mg/kg Bridion ™ are recommended. For immediate reversal, following administration of rocuronium, a dose of 16.0 mg/kg Bridion ™ is recommended, and the two-fold margin provided by the supratherapeutic dose of 32 mg/kg is considered to be sufficient. For the evaluation of the applied supra-therapeutic dose of 32 mg/kg Bridion ™, it is also important to note that, during the first 60 minutes post administration of Bridion ™ there is little difference in plasma levels of Bridion ™ between severely renal impaired and control subjects (thus neither in C_{max}).	

6.2 TABLE OF STUDY ASSESSMENTS

Table 1 Flowchart of subject

		Period 1	Period 1-6				
	Screening	Admission (Day -2)	Day -1	Day 1	Day 2	Day 3	Follow-up[a]
Medical history	•	Update					
Physical examination	•	Update					
Pregnancy test[b]	•	•					
Pharmacogenetic sampling				• (period 1)			
Clinical laboratory[c]	•	•	•[j]				•
Drug/alcohol screen	•	•					
Serology (hepatitis B-C/HIVI-II)	•						
Vital signs[d]	•	•[e]	•	•			•
Continuous 12-lead ECG			•[f]	•[g]	•[g]		
Safety 12-lead ECG	•	•	•	•[h]	•		•
Cardiac monitoring	• (24 h)			• (4h after dosing)			
SPO_2				• (2h after dosing)			
Dosing			Placebo	•			
PK sampling				•[i]			
Epinephrine sampling				•[i]			
(Serious) adverse events/ SPE	Whenever a (S)AE/SPE occurs						
Co-medication check	•	•	•	•	•	•	•
Hospitalization	•	•	•	•	•	•	

[a] Approximately three days after last dosing.
[b] For women only: At screening and at admission an urine sample was to be collected for pregnancy testing.
[c] Blood and urine samples were to be drawn/collected for safety lab (standard hematology, chemistry and urinalysis (dipstick)) at screening, admission and at follow up and pre-dose on Day -1 for Periods 2-6. At screening aPTT and PT were also to be measured
[d] BP, pulse rate, weight, height (at screening only), body temperature and respiration rate were to be recorded at screening and at follow up; BP and pulse rate were to be measured at Day -2 (Period 1), pre-dose on Days -1 and 1. Additional BP and pulse rate measurements could be performed if required based on the opinion of the investigator.
[e] Body weight was to be measured at Day-2 of Period 1 to be used for i.v. dosing volume of Org 25969, rocuronium, vecuronium or placebo.
[f] 39 ECGs were to be recorded on Day -1: 3 ECG recordings at 2, 5, 15 and 30 minutes and 1, 1½, 2, 3, 5, 8, 12, 16, 23½ hours post placebo dose.
[g] 39 ECGs were to be recorded on Day 1 for all treatments: 3 ECG recordings at 2, 5, 15 and 30 minutes and 1, 1½, 2, 3, 5, 8, 12, 16, 23½ hours post dose.
[h] If considered necessary, the investigator could decide to perform additional safety ECGs on Day 1.
[i] PK samples and epinephrine samples were to be taken in the double-blind part only at –5, 3, 6, 16 and 31 minutes and 1:01, 5:05 and 12:05 hours post dose. For moxifloxacin no PK and/or epinephrine blood samples were to be taken.
[j] Only for Periods 2-6.

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/s/

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MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 24, 2008

TO: Allison Meyer, Regulatory Project Manager
Dr. Robert Shibuya, Medical Officer

FROM: Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., Ph.D.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA#: 22-225

APPLICANT: Organon

DRUG: Bridion (sugammadex)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: Reversal of neuromuscular blockade induced by rocurinium or vecuronium

CONSULTATION REQUEST DATE: November 16, 2007

DIVISION ACTION GOAL DATE: April 25, 2008

PDUFA DATE: April 30, 2008

I. BACKGROUND:

Bridion is a new molecular entity. The sponsor, Organon, has submitted a new drug application for marketing approval of Bridion for reversal of neuromuscular blockade induced by rocurinium or vecuronium. Keith Candiotis, M.D. (protocol 194303, site 106) and R. Kevin Jones, M.D. (protocol 194302, site 103) were selected for inspection due to enrollment of a large number of subjects at their sites. In addition, two foreign clinical investigators' sites were selected for inspection because there were insufficient domestic data [Professor Manfred Blobner (protocol 194301) and Professor Jennifer Hunter (194310)]. The studies selected for the foreign sites were not conducted under an IND. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. It was noted that the data listings indicate that the high-enrolling site for protocol 194303 is UFL 104. The Clinical Study Report does not list site UFL 104. The sponsor informed the field investigator that "UFL 104" is the center code and "106" is the site number.

The protocols inspected include:

- **194301** entitled **"**A multi-center, randomized, parallel group, comparative, active controlled, safety-assessor blinded, phase IIIa, pivotal trial, in adult subjects comparing Org 25969 with neostigmine as reversal agent of a neuromuscular block induced by rocuronium or vecuronium at reappearance of T_2"
- **194310** entitled "Comparison of rocuronium and Org 25969 with cis-atracurium and neostigmine when neuromuscular block is reversed at reappearance of T_2"
- **194302 entitled "**A multicenter, randomized, parallel group, comparative, active controlled, safety-assessor blinded, phase IIIa, pivotal trial in adult subjects comparing Org 25969 with neostigmine as reversal agent of a neuromuscular block induced by maintenance dosing of rocuronium or vecuronium at 1-2 PTCs"
- **194303 entitled "**A multicenter, randomized, parallel group, comparative, active controlled, safety-assessor blinded, phase IIIa trial, in adult subjects comparing recovery from 1.2 $mg.kg^{-1}$ rocuronium followed by 16 $mg.kg^{-1}$ Org 25969 at 3 minutes with recovery from 1.0 $mg.kg^{-1}$ succinylcholine"

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Protocol #	Insp. Date	Final Classification
Keith Candiotis, M.D. Site UFL 106, University of Miami/Department of Anesthesiology Jackson memorial Hospital 1611 N.W. 12th Ave. Central Building Room C-300 Miami, FL 33136	194303	January 28-February 5, 2008	NAI

R. Kevin Jones, M.D. Site UCA 103 Saddleback Memorial Medical Center 24451 Health Center Drive Laguna Hills, CA 92653	194302	January 14-24, 2008	VAI
Professor Manfred Blobner Site DE 348, Department of Anesthesiology Technische Universitat Muchen Klinikum rechts der Isar D-81675 Munich, Germany	194301	February 4-8, 2008	Pending
Professor Jennifer Hunter Site GB 253 University of Liverpool Department of Anesthesia, University Clinical Department Liverpool, UK L69 3GA	194310	February 11-15, 2008	Pending
Organon USA, Inc. 56 Livingston Avenue Roseland, NJ 07068	194302 194303	January 29-February 21, 2008	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and/or complete review of EIR is pending.

1. Keith Candiotis, M.D., site UFL 106, 1
   University of Miami/Department of Anesthesiology
   Jackson memorial Hospital
   1611 N.W. 12th Ave. Central Building Room C-300
   Miami, FL 3313

   a. **What was inspected**: For protocol 194303, 36 subjects were screened; 30 subjects were randomized and 26 subjects completed the study. An audit of all subjects' records was conducted.

   b. **General observations/commentary**: No significant regulatory violations were noted.

   c. **Assessment of data integrity**: Data from this site appear acceptable in support of the pending application.

2. R. Kevin Jones, M.D., site UCA 103
   Saddleback Memorial Medical Center
   24451 Health Center Drive
   Laguna Hills, CA 92653

   a. **What was inspected**: For protocol 194302, 32 subjects were screened and enrolled. Twenty nine (29) subjects completed the study. An audit of 21 subject's records was conducted.

   b. **General observations/commentary**: Dr. Jones did not ensure that the investigation was conducted according to the investigational plan. Specifically,

      - The protocol specified that neuromuscular block will be maintained with either a bolus dose(s) of 0.15 mg.kg-1 rocuronium or a bolus dose(s) of 0.015 mg.kg-1 vecuronium. However, instead of the full doses required by the protocol, only partial doses of rocuronium or vecuronioum were administered to subjects 103016, 103017, 103020, 103023, and 103025 in violation of the protocol.

      - The protocol specified that after the last dose of rocuronium or vecuronium, subjects will be reversed at 1-2 PTCs (Post-tenatic Count) with a single bolus dose of either 4.0 mg.kg-1 Org 25969 or 70 µg.kg-1 neostigmine (total dose not to exceed 5 mg) plus 14 µg.kg-1 glycopyrrolate. However, subjects 103001, 103002, 103010, 03013, 103016, 103017, 103018, 103020, 103023, 103025, and 103102 were reversed at 3, 4, or 5 PTCs instead of the protocol required 1-2 PTCs.

   In addition, the efficacy data for subject 103015 could not be verified because the subject was transferred to the recovery room after 40% recovery and the TOF-Watch SX tracing was unreliable. Efficacy data for subjects 103019, and 103025 could not be verified during the inspection because TOF-Watch SX tracings did not include the time of recovery T4/T1 ratio to .90.

   c. **Assessment of data integrity**: The review division should evaluate the impact, if any, that the inability to verify data for the aforementioned subjects has on the acceptability of the efficacy data.

3. Professor Manfred Blobner, site DE 348,
   Department of Anesthesiology
   Technische Universitat Muchen
   Klinikum rechts der Isar
   D-81675 Munich, Germany

   a. **What was inspected**: For protocol 194301, 34 subjects were screened, 30 subjects were randomized, and 29 subjects completed the study. An audit of 20 subjects' records was conducted.

   b. **General observations/commentary**: No significant violations were noted.

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c. **Assessment of data integrity**: Data from this site appear acceptable in support of the pending application.

Observations noted for this site are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Prof. Jennifer Hunter, site GB 253
University of Liverpool
Department of Anesthesia,
University Clinical Department
Liverpool, UK L69 3GA

a. **What was inspected**: For protocol 194310, 32 subjects were screened, 29 subjects were randomized, and 28 subjects completed the study. An audit of 20 subjects' records was conducted.

b. **General observations/commentary**: No significant violations were noted.

c. **Assessment of data integrity**: Data from this site appear acceptable in support of the pending application.

Observations noted for this site are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. Organon USA, Inc.
56 Livingston Avenue
Roseland, NJ 07068

a. **What was inspected**: For protocol 194302, monitoring reports and correspondence for sites 106, 111, 103, 102, and 105 were reviewed. For protocol 194303, monitoring reports and correspondence for sites 106, 109, and 101were reviewed.

b. **General observations/commentary**: No significant regulatory violations were noted.

c. **Assessment of data integrity**: Data monitored by this sponsor appear acceptable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above, inspections of Dr. Keith Candiotti, Professor Manfred Blobner, and Professor Jennifer Hunter found no significant violations. Inspection of the sponsor,

Organon, found no significant regulatory violations. Data from these sites appear acceptable in support of the pending application.

Inspection of Dr. R. Kevin Jones found protocol violations. In addition, the efficacy data for subject 103015 could not be verified because the subject was transferred to the recovery room after 40% recovery and the TOF-Watch SX tracing was unreliable. Efficacy data for subjects 103019, and 103025 could not be verified during the inspection because TOF-Watch SX tracings did not include the time of recovery T4/T1 ratio to .90. The review division should evaluate the impact, if any, that the inability to verify data for the aforementioned subjects has on the acceptability of the efficacy data.

As previously mentioned, observations related to the inspections of Professor Blobner and Professor Hunter are based on communications with the field investigator. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR(s).

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

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/s/

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