Table of Contents

I) Division Director Memo p2

II) Draft Agenda p4

III) Draft Questions p6

IV) Briefing Document Clinical Summary
- 1) Executive Summary p8
- 2) Summary of FDA Review of Clinical Efficacy and Safety p9
- a) Efficacy p9
  - i) Explanation of Methodology and Endpoints p10
  - ii) Study 301 p10
  - iii) Study 302 p11
  - iv) Study 310 p12
  - v) Study 303 p12
  - vi) Clinical Narrative for Question 1 p12
  - vii) Clinical Narrative for Question 2 p14
- b) Safety p14
  - i) Pooled Phase 1-3 p14
  - ii) Pooled Phase 1 p15

V) Abbreviations p17

VI) Appendix p18

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products

MEMORANDUM

DATE: February 11, 2008

FROM: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members, and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)

RE: Overview of the March 11, 2008 ALSDAC Meeting to Discuss NDA 22-225 for Bridion for the reversal of neuromuscular blockade.

Bridion (also known as Organon 25969 and suggammadex sodium) is a novel compound developed for the reversal of neuromuscular blockade induced by rocuronium and vecuronium. It is a modified γ-cyclodextrin which is designed to form a 1:1 inclusion complex with the neuromuscular blocking molecule. Sequestration of the free neuromuscular blocker results in reversal of the neuromuscular blockade.

The applicant, Organon, is seeking two indications: a) routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and b) immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

During this meeting, representatives from the Agency and Organon will present:

- data from the non-clinical program for Bridion;
- data on the chemistry and the clinical pharmacology of Bridion, including information on potential drug-drug interactions derived from *in vitro* assessments and modeling of population pharmacokinetic/pharmacodynamic data; and
- data from the clinical trials performed to assess the safety and efficacy of Bridion.

Following these presentations, you will be asked to assess these findings, and to discuss the apparent risks and benefits of Bridion. Specific issues that the Agency would like the committee to address include whether the applicant has presented adequate data to support the indication of "immediate reversal of neuromuscular blockade," including the appropriateness of the primary endpoint with respect to its clinical relevance; whether the in vitro assessments and pharmacokinetic modeling are sufficient to adequately describe potential drug-drug interactions or whether clinical studies should be required; and whether the committee would recommend to the Agency that Bridion be approved for the indications requested by the applicant. In the event that the committee would recommend an approval, we would like the committee to consider whether there are any post-approval studies that should be required of the applicant.

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

Food and Drug Administration
Center for Drug Evaluation and Research

MEETING OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE (ALSDAC)

March 11, 2008
Washington DC Hilton-Silver Spring
8727 Colesville Road
Silver Spring, MD

AGENDA

New Drug Application (NDA) 22-225, sugammadex sodium injection (proposed tradename BRIDION), Organon USA Inc., proposed indication of routine reversal of shallow and profound neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at three minutes after administration of rocuronium.

8:30	**Call to Order and Introduction of Committees**	**John T. Farrar, M.D.** Acting Chair, ALSDAC
8:35	**Conflict of Interest Statement**	**Mimi Phan, Pharm.D., R.Ph.** Designated Federal Officer, ALSDAC
8:40	**Introduction to Meeting**	**Bob Rappaport, M.D.** Director, Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)/CDER/FDA

INDUSTRY PRESENTATION

9:00	**Sugammadex: A Novel Reversal Agent for NMB**	**TBD** Organon/Schering-Plough representative
	Introduction	**TBD** Organon/Schering-Plough representative
	Unmet Medical Need	**TBD** Organon/Schering-Plough representative
	Mechanism of Action, Pharmacology, Pharmacokinetics and Drug-Drug Interactions	**TBD** Organon/Schering-Plough representative
	Efficacy and Safety Clinical Overview	**TBD** Organon/Schering-Plough representative
	Summary	**TBD** Organon/Schering-Plough representative

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10:30 *Questions from the Committee*

10:45 **Break**

FDA PRESENTATIONS

11:00	**Sugammadex: Efficacy and Outlier Analysis**	R**ob Shibuya, M.D.** Medical Officer, Division of Anesthetic, Analgesic, and Rheumatology Products (DAARP)/CDER/FDA
11:20	**Sugammadex: Safety Considerations**	**Arthur Simone, M.D., Ph.D.** Medical Officer, Division of Anesthetic, Analgesic, and Rheumatology Products (DAARP)/CDER/FDA
11:40	*Questions from the Committee*	
12:00	Lunch	
1:00	**Open Public Hearing**	
2:00	**FDA Summary of Issues**	**Bob Rappaport, M.D.** Director, Division of Anesthetic, Analgesic, and Rheumatology Products (DAARP)/CDER/FDA
2:30	D*iscussion*	
3:30	*Questions to the Committee and Recommendations*	
5:00	**Adjourn**	

Questions for the Committee

1. The Applicant has conducted a clinical trial to evaluate the efficacy of Bridion to effect the "Immediate Reversal" of neuromuscular blockade (NMB). The primary efficacy endpoint was the time from start of administration of rocuronium bromide (RCB) or succinylcholine (Sux) to the recovery of T_1 to 10% if its baseline value. Bridion was administered to patients 3 minutes following administration of RCB.
    a. Does the primary endpoint have clinical relevance? If no, what other endpoints might be more useful?
    b. Based on the data submitted from this study, is there sufficient clinical information to assess whether Bridion, when used with RCB, provides a clear advantage when confronted with a "cannot ventilate/cannot intubate" situation in the clinical setting? If not, what additional information would be required to assess a possible role for Bridion in this scenario?

2. Based on the nonclinical data submitted by the applicant from the Bridion distribution, juvenile animal, reproductive toxicology, and dedicated bone studies:
    a. Has the risk for adult patients, including patients with fractures or surgical injury to bone been adequately characterized?
    b. Has the risk for pediatric patients been adequately characterized?
    c. Does the nonclinical data support the safety of Bridion for clinical trials in a pediatric population?
    d. If the answers to any of the above questions is "no," what additional information is required to support the use of Bridion in these populations?

3. Has the applicant provided enough data to support the use of Bridion for:
    a. the routine reversal of "shallow" neuromuscular blockade;
    b. the routine reversal of "profound" neuromuscular blockade; and
    c. the "immediate reversal" of neuromuscular blockade?

Briefing Document for the Anesthesia and Life Support Drug Advisory Committee Meeting

March 11, 2008

Bridion®
NDA 22-225

Department of Health & Human Services
Food & Drug Administration
Center for Drug Evaluation & Research
Division of Anesthesia, Analgesia and Rheumatology Products
Silver Spring, MD 20993

Executive Summary

The purpose of this advisory committee meeting is to discuss the marketing application for Bridion®, also known as Org25969, Sugammadex Sodium, a new molecular entity proposed for the following indications:

- The routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium.
- The immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

Available therapies for the first indication include several reversal agents that are presently marketed in the U.S. and are in widespread use; however, the only approved reversal agents are edrophonium and pyridostigmine, and their labeled indications do not distinguish between "shallow" or "profound" blockade. Neostigmine, although clinically used for neuromuscular blockade reversal, is not approved for this indication.

The second indication is entirely novel. These factors have shaped the clinical development program including trial design, choice of comparators, selection of endpoints, and replication of studies submitted in this application. We ask the Committee to consider the efficacy endpoints, the comparators, and the adequacy of the data submitted in its deliberations about the efficacy of this product.

The rationale for reversal of neuromuscular blockade is prevention of prolonged muscular weakness and its clinical consequences, including respiratory insufficiency and aspiration. Currently used reversal agents act through inhibition of acetyl cholinesterase. Their dose-response curve plateaus when the enzyme is fully inhibited, they are inactive when all receptors are blocked (no twitch following electrical stimulation of any type), and their half-life may be less than the neuromuscular blocking agent, leading to recurrence of neuromuscular blockade. There are clinically significant side effects attributable to the pharmacologic properties of the reversal agents as well as to the muscarinic receptor antagonists co-administered to counteract these side effects. We ask the Committee to consider available therapy in its deliberations about the safety and efficacy of this product.

According to the Applicant, pharmacologic reversal is administered for roughly 54% of the surgical procedures for which a neuromuscular blocker is used in this country. It follows that reversal agents are not considered medically necessary for 46% of surgeries, and a reasonable alternative to reversal is to allow the neuromuscular blocking agent to clear on its own and thereby permit spontaneous return of motor function. Therefore, we ask the Committee to include "no therapy" in its deliberations about the safety of this product (question 3).

It should be noted that the Agency's assessment of this submission is ongoing, and the content of the briefing document reflects this reality. At the time this memo was prepared, the 120-day Safety Update had not yet been submitted to the application, and safety issues identified by the applicant remain open. These include potential immediate and delayed hypersensitivity reactions to sugammadex as well as juvenile animal studies

demonstrating effects on bone and tooth enamel. Our current assessment is not in substantial disagreement with the Applicant regarding the data or the findings contained in this application, although it is possible this may change as reviews are finalized. We ask the Committee to consider the open issues identified above and in the narrative below in its deliberations over the need for additional information about this product.

The clinical development program for Bridion® was conducted in Europe, the U.S., Canada, and Japan and is comprised of 30 Phase 1, 2, and 3 clinical trials. The safety database from these clinical trials includes 2390 unique subjects of whom 2054 received Bridion®. Of the total Bridion® exposures, 209 received the drug alone for purposes of safety, tolerability, and PK assessment, and 1845 subjects received a neuromuscular blocking agent (NMBA), either rocuronium, vecuronium, or pancuronium,) prior to Bridion®. Doses of Bridion® ranged from 0.5 - 32 mg/kg. The primary safety analysis is comprised of all patients enrolled in the studies who received at least one dose Bridion®. Additional analyses were performed for all subjects enrolled in Phase 2 or 3 efficacy studies, including a separate analysis of the subset of 529 subjects enrolled in the four clinical trials considered pivotal for efficacy, of whom 288 received Bridion®. Relevant safety comparisons drawn from the pivotal trials were limited by the size of the trials and the small number of adverse events (AEs) overall.

Safety was assessed across treatment groups by clinical laboratory values, vital signs, ECG recordings, AEs, and serious adverse events (SAEs). There were no clinically significant changes in laboratory values attributable to study drug. There were three deaths overall during the clinical development program, two of which occurred in subjects who received Bridion®. None were considered to be study drug related. There were 24 reported cases of recurrence of neuromuscular blockade (NMB), 20 in subjects who had received a dose of Bridion® less than that proposed for reversal of shallow NMB (2.0 mg/kg).

Summary of FDA Review of Clinical Efficacy & Safety

Efficacy

There were a total of 23 Phase 2 and 3 trials identified by the applicant as relevant to the efficacy evaluation of Bridion®. The total study enrollment was 2128 subjects, of whom 1187 received a dose of Bridion®. Most of these studies were considered clinical pharmacology trials and were conducted to support the doses of Bridion® selected for the Applicant's pivotal trials or to study special populations such as the elderly, patients with cardiac or pulmonary disorders, or subjects with impaired renal function. The Phase 3 efficacy trials identified by the applicant as "pivotal" included Studies 301, 302, 303, and 310. The enrollment in these four trials included 529 subjects, of whom 288 received Bridion®.

The four pivotal efficacy studies are discussed in greater detail, below. Their alignment with regard to the two proposed indications is as follows:

- The routine reversal of shallow (Studies 301, 310; dose: 2 mg/mL) or profound (Study 302; dose 4 mg/mL) neuromuscular blockade induced by rocuronium or vecuronium.
- The immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium (Study 303; 16 mg/mL)

Explanation of Methodology and Endpoints:
The depth of neuromuscular blockade and the effect of the reversal agent was monitored via a TOF-Watch SX® accelerometer, a train-of-four twitch monitor device, which provides an electrical stimulus to the ulnar nerve while measuring contraction of the adductor pollicis muscle.

The primary efficacy parameter used for Studies 301, 302, and 310 was time to recovery from neuromuscular blockade starting from the time of administration of test article (Bridion®) until the return of the T_4:T_1 ratio to 0.9 (i.e., the point where the ratio of the 4th twitch in a train-of-four stimulation is 90% of the magnitude of the first twitch; considered clinically significant neuromuscular recovery). The T_4:T_1 ratio was measured by acceleromyography. Secondary endpoints included intermediate levels of recovery, specifically the time from test article administration to recovery of a T_4:T_1 ratio of 0.7 or 0.8. Other endpoints included clinical assessments of neuromuscular recovery such as the ability to maintain the head lifted from the pillow for 5 seconds and generalized weakness.

The primary efficacy parameter for Study 303 (see Appendix A), was the time from the start of administration of NMBA (rocuronium or succinylcholine) until recovery of T_1 to 10% of its baseline value, where T_1 is the first twitch in a TOF stimulation. A subject randomized to Bridion® would have been administered this agent 3 minutes after rocuronium was administered. Because the succinylcholine arm did not receive reversal agent, recovery times were referenced to NMBA. The secondary endpoint was time until recovery of T_1 to 90%.

The administration of reversal agent was timed to coincide with reappearance of T_2 for "shallow" NMB, 1-2 post-tetanic contractions (PTC) for "profound" NMB, and at 3 minutes after rocuronium infusion for "immediate" reversal. The doses of Bridion® used for these paradigms was 2 mg/kg for shallow, 4 mg/kg for profound, and 16 mg/kg for immediate reversal. The reversal agent used as a comparator in the pivotal clinical trials was neostigmine 50 – 70 mcg/kg administered with glycopyrrolate 10 – 14 mcg/kg.

Study 301
This study was conducted to support the routine reversal claim, "shallow" neuromuscular blockade the dosage of Bridion assessed was 2 mg/kg. NMB was induced by rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg). All study sites were in Europe. The patient population totaled 196 who were randomized, 189 who were treated, and 185 who completed the trial. Subjects were relatively healthy adults (ASA physical status 1-3) without serious concomitant systemic conditions who were scheduled for surgery

requiring general anesthesia in the supine position. Following screening, patients were randomized 1:1:1:1 to one of the following treatment groups:

Study 301

Group Number	N	Neuromuscular Blocking Agent (NBMA)	Reversal agent
1	48	Rocuronium	Bridion
2	48	Rocuronium	Neostigmine*
3	48	Vecuronium	Bridion
4	45	Vecuronium	Neostigmine*

*Glycopyrrolate was also administered for its anti-muscarinic effects

Patients were induced with intravenous medications including benzodiazepines, narcotics and a hypnotic agent followed by paralysis with the specified NBMA. Anesthesia was maintained with sevoflurane and parenteral agents including propofol and fentanyl. The level of neuromuscular blockade was monitored, and at the return of T_2, which was felt to approximate "shallow" blockade, the reversal agent was administered. The dose of Bridion® was 2 mg/kg. The dose of neostigmine was 50 mcg/kg. The elapsed time between the start of administration of the reversal agent and the recovery of the T_4:T_1 ratio to 0.9, as measured by acceleromyography, was the primary efficacy endpoint. Other clinical measures of recovery were assessed including a 5-second head lift and general weakness. Prior to, during, and following recovery from anesthesia, the patient was followed for safety. In these studies, the safety assessor was blinded.

Study 302

This study was conducted to support the routine reversal claim, "profound" neuromuscular blockade, the dosage of Bridion assessed was 4 mg/kg. NMB was induced using rocuronium (0.6 mg/kg) or vecuronium (0.1). Profound NMB was defined as 1-2 Post-Tetanic-Contractions (PTC). All study sites were in the US. A total of 187 patients were randomized, 157 were treated and 155 completed the study. The patients were relatively healthy adults scheduled to undergo elective surgery in the supine position (ASA 1-3).

Study 302

Group Number	N	Neuromuscular Blocking Agent (NBMA)	Reversal agent
1	37	Rocuronium	Bridion
2	37	Rocuronium	Neostigmine*
3	47	Vecuronium	Bridion
4	36	Vecuronium	Neostigmine*

*Glycopyrrolate was also administered for its anti-muscarinic effects

Anesthesia was induced and maintained as described above. The specified NMBA (rocuronium and vecuronium) was administered, and the level of neuromuscular blockade was monitored via a TOF nerve stimulator. After the final maintenance dose of NMBA, the blockade was verified as 1-2 PTC and the reversal agent was administered. The dose of Bridion® was 4 mg/kg. The dose of neostigmine was 70 mcg/kg. The

elapsed time between the start of administration of the reversal agent and the recovery of the T_4:T_1 ratio to 0.9 was again the primary endpoint.

Study 310

This study was conducted to support the routine reversal claim, "shallow" neuromuscular blockade, assessing a 2 mg/kg dose of Bridion. The NMB in this study was induced by the bezylisoquinolinium nondepolarizing NMBA cis-atricurium that was reversed with neostigmine. This study was conducted at 8 sites in Europe and enrolled a total of 84 patients (ASA 1-3), of whom 73 were treated and 72 completed the study. Subjects were otherwise healthy adults undergoing scheduled surgery. Subjects randomized to rocuronium received 0.6 mg/kg for induction of NMB whereas those randomized to cis-atricurium received 0.15 mg/kg. The level of neuromuscular blockade was again monitored via a TOF nerve stimulator and at the return of T_2, the reversal agent was administered ("shallow" block). The dose of Bridion® was 2 mg/kg. The dose of neostigmine was 50 mcg/kg. The elapsed time between the start of administration of the reversal agent and the recovery of the T_4:T_1 ratio to 0.9 was again the primary endpoint.

Study 310

Group Number	N	Neuromuscular Blocking Agent (NBMA)	Reversal agent
1	34	Rocuronium	Bridion
2	39	Cisatricurium	Neostigmine*

*Glycopyrrolate was also administered for its anti-muscarinic effects

Below is a summary table of data from the pivotal efficacy trials 301, 302, and 310

Summary Table of Efficacy

Study #	NMB	Bridion® (sec)	Neostigmine (sec)	p-value
301 shallow	Rocuronium Vecuronium	1:29 2:48	18:30 16:48	<0.0001
302 profound	Rocuronium Vecuronium	2:50 4:28	50:22 66:12	<0.0001
310 shallow	Rocuronium Cisatracurium	2:02	 8:46	<0.0001

The efficacy data all demonstrated a significant treatment effect that favored Bridion® over the active comparator. Studies 301 and 302 had been conducted in accordance with a Special Protocol Assessment (SPA) agreement.

Study 303

Please see Appendix A for description of Clinical Trial 303.

CLINICAL NARRATIVE FOR QUESTION 1

The applicant proposes a new clinical scenario referred to as "immediate reversal". The clinical trial was conducted by administration of an intubating dose of rocuronium

followed in three minutes by a 16 mg/kg dose of Bridion®, which is four times the dose proposed for reversal of a "profound" blockade.

The marketing application for Bridion® includes statements that appear to extrapolate the clinical scenario studied in Study 303 to an emergency cannot intubate/cannot ventilate or CICV scenario. For example, in the Clinical Overview it is stated:

> "As a result, use of Org 25969 (Bridion®) in a CICV situation following rocuronium administration may prevent the need for emergency non-invasive airway ventilation including rigid bronchoscopy, combitube ventilation, or transtracheal jet ventilation, and may prevent the need for emergency invasive airway access such as surgical or percutaneous tracheostomy or cricothyrotomy. In situations where succinylcholine is used for intubation and a CICV scenario develops, there is no antagonist available." (p. 90)

The Clinical Overview goes on to state:

> "As described above, the results from Trial 19.4.303 support the conclusion that replacement of succinylcholine with a combination of rocuronium followed by Org 25969 to reverse the neuromuscular blockade would potentially markedly reduce the morbidity and mortality caused by a CICV scenario" (p. 99).

We ask the Committee to consider the following in its deliberations about this proposed indication:

a. Does the primary endpoint have clinical relevance in terms of indicating whether the patient has recovered sufficient neuromuscular functioning to adequately support spontaneous ventilation and to allow emergence from anesthesia and extubation without risk of adverse events related to residual NMB? If no, what other endpoints might be more useful?
b. Would comparison of time from the administration of an NMB agent to the time of successful extubation provide more useful information for the clinician? If not, what, if anything, would.
c. Are the differences observed in times to recovery of T_1 to 10% between RCB followed by Bridion and Sux used alone, as measured in this study, of sufficient magnitude so as to alter the use of succinylcholine in clinical practice as suggested by the Applicant? If not, what additional information would be required to determine the advantages and disadvantages of the combination of RCB and Bridion (if needed) compared to Sux, e.g., time to adequate intubation conditions, risk of recurring NMB following initial recovery?
d. Based on the data submitted from this study, is there sufficient clinical information to assess whether Bridion, when used with RCB, provides a clear advantage when confronted with a "cannot ventilate/cannot intubate" situation in the clinical setting? If not, what additional information would be necessary (or useful) in assessing a possible role for Bridion in this scenario?

CLINICAL NARRATIVE FOR QUESTION 2

The toxicology section of the review of this application remains preliminary; however, the following concerns have been raised:

- Bridion® has high affinity for bone and is believed to bind to the hydroxyapatite in skeletal bone and teeth. Although the significance of this finding has not been fully characterized, studies conducted in juvenile rats demonstrate a significantly greater percentage deposition than in adults and a prolonged retention of drug with half-life averaging 172 days in long bones. Dedicated bone studies in adult animals have described transient changes in bone microarchitecture and bone strength parameters, although a safety margin for single-dose exposure in the human exists.
- Toxicology studies conducted in juvenile rats demonstrate that Bridion® interferes with the enamelization of teeth when administered repeatedly, and potentially when administered as a single dose at developmental stage when tooth enamel is forming. However, the applicant has defined human safety margins for this finding in both single- and multiple-dose studies based on systemic and predicted local concentrations of Org 25969.
- The Segment 3 (pre and postnatal development) studies showed an increase in neonatal mortality in the F1 generation and increased maternal cannibalization at 120 and 500 mg/kg without a clear explanation for this finding.

Safety

The safety review of the Bridion NDA was still in progress at the time the briefing package was due. This summary of the findings to date is therefore provided and will be updated, if necessary, with an FDA clinical safety presentation during the Committee's meeting.

The safety data collected in the 30 trials conducted during the Bridion clinical development program have been analyzed in a manner appropriate for the trial designs and for the safety assessments generally required for an NDA and specifically useful for an anesthetic product such as this. The Applicant has grouped the clinical trials as indicated below on the basis of whether an anesthetic or neuromuscular blocking agent (NMBA) was administered.

Pooled Phase 1-3: Data were pooled from the 26 trials in which Bridion or placebo were administered following an NMBA (rocuronium, vecuronium or pancuronium). These data allowed for an analysis of dose response, with particular interest on the proposed marketing doses of Bridion: 2.0 mg/kg, 4.0 mg/kg and 16 mg/kg. Within this dataset, two additional subsets were generated:

a. ***Bridion vs. Neostigmine***: Data were pooled from the two Phase 3 trials in which Bridion (N = 179) was directly compared to neostigmine (N = 167), the most widely used NMBA reversal agent.
b. ***Bridion vs. Placebo***: Data were pooled from the ten trials that included a placebo group in order to compare the safety of Bridion (N = 640) vs.

placebo (N = 140). This dataset was used by the Applicant for identifying potential adverse drug reactions.

Pooled Phase 1: The Phase 1 pooled dataset included data from six trials. All but one of these Phase 1 trials were randomized, double-blind, crossover trials in which healthy adult volunteers received single doses of trial medication but no anesthetic or NMBA. The other trial was an open-label, nonrandomized, single-center trial to determine the excretion balance, metabolite profile, and pharmacokinetics of an intravenous dose of ^{14}C-labeled Bridion. The pooled Phase 1 dataset includes 443 subjects (209 unique subjects) who received Bridion and 196 unique subjects who received placebo.

The Applicant reported that blinding for efficacy was not possible in the trials in which an NMBA was administered prior to Bridion, since the effect of the reversal agent was observed via a twitch monitor (TOF-Watch SX®) and through visual inspection of the subjects' clinical status. However, except for two of the trials, all were safety-assessor blinded for the subjective safety assessments (i.e., the safety assessor did not administer study drug).

In general, safety was assessed by the Applicant across trials by the reporting of adverse events (AEs), and assessment of changes from baseline in clinical laboratory values, vital signs, and electrocardiograms (ECGs). Events particularly relevant to the use of anesthesia in general and reversal agents in particular were also assessed. These included:

- reoccurrence of blockade and residual blockade based on the TOF Watch SX® measurements;
- anesthetic complications, which included the following preferred terms [with examples of verbatim terms]:
    - anesthetic complication (movement [of a limb or the body], coughing during the anesthetic procedure or during surgery, grimacing, suckling the endotracheal tube, including AEs that in MedDRA versions prior to 10.0 were coded to the preferred term of "light anesthesia"),
    - airway complications of anesthesia (coughing on induction, bucking, and spontaneous breathing),
    - delayed recovery from anesthesia (delayed awakening from anesthesia or extended recovery from anesthesia),
    - unwanted awareness during anesthesia (awareness during anesthesia, awake during operation), and
    - anesthetic complication cardiac (changes in cardiac rate and rhythm).
- AEs associated with ventilation, i.e., preferred terms not specifically noted to involve an anesthetic complication; and
- allergic reactions.

In addition to the routine analyses of adverse events related to cardiac, respiratory, renal and hepatic systems, and the events particularly relevant to the use of anesthesia and reversal agents, listed above, the Applicant focused special attention on the following aspects of safety for the reasons indicated:

1. the use of Bridion on patients with reduced renal function because the drug is nearly exclusively removed via the kidneys, cardiovascular effects;
2. the cardiac changes related to Bridion use because of the differences observed in QTc between Bridion and placebo; and
3. the possibility of sensitization to Bridion because of the reports of hypersensitivity reactions in some patients exposed to Bridion.

Review of the data thus far has not produced evidence that contradicts the Applicant's finding of relative safety for the proposed marketing doses of Bridion. In particular, the comparison of Bridion to placebo and neostigmine for treatment-emergent serious adverse events, for changes in electrocardiographic tracing morphology, and for use in patients with mild to moderate renal impairment has not generated any safety-related issues. Two areas of concern for safety have been identified based on the findings from either the clinical or preclinical trials: hypersensitization and effects of Bridion on bone and teeth, respectively. Both concerns are discussed below.

The possibility of sensitization to Bridion, due to reports of hypersensitivity reactions in some patients exposed to the drug, has been further explored by the Applicant in a sensitization trial. This trial was not submitted to the NDA at the time the Advisory Committee package was being prepared. The occurrence of this reaction, even in a relatively small number of subjects, could have a significant impact on the overall finding of safety if it is found to be related to Bridion.

Bridion was found to bind more strongly to the bone and teeth and hydroxyapetite, in particular, of juvenile animals than to those of adult animals in a preclinical study. Although a single pediatric trial was conducted, outside of the United States, the safety assessments made did not address the consequences for possibility of this kind of increased binding of Bridion in pediatric patients compared to adults. A complete assessment of the safety of Bridion in the pediatric population, at least in the younger members of this demographic, therefore, cannot be made at this time.

In summary, the Applicant appears to have made a thorough assessment of the safety of Bridion in a relatively healthy adult population and, with the possible exception of hypersensitivity, found the drug product to be safe compared to neostigmine and placebo. The safety evaluation of Bridion in the pediatric population cannot be completed at the present time due to the lack of data addressing juvenile animal findings for the effects of Bridion on teeth and bone.

ABBREVIATIONS

AE	Adverse Event
NMBA	Neuromuscular Blocking Agent
NMB	Neuromuscular Blockade
PTC	Post-Tetanic Contractions
SAE	Serious Adverse Event
SPA	Special Protocol Assessment
TOF	Train of Four

Appendix

Summary of Efficacy Review for Study Number: 19.4.303

Protocol Title: "A multicenter, randomized, parallel group, comparative, active controlled, safety assessor blinded, Phase IIIa trial in adult subjects comparing recovery from 1.2 mg/kg rocuronium followed by 16.0 mg/kg Bridion at 3 minutes with recovery from 1.0 mg/kg succinylcholine"

Primary Objective: To demonstrate faster recovery to T_1 10% after neuromuscular block induced by 1.2 mg/kg rocuronium (RCB) reversed at 3 minutes by 16 mg/kg of Bridion compared to succinylcholine

Secondary Objectives:

- To demonstrate faster recovery to T_1 90% after neuromuscular block induced by RCB/Bridion versus succinylcholine
- To evaluate the safety of a single dose of RCB/Bridion vs. succinylcholine

Study Design: Randomized, active controlled, parallel group, single dose, safety-assessor blinded

Study Conduct:

The study was divided into four phases, which are summarized below.

<u>Screening</u>: During the screening visit (within one week of surgery), the following procedures were to have been performed:

- Patient consented
- History and physical exam
- Vital signs
- Urine sample for safety and pregnancy
- Inclusion and exclusion criteria
- Assess pre-trial medications and adverse events

<u>Peri-anesthetic</u>: During the time immediately prior to and during the surgery, the following procedures were to have been performed (study-specific procedures in *italics*)

- *Patient randomized*
- Routine pre-anesthetic clinical procedures (place IV cannulas)
- Continuous ECG monitoring
- *Induce anesthesia with IV opioid, propofol, or other agents appropriate to the clinical scenario*
- *Affix, stabilize, and calibrate the Train-of-Four (TOF) device and start continuous monitoring*
- Continue routine anesthetic monitoring (vital signs, body temperature, etc.)
- Administer NMBA within 10 seconds

- Intubate
- Maintain anesthesia with IV opioid, propofol, or other appropriate agent.
- Monitor adverse events
- Administer Bridion (for patients receiving RCB) three minutes following the start of RCB/succinylcholine injection. [N.B. Patients administered succinylcholine did not receive a placebo treatment.]
- Collect blood, continue routine anesthetic and neuromuscular monitoring, collect adverse event and medication data at least until the recovery of T_4/T_1 to 0.9.

Post-anesthetic:

- Assess clinical signs of recovery prior to transfer to recovery room after extubation and prior to discharge from the recovery room.

Follow-up:

- Contact (in person if in hospital, by telephone if discharged) patient.
- Assess quality of recovery (via questionnaire), concomitant medication intake, and adverse events.

Outcome Measures:

Primary Efficacy Endpoint:

The primary efficacy endpoint was to be the elapsed time from administration of rocuronium or succinylcholine to recovery of T_1 to 10% of the initial T_1.

Secondary Endpoints:

- Time from administration of the NMBA to recovery of T_1 to 90% of the initial T_1
- Clinical signs of recovery

Other Efficacy Endpoints:

- Time from start of administration of rocuronium to recovery of the T_4/T_1 ratio to 0.7
- Time from start of administration of rocuronium to recovery of the T_4/T_1 ratio to 0.8
- Time from start of administration of rocuronium to recovery of the T_4/T_1 ratio to 0.9
- Time from start of administration of Bridion to the time of reappearance of T_3
- T_1 at the time of reappearance of T_3
- Health Economics Patient Reported Outcomes (Quality of Recovery questionnaire)

Statistical Analysis Plan and Definition of Analyzed Study Populations for Efficacy:

The primary analysis was to be performed on the ITT population, defined as all patients who received study drug and had at least one post-baseline efficacy assessment. Imputation rules for missing data were to be:

> For imputation of missing times from the start of administration of rocuronium or succinylcholine to the recovery of $_{T1}$ to 10% and to 90% a worst case scenario for rocuronium/Bridion and a best case scenario for succinylcholine will be applied.
>
> For the primary efficacy variable the following procedure will be followed. In case of missing data in the:
>
> - Rocuronium/Bridion group: calculate the 95th percentile (P95) of the available times from the start of administration of rocuronium to the recovery of T_1 to 10% of the baseline value in all subjects randomized to receive rocuronium and Bridion. Impute this P95 value for the missing times in this group.
> - Succinylcholine group: calculate the 5th percentile (P5) of the available times from the start of administration of succinylcholine to the recovery of T_1 to 10% of the baseline value in all subjects randomized to receive succinylcholine. Impute this P5 value for the missing times in this group.

Data from the two treatment groups (RCB/Bridion versus succinylcholine) were to have been compared using both the completed data and those with imputed data. The analysis with imputed data was to have been the primary analysis.

Secondary efficacy data were to have been analyzed similarly to those of the primary endpoint.

RESULTS:

Patient Exposure

Study 303 was conducted at 13 sites, 11 in the U.S. and 2 in Canada. Two of the U.S. centers did not enroll any patients. A total of 115 patients were randomized of which 189 were treated and 108 completed. The Intent-to-Treat population (all treated patients with at least one post-baseline efficacy evaluation) was 110 patients. Patient disposition per treatment group is summarized in Table 1 below.

Table 1: Patient disposition

	Treatment group		
	Rocuronium + Org 25969	Succinylcholine	Total
	n	n	n
Randomized	57	58	115
Treated	56	54	110
Completed	55	53	108

Data were taken from Appendix F, Table 1.1-A

Note: The number of subjects randomized is based on the treatment group according to the randomization schedule. The number of subjects treated and completed is according to the treatment they actually received.

One (101007) subject was randomized to the rocuronium + Org 25969 group but received succinylcholine. Two (101006 and 101008) subjects were randomized to the succinylcholine group but received rocuronium and Org 25969.

Source: Table 4 of CSR, page 74

Demographics/Medical History/Physical Exam

Given the small size of the trial, the treatment groups were reasonably similar and any differences in baseline characteristics would not be expected to change the findings.

Drop-Outs

Five patients dropped out (2 in the RCB/Bridion group and 3 in the succinylcholine group). The RCB/Bridion patients withdrew consent. The succinylcholine patients had a cancellation of the surgery, surgeon's request, and due to scheduling error.

Two patients were treated but did not complete the study. One (RCB/Bridion) was lost to follow up; one (succinylcholine) was discharged prior to completing the study and, presumably, lost to follow up.

Protocol Deviations

The major protocol violations are summarized in Table 2, taken verbatim from the clinical study report (page 76).

Table 2: Major protocol violations

Major protocol violation	Treatment group			
	Rocuronium + Org 25969 (N = 55)		Succinylcholine (N = 55)	
	n	(Subject no.)	n	(Subject no.)
One or more of the selected inclusion criteria not met	1	(105003)	1	(112004)
Violation of the randomization schedule	1	(101007)	2	(101006) (101008)
Administration of a neuromuscular blocking agent other than rocuronium or succinylcholine	1	(106027)	0	
Administration of a dose of rocuronium / Org 25969 / succinylcholine that deviated more than 10% from the dose prescribed in the protocol	1	(101011)	0	
Administration of Org 25969 more than 1 min from the time point specified in the protocol	1	(101002)	0	
Subject used medication expected to interfere with NMBAs, before scoring any efficacy variable	18	(103004) (103005) (103009) (103010) (106001) (106004) (106007) (106010) (106012) (106013) (106015) (109001) (109003) (109009) (111002) (112002) (113001) (116002)	11	(103002) (103003) (106005) (106006) (106008) (106009) (106014) (109002) (112001) (113002) (116001)
Total	23		14	

One patient randomized to receive RCB/Bridion received succinylcholine and two patients assigned succinylcholine received RCB/Bridion.

There was a numerical imbalance between the treatment-assignment groups, predominantly patients who received drugs expected to interfere with NMBAs (mostly inhaled anesthetic agents). The RCB/Bridion treated patients had more interfering drugs. Since these drugs would be expected to enhance the effect of the NMBA, the fact that the Bridion-treated patients received more interfering drugs would have biased the study results against Bridion.

The other violations were insufficient in number to be expected to alter the results.

The majority of the minor protocol violations were due to the administration of possibly interfering drugs after some, but not all, of the efficacy parameters had been collected (as opposed to prior to scoring any efficacy variable). Seventeen patients in the RCB/Bridion group were minor protocol violators compared to 11 in the succinylcholine

group. For the reason stated above, this would be expected to bias against Bridion. The other two minor protocol violations were unreliable data in one patient per treatment group.

PRIMARY EFFICACY RESULTS

Table 3, below, extracted from the Clinical Study Report, shows the summary data for the primary efficacy endpoint, time from NMBA administration to recovery of T_1 to 10%.

Table 3: Primary efficacy variable results

		Treatment group	
		Rocuronium + Org 25969 (N=55)	Succinylcholine (N=55)
Including imputed data	n	55	55
	Mean (SD)	4:22 (0:44)	7:04 (1:34)
	Median	4:11	7:06
	Min. – max.	3:28 - 7:43	3:45 - 10:28
Complete cases	n	54	53
	Mean (SD)	4:21 (0:43)	7:09 (1:33)
	Median	4:11	7:11
	Min. – max.	3:28 - 7:43	3:45 - 10:28

Source: CSR, page 86

While the magnitude of the treatment effect was not as great as in Studies 301 and 302, the statistical analysis of the primary endpoint data (ANOVA) showed high statistical significance as shown in Table 4, following.

Table 4: Statistical analysis, Study 303

	Trial 19.4.303	
	Rocuronium + Org 25969 (16.0 mg.kg^{-1})	Succinylcholine (1.0 mg.kg^{-1})
Time to T_1 of 10%		
n	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median	4.2	7.1
Min. – max.	3.5 – 7.7	3.8 – 10.5
p-value[a]	<0.0001	
Time to T_1 of 90%		
n	55	55
Mean (SD)	6.2 (1.8)	10.9 (2.4)
Median	5.7	10.7
Min. – max.	4.2 – 13.6	5.0 – 16.2
p-value[a]	<0.0001	

[a] P-value obtained from a 2-way ANOVA on the time to T_1 10% / 90%.

Source: Clinical Overview, page 57

Secondary Efficacy Endpoints

Summary statistics for the time from administration of the NMBA to return of T_1 to 90% is shown in Table 5, following.

Table 5: Secondary efficacy variable results for return of T_1 to 90% of baseline

		Treatment group	
		Rocuronium + Org 25969 (N=55)	Succinylcholine (N=55)
Including imputed data	n	55	55
	Mean (SD)	6:11 (1:50)	10:56 (2:25)
	Median	5:41	10:41
	Min. – max.	4:12 - 13:35	5:01 – 16:11
Complete cases	n	54	53
	Mean (SD)	6:08 (1:47)	11:02 (2:24)
	Median	5:39	10:53
	Min. – max.	4:12 - 13:35	5:01 - 16:11

Source: CSR, page 88

The analysis of the clinical signs of recovery showed that there was no difference between the quality of recovery between treatment groups (Table 6).

Table 6

	Time point [a)]			
	1		2	
	Treatment group		Treatment group	
	Rocuronium + Org 25969 (N=55) n	Succinylcholine (N=55) n	Rocuronium + Org 25969 (N=55) n	Succinylcholine (N=55) N
Subject's level of consciousness				
Awake and oriented	25	27	50	53
Arousable with minimal stimulation	19	21	4	2
Responsive only to tactile stimulation	10	7	0	0
Subject cooperative [b)]				
No	12	10	0	0
Yes	43	45	54	55
Subject able to perform the 5-sec head lift				
No	5	3	0	0
Yes	39	42	54	55
General muscle weakness				
No	38	39	54	54
Yes	6	6	0	1

a Data were taken from Appendix F, Table 6.2-B.1

a) 1: prior to transfer to the recovery room after extubation
2: prior to discharge from the recovery room

b) In case the subject was not cooperative, the 5-sec head lift test and general muscle weakness were not to be assessed.

Source: CSR, page 91

The other efficacy endpoints generally supported the primary.