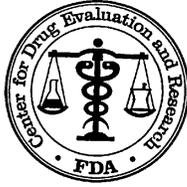


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022225Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

MEMORANDUM
STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number 22225/ 0046
Supplement Number 51
Drug Name: Sugammadex
Indication(s): Routine reversal of moderate or deep NMB by cocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium
Applicant: MERCK
Date(s): Letter Date: December 20, 2012
Stamp Date: December 20, 2012
Review Priority: Standard
Biometrics Division: Division of Biometrics V
Statistical Reviewer: Qing Xu, Ph.D.
Concurring Reviewers: Mark Rothmann, Ph.D., Statistical Team Leader
Rajeshwari Sridhara, Ph.D., Director, DBV
Medical Division: Division of Hematology Products
Clinical Team: George G. Shashaty, M.D., Clinical Reviewer
Kathy Robie Suh, M.D., Clinical Team Leader
Project Manager: Diana L Walker, Ph.D.

Table of Contents

MEMORANDUM	1
1 EXECUTIVE SUMMARY	4
2 INTRODUCTION	5
2.1 OVERVIEW.....	5
2.2 DATA SOURCES	5
3 STATISTICAL EVALUATION	6
3.1 DATA AND ANALYSIS QUALITY	6
3.2 EVALUATION OF EFFICACY	6
3.2.1 <i>Study Design and Endpoints</i>	6
3.2.2 <i>Statistical Methodologies</i>	7
3.2.3 <i>Patient Disposition, Demographic and Baseline Characteristics</i>	9
3.2.4 <i>Results and Conclusions</i>	13
3.3 EVALUATION OF SAFETY	ERROR! BOOKMARK NOT DEFINED.
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	17
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION	17
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	18
5 SUMMARY AND CONCLUSIONS	19

LIST OF TABLES

Table 1 Subject: Disposition from Screening to End of Trial.....	10
Table 2 Subjects Demographics and Characteristics using All-Patients-as-Treated Population	11
Table 3 Summary of Type of Surgery, ASA Class Between Two Groups (All-Subjects-Treated).....	12
Table 4 Summary of Stratification Variables, Usual Care Group and Country between Two Groups (All-Subjects-Treated).....	13
Table 5 Incidence (n, %) of Subjects with At Least One SUAEBa by Adjudicated Onset, Severity, Maximum Relationship, and Treatment Group. (All-Patients-as-Treated Population).....	14
Table 6 Analysis of Events of Bleeding Within 24 Hours of Trial Medication Administration (All-Patients-as-Treated Population)	15
Table 7 Sensitivity Analysis on Primary Endpoint: Adjudicated Events of Bleeding Within 24 Hours of Trial Medication Administration by Creatinine Clearance at Screening (All-Patients-as-Treated Population).....	16
Table 8 Key Secondary and Secondary Endpoint Analysis: Differece (95 CI) in APTT and PT (INR) versus by Time Point and for Sugammadex versus Usual Care (All-Patients-as Treated Population)	17
Table 9 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Gender	18
Table 10 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Age	18
Table 11 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Usual Care Group.....	18
Table 12 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Creatinine Clearance Class.....	18
Table 13 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Location of the Surgery.....	19

1 EXECUTIVE SUMMARY

This is a resubmission to provide the sponsor's response to the Complete Response Letter from FDA dated July 31, 2008 for NDA 22-225. The letter stated the following assessment would be required in the re-submission:

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

The Division of Hematology Products is being consulted by the Division of Neurological Products to review Study P07038 to determine whether or not the data submitted from the study address the concern for a potential increase in the frequency of bleeding related to the use of sugammadex (SU).

Subsequently, the sponsor provided additional in vitro data and proposal for clinical studies to address this safety concern. This submission includes a complete study report (CSR) and datasets for a study P07038: a randomized, controlled, parallel-group, double-blind trial of sugammadex (SU) or usual care (neostigmine) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin. The primary safety endpoint is the proportion of subjects with at least one adjudicated, major or non-major, unanticipated adverse event (AE) of bleeding with onset within 24 hours of trial medication administration. The primary safety analysis was to be performed on the All-Patients-as-Treated (APaT) population. The primary trial objective was to be addressed by using the Cochran-Mantel-Haenszel (CMH) method to estimate the relative risk stratified for renal function and type of prophylactic antithrombotic treatment. The analysis results showed the percentage of subjects who experienced an adjudicated unanticipated adverse event of bleeding with onset within 24 hours of trial medication administration was 2.9% in the sugammadex treatment group and 4.1% in the usual care group. The relative risk of adjudicated events of bleeding within 24 hours of 4 mg/kg sugammadex versus usual care for the primary safety endpoint was 0.70 with a 95% CI of 0.38 to 1.29. The results demonstrated that the treatment with sugammadex was not associated with an increased bleeding risk in comparison to usual care. This reviewer's analysis results were consistent with the sponsor's results for the primary safety endpoint.

2 INTRODUCTION

2.1 Overview

Sugammadex (MK-8616, SCH 900616, Org 25969) is the first-in-class Selective Relaxant Binding Agent (SRBA) that has been designed to bind specifically with the steroidal neuromuscular blocking agents (NMBAs) rocuronium and vecuronium with very high affinity.

In a clinical trial of healthy subjects (Trial 19.4.115), doses of 4 and 16 mg/kg of sugammadex resulted in mean prolongations of activated partial thromboplastin time (aPTT) and prothrombin time (PT) by up to 17% to 22%. A limited and transient aPTT and PT increase after 16 and/or 4 mg/kg sugammadex was confirmed in Trial P07025 and Trial P07044. These limited, mean aPTT and PT prolongations resolved quickly (i.e., ≤ 30 minutes), and pooled analysis of Phase 2/3 data from surgical subjects in the sugammadex development program did not indicate an increase in clinically meaningful events of bleeding. To further investigate the potential clinical relevance of these findings, Trial P07038 investigated the effect of 4 mg/kg sugammadex versus usual care used to reverse NMB (i.e., neostigmine or spontaneous reversal) on adjudicated events of bleeding and coagulation parameters in surgical subjects at increased risk for bleeding events due to concomitant administration of thromboprophylactic therapy.

In the current trial, the comparison between sugammadex and usual care was chosen in order to answer the question whether replacing usual care by treatment with sugammadex would introduce any change in the prespecified safety endpoints. Therefore, no distinction is made that usual care consisted of neostigmine or placebo. Since both active reversal and spontaneous recovery are considered usual care, both methods were included in this trial.

Subjects were assigned by the anesthesiologist into one of two groups according to plans for reversal of rocuronium- or vecuronium-induced NMB: planned active reversal (Usual Care Group 1) or planned spontaneous recovery (Usual Care Group 2). In Usual Care Group 1, subjects were randomized in a 1:1 ratio to receive either sugammadex or neostigmine in a blinded manner; in Usual Care Group 2, subjects were randomized in a 1:1 ratio to receive either sugammadex or placebo (normal saline [NaCl 0.9%]) in a blinded manner. Those subjects who were planned to undergo active reversal but due to unanticipated peri-operative events *required* spontaneous recovery (or vice versa) were to be discontinued from the trial. At or following completion of the surgical procedure (i.e., after wound closure), when it was imminently acceptable for the subject to begin to move spontaneously, a dose of 4 mg/kg sugammadex or neostigmine (Usual Care Group 1) or placebo (Usual Care Group 2) was to be administered as an IV dose over approximately 10 seconds into a fast running venous infusion.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: <\\CDSESUB1\EVSPROD\NDA022225\022225.ENX>

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The analysis dataset was adequate and the reviewer was able to perform all analyses using the submitted data. No additional data submission was needed.

3.2 Evaluation of Efficacy

The objective of current study submitted was to establish safety. Efficacy was already established.

3.3 Evaluation of Safety

Primary Trial Objective

The primary objective of this trial was to provide an estimate of the relative risk of adjudicated events of bleeding.

Key Secondary Trial Objectives

The key secondary objective was to characterize the effect of sugammadex versus usual care on aPTT at 10 and 60 minutes after trial medication administration.

Reviewer's Comments:

The efficacy was not the primary endpoint. For these objectives, there are no testing of formal hypotheses. Therefore, the aim of the trial for both objectives was to provide estimates with 95% confidence interval (CI) for clinical interpretation. Throughout, 95% CI and, where specified, P values were to be provided. These CIs and P values were not intended to test formal hypotheses, but to assist in the interpretation of trial results.

3.3.1 Study Design and Endpoints

Study Design

This trial was a randomized, controlled, parallel-group, multi-site, double-blind trial of sugammadex versus usual care (neostigmine or spontaneous recovery) for reversal of rocuronium- or vecuronium-induced NMB in subjects receiving thromboprophylaxis and undergoing intracapsular or extracapsular hip fracture surgery, total joint (hip/knee) or partial joint replacement surgery (e.g., hip/knee resurfacing), or total (hip/knee) replacement/revision surgery, or stage 1 revision only.

After a screening period of up to 7 days and on the day of surgery (Day 1), subjects were randomized to one of two treatment arms (sugammadex or usual care) in a 1:1 ratio. Randomization was stratified according to thromboprophylaxis (including Low Molecular Weight Heparin (LMWH), including Unfractionated Heparin (UFH), or not including either LMWH or UFH) and renal function (estimated creatinine clearance [CLCR] $<$ or \geq 60 mL/minute). After wound closure and when the surgical team determined that it was imminently acceptable for the subject to begin to move spontaneously, trial medication was to be administered within 10 seconds by means of a fast running infusion. After surgery, subjects were to be monitored according to routine anesthetic procedures at the trial site. A post-operative visit was to occur between 24 and 48 hours after trial medication administration, and a follow-up visit was to occur 4 to 7 weeks after trial medication administration. A pregnancy follow-up was scheduled for \geq 30 days after administration of trial medication. Unscheduled visits to assess suspected unanticipated adverse events of bleeding (SUAEB) could also occur at any time after administration of trial medication until the subject was discontinued from or completed the trial.

Since sugammadex was administered as a single dose and has a short half-life (terminal half-life = 1.8 hours), a significant causal relationship between sugammadex and an event of interest with onset later than 14 days after trial medication administration was considered to be very unlikely. Thus, the 4 to 7 week follow-up visit, which was intended to coincide with a subject's routine surgical follow-up (as travel was often difficult prior to this time) was changed in protocol amendment #4 to a final follow-up contact/visit up to 14 days post-surgery.

Endpoints

The primary safety endpoint for this trial was the proportion of subjects with at least one adjudicated, major or non-major, unanticipated event of bleeding with onset within 24 hours of trial medication administration.

The key secondary safety endpoint (and primary coagulation endpoint) is activated partial thromboplastin time (aPTT)

Secondary safety endpoint (and secondary coagulation endpoint) is prothrombin time (PT) and international normalized ratio (PT[INR]).

3.3.2 Statistical Methodologies

Data Sets:

The primary safety analysis and analyses of other safety endpoints were to be performed on the All-Patients-as-Treated (APaT) population, which consists of all randomized subjects who received at least one dose of randomized trial medication. For the analysis of safety data using

APaT population, subjects were included in the treatment group corresponding to the trial medication they actually received.

The APaT population was also to be used for the key secondary analysis of the primary (aPTT) and secondary coagulation endpoints, with the additional requirement that a subject had at least one valid baseline or post-baseline measurement within the assessment windows.

Statistical Analyses

The primary parameter of adjudicated events of bleeding within 24 hours after trial medication administration was to be analyzed using the CMH method on the relative risk of 4 mg/kg sugammadex versus usual care, providing an estimated relative risk and associated 95% CI. The analyses was to be stratified for all identified strata, i.e., renal function (CLCR < or \geq 60 mL/min) and type of prophylactic antithrombotic treatment (including LMWH, including UFH, or not including either LMWH or UFH). If the number of subjects in the UFH stratum was less than 6, this stratum was to be incorporated in the LMWH stratum.

Sensitivity analysis for the primary parameter was to be performed using the events of bleeding within 24 hours after trial medication administration as considered by the investigational site. This analysis was to be otherwise identical to the analysis of the primary endpoint (ie, a stratified CMH method to establish the relative risk and associated 95% CI of 4 mg/kg sugammadex versus usual care).

A second sensitivity analysis for the primary parameter was to be performed using Poisson regression with the robust variance estimator to estimate relative risks and associated 95% CI. This model was to be used to assess treatment by stratum interaction terms and to characterize the main effect of strata within the model. Both due to the incidence of adjudicated events of bleeding being relatively small and the presence of two stratification factors, the Poisson regression model could face convergence issues. If the model did not converge, the strategy was to drop one of the stratification factors from the model.

Sample Size and Power for the Primary Safety Endpoint

The sample size was chosen to provide an estimate of the relative risk of adjudicated bleeding events with sufficient precision of the upper bound of the 95% CI of the estimate by a factor of no more than 2, where precision is expressed as the ratio of the upper limit of the 95% CI divided by the relative risk estimate. The precision of the relative risk estimate was determined by sample size and the incidence of adjudicated bleeding events observed for subjects in the usual care treatment group. based upon review of the literature on hip fracture surgery and joint (hip/knee) replacement procedures, the incidence of events of bleeding in the pooled Phase 2/3 sugammadex development program, and considering the duration of the primary observation period in this trial, the incidence was expected to be approximately 5% or 1 out of every 20 subjects. Using this assumption, a sample size of 800 subjects should provide sufficient statistical power to achieve a precision of a factor of 1.83 for the relative risk. These precisions were computed for the case where there is no stratification using conventional methods to derive a 95% confidence interval as based on CMH method.

In case the event rate was substantially lower than the anticipated 5%, the sample size was to be increased such that the desired precision for the primary endpoint would be reached. This was to be done by enrolling subjects until the number of primary events reaches 33, or until the maximum of approximately 1200 subjects were enrolled. The number of 33 events was derived by taking all possible distributions of events across strata into account, which was to provide relative risk with the desired precision using the CMH method.

Reviewer's Comments

In this study, because there are no explicit hypotheses to be tested, no corrections for multiplicity were required.

3.3.3 Patient Disposition, Demographic and Baseline Characteristics

This trial was conducted at 22 sites in the European Union: 3 sites in Austria, 6 sites in Belgium, and 13 sites in Germany.

Subjects were randomized in a 1:1 ratio to sugammadex or usual care (neostigmine or placebo). Table 1 shows summarized subject disposition. A total of 1283 subjects were screened; 85 of the screened subjects were not randomized. A total of 1198 subjects were randomized (598 to sugammadex and 600 to usual care); 14 of the randomized subjects did not receive treatment (3 subjects in sugammadex group and 11 subjects in the Usual Care group). The most frequent reason for subjects discontinuing between randomization and treatment was withdrawal of consent (6 subjects (0.5%)). A total of 1184 subjects were treated: 596 with sugammadex and 588 per usual care. A total of 47 subjects did not complete the trial after administration of trial medication: 21 in the sugammadex group and 26 in the usual care group. The most frequent reason for subjects discontinuing after administration of trial medication was lost to follow-up (14 (2.3%) subjects in the sugammadex group and 20 (3.4%) in the usual care group). No subjects in the sugammadex group and 1 subject in the usual care group was discontinued because of an AE. A total of 1137 subjects completed the trial: 575 (96.5%) subjects for sugammadex and 562 (95.6%) subjects for usual care.

Table 1 Subject: Disposition from Screening to End of Trial

	Number (%) of Subjects		
	Sugammadex	Usual Care	Total
Screened			1283 (100.0)
Discontinued before randomization			85 (6.6)
Administrative			12 (0.9)
Adverse Event			2 (0.2)
Did Not Meet Protocol Eligibility			40 (3.1)
Non-Compliance With Protocol			1 (0.1)
Subject Withdrew Consent			30 (2.3)
Randomized			1198 (93.4)
Randomized	598 (100.0)	600 (100.0)	1198 (100.0)
Discontinued before treatment with IMP	3 (0.5)	11 (1.8)	14 (1.2)
Administrative	1 (0.2)	2 (0.3)	3 (0.3)
Adverse Event	1 (0.2)	2 (0.3)	3 (0.3)
Did Not Meet Protocol Eligibility	0	1 (0.2) ^a	1 (0.1)
Non-Compliance With Protocol	0	1 (0.2) ^b	1 (0.1)
Subject Withdrew Consent	1 (0.2)	5 (0.8)	6 (0.5)
Treated ^d	595 (99.5)	589 (98.2)	1184 (98.8)
Treated (APaT)	596 (100.0)^d	588 (100.0)^c	1184 (100.0)
Discontinued after treatment with IMP	21 (3.5)	26 (4.4)	47 (4.0)
Adverse Event	0	1 (0.2)	1 (0.1)
Did Not Meet Protocol Eligibility	0	2 (0.3) ^d	2 (0.2)
Lost To Follow-Up	14 (2.3)	20 (3.4)	34 (2.9)
Never Entered Follow Up	2 (0.3) ^e	1 (0.2) ^f	3 (0.3)
Non-Compliance With Protocol	1 (0.2) ^g	0	1 (0.1)
Subject Withdrew Consent	4 (0.7)	2 (0.3)	6 (0.5)
Completed study	575 (96.5)	562 (95.6)	1137 (96.0)

Source data: Sponsor's Clinical Study Report Table 10-1

Reviewer's Comments:

The results from this reviewer's analyses are all consistent with the results reported in Table 1.

Table 2 shows the demographic characteristics using the APaT population. Overall, more female (56%) than male (44%) subjects were enrolled in the trial. The vast majority of the subjects participating in both groups were white and not of Hispanic or Latino ethnicity. The average age of a subject was 67 years, and the average BMI was 27.6.

Table 2 Subjects Demographics and Characteristics using All-Patients-as-Treated Population

Subject Group	Number (%) of Subjects		
	Sugammadex n=596	Usual care n=588	Total n=1184
Sex (n,%)			
Female	326 (55)	340 (58)	666 (56)
Male	270 (45)	248 (42)	518 (44)
Race (n,%)			
White	595 (100)	584 (99)	1179 (100)
Non-White	1 (<1)	4 (1)	5 (<1)
Asian	1 (<1)	3 (1)	4 (<1)
Multiracial	0	1 (<1)	1 (<1)
Ethnicity (n,%)			
Hispanic or Latino	4 (1)	0	4 (<1)
Not Hispanic or Latino	592 (99)	588 (100)	1180 (100)
Age (yrs)			
Mean (SD)	66.7 (12.0)	66.6 (11.3)	66.7 (11.7)
Median	69.0	68.0	68.0
Range	18 - 92	24 - 93	18 - 93
Age (n,%)			
18 - <65	226 (38)	237 (40)	463 (39)
65 or Older	370 (62)	351 (60)	721 (61)
Weight (kg)			
Mean (SD)	79.34 (13.35)	79.09 (13.82)	79.22 (13.58)
Median	80.00	79.00	79.00
Range	43.0 - 117.0	47.0 - 119.0	43.0 - 119.0
Height (cm)			
Mean (SD)	169.30 (9.38)	169.04 (9.02)	169.17 (9.20)
Median	168.00	168.00	168.00
Range	148.0 - 198.0	146.0 - 198.0	146.0 - 198.0
BMI			
Mean (SD)	27.61 (3.65)	27.60 (3.79)	27.61 (3.72)
Median	27.66	27.53	27.63
Range	17.2 - 34.9	16.7 - 37.7	16.7 - 37.7

Source data: Sponsor's Clinical Study Report Table 10-2.

Reviewer's comments

The patient's demographics and other subject characteristics are relatively balanced between 2 groups.

Table 3 shows the distribution of subjects in the APaT population for type of surgery, American Society of Anesthesiologist classification.),

Table 3 Summary of Type of Surgery, ASA Class Between Two Groups (All-Subjects-Treated)

Subject Group	Number (%) of Subjects		
	Sugammadex n=596	Usual Care n=588	Total n=1184
Type of surgery (n,%)			
Hip fracture - intracapsular, dis- and replaced with total hip replacement or hemiarthroplasty	12 (2)	11 (2)	23 (2)
Hip fracture - intracapsular, fixed with internal fixation	6 (1)	7 (1)	13 (1)
Hip revision arthroplasty	33 (6)	32 (5)	65 (5)
Knee revision arthroplasty	28 (5)	29 (5)	57 (5)
Primary total hip arthroplasty	324 (54)	305 (52)	629 (53)
Primary total knee arthroplasty	193 (32)	204 (35)	397 (34)
ASA class (n,%)			
1	92 (15)	69 (12)	161 (14)
2	411 (69)	412 (70)	823 (70)
3	93 (16)	107 (18)	200 (17)

Source data: Table 10-3 of the clinical report.

Reviewer's Comments:

Primary total hip arthroplasty (54% sugammadex, 52% usual care) and primary total knee arthroplasty (32% sugammadex, 35% usual care) were the most frequent types of surgery in both treatment groups; these two types of surgery accounted for more than 86% of all surgeries. The majority of subjects in both treatment groups were American Society of Anesthesiologists (ASA) Class 2 (69% sugammadex, 70% usual care).

Table 4 shows the distribution of subjects in the APaT population for cratinine clearance class, prophylactic antithrombotic therapy, usual care group and country within and across treatment group.

Table 4 Summary of Stratification Variables, Usual Care Group and Country between Two Groups (All-Subjects-Treated)

Subject Group	Number (%) of Subjects		
	Sugammadex n=596	Usual Care n=588	Total n=1184
Creatinine clearance (mL/min)			
Mean (SD)	103.92 (36.99)	102.49 (33.84)	103.22 (35.47)
Median	100.35	98.90	99.51
Range	33.0 - 315.8	33.2 - 246.4	33.0 - 315.8
Missing	26	36	62
Baseline creatinine clearance class, as indicated during randomization (n,%)			
< 60 mL/min	103 (17)	105 (18)	208 (18)
>= 60 mL/min	493 (83)	483 (82)	976 (82)
Prophylactic antithrombotic therapy, as indicated during randomization (n,%)			
Including LMWH	581 (97)	573 (97)	1154 (97)
Including UFH	1 (<1)	0	1 (<1)
Including neither LMWH nor UFH	14 (2)	15 (3)	29 (2)
Usual care group, as indicated during randomization (n,%)			
Active reversal	292 (49)	319 (54)	611 (52)
Spontaneous recovery	304 (51)	269 (46)	573 (48)
Country (n,%)			
Austria	110 (18)	113 (19)	223 (19)
Belgium	94 (16)	84 (14)	178 (15)
Germany	392 (66)	391 (66)	783 (66)

Source data: Table 10-3 of the clinical report.

Reviewer's Comments:

The majority of subjects (82%) had a creatinine clearance \geq 60 mL/min (normal renal function), as indicated during randomization. Almost all the subjects in both treatment groups (97%) received LMWH, as indicated during randomization. There were no notable differences observed across treatment groups for any of these characteristics.

3.3.4 Results and Conclusions

Primary Prespecified Safety Endpoint: adjudicated events of bleeding with onset within 24 hours after administration of trial medication

Reviewer's Comments

This reviewer performed the following statistical analyses on the primary endpoints specified in the protocol (1) Incidence of all major and non-major bleeding events within 24 hours of treatment and up to 14 days of treatment, comparing the Sugammadex and Usual Care groups, as shown in Table 5 and Table 6; (2) Sensitivity Analysis on Primary Endpoint: Adjudicated Events of Bleeding Within 24 Hours of Trial Medication Administration by Creatinine Clearance at Screening (see Table 6) using Poisson regressions.

The results from this reviewer's analyses are all consistent with the results reported in Clinical Study Report (CSR) Chapter 11 by the sponsor. This reviewer found no major statistical issues in this part of analyses.

Table 5 Incidence (n, %) of Subjects with At Least One Suspected Unanticipated Adverse Event of Bleeding (SUAEB) by Adjudicated Onset, Severity, Maximum Relationship, and Treatment Group. (All-Patients-as-Treated Population)

Onset	Maximum Relationship	Sugammadex (N=596)		Usual Care (N=588)	
		Major	Total (Major+Non-major)	Major	Total (Major+Non-Major)
Within 24 Hours	Unlikely	0	1 (0.2%)	2 (0.3%)	3 (0.5%)
	Possible	12 (2.0%)	16 (2.7%)	18 (3.1%)	21 (3.6%)
	Probable	0	0	0	0
	Overall	12 (2.0%)	17 (2.9%)	20 (3.4%)	24 (4.1%)
Total (up to 14 days)	Unlikely	5 (0.8%)	7 (1.2%)	4 (0.7%)	5 (0.9%)
	Possible	13 (2.2%)	17 (2.9%)	19 (3.2%)	22 (3.7%)
	Probable	0	0	0	0
	Overall	18 (3.0%)	24 (4.0%)	23 (3.9%)	27 (4.6%)

Source data: Table 11-1 of the clinical report.

The percentage of subjects who experienced an adjudicated SUAEB with onset within 24 hours of trial medication administration (primary endpoint) was 2.9% in the sugammadex treatment group (17 of 596 subjects) and 4.1% in the usual care group (24 of 588 subjects) (see Table 6). The relative risk of adjudicated events of bleeding within 24 hours of 4 mg/kg sugammadex versus usual care (primary endpoint) was 0.70 with a 95% CI of 0.38 to 1.29 (see Table 6).

Table 6 Analysis of Events of Bleeding Within 24 Hours of Trial Medication Administration
(All-Patients-as-Treated Population)

	Sugammadex (N=596)	Usual Care (N=588)	Relative Risk Sugammadex vs. Usual Care (95% CI)
Adjudicated events of bleeding with onset within 24 hours of trial medication administration	17 (2.9%)	24 (4.1%)	0.70 (0.38, 1.29)
Events of bleeding with onset within 24 hours of trial medication administration according to investigator assessment	20 (3.4%)	31 (5.3%)	0.64 (0.37, 1.11)

Source data: Table 11-2 of the clinical report.

This estimated relative risk for the primary endpoint was consistent with the results of the two prespecified sensitivity analyses of the primary analysis. For the first sensitivity analysis, which was based on SUAEBs according to the investigators' assessment with onset within 24 hours of trial medication administration, the percentage of subjects who experienced an adjudicated SUAEB within 24 hours was 3.4% in the sugammadex treatment group (20 of 596 subjects) and 5.3% in the usual care group (31 of 588 subjects) with an estimated relative risk of 0.64 (95% CI: 0.37 to 1.11; see Table 6). The second prespecified sensitivity analysis using Poisson regression and adjudicated SUAEBs provided an estimated relative risk that was identical to the primary analysis (i.e., 0.70 with a 95% CI of 0.38 to 1.29).

There was no significant interaction of sugammadex use with creatinine clearance at screening (< or ≥ 60 mL/min, p=0.85) on bleeding events based on the prespecified Poisson regression model; the relative risks of an adjudicated SUAEB of sugammadex versus usual care were very similar for subjects with creatinine clearance < 60 mL/min and ≥ 60 mL/min at screening (Table 7). Note that the incidences of adjudicated SUAEBs were higher for subjects with a creatinine clearance < 60 mL/min (5.8% sugammadex, 7.6% usual care) versus subjects with creatinine clearance ≥ 60 mL/min (2.2% sugammadex, 3.3% usual care;) the corresponding estimated relative risk for subjects with creatinine clearance < 60 mL/min versus subjects with creatinine clearance ≥ 60 mL/min was 2.4 (95% CI: 1.3 to 4.5), suggesting that the risk of an adjudicated event of bleeding within 24 hours after trial medication was stopped was notably increased for subjects with a low baseline creatinine clearance irrespective of treatment.

Table 7 Sensitivity Analysis on Primary Endpoint: Adjudicated Events of Bleeding Within 24 Hours of Trial Medication Administration by Creatinine Clearance at Screening (All-Patients-as-Treated Population)

	Sugammadex (N=596)		Usual Care (N=588)		Relative Risk Sugammadex vs. Usual Care (95% CI)	Interaction (p-value)
	N	n(%)	N	n(%)		
Creatinine clearance ≥ 60 mL/min	493	11(2.2%)	483	16(3.3%)	0.67 (0.31, 1.45)	0.85
Creatinine clearance <60 mL/min	103	6(5.8%)	105	8(7.8%)	0.77 (0.27, 2.21)	

Source data: Table 11-3 of the clinical report.

Key Secondary (aPTT) and Secondary (PT and PT (INR)) Prespecified Safety Endpoints

Table 8 shows the summarized analyses results for the key secondary efficacy endpoint. Using aPTT, there was an estimated increase with sugammadex as compared to usual care treatment of 5.5% (95% CI: 3.7% to 7.3%) at 10 minutes after administration of trial medication and of 0.9% (95% CI: -0.9% to 2.8%) at 60 minutes after administration of trial medication (adjusted for baseline aPTT, site, strata, and type of surgery).

For the secondary endpoints of PT and PT(INR), there was an estimated increase in the mean change from baseline with sugammadex versus usual care of 3.0% (95% CI: 1.3% to 4.7%) at 10 minutes after administration of trial medication and of 0.9% (95% CI: -1.0% to 2.9%) at 60 minutes after administration of trial medication (adjusted for baseline aPTT, site, strata, and type of surgery).

Table 8 Key Secondary and Secondary Endpoint Analysis: Difference (95 CI) in APTT and PT (INR) versus by Time Point and for Sugammadex versus Usual Care (All-Patients-as Treated Population)

		Sugammadex (vs Baseline)		Usual Care (vs Baseline)		Difference between Sugammadex and Usual Care	
		Estimate ^a	95% CI ^a	Estimate ^a	95% CI ^a	Estimate ^a	95% CI ^a
aPTT ^b	10 min	4.7%	(3.4%, 5.9%)	-0.8%	(-2.0%, 0.4%)	5.5%	(3.7%, 7.3%)
	60 min	-1.9%	(-3.2%, -0.6%)	-2.8%	(-4.1%, -1.5%)	0.9%	(-0.9%, 2.8%)
PT(INR) ^{b,c}	10 min	4.5%	(3.3% , 5.8%)	1.5%	(0.3%, 2.7%)	3.0%	(1.3%, 4.7%)
	60 min	2.7%	(1.2%, 4.1%)	1.7%	(0.3%, 3.2%)	0.9%	(-1.0%, 2.9%)

aPTT=activated partial thromboplastin time; CI=confidence interval; PT(INR)=prothrombin time (international normalized ratio).

^a Estimates and confidence intervals are geometric means, adjusted for trial center, usual care group (active reversal versus spontaneous recovery), renal function (< or ≥ 60 mL/min), antithrombotic therapy (LWMH/UFH vs. other), surgical procedure (hip fracture, hip or knee replacement/revision, or hip or knee stage 1 revision [total or partia]), and treatment-by-time interaction.

^b A total of 567 subjects treated with sugammadex and 548 treated with usual care contributed to the cLDA analyses with a valid parameter value, both for aPTT as well as for PT(INR).

^c Estimates for PT and INR are identical; values for PT were used in analysis since these were provided with higher precision.

Data Source: Applicant Clinical Study Report: Table 11-4

Reviewer's Comments

In this study, because there are no explicit hypotheses to be tested, no corrections of multiplicity were required for these secondary endpoints.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Reviewer's Comments

To determine whether the results of the primary safety analysis were consistent across various subgroups, this reviewer conducted the descriptive analyses for the primary safety endpoint.

4.1 Gender, Race, Age, and Geographic Region

Reviewer's Subgroup Descriptive Analyses and Comments:

Table 9 shows the reviewer's analysis of the distribution of total bleeding events (major bleeding + non-major bleeding) by gender for both sugammadex group and usual care group. For female, there are 6 (1.9%) subjects with bleeding event in sugammadex group compared with 15 (4.4%) subjects with bleeding event in usual care group

Table 9 Reviewer's Summary of Analyses Results for Primary Efficacy Endpoint by Gender

Major + Non-major bleeding	Sugammadex (N=596)	Usual Care (N=588)
Female	6 (6/325=1.9%)	15 (15/341=4.4%)
Male	11 (11/270=4.1%)	9 (9/248=3.6%)

Table 10 shows the reviewer's analysis of the distribution of total bleeding events (major bleeding + non-major bleeding) by age for both sugammadex group and usual care group.

Table 10 Reviewer's Summary of Analyses Results for Primary Efficacy Endpoint by Age

Major + Non-major bleeding	Sugammadex (N=596)	Usual Care (N=588)
Age 18-65	4 (4/226=1.8%)	6 (6/237=2.5%)
Age 65 years or older	13 (13/369=3.5%)	18 (18/352=5.1%)

4.2 Other Special/Subgroup Populations

Table 11 shows the reviewer's analysis of the distribution of total bleeding events (major bleeding + non-major bleeding) by usual care group, as indicated during randomization, for both sugammadex group and usual care group.

Table 11 Reviewer's Summary of Analyses Results for Primary Efficacy Endpoint

Major + Non-major bleeding	Sugammadex (N=596)	Usual Care (N=588)
Active Reversal (usual care group 1)	7 (7/291=2.4%)	12 (12/320=3.8%)
Spontaneous Recovery (usual care group 2)	10 (10/304=3.3%)	12 (12/269=4.5%)

Table 12 shows the reviewer's analysis of the distribution of total bleeding events (major bleeding + non-major bleeding) by baseline creatinine clearance class for both sugammadex group and usual care group.

Table 12 Reviewer's Summary of Analyses Results for Primary Efficacy Endpoint by Creatinine Clearance Class

Major + Non-major bleeding	Sugammadex (N=596)	Usual Care (N=588)
Renal \geq 60 ML/MIN	6 (6/103=5.8%)	8 (8/105=7.6%)
Renal $<$ 60 ML/MIN	11 (11/492=2.2%)	16 (16/484=3.3%)

Table 13 shows the reviewer’s analysis of the distribution of total bleeding events (major bleeding + non-major bleeding) by location of the surgery for both sugammadex group and usual care group.

Table 13 Reviewer’s Summary of Analyses Results for Primary Efficacy Endpoint by Location of the Surgery

Major +Non-major	Sugammadex (N=596)	Usual Care (N=588)
Surglocation Hip	7 (7/375=1.9%)	12 (12/355=3.4%)
Surglocation Knee	10 (10/220=4.6%)	12 (12/234=5.1%)

5 SUMMARY AND CONCLUSIONS

This is a resubmission with sponsor’s response to the Complete Response Letter from FDA dated July 31, 2008 for NDA 22-225. The letter stated the following assessment would be required in a re-submission:

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

The Division of Hematology Products is being consulted by the Division of Neurological Products to review Study P07038 to determine whether or not the data submitted from the study address the concern for a potential increase in the frequency of bleeding related to the use of SU

Subsequently, the sponsor provided additional in vitro data and proposal for clinical studies to address this safety concern. This submission includes a complete study report (CSR) and datasets for study p07038: a randomized, controlled, parallel-group, double-blind trial of sugammadex or usual care (neostigimine) to assess the incidence of bleeding in patients who were undergoing major orthopedic surgery and who were to receive thromboprophylaxis with heparin or low molecular weight heparin. The primary safety endpoint is the proportion of subjects with at least one adjudicated, major or non-major , unanticipated adverse event (AE) of bleeding with onset within 24 hours of trial medication administration. The primary safety analysis was to be performed on the All-Patients-as-Treated (APaT) population. The primary trial objective was to be addressed by using the Cochran-Mantel-Haenszel (CMH) method to estimate the relative risk stratified for renal function and type of prophylactic antithrombotic treatment. The analysis results showed the percentage of subjects who experienced an adjudicated unanticipated adverse event of bleeding with onset within 24 hours of trial medication administration was 2.9 in the sugammadex treatment group and 4.1% in the usual care group. the relative risk of adjudicated events of bleeding within 24 hours of 4 mg/kg sugammadex versus usual care for the primary safety endpoint was 0.70 with a 95% CI of 0.38 to 1.29. The results demonstrated that the treatment with sugammadex was not associated with an increased bleeding risk in comparison to

usual care. This reviewer's analysis results were consistent with the sponsor's results for the primary safety endpoint.

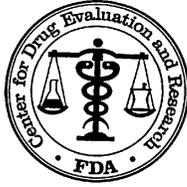
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

QING XU
08/30/2013

LEI NIE
08/30/2013

RAJESHWARI SRIDHARA
08/30/2013



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #: 22-225
Supplement #: 46
Drug Name: Sugammadex sodium injection
Indication(s): Routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at 3 minutes after administration of rocuronium
Applicant: Organon USA Inc.
Date(s): Letter date: December 20, 2012
PDUFA date: September 20, 2013
Review Priority: Priority
Biometrics Division: II
Statistical Reviewer: Yan Zhou, Ph.D.
Concurring Reviewer: Janice Derr, Ph.D.
Medical Division: Division of Anesthesia , Analgesia, and Addiction Products
Clinical Team: Medical Officer: Arthur Simone, M.D.
Medical Team Leader: Christopher Breder, M.D.
Deputy Division Director: Rigoberto Roca, M.D.
Project Manager: Diana Walker, Ph.D.
Keywords: NDA review, clinical studies

Table of Contents

1. EXECUTIVE SUMMARY	4
2. INTRODUCTION	4
2.1 OVERVIEW.....	4
2.2 DATA SOURCES	5
3. STATISTICAL EVALUATION	6
3.1 DATA AND ANALYSIS QUALITY	6
3.2 EVALUATION OF EFFICACY	6
3.3 EVALUATION OF SAFETY	10
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	10
4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION	10
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	11
5. SUMMARY AND CONCLUSIONS	11
5.1 STATISTICAL ISSUES	11
5.2 COLLECTIVE EVIDENCE.....	11
5.3 CONCLUSIONS AND RECOMMENDATIONS	11
5.4 LABELING RECOMMENDATIONS	11
APPENDIX	17

LIST OF TABLES

Table 1: List of the study included in this review.....	5
Table 2: Subjects' disposition.....	7
Table 3: Summary statistics of the T_4/T_1 at tracheal extubation.....	9
Table 4: Frequency table of the T_4/T_1 at tracheal extubation	9
Table 5: Primary analysis results.....	9
Table 6: For secondary efficacy variable: recovery time of the T_4/T_1 ratio to 0.9 (minute: second)	10
Table 7: Reviewer's subgroup analyses	10

1. EXECUTIVE SUMMARY

Organon has resubmitted a New Drug Application (NDA) for Sugammadex sodium injection seeking an indication for routine reversal of moderate or deep neuromuscular blockade (NMB) induced by rocuronium or vecuronium and immediate reversal of NMB at 3 minutes after administration of rocuronium. I conclude that the study provides additional evidence of efficacy of Sugammadex in comparison to neostigmine.

The resubmission contained 10 additional efficacy studies that have been conducted since the original NDA submission. To provide additional evidence of efficacy, one study (Study 194334) was added to the previous labeling in the original NDA submission. This review focuses only on Study 194334 which was a randomized, multi-center, parallel group, active controlled, safety-assessor blinded, anesthesiologist-train of four (TOF)-Watch SX blinded study to demonstrate superiority of Sugammadex over neostigmine in subjects undergoing elective open abdominal procedures.

The primary efficacy endpoint was the ratio of T_4 to T_1 at tracheal extubation. Secondary efficacy variables were the time from start of administration of the investigational medicinal product (IMP) to recovery of the T_4/T_1 ratio to 0.9, the time from start of administration of the IMP to recovery of the T_4/T_1 ratio to 0.8, and the time from start of administration of the IMP to recovery of the T_4/T_1 ratio to 0.7.

In addition to the summary statistics of the T_4/T_1 ratio, the primary analysis utilized a Chi-square test to analyze the binary variable “ T_4/T_1 ratio < 0.9” at the time of tracheal extubation. The applicant applied the 5th and 95th percentile of observed T_4/T_1 ratios within the group to impute missing values of the T_4/T_1 ratio in the Sugammadex group and neostigmine group respectively. In my opinion, this method is reasonable as it did not assign any treatment benefit to subjects with missing values. In three efficacy studies (Study 301, Study 302 and Study 310) in the original NDA submission, the primary efficacy endpoint was defined as the recovery time of the T_4/T_1 ratio to 0.9. To be consistent and seek additional evidence of efficacy, I also analyzed the secondary efficacy variable “the time from start of administration of the IMP to recovery of the T_4/T_1 ratio to 0.9” using an analysis of variance (ANOVA) model. The missing data of recovery times were imputed by a strategy that a worst-case scenario was applied to the Sugammadex group and a best-case scenario was applied to the neostigmine group. This imputation method did not assign any treatment benefit to subjects with missing values.

Based on my review, I conclude that Sugammadex is effective in reversing neuromuscular blockade induced by rocuronium when compared to neostigmine.

2. INTRODUCTION

2.1 Overview

When the surgical procedure is complete, reversal agents are often given to accelerate the recovery of drug-induced NMB. Neostigmine is frequently used for this purpose. However, it

can result in adverse cardiovascular and respiratory effects. Sugammadex is a new type of agent for the reversal of NMB. It might offer the possibility of quick reversal in situations where blockade has become dangerous. In October 2007, Organon submitted the original NDA for Sugammadex sodium injection to seek the indication of reversing NMB produced by rocuronium or vecuronium. The submitted efficacy studies provided ample evidence that Sugammadex is effective in reversing NMB, but there existed two safety issues: (1) potential hypersensitivity reactions after Sugammadex administration and (2) possible effects of Sugammadex on coagulation. These two issues were outlined as reasons for the Not-Approval decision in the Not-Approvable letter issued by the Food and Drug Administration (FDA) on July 31, 2008. In the Not-Approvable letter, the FDA also provided comments and requests that were related to cardiac arrhythmias, corrected QT interval prolongation, special populations with renal failure or hepatic impairment, related safety and efficacy trials in pediatric populations, and additional preclinical work. Subsequently, the sponsor and the FDA had several interactions and communications in which an agreement was reached on the scope of additional data required to address the Not-Approvable issues as well as some of the additional studies recommended by the FDA. These data have currently been resubmitted as a complete response to the deficiencies outlined in the Not-Approvable letter.

The resubmission contained 10 additional efficacy studies that have been conducted since the original submission. To provide additional evidence of efficacy, one study (Study 194334) was added into the previous labeling in the original NDA submission. The study was a randomized, multi-center, parallel group, active controlled, safety-assessor blinded, anesthesiologist-TOF-Watch SX blinded study to demonstrate superiority of Sugammadex over neostigmine in subjects undergoing elective open abdominal procedures.

Study 194334 was conducted from May 2008 to September 2008 at 10 centers in the United States. My statistical review focuses only on this study.

Table 1: List of the study included in this review

Study Number (Dates Conducted)	Number of Centers (Locations)	Sample Size	Type of Control	Design
194334 (05/2008 – 09/2008)	US: 10 sites	Randomization: Sugammadex n=54 Neostigmine n=52	Neostigmine	Randomized, active-controlled, multicenter, parallel group, safety-assessor blinded, anesthesiologist-TOF- Watch SX blinded

Source: Reviewer's analysis

2.2 Data Sources

All data was supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room:

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The electronic data submitted by the applicant was of sufficient quality to allow a thorough review. I was able to locate the primary outcome as well as the secondary variables of interest.

3.2 Evaluation of Efficacy

My review focuses on the Study 194334 which was a part of the current resubmission of NDA.

Study Design and Endpoints

The primary objective of Study 194334 was to compare the incidence of residual NMB at the time of tracheal extubation between the 4 mg/kg Sugammadex and the 50 µg/kg neostigmine group, while the NMB was induced by rocuronium bromide.

The study enrolled 114 adult subjects from 10 sites in the United States. Subjects underwent elective open abdominal surgical procedures that require general anesthesia. The surgical procedures were mainly gastrointestinal, gynecological, hernia repairs, or urological in nature. One hundred and six eligible subjects were randomly assigned to the Sugammadex or neostigmine group. Subjects received a single intubating bolus dose of 0.6 mg/kg rocuronium and maintenance dose(s) of 0.15 mg/kg rocuronium as necessary. At the end of the surgical procedure, the NMB was reversed with a single bolus dose of 4 mg/kg Sugammadex at 1-2 post tetanic counts (PTCs) after the last dose of rocuronium or with a single bolus dose of 50 µg/kg neostigmine administered as per standard care.

The primary efficacy endpoint was the T_4/T_1 ratio at tracheal extubation. Secondary efficacy endpoints were time from start of administration of the IMP to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 respectively. The T_4/T_1 ratio of 1 was defined as complete recovery from NMB, and the T_4/T_1 ratio of less than 0.9 was defined as residual paralysis.

Patient Disposition, Demographic and Baseline Characteristics

The demographic and baseline characteristics for all treated subjects are presented in the appendix. The majority of the subjects were white (86%), and approximately 60% of all subjects were female. The mean age was 51 years.

The disposition of subjects is shown in Table 2. A total of 114 subjects enrolled in the study, of which 106 subjects were randomized and 100 subjects were treated. A total of 54 subjects were randomized to take a dose of Sugammadex 4.0 mg/kg and 52 subjects were randomized to take a dose of neostigmine 50 µg/kg.

Table 2: Subjects' disposition

	Not treated	4.0 mg/kg Sugammadex	50 µg/kg Neostigmine	Total
Enrolled	8	54	52	114
Randomized	0	54	52	106
Treated	NA	51	49	100
Completed	NA	51	49	100

Source: Reviewer's Analysis

NA: not applicable

Eight subjects agreed to participate and sign the informed consent form but were not randomized because of the following reasons: unable to complete the post-anesthetic visit (102013), the Web Randomization System malfunctioned (105003), the subject's medical insurance would not pay for the cost of surgical procedure (106006), the subject had neuromuscular disorder (110002), withdrew consent to participate (110003), the surgeon decided to perform a laparoscopic procedure (111004) and the BMI was $\geq 35 \text{ kg/m}^2$ (111007, 111016).

Six subjects agreed to participate and sign the informed consent form, were randomized but the investigator decided to terminate the subjects' participation because of the following reasons: unable to perform neuromuscular transmission monitoring because of the subjects' position during the surgical procedure (102005, 102011), unable to calibrate the TOF-Watch SX device (109002), withdrew consent to participate (109003), unable to complete the post-anesthetic visit (110008), and occurrence of pre-treatment events (111010). All other 100 treated subjects completed the study.

Statistical Methodologies

In addition to the summary statistics of the primary efficacy variable, the binary variable "T₄/T₁ ratio < 0.9 at time of tracheal extubation" was compared between two treatment groups using a Chi-square test. The primary analysis population was the intention-to-treat (ITT) population which included all randomized subjects who received Sugammadex or neostigmine and had at least one efficacy measurement.

The applicant used the following strategies to impute the missing data for the T₄/T₁ ratio. For subjects in the Sugammadex group, their missing T₄/T₁ ratios were imputed by the 5th percentile of observed T₄/T₁ ratios within the group. While for subjects in the neostigmine group, their missing T₄/T₁ ratios were imputed by the 95th percentile of observed T₄/T₁ ratios within the group. As the lower values of the T₄/T₁ ratio represent worse effects of reversing NMB, the primary imputation method used a bad score to impute the missing values of the T₄/T₁ ratio for subjects in the Sugammadex group. In my opinion, the primary imputation was a reasonable method because it did not attribute any treatment benefit to subjects with missing values.

In the original NDA submission, the recovery time of the T₄/T₁ ratio to 0.9 was the primary efficacy endpoint in three efficacy studies (Study 301, Study 302 and Study 310). To be consistent and seek additional evidence of efficacy, I also analyzed the secondary efficacy variable "the time from start of administration of the IMP to recovery of the T₄/T₁ ratio to 0.9" using an ANOVA model. Treatment, center and their interaction effects were detected in the

ANOVA model. The missing data of recovery times were imputed by a strategy that a worst-case scenario was applied to the Sugammadex group and a best-case scenario was applied to the neostigmine group. Again, this imputation method did not assign any treatment benefit to subjects with missing values. The imputation method was described as follows:

Suppose that for a subject the time from the start of administration of IMP to recovery of the T_4/T_1 ratio to 0.9 (secondary efficacy variable) was missing. For imputation three cases were of importance, namely:

1. Time to T_4/T_1 ratio to 0.8 is available:

Sugammadex group: first calculate for all subjects randomized to receive sugammadex and with times to recovery of the T_4/T_1 ratio to 0.8 and 0.9 available, the difference in time between these two recovery times. Next, add the 95th percentile (P95) of these differences to the time to recovery of the T_4/T_1 ratio to 0.8 of the subjects with missing times to recovery of the T_4/T_1 ratio to 0.9. This will be used as imputation of the missing time to recovery of the T_4/T_1 ratio to 0.9.

Neostigmine group: same as for sugammadex group but now use only subjects randomized to receive neostigmine and calculate the 5th percentile (P5) of the differences in time to recovery of the T_4/T_1 ratio to 0.8 and 0.9.

2. Time to T_4/T_1 ratio to 0.7 is available, but the time to T_4/T_1 ratio to 0.8 is missing:

Sugammadex group: first calculate for all subjects randomized to sugammadex and with times to recovery of the T_4/T_1 ratio to 0.7 and 0.9 available, the difference in time between these two recovery times. Next, add the P95 of these differences to the time to recovery of the T_4/T_1 ratio to 0.7. This will be used as imputation of the missing time to recovery of the T_4/T_1 ratio to 0.9.

Neostigmine group: same as for sugammadex group but now use only subjects randomized to receive neostigmine and calculate the P5 of the differences in time to recovery of the T_4/T_1 ratio to 0.7 and 0.9.

3. Times to T_4/T_1 ratio to 0.7 and to 0.8 are both missing:

Sugammadex group: impute the P95 of the time to recovery of the T_4/T_1 ratio to 0.9 observed in all subjects randomized to receive sugammadex.

Neostigmine group: impute the P5 of the time to recovery of the T_4/T_1 ratio to 0.9 observed in all subjects randomized to receive neostigmine.

Results and Conclusions

Of 100 randomized and treated subjects, three subjects in the neostigmine group did not have at least one efficacy measurement. Therefore, the ITT analysis set included 97 subjects (51 subjects in the Sugammadex group and 46 subjects in the neostigmine group).

Table 3 and Table 4 show the results of summary statistics for the T_4/T_1 ratio. Two sets of analyses were presented: imputed data and complete cases for the ITT analysis set. Table 5 shows the results of primary efficacy analyses. My results confirmed the applicant's results. Both two treatment groups had the same number of subjects with the missing values for the T_4/T_1 ratio. The median T_4/T_1 ratio at tracheal extubation was 1.00 in the Sugammadex group when missing data were imputed and 1.03 for the complete cases. The median T_4/T_1 ratio at tracheal extubation was 0.87 in the neostigmine group when missing data were imputed and 0.76 for the complete cases. The results also show that there was a high incidence of residual NMB (T_4/T_1 ratio < 0.9)

at tracheal extubation in the neostigmine group compared with the Sugammadex group. With the imputed data for the missing T_4/T_1 ratio, it was indicated that Sugammadex was statistically significantly different from neostigmine.

Table 3: Summary statistics of the T_4/T_1 ratio at tracheal extubation

	Complete Cases		Including imputed data	
	Sugammadex	Neostigmine	Sugammadex	Neostigmine
N	43	38	51	46
Mean (SD)	1.03 (0.15)	0.73 (0.24)	1.02 (0.15)	0.78 (0.24)
Median	1.03	0.76	1.00	0.87
Min - Max	0.38 - 1.41	0.13 - 1.06	0.38 - 1.41	0.13 - 1.06

Source: Clinical Study Report Table 10 and Reviewer's Analyses

Table 4: frequency table of the T_4/T_1 ratio at tracheal extubation

	Complete Cases		Including imputed data	
	Sugammadex	Neostigmine	Sugammadex	Neostigmine
N	43	38	51	46
<= 0.6	1 (2%)	10 (26%)	1 (2%)	10 (22%)
(0.6, 0.7]	0 (0%)	5 (13%)	0 (0%)	5 (11%)
(0.7, 0.8]	0 (0%)	5 (15%)	0 (0%)	5 (11%)
(0.8, 0.9)	1 (2%)	6 (16%)	1 (2%)	6 (13%)
>= 0.9	41 (95%)	12 (32%)	49 (96%)	20 (43%)

Source: Clinical Study Report Table 11 and Reviewer's Analyses

Table 5: Primary analysis results

	Including imputed data	
	Sugammadex	Neostigmine
N	51	46
< 0.9	2 (4%)	26 (57%)
>= 0.9	49 (96%)	20 (43%)

Source: Reviewer's Analysis

Note: P-value < 0.0001 using Fisher-exact test

To further assess the efficacy of Sugammadex, I also analyzed the secondary efficacy variable “the time from start of administration of the IMP to recovery of the T_4/T_1 ratio to 0.9”. The results are shown in the Table 6. Twenty nine subjects (2 in the Sugammadex group and 27 in the neostigmine group) had missing times with respect to the recovery of the T_4/T_1 ratio to 0.9. The reasons for these missing times were: the T_4/T_1 ratio never reached 0.9, the time to recovery of the T_4/T_1 ratio to 0.9 was not measured, or the time to the T_4/T_1 ratio of 0.9 was considered unreliable by the Central Independent Adjudication Committee. Two sets of analyses were presented: imputed data and complete cases for the ITT group. The median time from administration of Sugammadex to recovery of the T_4/T_1 ratio to 0.9 was 2 minutes and 5 seconds when missing data were imputed and 2 minutes and 2 seconds for the complete cases. The median time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.9 was 5 minutes and 43 seconds when missing data were imputed and 6 minutes and 48 seconds for the complete cases. In the ANOVA model, the interaction term between treatment and site was not

statistically significant, and Sugammadex was statistically significantly different from neostigmine.

Table 6: For secondary efficacy variable: recovery time of the T4/T1 ratio to 0.9 (minute: second)

	Complete Cases		Including imputed data	
	Sugammadex	Neostigmine	Sugammadex	Neostigmine
N	49	19	51	46
Mean (SD)	2:28 (1:09)	9:36 (6:44)	2:32 (1:11)	7:57 (6:55)
Median	2:02	6:48	2:05	5:43
Min - Max	0:44 – 5:21	1:17 – 23:11	0:44 – 5: 21	1:17 – 23:11
LS Means (SE)	-	-	2:54 (0:45)	8:27 (0:47)
P-value	-	-		< 0.0001

Source: Clinical Study Report Table 16 and Reviewer’s Analysis

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by Dr. Arthur Simone. The reader is referred to Dr. Simone’s review for detailed information regarding the adverse event profile.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant did not conduct any subgroup analyses. I conducted subgroup analyses for the secondary efficacy variable “the time from start of administration of the IMP to recovery of the T₄/T₁ ratio to 0.9”. My subgroup analyses did not reveal any issues that were concerning.

4.1 Gender, Race, Age, and Geographic Region

Table 7 presents exploratory analyses for the secondary endpoint by gender. I utilized the same ANOVA model as in the analysis of the secondary efficacy variable with additional terms for gender and its interaction with treatment. There was no statistically significant interaction between treatment and gender. Race was not included in the assessment of subgroups because the majority of the study population (86%) was white. Age was not included because all subjects in the study were younger than 65 years. Region was also not included because all subjects were from the US.

Table 7: Reviewer's subgroup analyses

Endpoint	Sugammadex		Neostigmine	
	n	Mean (SD)	n	Mean (SD)
Time to recovery of the T₄/T₁ ratio to 0.9 (minutes: second)				
Gender				
Female	29	2:33 (1:02)	28	8:06 (7:26)
Male	22	2:31 (1:23)	18	7:43 (6:14)

Source: Reviewer’s analysis

4.2 Other Special/Subgroup Populations

No other subgroup analyses were requested by Dr. Simone.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Study 194334 was a superiority study which was designed to and did show statistically significant differences between Sugammadex and the active comparator neostigmine. The number of missing values for the primary efficacy endpoint was balanced between two treatment groups. The applicant applied the 5th and 95th percentile of observed T₄/T₁ ratios within the group to impute missing values of the T₄/T₁ ratio in the Sugammadex group and neostigmine group respectively. As the lower values of the T₄/T₁ ratio represent worse effects of reversing NMB, the primary imputation used a bad score to impute the missing values of the T₄/T₁ ratio for subjects in the Sugammadex group. In my opinion, the primary imputation was a reasonable method because it did not attribute any treatment benefit to subjects with missing values.

The secondary efficacy variable “the time from start of administration of the IMP to recovery of the T₄/T₁ ratio to 0.9” was also reviewed to seek additional evidence of efficacy. The missing data of recovery times were imputed by a strategy that a worst-case scenario was applied to the Sugammadex group and a best-case scenario was applied to the neostigmine group. This imputation method did not assign any treatment benefit to subjects with missing values.

5.2 Collective Evidence

The efficacy studies reviewed in the original NDA 22-225 along with the efficacy study reviewed in the current resubmission provide ample evidence that Sugammadex is effective to reverse NMB.

5.3 Conclusions and Recommendations

Based on my review, I conclude that Sugammadex is effective in reversing neuromuscular blockade produced by rocuronium.

5.4 Labeling Recommendations

The applicant submitted the draft wording that has been revised since the original submission. I have the following comments for Section 14.1 and 14.2. My comments and suggestions follow the applicant’s proposed wording and are italicized and bolded.

14 CLINICAL STUDIES

14.1 (b) (4)

(b) (4)

1. Comparative Study of [TRADENAME] versus Neostigmine as a Reversal Agent (b) (4)
Neuromuscular Blockade Induced (b) (4) *by Rocuronium or Vecuronium at 1-2 PTCs*

A multicenter, randomized, parallel-group, comparative, active-controlled, safety-assessor blinded study comparing [TRADENAME] and neostigmine enrolled 157 patients (86 women and 71 men, (b) (4) and the median ages (b) (4) 54 and 56 years. (b) (4) Patients underwent elective (b) (4) surgical procedures (b) (4) general anesthesia. The surgical procedures were mainly abdominal (gynecological, colorectal, urological), orthopedic, reconstructive, or neurological (b) (4). Patients were randomly assigned to the rocuronium or vecuronium group. (b) (4) at 1-2 PTCs, 4 mg/kg [TRADENAME] or 70 mcg/kg neostigmine was administered in a randomized order as a single bolus injection. The time from start of administration of [TRADENAME] or neostigmine to recovery of the T₄/T₁ ratio to 0.9 was assessed.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2. Comparative Study of [TRADENAME] versus Neostigmine as a Reversal Agent of Neuromuscular Blockade Induced by Rocuronium or Vecuronium at Reappearance of T₂

A multicenter, randomized, parallel-group, (b) (4) active-controlled, safety-assessor blinded study comparing [TRADENAME] and neostigmine enrolled 189 patients (87 women and 102 men, (b) (4) ASA class 1 and 2, and the median ages (b) (4) were 50 and 51 years, (b) (4) Patients underwent elective (b) (4) surgical procedures (b) (4) general anesthesia. The surgical procedures were mainly endocrine, ocular, ENT, abdominal (gynecological, colorectal, urological) orthopedic, vascular, or dermatological in nature. Patients were randomly assigned to the rocuronium or vecuronium group. (b) (4) at the reappearance of T₂, 2 mg/kg [TRADENAME] or 50 mcg/kg neostigmine was administered in a randomized order as a single bolus injection. The time from start of administration of [TRADENAME] or neostigmine to recovery of the T₄/T₁ ratio to 0.9 was assessed.

(b) (4)

and ASA class 2, and the median ages in the [TRADENAME] and neostigmine groups were 49

(b) (4)

(b) (4)

(b) (4)

(b) (4)
study in 110 patients (64 women and 46 men,
class 1 and 2, and the median age was 43 years)

(b) (4)

Patients underwent surgical procedures under general anesthesia requiring a short duration of neuromuscular relaxation (b) (4)

. The laparoscopic or open surgical procedures were mainly gynecological, orthopedic, or reconstructive (b) (4) Recovery to T₁ of 10% (b) (4)

(b) (4)

Recovery to T₁ of 10% (relative to the time of administration of rocuronium or succinylcholine) was faster in the rocuronium/[TRADENAME] group compared with succinylcholine alone (Table 8).

Table 8: Time (minutes) from Start of Administration of Rocuronium or Succinylcholine to Recovery of T₁ to 10%

	Treatment Regimen	
	Rocuronium (1.2 mg/kg) and [TRADENAME] (16 mg/kg)	Succinylcholine (1 mg/kg)
N	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median (Range)	4.2 (3.5 – 7.7)	7.1 (3.8 – 10.5)



(b) (4)

The above is accurate and consistent with the study report.

Appendix

Summary of Demographics and Baseline Characteristics

Study 194334 (Source: Clinical Study Report Table 8)

Parameter	Statistic	Treatment group		Total (N=100)
		4.0 mg/kg sugammadex (N=51)	50 µg/kg neostigmine (N=49)	
Age (yrs)	N	51	49	100
	Mean (SD)	49 (11)	52 (9)	51 (10)
	Median	51	54	53
	Min. - max.	24 - 65	28 - 65	24 - 65
Weight (kg)	n	51	49	100
	Mean (SD)	75 (16)	80 (13)	77 (15)
	Median	79	77	78
	Min. - max.	48 - 110	59 - 107	48 - 110
Height (cm)	n	51	49	100
	Mean (SD)	171 (10)	169 (10)	170 (10)
	Median	170	168	170
	Min. - max.	150 - 196	150 - 191	150 - 196
Gender (n (%))	Female	29 (57)	31 (63)	60 (60)
	Male	22 (43)	18 (37)	40 (40)
Race (n (%))	White	44 (86)	42 (86)	86 (86)
	Black	3 (6)	2 (4)	5 (5)
	Asian	1 (2)	1 (2)	2 (2)
	Other	3 (6)	4 (8)	7 (7)
Ethnicity (n (%))	Hispanic or Latino	2 (4)	2 (4)	4 (4)
	Not Hispanic or Latino	49 (96)	47 (96)	96 (96)
ASA Class (n (%))	1	3 (6)	8 (16)	11 (11)
	2	37 (73)	33 (67)	70 (70)
	3	11 (22)	8 (16)	19 (19)
	4	0 (0)	0 (0)	0 (0)

Signature/Distribution List

Primary Statistical Reviewer: Yan Zhou, Ph.D.
Mathematical Statistician

Concurring Reviewer: Janice Derr, Ph.D.
Team Leader

Date: August 21, 2013

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

/s/

YAN ZHOU
08/22/2013

JANICE A DERR
08/22/2013



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Stability Studies

NDA/Serial Number: 22-225/000
Drug Name: Bridion (sugammadex sodium) 100 mg/mL
Solution for Injection
Indication: Reversal of Shallow or Profound
Neuromuscular Blockage
Applicant: Organon
Date: October 30, 2007
Classification: Priority
Statistical Reviewer: Roswitha Kelly, M.S., OTS/OB/DB6
Concurring Reviewer: Yi Tsong, Ph.D., OTS/OB/DB6
Medical Division: Division of Anesthesia, Analgesia, and
Rheumatology Products
Chemistry Reviewer: Alan Schroeder, Ph.D., OPS/ONDAQ/DPA1
Chemistry Branch Chief: Ali Al-Hakim, Ph. D., OPS/ONDAQ/DPA
Project Manager: Allison Meyer, OND/ONDEII/DAARP

Keywords: Bridion Injection, drug product stability, non-linear shelf life estimation

Distribution: NDA 22-225/Bridion Injection

OND/ONDEII/DAARP/A. Meyer

ONDQA/A. Schroeder, Ph.D./A. Al-Hakim, Ph.D.

OTS/OB/DB6/R. Kelly/Y. Tsong, Ph.D./S. Machado, Ph.D./E. Nevius, Ph.D./R. Tiwari, Ph.D.

File directory: My Documents/N22225_stab_6.doc

Table of Contents

1. EXECUTIVE SUMMARY	6
1.1. Conclusions and Recommendations	6
1.2. Brief Overview of Stability Studies	6
1.3. Statistical Issues and Findings	7
2. INTRODUCTION	8
2.1. Overview	8
2.2. Data Sources	9
3. STATISTICAL EVALUATION	9
3.1. The Drug Product	9
3.1.1. Sponsor's Results	10
3.1.2. Reviewer's Results	11
4. STATISTICAL ISSUES	16
5. CONCLUSION	17
6. ACKNOWLEDGEMENTS	18
7. APPENDIX	19
7.1. Reviewer's Linear Analysis Results for Primary Batches from Oss, the Netherlands	19
7.2. Reviewer's Linear Analysis Results for Supportive Batches from Oss, the Netherlands	37

Table of Tables

Table 1: Summary Results of Shelf Life Estimation for Primary Stability Data from Oss, the Netherlands	12
Table 2: Summary Results of Shelf Life Estimation for Supporting Stability Data from Oss, the Netherlands	13
Table 3: Shelf Life Estimation Based on Degradant Stability Data from Swords, Ireland.	15
Table 4: Shelf Life Estimation Based on C_Org25969 Assay for Primary Batches from Oss, 2mL	19
Table 5: Shelf Life Estimation Based on C_Org25969 Assay for Primary Batches from Oss, 5mL	20
Table 6: Shelf Life Estimation Based on Total Assay for Primary Batches from Oss, 2mL	21
Table 7: Shelf Life Estimation Based on Total Assay for Primary Batches from Oss, 5mL	22
Table 8: Shelf Life Estimation Based on Degradant (b) (4) for Primary Batches at Oss, 2mL	23
Table 9: Shelf Life Estimation Based on Degradant (b) (4) for Primary Batches at Oss, 5mL	24

Table 10: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches at Oss, 2mL	25
Table 11: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches at Oss, 5mL	26
Table 12: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches at Oss, 2mL	27
Table 13: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) Primary Batches at Oss, 5mL	29
Table 14: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches from Oss, 2mL.....	31
Table 15: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches from Oss, 5mL.....	32
Table 16: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches from Oss, 2mL.....	33
Table 17: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for Primary Batches from Oss, 5mL.....	34
Table 18: Shelf Life Estimation Based on Total Degradation for Primary Batches from Oss, 2mL.....	35
Table 19: Shelf Life Estimation Based on Total Degradation for Primary Batches from Oss, 5mL.....	36
Table 20: Shelf Life Estimation Based on C_Org25969 Assay for Supporting Batches from Oss, 2mL.....	37
Table 21: Life Estimation Based on C_Org25969 Assay for Supporting Batches from Oss, 5mL.....	38
Table 22: Shelf Life Estimation Based on Total Assay for Supporting Batches from Oss, 2mL.....	39
Table 23: Shelf Life Estimation Based on Total Assay for Supporting Batches from Oss, 5mL.....	40
Table 24: Life Estimation Based on Degradant [REDACTED] (b) (4) 2 for Supporting Batches from Oss, 2mL	41
Table 25: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 5mL	42
Table 26: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 2mL	43
Table 27: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 5mL	44
Table 28: : Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 2mL	45
Table 29: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 5mL	47
Table 30: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 2mL	49
Table 31: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 5mL	50
Table 32: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batches from Oss, 2mL.....	51

Table 33: Life Estimation Based on Degradant (b) (4) for Supporting Batches from Oss, 5mL	52
Table 34: Life Estimation Based on Total Degradants for Supporting Batches from Oss, 2mL	53
Table 35: Life Estimation Based on Total Degradants for Supporting Batches from Oss, 5mL	54

Table of Figures

Figure 1: Shelf Life Estimation for C_Org25969 Assay from a Primary Batch from Oss, 2mL	19
Figure 2: Life Estimation for C_Org25969 Assay from a Primary Batch from Oss, 5mL	20
Figure 3: Life Estimation for Total Assay from a Primary Batch from Oss, 2mL	21
Figure 4: Life Estimation for Total Assay from Pooled Primary Batches from Oss, 5mL	22
Figure 5: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 2mL	23
Figure 6: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 5mL	24
Figure 7: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 2mL	25
Figure 8: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 5mL	26
Figure 9: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 2mL	27
Figure 10: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch with Almost Zero Slope at Oss, 2mL	28
Figure 11: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch at Oss, 5mL	29
Figure 12: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch with Almost Zero Slope at Oss, 5mL	30
Figure 13: Shelf Life Estimation Based on Degradant (b) (4) for the Pooled Primary Batches from Oss, 2mL	31
Figure 14: Shelf Life Estimation Based on Degradant (b) (4) 1 for the Pooled Primary Batches from Oss, 5mL	32
Figure 15: Shelf Life Estimation Based on Degradant (b) (4) for the Pooled Primary Batches from Oss, 2mL	33
Figure 16: Shelf Life Estimation Based on Degradant (b) (4) for a Primary Batch from Oss, 5mL	34
Figure 17: Shelf Life Estimation Based on Total Degradation for a Primary Batch from Oss, 2mL	35

Figure 18: Shelf Life Estimation Based on Total Degradation for a Primary Batch from Oss, 5mL	36
Figure 19: Life Estimation Based on C_Org25969 Assay for a Supporting Batch from Oss, 2mL	37
Figure 20: Life Estimation Based on C_Org25969 Assay for a Supporting Batch from Oss, 5mL	38
Figure 21: Life Estimation Based on Total Assay for a Supporting Batch from Oss, 2mL	39
Figure 22: Life Estimation Based on Total Assay for a Supporting Batch from Oss, 5mL	40
Figure 23: Shelf Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 2mL	41
Figure 24: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 5mL	42
Figure 25: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 2mL	43
Figure 26: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 5mL	44
Figure 27: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batch 708682001 from Oss, 2mL	45
Figure 28: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batch 708683001 from Oss, 2mL*	46
Figure 29: Life Estimation Based on Degradant [REDACTED] (b) (4) 1 for Supporting Batch 708684001 from Oss, 2mL	46
Figure 30: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batch 708685001 from Oss, 5mL	47
Figure 31: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batch 708686001 from Oss, 5mL*	48
Figure 32: Life Estimation Based on Degradant [REDACTED] (b) (4) for Supporting Batch 708687001 from Oss, 5mL	48
Figure 33: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 2mL	49
Figure 34 : Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 5mL	50
Figure 35: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 2mL	51
Figure 36: Life Estimation Based on Degradant [REDACTED] (b) (4) for a Supporting Batch from Oss, 5mL	52
Figure 37: Life Estimation Based on Total Degradants for a Supporting Batch from Oss, 2mL	53
Figure 38: Life Estimation Based on Total Degradants for a Supporting Batch from Oss, 5mL	54

1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The primary stability data collected at Oss, the Netherlands, were stored (b) (4) (in the dark) for 18 months at several long-term conditions of which 30°C/75%RH was the most extreme. All shelf life estimates exceeded the desired 36 months. However, from a regulatory point of view, only a 12 month extrapolation to 30 months would be appropriate.

The supporting stability data collected at Oss, the Netherlands, were similarly stored (b) (4) for 24 months. All shelf life estimates exceeded the desired 36 months. It needs to be decided whether the sponsor's reasoning holds, that there is no essential difference between the supporting, primary, and commercial batches, and that therefore the 36 month expiry is applicable in general to the product manufactured at Oss. This argument is not based on any statistical comparison, but only on the circumstances of how batches were labeled supporting and primary.

The primary stability data collected at Swords, Ireland, were stored (b) (4) (in the dark) for 6 months at the same long-term conditions of which 30°C/75%RH was the most extreme. The sponsor and the reviewer agreed that these data were too sparse for shelf life estimation. However, the reviewer does not agree with the sponsor that the requested 36 month expiry is also applicable, based solely on visual similarities between these data and those observed and evaluated at Oss.

The supporting stability data collected at Swords, Ireland, were similarly stored (b) (4) for 12 months. The early assay data needed to be discarded and hence this attribute could not provide a shelf life estimate. Some degradant data provided shelf life estimates. However, these data are sparse, as only one sub-batch is available per presentation and per final sterilization condition. Given that the assay data cannot provide a shelf life estimate at this point and that there is only one sub-batch per attribute, it is the reviewer's opinion that the stability data collected at Swords are insufficient at this time to estimate an expiry. Further, the reviewer concluded that the Swords data cannot be considered equivalent to the stability data from Oss. There is a great imbalance between the amount of stability data available at either site, and no equivalency study has been designed on an appropriate endpoint. In the reviewer's opinion only separate shelf lives can be estimated for each of the two sites which may turn out to be the same. However, first sufficient stability data from the primary batches have to be collected and evaluated before a valid expiry can be estimated for the product manufactured at Swords, Ireland.

1.2. Brief Overview of Stability Studies

Bridion (sugammadex sodium) comes in one strength (100 mg/mL) and is filled into 2mL and 5mL presentations. There are 18 month stability data available from three primary batches and 24 month from three supporting batches manufactured at Oss, the

Netherlands. From Swords, Ireland, there is one primary and one supporting batch per presentation. Each batch was divided into two sub-lots receiving one of two types of final sterilization conditions. The primary batches from Swords had six month data whereas the supporting batches provided 12 month stability data. The supporting batches do not have valid assay results for the first six months.

The product is stored in the dark at four long-term conditions (5°C/ambient RH, 25°C/60%RH, 30°C/40%RH, and 30°C/75%RH) of which the 30°C/75%RH condition was considered the most severe. The sponsor will maintain all long-term studies for 36 months and the accelerated storage condition (40°C/75%RH) for 6 months.

1.3. Statistical Issues and Findings

There are two major statistical issues with this submission. The first one relates to the sponsor's statistical model to estimate shelf life. The sponsor used storage condition as a factor in the model which goes against ICH recommendations. In addition, the intercept term in the model is restricted to the release data only, i.e. not the usual intercept formed in linear regression. Due to these shortcomings the reviewer re-analyzed all stability data collected under the 30°C/75%RH condition. She first applied the standard linear regression to the data of all attributes. However, when the data appeared strongly non-linear, the reviewer fit similar non-linear models to the data as the sponsor had. The reviewer's non-linear models used only the data from the most extreme long-term storage condition and put no restrictions on the intercept. The shelf life estimates were based on the better-fitting model.

The second major statistical issues relates to estimating a shelf life from the data collected at Swords, Ireland, and making any comparative statements with the data from Oss, the Netherlands. In the reviewer's opinion, there are no appropriate or sufficient data from Swords to estimate a shelf life for the product manufactured in Ireland. For the primary data the reviewer agreed with the sponsor that there were insufficient data points to estimate a shelf life. The supporting batches had insufficient assay data and any shelf life estimates would be based on only degradation products. Hence no representative shelf life can be estimated at this point. In the reviewer's opinion, the data from Swords (Ireland) cannot not be considered equivalent to those from Oss (Netherlands) as no proper equivalency study has been set up and as the data at Swords are extremely sparse. Separate expiries need to be established for product manufactured at Swords when valid and sufficient data have been collected.

The sponsor makes a case that the supportive data from Oss (Netherlands) are equally representative of the commercial product as are the primary stability data. It needs to be determined whether this reasoning is acceptable from the regulatory point of view as only the supportive data have sufficient observations (24 months) for an extrapolation to the desired 36 month shelf life.

Most degradant stability data followed non-linear patterns where the initial values were much lower than those obtained on stability. However, the post-release data were often very similar or even numerically equal. It needs to be decided whether this pattern is scientifically acceptable and explainable. It usually could be modeled statistically and the non-linear approach often provided a better fit to the degradant data than did the linear model. However, there were instances where sparse data contributed to lack of convergence of the non-linear model.

The sponsor states the labeled storage conditions as (b) (4). However, the studied range of long-term storage conditions was (b) (4). This may have been a misprint by the sponsor but needs to be clarified.

2. INTRODUCTION

2.1. Overview

In support of the requested shelf life of 36 months the sponsor submitted stability data for each presentation (2mL and 5mL) from three primary and three supporting batches manufactured at Oss, the Netherlands. When batches 708682001 and 708687001 were tested for release there was no adequate method in place for 100% visual inspection of visible particles. Hence these batches were defined as supporting. In the meantime, the current method for visible particles showed results within acceptance criteria. Differences in the manufacturing method of these batches as compared to the current process were determined to have no influence on the product quality. Hence, the sponsor considered the supporting stability batches equally as representative of the stability of the commercial batches as are the primary batches. The primary batches had 18 month and the supporting batches had 24 month stability data at the time of submission.

At Swords, Ireland, one primary and one supporting batch were manufactured for each presentation. The assay results from batches 422421 and 422423 were declared invalid for the initial, 3- and 6-month time points because of an analytical artifact. The stability study was continued but these batches were defined as supporting and new primary batches were put on stability. The primary batches had 6 month and the supporting batches 12 month stability data at the time of submission. Each of the batches manufactured at Swords, Ireland, was split into two sub-batches depending with which of two methods they wer (b) (4)

(b) (4) The data from the primary batches were considered too sparse for statistical analysis and from the supporting batches only the degradation results were analyzable.

In order to meet tropical zones requirements, long term data are being collected for two intermediate ICH conditions, namely (b) (4)

condition was considered the most severe long-term condition. The reviewer analyzed the data from the 30°C/75%RH storage condition only, as the results should represent a worst case. The sponsor will maintain all long-term studies for 36 months and the accelerated storage condition (40°C/75%RH) for 6 months.

2.2. Data Sources

The sponsor submitted stability data for the drug product manufactured at Oss, the Netherlands, in two SAS transport files, one file containing the primary and the other file containing the supporting stability data. Data were collected under all storage conditions, but the files contained data only from the 5°C/ambient, 25°C/60%RH and 30°C/75%RH storage conditions. Of these the reviewer analyzed only the results of the 30°C/75%RH condition as the sponsor provided detailed statistical analyses and shelf life estimation for it and the condition is considered the most severe for long term stability. Also, the submitted data represented [REDACTED] (b) (4)

The data from the site at Swords, Ireland, were not submitted as an electronic data file. The primary batches had only 6 month data (3 time points) and were therefore considered too sparse for any statistical analysis. The assay data from the supporting batches were incomplete and were therefore not statistically analyzed. However, the 12 month data for the degradation products from the supporting batches were analyzed by both the sponsor and the reviewer.

3. STATISTICAL EVALUATION

3.1. The Drug Product

The drug product is manufactured in one strength (100 mg/mL) and is filled into 2 mL and 5 mL presentations. Stability batches manufactured at Oss, the Netherlands, were stored in the dark at 5°C/ambient, 25°C/60%RH, 30°C/40%RH and 30°C/75%RH conditions for 18 (primary batches) and 24 months (supporting batches). In addition, the product was exposed for 6 months to the accelerated condition of 40°C/75%RH. When the product was stored under the 30°C/40%RH condition testing was greatly reduced because the 30°C/75%RH condition was considered more stressful. Stability data were collected and analyzed for the assays of Org 25969 and Org 48302 and for the degradation products [REDACTED] (b) (4)

[REDACTED] Statistical evaluations were also performed on the sum of Org 25969 and Org 48302 and on the total impurities. The 30°C/75%RH storage condition was considered the most severe and was used for shelf life estimation by the sponsor and the reviewer. The sponsor also presented some summary statistics for change over time for the 5°C/ambient and the 25°C/60%RH conditions but no shelf life estimation. Because there was no adequate method for 100% visual inspection of visible particles in place at the time of release, batches 708682001 and 708687001 were defined as supporting. In the meantime, the current method for visible particles showed results

within acceptance criteria. Hence, according to the sponsor there is no meaningful difference between the primary and supporting batches from Oss.

The product manufactured at Swords, Ireland, follows a similar stability protocol as is in place for Oss, the Netherlands, but there is only one batch per presentation on stability. In addition, each batch was split into two sub-batches depending under which condition the sub-batch (b) (4). The assay results of batches 422421 and 422423 were declared invalid because of an analytical artifact at the initial, 3- and 6-month time points. The stability study was continued but these batches were defined as supporting and new primary batches were put on stability. The new primary batches had only six month data at the time of the submission and were therefore not statistically analyzed. The supporting batches had 12 month data but not for assay, which had only the 9- and 12-month time points. The sponsor and the reviewer analyzed the 12 month data for degradation products from the supportive batches.

3.1.1. Sponsor's Results

The sponsor's mathematical model for shelf life estimation was novel in that it contained storage condition (5°C/ambient RH, 25°C/60%RH, and 30°C/75%RH) as a factor, used the release data only once, and allowed for non-linearity in time. The linear or non-linear parameter estimated by this mathematical model were used in the sponsor's line graphs for primary and supporting batches by attribute, storage condition and site (p81-stability-summary-and-conclusion.pdf report). For shelf life estimation the sponsor concentrated on each batch separately when stored (b) (4) in the dark at the 30°C/75%RH.

At Oss, the Netherlands, three primary and three supporting batches of each presentation (2mL and 5mL) were on stability for 18 and 24 months respectively. For each of the three analyzed storage conditions (note: 30°C/40%RH was excluded as it had greatly reduced testing and the 30°C/75%RH was considered a more severe storage condition) and for each attribute, the sponsor listed the estimated average change (based on linear or non-linear models) over 36 months and the 95% confidence interval around each estimate. If the batches could be pooled, the average change was an average of the three batches; otherwise it was an average over time for each batch separately. For the non-linear model, this average is applicable only to the 36 months for which it was computed, whereas for the linear model this average can be adjusted to any time frame. To estimate the shelf lives, the individual and combined active ingredients were fitted with linear models which were presented graphically. For the degradation products, the sponsor concluded that non-linear models were appropriate. The models were nonlinear in storage time, but linear in a power transformation of the storage time. The power parameter was also estimated from the data and the model was considered linear when the power parameter did not significantly differ from '1'. The sponsor presented these regression graphs and one-sided 95% confidence limits as well as the acceptance criteria for each primary and supporting batch. The sponsor concluded that based on the analyses of the 18 month primary data and 24 month supporting data collected at Oss, the Netherlands, the observed decrease in the Org 25969 drug substance content and the observed increases in degradation products warranted an extrapolated shelf life of 36 months.

At Swords, Ireland, one primary and one supporting stability batch of each presentation were on stability for 6 and 12 months respectively. Each batch was subdivided into two sub-lots depending which of two final sterilization cycles were applied. One sub-lot was sterilized (b) (4) whereas the other sub-lot was sterilized (b) (4). Batches 422421 (2mL) and 422423 (5mL) had originally been primary batches but their initial, 3- and 6-month assay results were declared invalid because of an analytical artifact. The stability study was continued but the batches were defined as supporting and new primary stability batches were manufactured. The sponsor presented line graphs for the first 6 months of the primary batches' assay results and months 9 and 12 from the supporting batches. Similar line graphs were presented for each degradation product under the various storage conditions. No statistical analyses were performed on the primary batches, as 6 month data were insufficient to support the estimation of a shelf life. The supporting batches had only the 9- and 12- month time points for assay and therefore no statistical analysis was performed for this attribute. However, for each degradation product (by sub-lot) the sponsor submitted the average change over 36 months and the corresponding 95% confidence interval. In addition, they performed shelf life estimation based on each degradation product by supporting sub-batch. Most models were nonlinear in storage time, but linear in a power transformation of the storage time. The results were presented as graphs with 95% upper specification limits (the reviewer presumes that the sponsor's reference to the 'lower' confidence limit in Section 5 (p. 63 of the CMC Module P81 v01 INT00046682) is a misprint). The sponsor concluded that degradation products tended to be slightly higher for the batches (i.e. sub-batches) with (b) (4) conditions than for batches with (b) (4) conditions. The supporting data are described in Report P84C v02, INT00052569 (for the sub-batches with (b) (4) and Report P84D v03, INT00053122 (for the sub-batches with (b) (4)).

Report P84E v01, INT00025625 and Report P84F v01, INT00025859 contain the raw data and summary of the two primary sub-lots manufactured at Swords, Ireland, which underwent the (b) (4), respectively. As there are only 6 month data, the sponsor did not perform any statistical analyses but in each case concluded that the two batches representing the two vial sizes were comparable to each other and stable for at least 6 months when stored between 5°C and 30°C in the dark. The sponsor further concluded that the results were comparable between the two (b) (4) conditions.

The sponsor stated that there is no real difference between the primary and supporting stability batches from both Oss and Swords and that their conclusions are based on the data as if they were one single set.

3.1.2. Reviewer's Results

The reviewer independently analyzed the assay and degradation data from the primary and supporting batches manufactured at Oss, the Netherlands, and some of the degradation data from Swords, Ireland, when stored (b) (4) in the dark at 30°C/75%RH.

She employed the standard linear regression approach and evaluated a non-linear model, similar to the sponsor's, when suggested by the data. It is noted that the linear model provided an excellent fit for many attributes (see Appendix I for detail). At other times the R²'s were small due to the slopes being close to zero. This is not to say, that most degradation products did not seem to follow a non-linear pattern. In the cases when it was imperative to decide which was the more appropriate model the reviewer compared the log-likelihoods of the linear and non-linear models and estimated the shelf life based on the more appropriate model. The non-linear model used by the reviewer was similar in form to the one the sponsor had employed, but used only the data from the most extreme long-term storage condition (30°C/75%RH). This approach followed the ICH Q1E guidance and as a by-product, there was no issue regarding the use of the release data more than once.

Table 1 summarizes the reviewer's estimated shelf lives based on the standard linear model and a non-linear model, if the linear model seemed inappropriate or if it led to extrapolated shelf lives close to or less than the desired 36 months. The analyses were performed per attribute and per presentation of the primary batches from Oss when stored (b) (4) in the dark at 30°C/75%RH for 18 months.

The sponsor did not submit the release data for degradant (b) (4) from the primary batches. The data covering months 3 to 18 of the primary batches looked quite linear and estimated long shelf lives. These may be overestimations but fitting an appropriate non-linear model with the proper release data would most likely lead to a shelf life of at least the desired length. For all attributes and based on the appropriate statistical analysis of the primary stability data from Oss, an extrapolated shelf life of well over 36 months is supported. Based on strict regulatory guidance, a maximum extrapolation of 12 months would lead to an expiry of 30 months.

Table 1: Summary Results of Shelf Life Estimation for Primary Stability Data from Oss, the Netherlands

Attribute	Batches	Prese ntation	Linear Model	R ²	Linear Shelf Life	Non-linear Shelf Life	Comment
Total Content	Primary	2mL	parallel slopes	0.4009	118	n/a	
Total Content	Primary	5mL	pooled	0.2885	102	n/a	
C_Org2596 Content	Primary	2mL	parallel slopes	0.5285	184	n/a	Lower Spec: 82%
C_Org2596 Content	Primary	5mL	parallel slopes	0.6145	148	n/a	Lower Spec: 82%
Deg: (b) (4)	Primary	2mL	parallel slopes				(b) (4)
Deg: (b) (4)	Primary	5mL	parallel slopes				
Deg: (b) (4)	Primary	2mL	parallel slopes				
Deg: (b) (4)	Primary	5mL	parallel slopes				
Deg: (b) (4)	Primary	2mL	Individual lines				
Deg:	Primary	5mL	Individual				

(b) (4)			lines	(b) (4)
Deg: (b) (4)	Primary	2mL	pooled	
Deg: (b) (4)	Primary	5mL	pooled	
Deg: (b) (4)	Primary	2mL	-	
Deg: (b) (4)	Primary	5mL	-	
Deg: (b) (4)	Primary	2mL	pooled	
Deg: (b) (4)	Primary	5mL	parallel slopes	
Total Degradants	Primary	2mL	parallel slopes	
Total Degradants	Primary	5mL	parallel slopes	

* According to the sponsor, degradant (b) (4) changes into (b) (4) and (b) (4) and therefore has no data after 3 months. This degradants is not used for shelf life estimation.

** In the data submitted, the release values had been omitted. Hence most of the non-linear shape was lost.

Table 2 summarizes the reviewer’s estimated shelf lives for the supporting batches from Oss, the Netherlands, based on the standard linear model and a non-linear model, if the linear model seemed inappropriate or if it led to extrapolated shelf lives close to or less than the desired 36 months. The analyses were performed per attribute and per presentation when the supporting batches were stored (b) (4) in the dark at 30°C/75%RH for 24 months.

For degradant (b) (4) one of the three supporting batches had the release point missing. The linear model estimated short shelf lives for one of the batches per presentation whose graphs suggested a non-linear fit. The reviewer fit a linear model to two of the batches and a non-linear model to the one batch per presentation which strongly suggested a non-linear degradation pattern. All shelf life estimates based on the 24 months data supported extrapolated expiries of over 36 months. It needs to be decided whether these supporting data qualify to set the expiry for the whole product manufactured at Oss, as the primary batches lag behind in time points.

Table 2: Summary Results of Shelf Life Estimation for Supporting Stability Data from Oss, the Netherlands

Attribute	Batches	Presenta tion	Linear Model	R ²	Linear Shelf Life	Non-linear Shelf Life	Comment
Total Content	Supporting	2mL	parallel slopes	0.6240	86	n/a	
Total Content	Supporting	5mL	parallel slopes	0.6206	103	n/a	
C_Org2596 Content	Supporting	2mL	parallel slopes	0.7691	106	n/a	82%
C_Org2596 Content	Supporting	5mL	parallel slopes	0.6911	126	n/a	82%
Deg: (b) (4)	Supporting	2mL	parallel slopes	(b) (4)	(b) (4)	(b) (4)	
Deg: (b) (4)	Supporting	5mL	parallel slopes				
Deg: (b) (4)	Supporting	2mL	parallel slopes				
Deg: (b) (4)	Supporting	5mL	parallel slopes				
Deg: (b) (4)	Supporting	2mL	Individual lines				
Deg: (b) (4)	Supporting	2mL	Individual lines				
							Missing release data

Deg: (b) (4)	Supporting	2mL	Batches 708682001 and 708683001	(b) (4)	substituted
Deg: (b) (4)	Supporting	2mL	Batch 708684001 only	(b) (4)	Missing release data substituted
Deg: (b) (4)	Supporting	5mL	Individual lines	(b) (4)	Missing release data substituted
Deg: (b) (4)	Supporting	2mL	Individual lines	(b) (4)	
Deg: (b) (4)	Supporting	5mL	Individual lines	(b) (4)	
Deg: (b) (4)	Supporting	2mL	-	(b) (4)	Insufficient data
Deg: (b) (4)	Supporting	5mL	-	(b) (4)	Insufficient data
Deg: (b) (4)	Supporting	2mL	Individual lines	(b) (4)	
Deg: (b) (4)	Supporting	5mL	parallel slopes	(b) (4)	
Total Degradants	Supporting	2mL	parallel slopes	(b) (4)	
Total Degradants	Supporting	5mL	parallel slopes	(b) (4)	

* According to the sponsor, degradant (b) (4) degrades further into (b) (4) and (b) (4) and therefore has no data after 3 months. This degradants is not used for shelf life estimation.

** In the data submitted, the release data were omitted for one of the three batches. The reviewer substituted the average of the other two batches for the missing data point in the linear model. The non-linear model was applied to each batch separately without any substituted release data.

*** Linear shelf life longer than desired 36 months. Non-linear shelf life estimate likely to be even longer.

The reviewer agreed with the sponsor that the assay data from the primary and the supporting batches from **Swords, Ireland**, should not be analyzed statistically at this point. There is only one lot per presentation and each lot had been split into two sub-lots depending which of two sterilization methods were applied. The primary batches have only six month data (three data points) which is barely sufficient to fit a linear model but insufficient to estimate a confidence limit and a shelf life. The early assay data from the supporting batches needed to be deleted and hence these batches have only the 9- and 12-month time points, which are insufficient for linear regression analysis. The sponsor plotted the piecemeal assay results from the primary and supporting sub-lots in one graph. The pictures show that the observed assay results are not out of the ordinary. However, no shelf life can be estimated based on the collective data, and they can only visually be compared to the findings observed at Oss, the Netherlands. In the reviewer's opinion, the assay data collected so far at Swords, Ireland, cannot be used to make a statement of similar or supporting stability compared to the assay results from Oss, the Netherlands. The reviewer disagrees with the sponsor that the assay data from Swords support an extrapolated shelf life of 36 months without any analysis and both the sponsor and the reviewer agreed that a proper analysis of either primary or supporting assay data was not possible at this point.

Table 3 presents the results of some of the degradation products from the supporting batches at **Swords, Ireland**. These are the only data that were amenable to statistical

analysis. They are based on single sub-lots for each presentation and each of the two final sterilization conditions. The reviewer was not able to have the non-linear model converge in each case. In cases where the raw data were identical or almost identical after the initial release data, the reviewer did not attempt to fit a non-linear model. More importantly one needs to remember that there is only one (sub-)batch per attribute and sterilization condition and only five time points per batch. The linear model uses two of the available four degrees of freedom and the non-linear model three. Hence, the shelf life estimates can be viewed as suggestive at best, and more data are necessary to provide expiries which can be trusted. In the reviewer’s opinion, the degradant stability data from Swords, Ireland, are too sparse for a definite estimation of an expiry and currently the assay data are insufficient for estimation. With these reservations in mind, the degradants support an 18 month shelf life based on the linear model. Though, the data appear visually consistent with the findings from Oss, the Netherlands, the reviewer does **not** agree with the sponsor that at this point in time one can assign or infer the desired shelf life of 36 months to both sites.

Table 3: Shelf Life Estimation Based on Degradant Stability Data from Swords, Ireland.

BATCH	DEGRADANT	Linear Log-likelihood, Regression Line	Non-linear Log-likelihood	‘Linear’ Expiry	‘Non-linear’ Expiry
Supportive 2mL, Swords	“S”,				
Supportive, 5mL, Swords	“S”,				
Supportive, 2mL, Swords	“O”,				
Supportive, 5mL, Swords	“O”,				
Supportive 2mL, Swords	“S”,				
Supportive, 5mL, Swords	“S”,				
Supportive, 2mL, Swords	“O”,				
Supportive, 5mL, Swords	“O”,				
Supportive, 2mL, Swords	“S”,				
Supportive, 5mL, Swords	“S”,				
Supportive 2mL, Swords	“O”,				
Supportive, 5mL, Swords	“O”,				
Supportive, 2mL, Swords	“S”,				
Supportive, 5mL, Swords	“S”,				
Supportive, 2mL, Swords	“O”,				

(b) (4)

Supportive, 5mL, Swords	“O”,	Total Degradants
----------------------------	------	------------------

4. STATISTICAL ISSUES

Both the primary and supporting data collected at Oss, the Netherlands, supported the desired shelf life of 36 months. However, the primary batches had been on stability for only 18 months and hence a strict regulatory extrapolation would allow an expiry of only 30 months. However, the sponsor argued that the supporting batches are equally representative of the commercial lots as are the primary stability batches. It needs to be decided whether the sponsor's reasoning is acceptable because it determines whether the maximally extrapolated shelf life can be 30 or 36 months.

The reviewer assumed that the non-linear model suggested by most degradant data is acceptable from the chemistry and scientific point of view. Most of the non-linearity seems to be due to release values being much lower than following observations. There were several cases where a low release value was followed by higher and identical stability values. It is outside the reviewer's expertise to decide whether such stability patterns make scientific sense.

For the many of the degradants studied, the non-linear model fit the data better than the linear model. The non-linear model with individual growth factors did not significantly improve the fit over the non-linear model with a common growth factor. This decision was based on comparing the log-likelihoods of the linear and non-linear model with the common growth factor and the log-likelihoods of the two non-linear models. It is noted that the linear models had provided excellent fit in many cases, but that the non-linear model fit the degradant data so well, that the error term was practically zero.

In the reviewer's opinion there are insufficient data collected so far at Swords, Ireland, for a robust shelf life estimate. There is only one (sub-)batch per attribute and sterilization condition and only five time points per supporting batch. The linear model uses two of the available four degrees of freedom and the non-linear model three. Hence, the shelf life estimates can be viewed as suggestive, but more data are necessary to provide expiries which can be trusted. At best, an 18 month expiry was supported based on linear models and only on the degradant attributes of the supporting batches. As the supporting batches will never have complete assay data, in the reviewer's opinion, it would better to estimate a proper and separate shelf life for the product manufactured at Swords when more of the primary data have been collected.

As mentioned above, there were occasions when the non-linear modeling may have failed due to insufficient data, especially at Swords where only a single (sub-)batch with 5 data points represented each configuration. At Oss, release data for degradants were missing which may also have contributed to the lack of convergence of some cases.

The reviewer did not perform a formal comparison of the degradants data from Swords with those from Oss. No acceptable difference had been declared nor had an equivalency study been designed. It is presumed that only one sterilization condition, namely the (b) (4) was used at Oss, and that the (b) (4) condition data are for informative purposes only. Hence the data from only a single sub-batch from Swords would be compared to the data from three primary and three supporting batches from Oss, which is not likely to provide a satisfactory answer due to the imbalance even if some equivalency measure were established. In the reviewer's opinion, the data from Swords remain handicapped until the primary lots have sufficient time points to estimate proper shelf lives on all attributes, including assay. Visual comparisons between the stability data collected at Oss and at Sword are helpful to assess that there are no apparent outliers. However, in the reviewer's opinion two separate shelf lives, one for each site, need to be established. These shelf life estimates may well turn out to be identical, but at this point it is improper to infer the shelf life estimated for the product from Oss unto the product manufactured at Swords due to the inadequate data at the latter site.

5. CONCLUSION

The reviewer estimated shelf lives based on assay and most degradation products collected at Oss, the Netherlands. When the data suggested strongly that a linear model would not be adequate, despite high R^2 's, she fit a non-linear model similar to the sponsor's. However, only one long-term storage condition was considered and there was no issue regarding repeated use of release data. Assuming that the form of the non-linear models suggested by the data make scientific sense, they estimated shelf lives of at least 36 months for the primary or supporting data from Oss. It needs to be decided whether the expiry can be based on the supporting data from Oss as the primary data had only 18 months at the time of submission.

The stability data from the primary batches manufactured at Swords, Ireland, had insufficient time points for shelf life estimation. The supporting batches had only two data points for assay and hence were insufficient for regression analysis. There were 12 month data for degradation products from the supporting batches which were analyzed by the reviewer. As there was only one sub-batch for each configuration and sterilization condition, in the reviewer's opinion any estimated shelf life is not reliable. In general, the data from Swords are visually similar to those from Oss. However, only the roughest visual comparisons between the data from Swords and Oss can be made and in the reviewer's opinion, at this time no shelf life can be set for the product manufactured at Swords, much less a comparison made between the stability of the product manufactured at Swords and at Oss.

In summary, the reviewer agrees with the sponsor that all attributes measured on the stability batches from Oss supported an extrapolated shelf life of over 36 months. Note, the primary batches have 18 months data and a strict regulatory point of view would support an extrapolation to only 30 months. Hence, the sponsor's arguments that the

supporting data from Oss are as representative of the commercial product as are the primary stability data need to be evaluated.

The sponsor's non-linear model was unacceptable as it had storage condition as a factor in the model, which is against ICH Q1E recommendations. The reviewer analyzed only the results from the most severe long-term storage condition. Though the sponsor also presented the results by storage condition, their findings are based on a different statistical model and hence need not be identical to the reviewer's. In addition, the sponsor used the release data for each batch only once. Since the reviewer analyzed the data of only one storage condition, this issue did not arise.

The reviewer's non-linear model followed the sponsor's general approach in that the model was non-linear in time and that the growth factor was estimated based on the data. However, it needs to be decided, whether the stability curves of most degradants, which in the extreme had a low release point and thereafter much higher but identical values over time, are scientifically acceptable.

6. ACKNOWLEDGEMENTS

The reviewer would like to acknowledge the valuable guidance and computational support for the non-linear modeling provided by Drs. Jinglin Zhong (DBVI) and Lei Nie (DBIV).

7. APPENDIX

7.1. Reviewer's Linear Analysis Results for Primary Batches from Oss, the Netherlands

Table 4: Shelf Life Estimation Based on C_Org25969 Assay for Primary Batches from Oss, 2mL

Source	SS	DF	MS	F-Statistic	P-Value
A	5.2195	4	1.3049	3.3444	0.0465
B	4.8412	2	2.4206	6.2040	0.0141
C	0.3783	2	0.1892	0.4848	0.6274
RESIDUAL	4.6820	12	0.3902		

Fitted Line	R-Square	Batch	Estimated Expiry Period
$Y = 96.1405 - 0.0363 \times \text{Time}$	0.5285	827870001	184
$Y = 96.3261 - 0.0363 \times \text{Time}$	0.5285	827871001	186
$Y = 97.3217 - 0.0363 \times \text{Time}$	0.5285	827872001	199
	.	-MIN-	184

Figure 1: Shelf Life Estimation for C_Org25969 Assay from a Primary Batch from Oss, 2mL

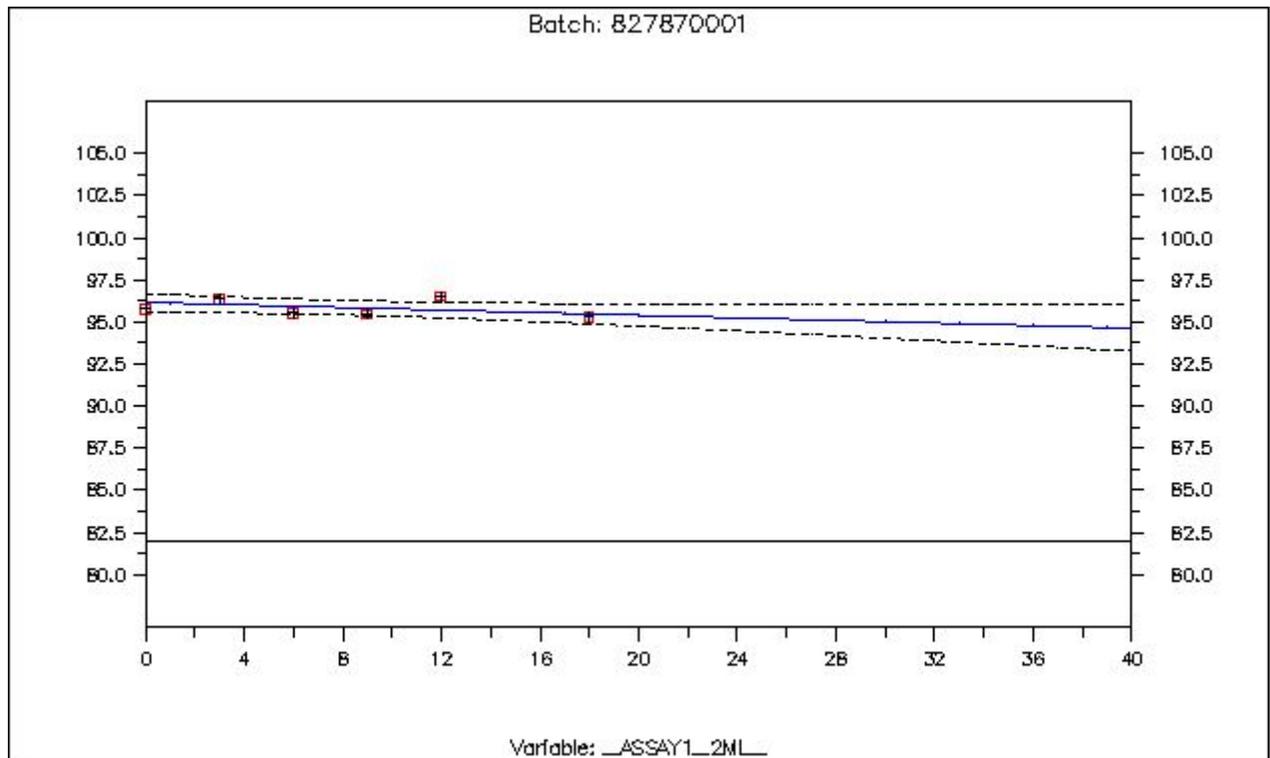


Table 5: Shelf Life Estimation Based on C_Org25969 Assay for Primary Batches from Oss, 5mL

Source	SS	DF	MS	F-Statistic	P-Value
A	4.9671	4	1.2418	3.9169	0.0293
B	4.5759	2	2.2879	7.2168	0.0088
C	0.3912	2	0.1956	0.6170	0.5558
RESIDUAL	3.8044	12	0.3170		

Fitted Line	R-Square	Batch	Estimated Expiry Period
$Y = 96.5060 - 0.0579 \times \text{Time}$	0.6145	827873001	153
$Y = 96.0449 - 0.0579 \times \text{Time}$	0.6145	827874001	148
$Y = 97.2676 - 0.0579 \times \text{Time}$	0.6145	827875001	161
	.	-MIN-	148

Figure 2: Life Estimation for C_Org25969 Assay from a Primary Batch from Oss, 5mL

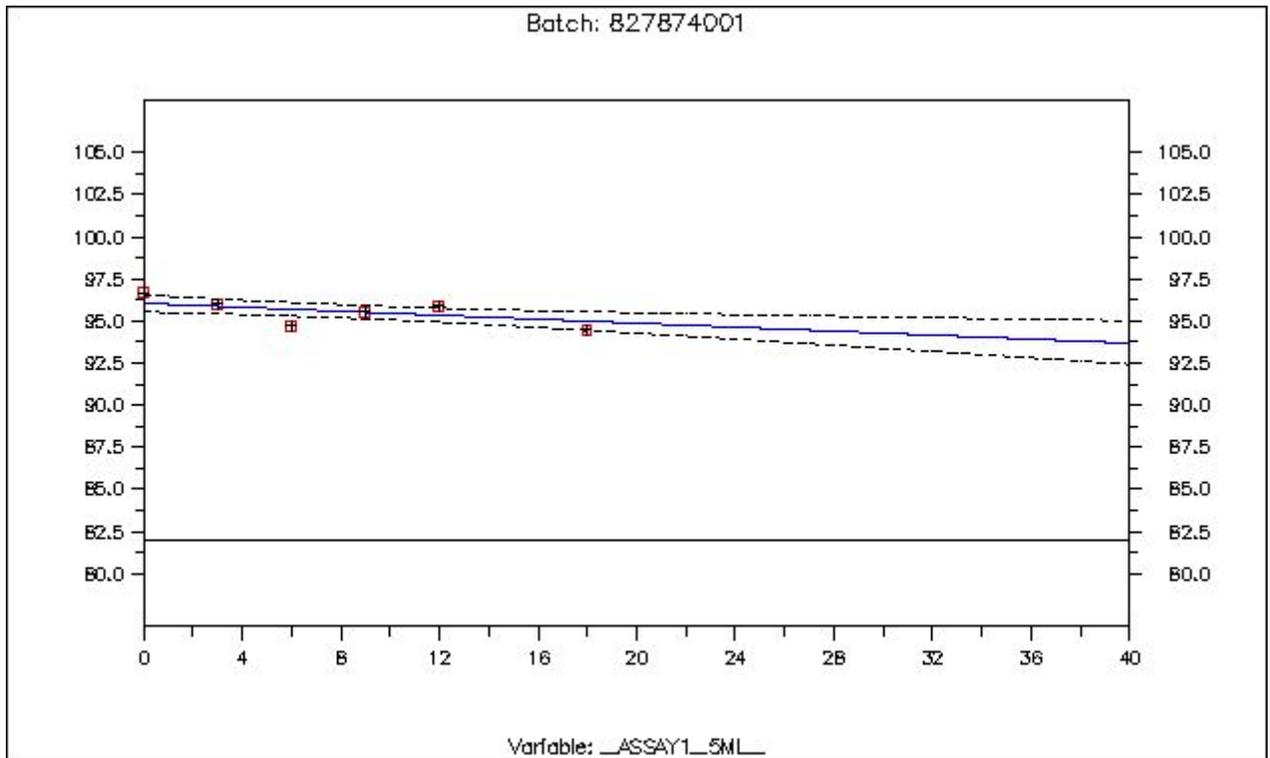


Table 6: Shelf Life Estimation Based on Total Assay for Primary Batches from Oss, 2mL

Source	SS	DF	MS	F-Statistic	P-Value
A	3.1606	4	0.7901	1.9374	0.1688
B	2.7451	2	1.3725	3.3654	0.0691
C	0.4155	2	0.2077	0.5094	0.6133
RESIDUAL	4.8941	12	0.4078		

Fitted Line	R-Square	Batch	Estimated Expiry Period
$Y = 99.0460 - 0.0358 \times \text{Time}$	0.4009	827870001	118
$Y = 99.8510 - 0.0358 \times \text{Time}$	0.4009	827871001	128
$Y = 99.8960 - 0.0358 \times \text{Time}$	0.4009	827872001	129
	.	~MIN~	118

Figure 3: Life Estimation for Total Assay from a Primary Batch from Oss, 2mL

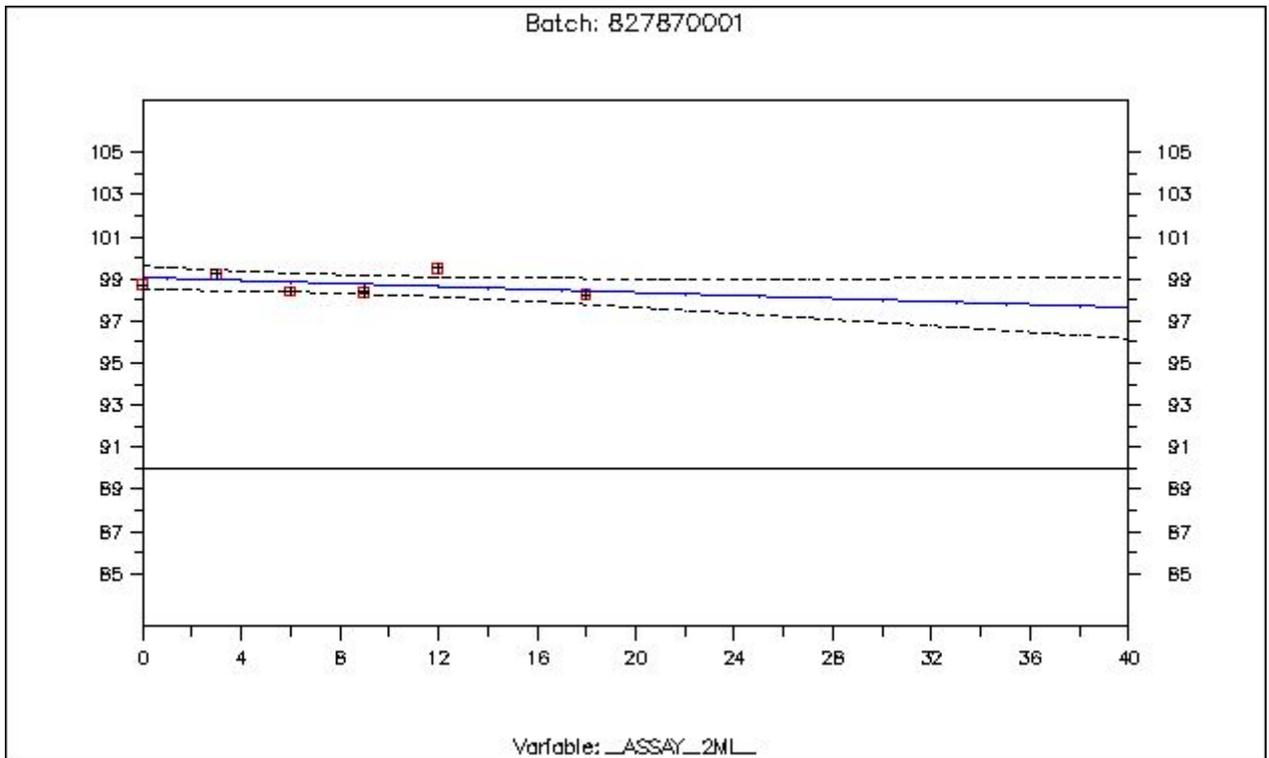
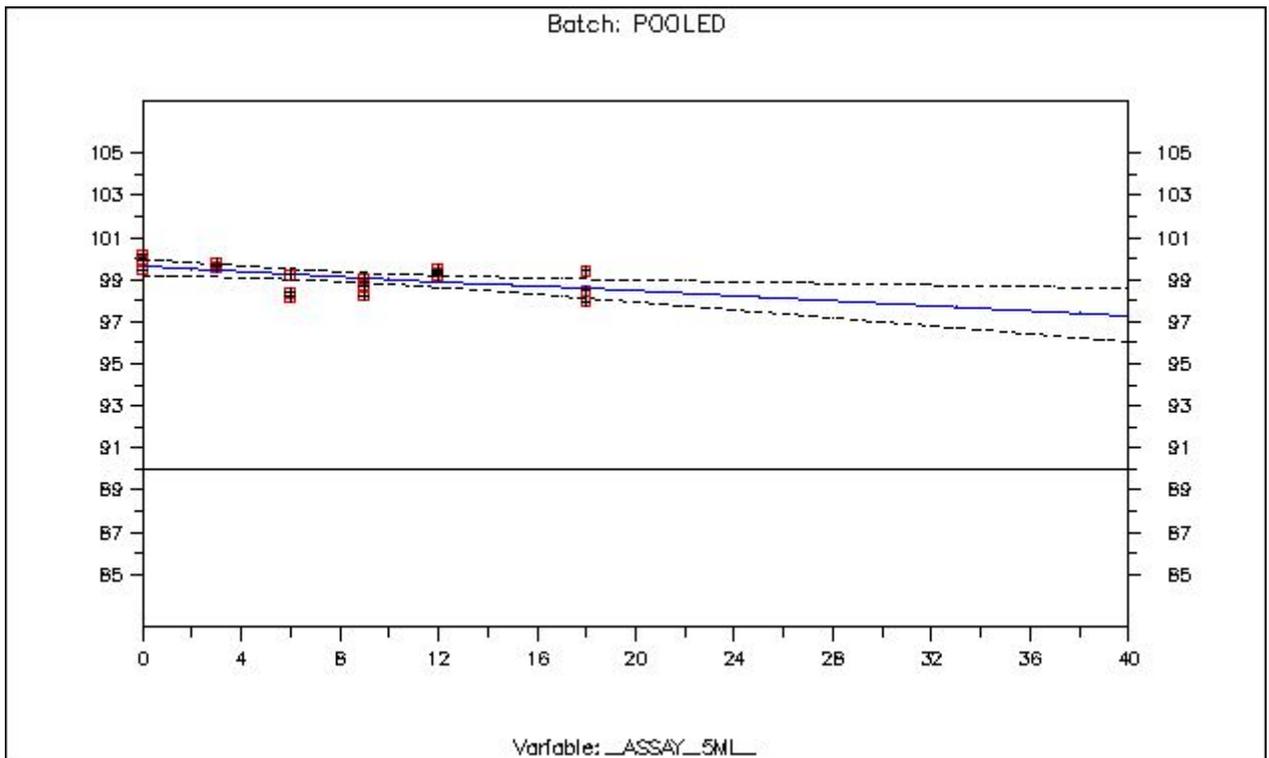


Table 7: Shelf Life Estimation Based on Total Assay for Primary Batches from Oss, 5mL

Source	SS	DF	MS	F-Statistic	P-Value
A	1.0177	4	0.2544	0.7506	0.5763
B	0.5868	2	0.2934	0.8656	0.4455
C	0.4309	2	0.2155	0.6357	0.5465
RESIDUAL	4.0674	12	0.3390		
Fitted Line		R-Square	Batch	Estimated Expiry Period	
Y = 99.5999 - 0.0572 x Time		0.2885	POOLED	102	
		.	~MIN~	102	

Figure 4: Life Estimation for Total Assay from Pooled Primary Batches from Oss, 5mL



32 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

Roswitha Kelly
6/9/2008 01:41:11 PM
BIOMETRICS

Yi Tsong
6/9/2008 05:36:48 PM
BIOMETRICS



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIostatISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA: 22-225

Name of drug: Bridion (sugammadex sodium) injection (Org 25969)

Indication: reversal of neuromuscular blockade

Applicant: Organon

Dates: letter 30 October 2007; user fee goal (6 months) 30 March 2008

Review priority: P

Biometrics division: Division of Biometrics II

Statistical reviewer: Thomas Permutt

Concurring reviewers: none

Medical division: Anesthesia, Analgesia and Rheumatology Products

Clinical team: Rob Shibuya, M.D.; Arthur Simone, M.D.; Mary Purucker, M.D. (cross-discipline team leader)

Project manager: Allison Meyer

Keywords: NDA review, clinical studies

1 EXECUTIVE SUMMARY	3
1.1 Conclusions and Recommendations	3
1.2 Brief Overview of Clinical Studies	3
1.3 Statistical Issues and Findings	3
2 INTRODUCTION	4
2.1 Overview	4
2.2 Data Sources	4
3 STATISTICAL EVALUATION	5
3.1 Evaluation of Efficacy	5
3.1.1 <i>Study 301</i>	5
3.1.2 <i>Study 302</i>	6
3.1.3 <i>Study 310</i>	6
3.1.4 <i>Study 303</i>	7
3.2 Evaluation of Safety	7
4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	7
5 SUMMARY AND CONCLUSIONS	8
5.1 Statistical Issues and Collective Evidence	8
5.2 Conclusions and Recommendations	8

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Sugammadex was effective in reversing neuromuscular blockade produced by rocuronium or vecuronium. The proposed labeling accurately describes the results of the clinical trials. With single studies in each clinical setting, however, it is not clear that the evidence is up to the usual standard for comparative claims.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The application mentions 8 phase 2 trials, 4 “bridging” trials and 11 phase 3 trials. The proposed labeling discusses four of these trials in detail. Two of these trials (301, 302) were comparisons to neostigmine in routine reversal of blockade with rocuronium or vecuronium, with different criteria for the time at which reversal was attempted. One trial (310) compared rocuronium reversed by sugammadex to cisatracurium reversed by neostigmine. One trial (303) compared rocuronium reversed by sugammadex to succinylcholine without reversal. The clinical review is mainly focused on these four studies.

1.3 STATISTICAL ISSUES AND FINDINGS

The principal studies reviewed were all of different designs: there were no replicated studies. They are individually persuasive, however. Furthermore, though they investigated slightly different clinical settings, both the mechanism of action and the clinical effect of the test drug are the same in each setting: reversal of neuromuscular blockade. There is ample evidence that sugammadex produces this effect.

2 INTRODUCTION

2.1 OVERVIEW

Sugammadex is a new kind of agent for the reversal of neuromuscular blockade. It is a cyclodextrin, a cyclic oligomer of sugar molecules. Molecules of sugammadex apparently entrap molecules of certain neuromuscular blocking agents (NBAs), specifically rocuronium and vecuronium, neutralizing their effect and thus hastening the return of neuromuscular function. This might be useful in the routine management of surgical anesthesia: a patient who no longer needs to be paralyzed can have normal function restored earlier than the NBA would wear off by itself. Neostigmine, an unapproved agent, is frequently used for this purpose. More importantly, sugammadex might offer the possibility of quick reversal in situations where blockade has become dangerous. The short-acting NMB succinylcholine is usually used in situations where this need is contemplated, but rocuronium followed by sugammadex might be an alternative.

2.2 DATA SOURCES

The application mentions 8 phase 2 trials, 4 “bridging” trials and 11 phase 3 trials. The proposed labeling discusses four of these trials in detail. Two of these trials (301, 302) were comparisons to neostigmine in routine reversal of blockade with rocuronium or vecuronium, with different criteria for the time at which reversal was attempted. (b) (4)

One trial (303) compared rocuronium reversed by sugammadex to succinylcholine without reversal. (b) (4) A Special Protocol Agreement covers studies 301 and 302.

These were all “superiority” studies in the sense that they were designed to and did show statistically significant differences between the test drug and the active comparator. This is one appropriate design for showing that the test drug has an effect, assuming there is no realistic possibility that the comparator has a paradoxical effect. That is, if the test drug is better than something, and something is not worse than nothing, the test drug must be better than nothing. Whether the trials support direct claims of superiority, however, is rather a different question, with complicated aspects both scientific and regulatory. The comparator neostigmine in routine reversal is not an approved agent. The trials using different NMBs may imply comparative claims about the NMBs themselves rather than about the reversal agents. Finally, the primary analyses, though clearly sufficient to show that the test drug is effective, may not adequately address the question of whether it is better than the alternative.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY 301

Study 301 was a randomized, parallel-group trial in two strata in elective surgery patients. Ninety-eight patients were randomized to receive rocuronium as a NBA and 100 to receive vecuronium. Within each of these strata approximately half the patients were randomized to reversal with sugammadex, the other half with neostigmine. The reversal agent was administered at the return of T_2 , a second twitch of the thumb on electrical stimulation of the ulnar nerve in a train-of-four pattern (four shocks a half-second apart).

The primary measure of outcome was the time from administration until the ratio of T_4 to T_1 (the magnitudes of the fourth and first twitches) reached 0.9. The primary analysis was separate t-tests on the logarithm of this time in the rocuronium and vecuronium strata. The results are shown in the table below, copied from the submission (module 2.7.3, p. 32).

Recovery of the T_4/T_1 ratio to 0.9 (min), Clinical Trial 19.4.301 (ITT group)

	Rocuronium		Vecuronium	
	Org 25969	Neostigmine	Org 25969	Neostigmine
n	48	48	48	45
Geometric mean	1.5	18.5	2.8	16.8
Median	1.4	17.6	2.1	18.9
Min. – max.	0.9 – 5.4	3.7 – 106.9	1.2 – 64.2	2.9 – 76.2

In each stratum the difference between treatments was statistically significant at level 0.001. With the test drug neuromuscular function as measured by this outcome returned usually within a couple of minutes, whereas with neostigmine it was usually more than a quarter-hour.

3.1.2 STUDY 302

Study 302 was of similar design to Study 301 except that reversal was attempted at a different timepoint: one to two twitches following tetanic stimulation (1–2 posttetanic contractions or PTC). Neostigmine is not widely used in this way. The table below (module 2.7.3, p. 42) shows the results. Again the differences between sugammadex and neostigmine are highly significant statistically ($p < 0.001$) as well as massive, though again the ranges overlap a little.

Recovery of the T4/T1 ratio to 0.9 (min), Clinical Trial 19.4.302 (ITT group)

	Rocuronium		Vecuronium	
	Org 25969	Neostigmine	Org 25969	Neostigmine
n	37	37	47	36
Geometric mean	2.9	50.4	4.5	66.2
Median	2.7	49.0	3.3	49.9
Min. – max.	1.2 – 16.1	13.3 – 145.7	1.4 – 68.4 ^a	46.0 – 312.7

3.1.3 STUDY 310

Study 310 compared two regimens of neuromuscular blockade and reversal: rocuronium reversed by sugammadex or cisatracurium reversed by neostigmine. The results are shown below (module 2.7.3, p. 34).

Recovery of the T4/T1 ratio to 0.9 (min), Clinical Trial 19.4.310 (ITT group)

	Treatment group	
	Rocuronium / Org 25969	Cisatracurium / Neostigmine
n	34	39
Geometric Mean	2.0	8.8
Median	1.9	7.2
Min. – max.	0.7 – 6.4	4.2 – 28.2

The treatments were obviously and statistically significantly different ($p < 0.001$). This is not in itself evidence of efficacy of sugammadex because the effects of the reversal agents are confounded with those of the NMB. (b) (4)



3.1.4 STUDY 303

Like study 310, study 303 was not designed to furnish direct evidence of the efficacy of sugammadex, as different NMBs were used in the two arms. Rocuronium reversed with sugammadex 3 min after administration was compared to succinylcholine with spontaneous recovery, with respect to the time to recovery of modest neuromuscular function, namely a single twitch (T_1) at least 10 percent of baseline. The results are shown below (module 2.7.3, p. 44).

Recovery from start NMBA to T_1 to 10% (min), Clinical Trial 19.4.303 (ITT group)

	Treatment group	
	Rocuronium + Org 25969	Succinylcholine
n	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median	4.2	7.1
Range	3.5-7.7	3.8-10.5

Recovery with rocuronium and sugammadex was statistically significantly faster ($p < 0.001$) than spontaneous recovery with succinylcholine.

3.2 EVALUATION OF SAFETY

Adverse events are discussed in the medical officers' reviews. I call attention, however, to one potential issue of safety that has a statistical aspect. If sugammadex is to be used in situations where immediate reversal of neuromuscular blockade may be necessary for the safety of the patient, then lack of effect in those conditions constitutes a safety problem.

The distribution of recovery times with rocuronium and sugammadex in study 303 was skewed to the right, with the range going from only slightly less than the median to almost double. The cases at the right-hand end deserve careful attention from medical reviewers. Beyond noting their existence, statistics are not much help in understanding the implications of these cases. The question here is not whether sugammadex usually works, or works faster on average than recovery from succinylcholine. Rather, the issue is what happens if it does not work, or works slowly.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

See the clinical pharmacologist's review.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The principal studies reviewed were all of different designs: there were no replicated studies. They are individually persuasive, however. Furthermore, though they investigated slightly different clinical settings, both the mechanism of action and the clinical effect of the test drug are the same in each setting: reversal of neuromuscular blockade. There is ample evidence that sugammadex produces this effect.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Sugammadex was effective in reversing neuromuscular blockade produced by rocuronium or vecuronium. The proposed labeling accurately describes the results of the clinical trials. With single studies in each clinical setting, however, it is not clear that the evidence is up to the usual standard for comparative claims.

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

/s/

Thomas Permutt
3/13/2008 02:00:17 PM
BIOMETRICS