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 #	NDA 022-225
Supplement #	8
Drug Name	Bridion® (Sugammadex) injection
Indication(s)	For the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery
Applicant	Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)
Date(s)	Submission: August 26, 2020
	PDUFA due date: June 26, 2021
Review Priority	Standard
Biometrics Division	Division of Biometric I
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Keywords	active control/superiority, censored observations, imputation/data imputation, Kaplan-Meier product limit, logrank test, stratification, subgroup analyses, survival analysis

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1 EXECUTIVE SUMMARY

This review assesses a Phase IV Study P089 of sugammadex for the reversal of moderate neuromuscular blockade (NMB) in participants aged 2 to less than 17 years old. Efficacy was demonstrated at reducing the time to recovery compared to the active control neostigmine.

Bridion® (sugammadex, single-dose injection, 100 mg/mL, NDA022225) was approved on December 15, 2015, for the reversal of NMB induced by rocuronium or vecuronium in adults undergoing surgery. Study P089 was designed to fulfill the post-marketing pediatric requirement. It was a randomized, active comparator-controlled, parallel group, multisite, double-blinded trial. The primary efficacy endpoint was time to recovery to a train-of-four (TOF) ratio of 0.9 or above. The secondary endpoints were time to recovery to a TOF ratio of 0.8 or above and time to recovery to a TOF ratio of 0.7 or above. The efficacy analyses were based on all randomized participants who received at least 1 dose of study intervention in the setting of moderate block.

The applicant evaluated the efficacy by comparing sugammadex to neostigmine using log transformed time to recovery values via Analysis of Variance (ANOVA), adjusting for neuromuscular blocking agent (NMBA) (rocuronium or vecuronium) and age. The primary analysis demonstrates that the time to recovery to a TOF ratio of 0.9 or above was statistically significantly faster ($p<0.0001$) in participants dosed with sugammadex 2 mg/kg compared to neostigmine with a ratio of geometric means equal to 0.22 and 95% confidence interval (CI) of (0.16, 0.32). The applicant also performed sensitivity and subgroup analyses, the results of which are consistent with the primary finding. Based on the Kaplan-Meier estimates, 90.9% (30/33) of participants dosed with sugammadex 2 mg/kg recovered to a TOF ratio of ≥0.9 within 3 minutes compared with 8.8% (3/34) of participants in the neostigmine group. The statistical team has verified the applicant's analyses and has some comments on the labeling including the description of the study participants and the statistics reported for the efficacy comparison.

The statistical team confirms that Study P089 supports the use of sugammadex for the reversal of moderate NMB in pediatric participants aged 2 to less than 17 years old based on the efficacy data.

2 INTRODUCTION

A single study was submitted to support the use in pediatric patients aged 2 to less than 17 years old. This review focuses on the efficacy evaluation.

2.1 Overview

Bridion® (sugammadex, single-dose injection, 100 mg/mL), NDA022225, was approved on December 15, 2015, for the reversal of NMB induced by rocuronium or vecuronium in adults undergoing surgery. Several post-marketing requirements (PMRs) were issued upon approval including one pediatric study. In addition, a Pediatric Written Request (PWR) was issued on October 28, 2016 and the following post marketing requirement was requested on July 11, 2018.

Study P089 was designed to fulfill the pediatric requirement and support an update to the approved product labeling in patients aged 2 to less than17 years old. The applicant has proposed a separate Study P189 in patients from birth to less than 2 years old, of which the results haven't been submitted yet by May 2, 2021.

3003-8 A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of BRIDION injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages 2 to less than 17 years old.

Table 1 List of All Studies Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
P089MK8616 (Part B)	Phase IV	Day 1: Single dose injection	2 weeks	sugammadex 2 mg/kg: 54 sugammadex 4 mg/kg: 199 neostigmine: 35	Patients ages 2 to less than 17 years old. Deep block (sugammadex 4 mg/kg) data were not contribute to the primary efficacy analysis.

2.2 Data Sources

The applicant submitted this NDA supplement to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: \\CDSESUB1\evsprod\NDA022225\0290. All data are in SAS transport files in the CDISC and ADaM data format.

3 STATISTICAL EVALUATION

The title of Study P089 is 'A Phase 4 Double-Blinded, Randomized, Active Comparator-Controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants'.

3.1 Data and Analysis Quality

The statistical team can reproduce the applicant's results using the submitted data. No additional data submission was needed.

The protocols for the required pediatric assessments were submitted to IND068029. Dr. James Travis concurred the protocol dated March 9, 2017 (SDN699, eCTD0663). The review was dated April 5, 2017 in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). (https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804328b3&_afrRedirect=2660367633396813)

The revised protocols after March 9, 2017 were not assigned to statistical team for review. The main statistics related changes, between the protocol dated March 10, 2017 and the final protocol dated August 18, 2017, include

- moving efficacy hypothesis from a secondary objective to the primary objective;
- removing sugammadex 16 mg/kg treatment arm from the protocol;
- adding text regarding trial stopping criteria.

These changes are acceptable and have been concurred by the clinical review team. Study P089 was conducted during February 12, 2018 to January 28, 2020. The supplemental statistical analysis plan was finalized on March 12, 2020. The final data were extracted and unmasked to the study team after the final database lock on March 19, 2020.

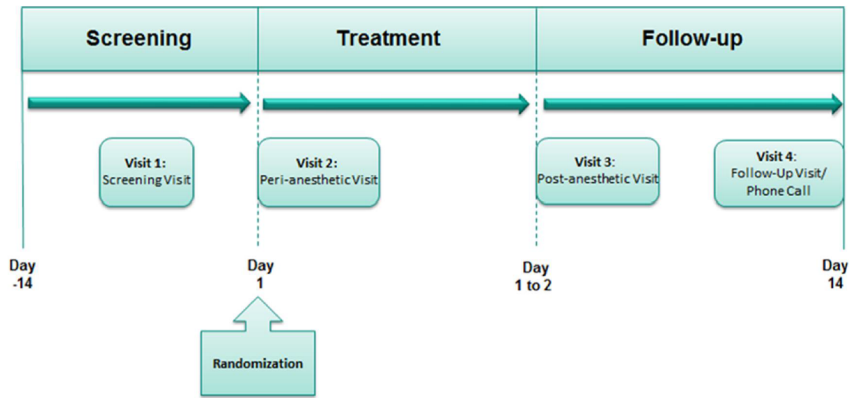
3.2 Evaluation of Efficacy

The applicant conducted the study and analyzed the data according to the concurred protocol. The statistical team confirmed that the efficacy in pediatric patients aged 2 to less than 17 years old was established.

3.2.1 Study Design and Endpoints

Study P089 was a randomized, active comparator-controlled, parallel group, multisite, double-blinded trial of sugammadex in pediatric participants from 2 to less than 17 years of age for the reversal of NMB induced by rocuronium or vecuronium. Male and female participants between the ages of 2 and less than 17 years at Visit 2, of American Society of Anesthesiologists (ASA) Class 1, 2, or 3, who underwent a planned nonemergent surgical procedure or clinical situation requiring moderate or deep NMB with either rocuronium or vecuronium were enrolled in this study. Figure 1 illustrates the study design.

Figure 1 Study Design



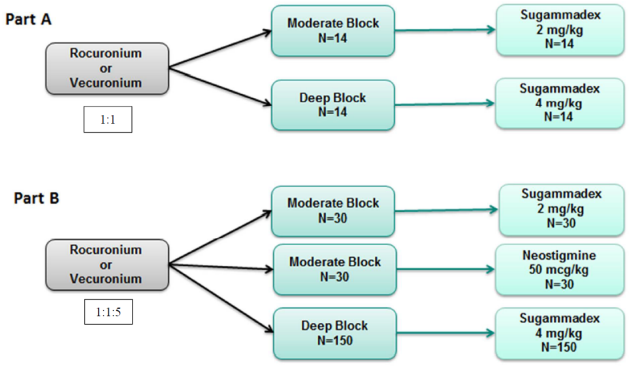
Source: Figure 9-1 in the Clinical Study Report for P089MK8616, page 28 out of 459.

The study consisted of two parts, Part A and B. Part A only collected and evaluated pharmacokinetics (PK) data. Figure 2 illustrates the planned study interventions randomization. In Part B, participants were randomized to one of the three intervention groups in an overall 1:1:5 ratio to:

- moderate block and reversal with 2 mg/kg sugammadex; or
- moderate block and reversal with neostigmine + glycopyrrolate or atropine sulfate (hereafter, referred to as neostigmine) [active control]; or
- deep block and reversal with 4 mg/kg sugammadex

Note: The inclusion of the deep block and reversal with 4 mg/kg sugammadex arm was for safety reasons. Therefore, this arm was not included in efficacy evaluation.

Figure 2 Planned Study Interventions Randomization



Note: Approximately 30% of the overall planned sample was to be enrolled in the vecuronium stratum.

Source: Figure 9-2 in the Clinical Study Report for P089MK8616, page 29 out of 459.

The primary endpoint was the time to recovery to a TOF ratio of 0.9 or above for the reversal of moderate NMB in sugammadex group compared to neostigmine group. The secondary endpoints were the time to recovery to a TOF ratio of 0.8 or above and the time to recovery to a TOF ratio of 0.7 or above.

3.2.2 Statistical Methodologies

Analysis Datasets: Both the primary and supportive analyses were based on the All Participants Treated (APT) population that included all randomized participants who received at least 1 dose of study intervention, in the setting of moderate block was conducted with data from Part B. Deep block data did not contribute to the efficacy analysis.

Primary Analysis: The applicant evaluated the efficacy by comparing sugammadex to neostigmine using log transformed values via ANOVA, adjusting for NMBA and age.

Sensitivity Analyses: The applicant reanalyzed the efficacy using a stratified log-rank test (adjusting for age group and NMBA), Kaplan-Meier curves, and a Cox regression model with Efron's method of tie handling with age as a covariate and NMBA as a stratification factor.

Multiplicity Adjustment: The applicant conducted a single efficacy assessment and so no multiplicity adjustment was required.

Missing Data Imputation: The statistical analysis plan (SAP) described the following imputation procedure on pages 6-7 out of 25.

"If the time from the start of administration of study drug to recovery of the TOF ratio ≥0.9 is missing, there are 3 cases for imputation purposes:

1. Time to TOF ratio ≥0.8 is available:
    a. Sugammadex group: First, for all participants randomized to receive sugammadex and with times to recovery of the TOF ratio ≥0.8 and ≥0.9 available, the difference between these 2 recovery times will be calculated. Next, the 95th percentile (P95) of these differences will be added to the time to recovery of the TOF ratio ≥0.8 of the participants with missing times to recovery of the TOF ratio ≥0.9. This will be used as the imputed missing time to recovery of the TOF ratio ≥0.9.
    b. Neostigmine group: Same as for the sugammadex group, but now only participants randomized to receive neostigmine will be used, and the 5th percentile (P5) of the differences in time to recovery of the TOF ratio of ≥0.8 and ≥0.9 will be calculated.
2. Time to TOF ratio ≥0.7 is available, but the time to TOF ratio ≥0.8 is missing:
    a. Sugammadex group: First, for all participants randomized to sugammadex and with times to recovery of the TOF ratio ≥0.7 and ≥0.9 available, the difference in time between these 2 recovery times will be calculated. Next, the P95 of these differences will be added to the time to recovery of the TOF ratio ≥0.7. This will be used as imputation of the missing time to recovery of the TOF ratio ≥0.9.
    b. Neostigmine group: Same as for sugammadex group, but now only participants randomized to receive neostigmine will be used and the P5 of the differences in time to recovery of the TOF ratio ≥0.7 and ≥0.9 will be calculated.
3. Times to TOF ratio ≥0.7 and ≥0.8 are both missing:
    a. Sugammadex group: The P95 of the time to recovery in all participants randomized to sugammadex with an observed recovery time of the TOF ratio ≥0.9 will be imputed.
    b. Neostigmine group: The P5 of the time to recovery in all participants randomized to receive neostigmine with an observed recovery time of the TOF ratio ≥0.9 will be imputed.

A corresponding procedure will be followed for imputation of missing times from the start of administration of study drug to recovery of the TOF ratio ≥0.8 (secondary efficacy variable). For imputation of missing times, P95 (sugammadex) or P5 (neostigmine) of the differences in time between recovery of the T4/T1 ratio ≥0.7 and ≥0.8 will be used.

For imputation of missing times from the start of administration of study drug to recovery of the TOF ratio ≥0.7 (secondary efficacy variable), the P95 observed time for the participants randomized to the sugammadex group will be imputed. For participants randomized to the neostigmine group the P5 observed time will be imputed. Imputation of missing times of the primary and secondary efficacy variables, however, should always result in a non-descending sequence of times to recovery of the TOF ratios of ≥ 0.7, ≥0.8, and ≥0.9."

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study P089 was conducted at 26 centers in 8 countries. Table 2 summarizes the patient disposition. As mentioned in Section 3.2.1 of this review, Part A was for PK evaluation only; in Part B, the inclusion of 4 mg/kg sugammadex arm in the setting of deep block was for safety reasons and that arm did not contribute to the efficacy evaluation. Therefore, all efficacy analyses were based on the two groups with moderate block in Part B, which were conducted in 70 randomized pediatric participants, among whom 67 received at least one dose of treatment.

Table 3 summarizes the demographic and baseline characteristics for the efficacy analysis population. Mean and standard deviation (SD) as well as median and range are reported for continuous variables; frequency and proportion are reported for categorical variables. Among the 67 participants treated, mean age was 8 years old; mean weight was 35 kg; 57% were male; and 92% were Caucasian. Table 3 is different from the applicant's Table 10-4 (Subject Characteristics) because the applicant combined 276 treated participants in Parts A and B.

Table 2 Patient Disposition

	Part A		Part B			Total
	Sugammadex 2mg/kg (Moderate block)	Sugammadex 4mg/kg (Deep block)	Sugammadex 2mg/kg (Moderate block)	Sugammadex 4mg/kg (Deep block)	Neostigmine (Moderate block)	
Randomized	19	23	35	176	35	288
Analysis Population			**33**		**34**	**67**
Completed			32		33	65

Source: Statistical team's analysis using applicant's adam-adsl.

Table 3 Demographic and Baseline Characteristics

	Sugammadex 2mg/kg (n=33)	Neostigmine (n=34)	Total
Age (Years)			
Mean (Standard Deviation)	8.0 (4.5)	8.5 (4.3)	8.3 (4.4)
Median (Range)	7 (2, 15)	8 (2, 16)	8 (2, 16)
Age Group			
2 to <6 years	13 (39%)	12 (35%)	25 (37%)
6 to <12 years	10 (30%)	13 (38%)	23 (34%)
12 to <17 years	10 (30%)	9 (26%)	19 (28%)
Gender			
Male	20 (61%)	18 (53%)	38 (57%)
Female	13 (39%)	16 (47%)	29 (43%)
Race			
White	29 (91%)	32 (94%)	61 (92.4%)
Others	3 (9%)	2 (6%)	5 (7.6%)
Weight (kg)			
Mean (Standard Deviation)	35.0 (22.1)	35.4 (21.8)	35.2 (21.8)
Median (Range)	27 (11, 85)	29 (11, 99)	29 (11, 99)
Region			
United States	9 (27%)	5 (15%)	14 (21%)
Others	24 (73%)	29 (85%)	53 (79%)
ASA			
1	24 (73%)	24 (71%)	48 (72%)
2	6 (18%)	9 (26%)	15 (22%)
3	3 (9%)	1 (3%)	4 (6%)
NMBA			
Rocuronium	20 (61%)	20 (59%)	40 (60%)
Vecuronium	13 (39%)	14 (41%)	27 (40%)

Source: Statistical team's analysis using applicant's adam-adsl for all participants treated in Part B.

3.2.4 Results and Conclusions

The statistical team confirmed the applicant analyses. The time to recovery to a TOF ratio of 0.9 or above is faster among pediatric participants (2 to <17 years) dosed with sugammadex 2 mg/kg compared to neostigmine for the reversal of moderate NMB induced by rocuronium or vecuronium.

Missing Data Imputation: The statistical team checked the applicant's missing data imputation in **bold** in Table 4, all of which were imputed according to the procedure described in the SAP. Among the 67 randomized participants who received at least 1 dose of study intervention in Part B (33 received sugammadex 2 mg/kg and 34 received neostigmine), 5 subjects had missing the primary or key secondary endpoints, all of whom received neostigmine.

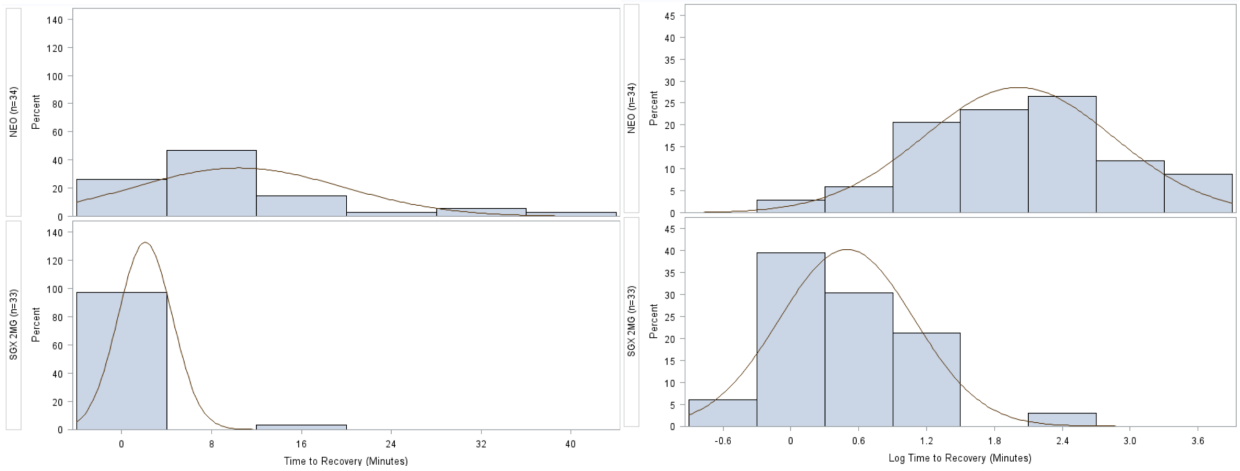
Table 4 Missing Data Imputation

Site Number	Subject ID	Treatment	Age	NMBA	TOF≥0.7	TOF≥0.8	TOF≥0.9
0038	(b) (6)	neostigmine	8	Vecuronium	19.4000	28.9000	**29.1500**
0150		neostigmine	14	Rocuronium	5.6000	9.8667	**18.3667**
0355		neostigmine	2	Vecuronium	8.0500	**8.3000**	**8.3000**
0355		neostigmine	5	Vecuronium	4.3167	**4.5667**	**4.5667**
0500		neostigmine	11	Rocuronium	5.4833	12.2333	**12.7333**

Source: Statistical team's analysis using applicant's adam-adeff.

Primary Analysis: The statistical team checked the data distribution and found that the primary endpoint time to recovery to a TOF ratio of 0.9 or above was not normally distributed, whereas the log transformed time to recovery was normally distributed. Figure 3 illustrates the distribution of the raw data on the left and the log transformed data on the right. Therefore, the log transformed values were used in the efficacy analysis.

Figure 3 Distribution of Primary Endpoint



Source: Statistical team's analysis using applicant's adam-adeff, using all participant treated in Part B.

Based on ANOVA of log transformed values, adjusting for age and NMBA, the time to recovery to a TOF ratio of 0.9 or above was statistically significantly faster ($p<0.0001$) in participants dosed with sugammadex 2 mg/kg compared to neostigmine (ratio of geometric means = 0.22, 95% CI: 0.16, 0.32). Table 5 summarizes the results from the primary analysis, including geometric least squares (LS) mean for each treatment group, ratio of geometric means and 95%

CI. The geometric LS mean for each treatment group in Table 5 differs slightly from the observed geometric mean reported in Table 11-1 (Primary Analysis) of the applicant's clinical study report. The difference between observed geometric means and geometric LS means is that geometric LS means are adjusted by NMBA and age in this case. Therefore, geometric LS means are more comparable and should be reported in the statistical comparison results. For convenience, the results for secondary endpoints are also included in Table 5.

Table 5 Primary Analysis Results of the Primary Endpoint and Secondary Endpoints

Endpoint	Sugammadex 2mg/kg (n=33) Geometric LS Mean (95% CI)	Neostigmine (n=34) Geometric LS Mean (95% CI)	Ratio of Geometric LS Means (95% CI)	p-Value
Primary Endpoint: Time to recovery to a TOF Ratio of 0.9 or above	1.7 (1.3, 2.1)	7.4 (5.8, 9.6)	0.2 (0.2, 0.3)	<0.0001
Secondary Endpoint: Time to recovery to a TOF Ratio of 0.8 or above	1.3 (1.1, 1.7)	5.0 (4.0, 6.4)	0.3 (0.2, 0.4)	<0.0001
Secondary Endpoint: Time to recovery to a TOF Ratio of 0.7 or above	1.1 (0.9, 1.4)	3.7 (3.0, 4.6)	0.3 (0.2, 0.4)	<0.0001

Source: Statistical team's analysis using applicant's adam-adeff for all participants treated in Part B. All the statistics are based on an ANOVA of log transformed time to recovery values, adjusting for age and NMBA. The P-values are two-sided.

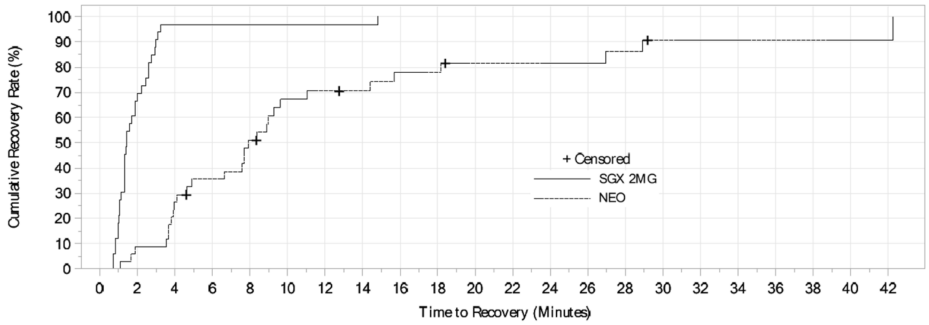
Sensitivity Analyses: The sensitivity analysis results were consistent with the primary finding. Based on Kaplan-Meier estimates, 90.9% (30/33) of participants dosed with sugammadex 2 mg/kg recovered to a TOF ratio of 0.9 or above within 3 minutes compared with 8.8% (3/34) of participants in the neostigmine group. The time to recovery to a TOF ratio of 0.9 or above was statistically significantly faster (p<0.0001) in participants dosed with sugammadex 2 mg/kg compared to neostigmine (hazard ratio = 7.34, 95% CI: 3.75, 14.39). Table 6 summarizes the results from sensitivity analyses and Figure 4 illustrates the Kaplan-Meier curves for the primary endpoint. For convenience, the results for secondary endpoints are also included in Table 6.

Table 6 Sensitivity Analyses

Endpoint	Sugammadex 2mg/kg (n=33) Median (95% CI)	Neostigmine (n=34) Median (95% CI)	Hazard Ratio (95% CI)	p-Value
Primary Endpoint: Time to recovery to a TOF Ratio of 0.9 or above	1.4 (1.3, 1.9)	7.9 (4.6, 9.6)	7.3 (3.7, 14.4)	<0.0001
Secondary Endpoint: Time to recovery to a TOF Ratio of 0.8 or above	1.2 (1.1, 1.4)	4.7 (3.2, 6.4)	6.1 (3.2, 11.5)	<0.0001
Secondary Endpoint: Time to recovery to a TOF Ratio of 0.7 or above	1.1 (0.8, 1.1)	3.2 (2.6, 4.3)	5.6 (3.1, 10.2)	<0.0001

Source Statistical team's analysis using applicant's adam-adeff for all participants treated in Part B. The median times to recovery and their 95% CI are based on the Kaplan-Meier product-limit method for censored data. The hazard ratio and its 95% CI are based on Cox regression model with Efron's method of tie handling with age as a covariate and NMBA as a stratified factor. Two-sided p-values are based on stratified log-rank test, adjusting for age and NMBA.

Figure 4 Kaplan-Meier Curves for Primary Endpoint



Source Figure 11-1 in the Clinical Study Report for Study P089MK8616, page 52 out of 459, using all participants treated in Part B.

3.3 Evaluation of Safety

See clinical review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses presented in this section are all exploratory. The main objective of the exploratory subgroup analysis is to assess consistency across subgroups with respect to the primary analysis results. Because of the exploratory purpose of the subgroup analyses, the p-values are not presented here.

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses were performed by age, gender, geographic region and NMBA using the APT population. The estimated treatment effects in the primary endpoint the time to recovery to a TOF ratio 0.9 or above were consistent across these subgroups. There were no important differences in the results within these subgroups compared to the overall analysis.

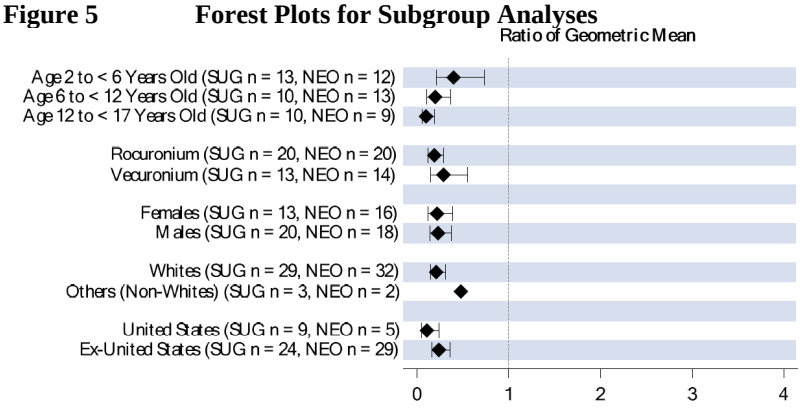
Table 7 summarizes the results from the subgroup analyses and Figure 5 demonstrates the ratio of geometric means and its 95% CI for each subgroup. The results were presented only for those subgroups with at least 10% subjects in each subgroup. The subgroup analysis for race was not applicable due to limited sample size for non-white subgroup (n=5).

Table 7 Subgroup Analyses

	Sugammadex 2mg/kg		Neostigmine		Ratio of Geometric LS Mean (95% CI)
	n	Geometric LS Mean (95% CI)	n	Geometric LS Mean (95% CI)	
Age Group					
2 to <6 years	13	2.0 (1.3, 3.1)	12	5.0 (3.2, 7.9)	0.4 (0.2, 0.8)
6 to <12 years	10	1.4 (0.9, 2.2)	13	7.0 (4.6, 10.6)	0.2 (0.1, 0.4)
12 to <17 years	10	1.6 (1.1, 2.5)	9	14.7 (9.4, 23.0)	0.1 (0.1, 0.2)
Gender					
Male	20	1.6 (1.2, 2.3)	18	7.2 (5.0, 10.2)	0.2 (0.1, 0.4)
Female	13	1.7 (1.1, 2.6)	16	7.8 (5.2, 11.7)	0.2 (0.1, 0.4)
Region					
United States	9	1.8 (1.2, 2.8)	5	16.9 (9.1, 31.2)	0.1 (0.1, 0.2)
Others	24	1.5 (1.1, 2.1)	29	6.3 (4.8, 8.2)	0.2 (0.2, 0.4)
NMBA					
Rocuronium	20	1.5 (1.1, 2.1)	20	8.1 (6.0, 11.0)	0.2 (0.1, 0.3)
Vecuronium	13	1.9 (1.2, 3.0)	14	6.5 (4.2, 10.1)	0.3 (0.2, 0.6)

Source: Statistical team's analysis using applicant's adam-adeff for all participants treated in Part B. All the statistics are based on an ANOVA of log transformed time to recovery values, adjusting for age and NMBA.

Figure 5 Forest Plots for Subgroup Analyses



Source: Figure 11-2 in the Clinical Study Report for P089MK8616, page 53 out of 459, using all participants treated in Part B.

4.2 Other Special/Subgroup Populations

Subgroup analysis by stratification factor NBMA was included in Section 4.1.

5 SUMMARY AND CONCLUSIONS

The statistical team confirms that Study P089 supports the use of sugammadex for the reversal of moderate NMB in pediatric participants aged 2 to less than 17 years old based on the efficacy data.

5.1 Statistical Issues

The statistical team didn't find any statistical issues that impact the overall conclusions.

5.2 Collective Evidence

Not applicable.

5.3 Conclusions and Recommendations

Based on the efficacy analyses, the time to recovery to a TOF ratio of 0.9 or above was statistically significantly faster ($p<0.0001$) in participants dosed with sugammadex 2 mg/kg compared to neostigmine with a ratio of geometric means equal to 0.22 and 95% CI of (0.16, 0.32). The results from sensitivity and subgroup analyses are consistent with the primary finding. Therefore, Study P089 supports the use of sugammadex for the reversal of moderate NMB in pediatric participants aged 2 to less than 17 years old.

5.4 Labeling Recommendations (as applicable)

The applicant proposed the following additional labeling in Section 14.1 (Controlled Clinical Studies):

"Comparative Study of BRIDION versus Neostigmine as a Reversal Agent for Neuromuscular Blockade Induced by Rocuronium or Vecuronium in Pediatric Patients 2 to <17 Years of Age Time to recovery from neuromuscular blockade induced by rocuronium or vecuronium followed by administration of BRIDION or neostigmine was assessed in a randomized, double-blind, active comparator controlled study. The study was conducted in 288 randomized pediatric patients 2 to <17 years of age, of which 276 patients received treatment (153 boys and 123 girls; ASA class 1, 2, and 3; 89.5% were Caucasian; median weight was 25 kg; median age was 7 years). The primary efficacy objective was to evaluate the effect of BRIDION compared to neostigmine for reversal of moderate neuromuscular blockade as measured by time to recovery to a TOF ratio of 0.9 or above.

Recovery to a TOF ratio of 0.9 or above was statistically significantly faster (b) (4) in pediatric patients dosed with BRIDION 2 mg/kg compared with neostigmine for reversal of moderate block based on a geometric mean of 1.(b)(4)minutes for BRIDION 2 mg/kg and 7.(b)(4)minutes for neostigmine (ratio of geometric means was 0.22, 95% CI (0.16, 0.32)). (b) (4) (b) (4) These effects were consistent across age cohorts studied (2 to <6; 6 to <12; 12 to <17 years of age) and neuromuscular blocking agent (rocuronium and vecuronium)."

The statistical team has the following recommendations regarding the proposed additional labeling in Section 14.1 (Controlled Clinical Studies):

- Study Participants: Change the study participants to the two moderate block groups in Part B, which was used in the efficacy analyses of BRIDION compared to the active control neostigmine, because Part A was for PK only, and the deep block arm in Part B was for safety reasons and did not contribute to the efficacy comparison. That is, in the first paragraph, change

  'The study was conducted in 288 randomized pediatric patients 2 to <17 years of age, of which 276 patients received treatment (153 boys and 123 girls; ASA class 1, 2, and 3; 89.5% were Caucasian; median weight was 25 kg; median age was 7 years).'

  to

  'The study was conducted in 70 randomized pediatric patients 2 to <17 years of age, of which 67 patients received BRIDION 2 mg/kg or neostigmine (38 boys and 29 girls; ASA class 1, 2, and 3; 92% were Caucasian; mean weight was 35 kgs and mean age was 8 years).'

- Efficacy Comparison: Report the model based geometric least squares means (1.7 vs 7.4) from the primary analysis, (b) (4). In addition, in the result statement, change 'pediatric patients' to 'pediatric patents 2 to < 17 years of age' to specify the study participants. The (b) (4) should be removed to be consistent with our previous practice. That is, in the second paragraph, change

‘Recovery to a TOF ratio of 0.9 or above was statistically significantly faster (b) (4) in pediatric patients dosed with BRIDION 2 mg/kg compared with neostigmine for reversal of moderate block based on a geometric mean of 1 (b) (4) minutes for BRIDION 2 mg/kg and 7. (b) (4) minutes for neostigmine (ratio of geometric means was 0.22, 95% CI (0.16, 0.32)).’

to

‘Recovery to a TOF ratio of 0.9 or above was statistically significantly faster in pediatric patients 2 to < 17 years of age dosed with BRIDION 2 mg/kg compared with neostigmine for reversal of moderate block based on a geometric mean of 1.7 minutes for BRIDION 2 mg/kg and 7.4 minutes for neostigmine (ratio of geometric means was 0.22, 95% CI (0.16, 0.32)) .’

- (b) (4)

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