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 #:	NDA 022225
Supplement #:	14
Drug Name:	BRIDION® (Sugammadex)
Indication(s):	Reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in pediatric patients from birth to less than 2 years of age
Applicant:	Merck Sharp & Dohme Corp., a Subsidiary of Merck & Co., Inc., NJ, USA (MSD)
Date(s):	Received: 06/12/2024 Filling planning: 07/18/2024 Filling review due: 08/09/2024 Filling: 08/09/2024 Day-74: 08/23/2024 Midcycle: 09/19/2024 Pediatric Exclusivity Board Meeting: 10/16/2024 PeRC Meeting: 10/29/2024 PDUFA due date: 12/12/2024
Review Priority:	Priority
Biometrics Division:	Division of Biometrics I
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Concurring Reviewers:	Xinyu Tang, PhD, Secondary Reviewer, Team Lead Sue Jane Wang, PhD, Tertiary Reviewer, Deputy Director
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Clinical Team:	Lisa Banta, MD, Primary Reviewer, Medical Officer Alla Bazini, MD, Secondary Reviewer, Team Lead, Rigoberto Roca, MD, Tertiary Reviewer, Director

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Keywords: active control/superiority, censored observations, Kaplan-Meier product limit, logrank test, proportional hazards, stratification, subgroup analyses, survival analysis

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1 EXECUTIVE SUMMARY

BRIDION® (sugammadex, single-dose injection, 100 mg/mL, NDA022225) was originally approved on December 15, 2015, for the reversal of moderate neuromuscular blockade (NMB) induced by rocuronium or vecuronium in adults undergoing surgery. On June 25, 2021, BRIDION® was approved for an extended indication to pediatric patients aged over 2 years. On June 12, 2024, Merck, Sharp & Dohme LLC submitted an efficacy supplemental New Drug Application (sNDA), which includes the final study report for Study MK-8616-169 (hereafter referred to as Study 169) entitled, "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 Blockage in Pediatric Participants Aged Birth to <2 Years." This study was conducted to fulfill the following Post Marketing Requirement (PMR) 3003-09 issued on July 11, 2018, and deferral extension issued on August 31, 2023:

> 3003-09: 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 birth to less than 2 years old.

Based on the results from Study 169, the applicant proposed to update the BRIDION Prescribing Information to provide for the use of BRIDION for the reversal of NMB induced by rocuronium or vecuronium in pediatric patients from birth to less than 2 years of age.

Study 169 consists of a 2-part structure (Part A and Part B). Part A is a 2-panel, open-label, single-arm, multisite study to evaluate pharmacokinetics (PK) and safety of sugammadex when used for reversal of NMB. Part B is a randomized, double-blinded, active comparator-controlled, multisite study to evaluate the efficacy and safety of sugammadex as determined by time to neuromuscular recovery (TTNMR) in the moderate and deep block setting. This statistical review focuses on the efficacy results from Part B of Study 169.

In Part B of Study 169, a total of 95 participants were randomized to 1 of the following intervention arms in a 1:1:1 ratio:

- Moderate block and reversal with 2 mg/kg sugammadex (n=32); or
- Moderate block and reversal with 50 mcg/kg neostigmine (n=32); or
- Deep block and reversal with 4 mg/kg sugammadex (n=32).

The primary efficacy endpoint was TTNMR, defined as the interval from administration of reversal agent to time of neuromuscular recovery, comparing 2 mg/kg sugammadex (hereafter referred to as sugammadex) to 50 mcg/kg neostigmine (hereafter referred to as neostigmine) for moderate NMB. The analyses of the primary efficacy endpoint were based on all participants treated (APT) which included 29 and 31 participants in the sugammadex and neostigmine groups, respectively, who were randomized and received at least 1 dose of study intervention, often referred to as modified intent-to-treat participants.

Based on a stratified Cox regression model, TTNMR was shown statistically significantly faster in the sugammadex group compared to the neostigmine group (p=0.0021). The hazard ratio (sugammadex versus neostigmine) was estimated to be 2.4 (95% confidence interval [CI]:1.37, 4.18). The applicant performed a supportive analysis for TTNMR based on the product-limit

(Kaplan-Meier) and logrank test. The applicant also performed a sensitivity analysis for TTNMR only including those with neuromuscular recovery assessment using train-of-four stimulation/ peripheral nerve stimulator (TOF/PNS) devices. The results from the supportive analysis and sensitivity analysis were consistent with the primary analysis findings.

Based on our statistical review, we agree that the efficacy results from Part B of Study 169 support the use of sugammadex for the reversal of moderate NMB in pediatric participants from birth to less than 2 years of age.

2 INTRODUCTION

2.1 Overview

BRIDION® (sugammadex, single-dose injection, 100 mg/mL, NDA022225) was originally approved on December 15, 2015, for the reversal of moderate NMB induced by rocuronium or vecuronium in adults undergoing surgery. On June 25, 2021, BRIDION® was approved for an extended indication to pediatric patients aged over 2 years. On June 12, 2024, Merck, Sharp & Dohme LLC submitted an efficacy sNDA, which includes the final study report for Study MK-8616-169 (hereafter referred to as Study 169) entitled, "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 Blockage in Pediatric Participants Aged Birth to <2 Years." This study was conducted to fulfill the following Post Marketing Requirement (PMR) 3003-09 issued on July 11, 2018, and deferral extension issued on August 31, 2023:

> 3003-09: 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 birth to less than 2 years old.

Based on the results from Study 169, the applicant proposed to update the BRIDION Prescribing Information to provide for the use of BRIDION for the reversal of NMB induced by rocuronium or vecuronium in pediatric patients from birth to less than 2 years of age.

Study 169 consists of a 2-part structure (Part A and Part B). Part A evaluated the safety and confirmed the doses of sugammadex. Part B assessed safety and efficacy parameters of sugammadex. This statistical review focuses on the efficacy results from Part B of Study 169 shown in Table 1.

Table 1 List of All Studies Included in Analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Randomized Subjects per Arm	Study Population
MK-8616-169 (Part B)	Phase 4	Single	2 weeks	Sugammadex	Patients from birth to less

	MC, R, DB, PG, AC	dose injection on Day 1		2 mg/kg (moderate block): 31 Sugammadex 4 mg/kg (deep block): 32 Neostigmine + (Glycopyrrolate or Atropine) (moderate block): 32	than 2 years of age undergoing a surgery or clinical procedure requiring a neuromuscular blocking agent (rocuronium or vecuronium) for either moderate or deep block.

* MC: multicenter; R: randomized; DB: double-blind; PG: parallel-group; AC: active-controlled
Note: Data from the deep block sugammadex 4 mg/kg arm were not included in the analyses of the efficacy endpoints.

2.2 Data Sources

The applicant submitted this sNDA to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location: \\CDSESUB1\evsprod\NDA022225\0632. The applicant submitted both SDTM and ADaM datasets in SAS transport files complying with the CDISC standards.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

We do not identify issues with the quality and integrity of the submitted data. With the submitted data, we can reproduce the applicant's efficacy results for Part B of Study 169 using the submitted data.

The protocols for the required pediatric assessments were submitted to IND068029. The clinical reviewer, Dr. James Travis concurred on the protocol dated Jan 26, 2018 (SDN710, eCTD0674). His clinical review was submitted in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) on March 14, 2018.

Any revised protocols submitted after Jan 26, 2018 were not assigned to the statistical team for review. The main statistics related changes, between the protocol dated Jan 26, 2018 and the final protocol dated October 27, 2022, include

- Study endpoint of "time to neuromuscular recovery" moved to primary efficacy endpoint;
- Study endpoint of "time to extubation" moved to secondary efficacy endpoint;
- Protocol updated to assist sites with managing participant assignment in the case of delayed or rescheduled surgeries or clinical procedures.

These changes are acceptable and have been concurred by the clinical review team. Study P169 was conducted during July 23, 2019 to Sep 21, 2023. The supplemental statistical

analysis plan was finalized on Oct 17, 2023. The final data were extracted and unblinded to the study team after the final database lock on Oct 24, 2023/Nov 17, 2023.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 169 was a randomized, active comparator-controlled, parallel-group, multisite, double-blinded study to evaluate the PK, safety, and efficacy of sugammadex in pediatric participants aged birth to <2 years for the reversal of moderate and deep NMB. Participants were planned to be randomized across multiple global sites. The maximum duration of the study for each participant was approximately 14 days.

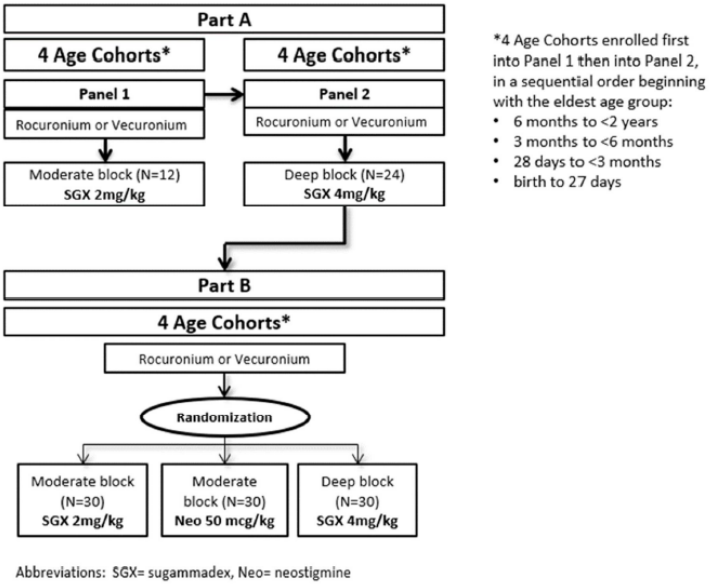
The study design of Study 169 is shown in Figure 1. This study consisted of 2 parts (Part A and Part B), and 4 age cohorts per part (6 months to <2 years, 3 months to <6 months, 28 days to <3 months, and birth to 27 days). Part A evaluated the safety and confirmed the doses of sugammadex. Part B assessed safety and efficacy parameters. Our statistical review focuses on Part B of Study 169.

In Part B of Study 169, approximately 126 participants were planned to be randomized to 1 of the following intervention arms in a 1:1:1 ratio:

- Moderate block and reversal with 2 mg/kg sugammadex; or
- Moderate block and reversal with 50 mcg/kg neostigmine; or
- Deep block and reversal with 4 mg/kg sugammadex.

Randomization was stratified by age, beginning with the oldest cohort (6 months to <2 years; 3 months to <6 months; 28 days to <3 months, birth to 27 days) and NMBA (rocuronium or vecuronium). The primary efficacy endpoint was TTNMR, defined as interval from administration of reversal agent to time to neuromuscular recovery. The secondary efficacy endpoint was the time to extubation, defined as interval from administration of reversal agent to removal of the endotracheal tube. Both efficacy endpoints were analyzed comparing the 2 mg/kg sugammadex to the 50 mcg/kg neostigmine for moderate NMB.

Figure 1 Study Design



Source: Figure 9-1 in the Clinical Study Report for P169MK8616, page 33 out of 381

3.2.2 Statistical Methodologies

Analysis Datasets: The primary and supportive efficacy analyses were based on APT population that included all randomized participants who received at least 1 dose of study intervention. Participants were included in the intervention group to which they were randomized for the analysis of efficacy data using the APT population. No treated participants were excluded from the APT population.

Primary Analysis: The applicant evaluated the efficacy by comparing sugammadex to neostigmine on TTNMR and the time to extubation via Cox Proportional Hazards (Cox PH) Model, adjusting for age (continuous) and stratified by NMBA (rocuronium and vecuronium). In addition, the Cox PH model for time to extubation will include a covariate of endotracheal extubation type (deep and not deep).

Sensitivity Analysis: The applicant analyzed the primary efficacy endpoint by including participants with neuromuscular recovery assessment using TOF/PNS devices only.

Supportive Analysis: The applicant performed stratified log-rank test (adjusting for age cohort and NMBA) as well as a Kaplan-Meier (KM) curve for the efficacy endpoints.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 169 was conducted at 39 centers in 12 countries. Table 2 summarizes the patient disposition. 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, efficacy analyses of Part B were based on the two groups with moderate block. The APT population included 29 and 31 participants in the sugammadex and neostigmine groups, respectively, who were randomized and received at least 1 dose of treatment intervention.

Table 2 Participant Disposition

	Part A		Part B			
	Sugammadex 2mg/kg (Moderate block)	Sugammadex 4mg/kg (Deep block)	Sugammadex 2mg/kg (Moderate block)	Sugammadex 4mg/kg (Deep block)	Neostigmine (Moderate block)	Total
Randomized	16	34	31	32	32	145
Analysis Population			**29**		**31**	**60**
Completed			29		31	60

Source: Table 14.1-4 in the Clinical Study Report for P169MK8616, page 91 out of 381; Table 14.1-7 in the Clinical Study Report for P169MK8616, page 96 out of 381

Table 3 summarizes the demographic and baseline characteristics for the APT Population. Among the 60 participants in the APT population, mean age was 8 years old; mean weight was 35 kg; 57% were male; and 92% were Caucasian.

Table 3 Participant Characteristics For APT Population of Part B

	Sugammadex 2mg/kg (n=29)	Neostigmine (n=31)	Total (n=60)
Sex			
Male	24 (82.8%)	19 (61.3%)	43 (71.7%)
Female	5 (17.2%)	12 (38.7%)	17 (28.3%)
Age (days)			
Mean (Standard deviation)	164.0 (176.1)	179.3 (193.9)	171.9 (184.1)
Median (Range)	113 (1, 564)	94 (1, 720)	95 (1, 720)
Age Group			
Birth to 27 days	7 (24.1%)	5 (16.1%)	12 (20.0%)
28 days to < 3 months	6 (20.7%)	9 (29.0%)	15 (25.0%)
3 months to < 6 months	8 (27.6%)	8 (25.8%)	16 (26.7%)
6 months to < 2 years	8 (27.6%)	9 (29.0%)	17 (28.3%)
Race			
White	20 (69.0%)	16 (51.6%)	36 (60.0%)
Others (Non-white)	9 (31.0%)	15 (48.4%)	24 (40.0%)
Weight (kg)			
Mean (Standard deviation)	6.2 (2.7)	6.4 (3.1)	6.3 (2.9)
Median (Range)	5.6 (2.3, 11.9)	5.7 (2.1, 13.4)	5.65 (2.1, 13.4)
Region			
United States	8 (27.6%)	9 (29.0%)	17 (28.3%)
Non-United States	21 (72.4%)	22 (71.0%)	43 (71.7%)
ASA Class			
ASA Class 1	9 (31.0%)	10 (32.3%)	19 (31.7%)
ASA Class 2	16 (55.2%)	15 (48.4%)	31 (51.7%)
ASA Class 3	4 (13.8%)	6 (19.4%)	10 (16.7%)
Neuromuscular Blocking Agent			
Rocuronium	21 (72.4%)	19 (61.3%)	40 (66.7%)
Vecuronium	8 (27.6%)	12 (38.7%)	20 (33.3%)

n = the number of treated participants.

Source: Table 14.1-11 in the Clinical Study Report for P169MK8616, page 105 out of 381

Note: Summary statistics for Age and Weight in the Total column were calculated by the statistical reviewer using applicant's adam-adsl.

3.2.4 Results and Conclusions

Primary and supportive analyses for the primary efficacy endpoint: Table 4 summarizes the results from the primary analysis for the primary efficacy endpoint, including the number of treated participants in Part B, the number of events, Kaplan-Meier estimate, hazard ratio (95% CI), and p-value. Based on Cox PH model, TTNMR was significantly faster (p=0.0021) in the sugammadex group compared with the neostigmine group (hazard ratio = 2.40, 95% CI: 1.37, 4.18). Supportive analysis of the primary efficacy endpoint based on the log-rank test yielded a similar result (p=0.0002).

Based on the Kaplan-Meier estimates (Figure 3), the median TTNMR is 1.4 minutes and 4.4 minutes in the sugammadex and neostigmine groups, respectively. In addition, 79.3% (23/29) participants in the sugammadex group reached neuromuscular recovery within 4 minutes compared with 41.9% (13/31) participants in the neostigmine group.

Table 4 Primary Analysis Results of the Primary Endpoint

Treatment	N	Number of Events (%)	TTNMR (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	1.4 (1.1, 2.0) [1.0, 2.5]
Neostigmine + (Glycopyrrolate or Atropine)	31	30 (96.8)	4.4 (2.7, 7.9) [2.4, 8.5]

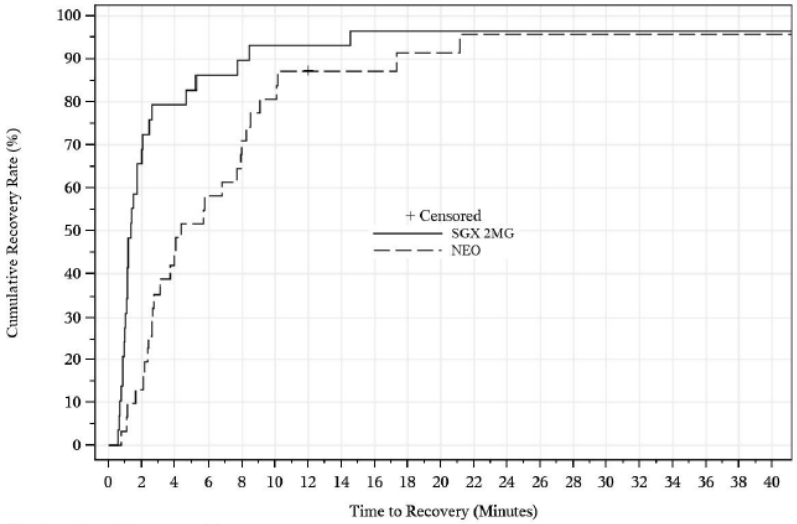
Pairwise Comparisons	Hazard ratio (95% CI[a])	p-value
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	2.40 (1.37, 4.18)	0.0021

N = the number of participants treated; CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile.
Hazard ratio (95% CI) and two-sided p-value were obtained based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous) and stratified by neuromuscular blocking agent.

Source: Table 2 on the sponsor's RESPONSE TO FDA REGARDING PRIMARY AND SECONDARY ENDPOINT ANALYSIS received on Oct 16, 2024

Figure 2 Kaplan-Meier Plot of Time (in Minutes) to Neuromuscular Recovery

Kaplan-Meier Plot of Time (in Minutes) to Neuromuscular Recovery
(All Participants Treated, Part B)



Number of participants at risk

SGX 2MG	29	10	6	4	3	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1
NEO	31	27	18	13	9	6	4	3	3	2	2	1	1	1	1	1	1	1	1	1	1

Number of events inside period

SGX 2MG	19	4	2	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
NEO	4	9	5	4	3	2	0	0	1	0	1	0	0	0	0	0	0	0	0	0	1

TTNMR is censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
TTNMR = time to neuromuscular recovery; SGX 2MG = sugammadex 2 mg/kg; NEO = neostigmine.

Source: Figure 11-1 in the Clinical Study Report for P169MK8616, page 58 out of 381

Sensitivity analysis for the primary efficacy endpoint: Table 5 summarizes the results from the sensitivity analysis for the primary efficacy endpoint, including the number of treated participants in Part B, the number of events, Kaplan-Meier estimate, hazard ratio (95% CI), and p-value. The sensitivity analysis included all the treated participants with Neuromuscular Recovery Assessment Using TOF/PNS Devices. Based on Cox PH model, the time to neuromuscular recovery was significantly faster (p=0.0043) in the sugammadex group compared with the neostigmine group (hazard ratio = 2.27, 95% CI: 1.29, 3.97). Based on Kaplan-Meier estimates, the median TTNMR is 1.4 minutes and 4.4 minutes in the sugammadex and neostigmine groups, respectively. These results are consistent with those from the primary analysis of the primary efficacy endpoint.

Table 5 Sensitivity Analysis Results of the Primary Endpoint

Treatment	N	Number of Events (%)	TTNMR (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	1.4 (1.1, 2.0) [1.0, 2.5]
Neostigmine + (Glycopyrrolate or Atropine)	29	28 (96.6)	4.4 (2.7, 7.9) [2.4, 8.3]
Pairwise Comparisons		Hazard ratio (95% CI)	p-value

Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	2.27 (1.29, 3.97)	0.0043

N = the number of participants treated; CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile.
Hazard Ratio (95% CI) and two-sided p-value based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous) and stratified by neuromuscular blocking agent.

Source: Table 3 on the sponsor's RESPONSE TO FDA REGARDING PRIMARY AND SECONDARY ENDPOINT ANALYSIS received on Oct 16, 2024

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Primary analysis for the secondary efficacy endpoint: Table 6 summarizes the results from the primary analysis for the secondary efficacy endpoint, including the number of treated participants in Part B, the number of events, Kaplan-Meier estimate, hazard ratio (95% CI), and p-value. Based on Cox PH model, the time to extubation was similar (p=0.3381) in both the sugammadex and neostigmine groups (hazard ratio = 1.30, 95% CI: 0.76, 2.21).

Based on Kaplan-Meier estimates (Figure 4), the median time to neuromuscular is 7.9 minutes and 10.5 minutes in the sugammadex and neostigmine groups, respectively. In addition, 79.3% (23/29) participants in the sugammadex group were extubated within 15 minutes from study intervention administration compared with 71.0% (22/31) participants in the neostigmine group.

Table 6 Primary Analysis Results of the Secondary Endpoint

Treatment	N	Number of Events (%)	Time to Extubation (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	7.9 (5.7, 11.6) [4.7, 12.6]
Neostigmine + (Glycopyrrolate or Atropine)	31	31 (100.0)	10.5 (7.9, 13.5) [7.1, 17.4]

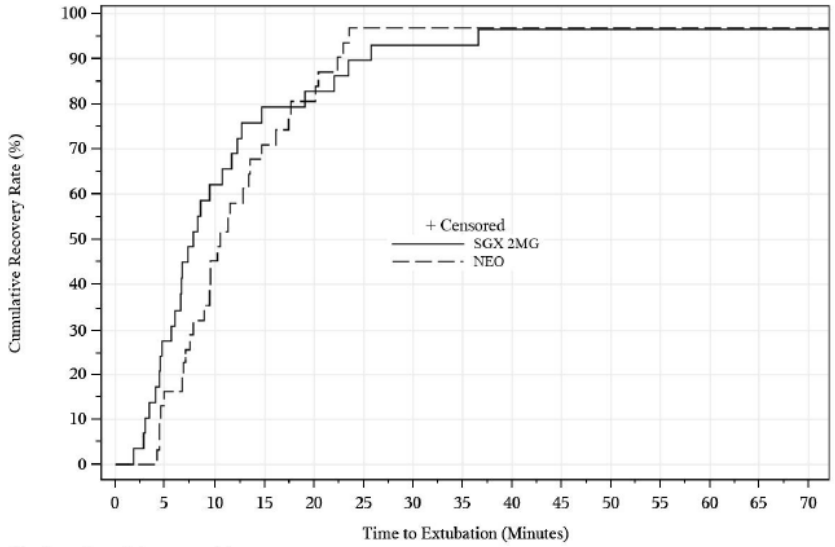
Pairwise Comparisons	Hazard ratio (95% CI)	p-value
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)	1.30 (0.76, 2.21)	0.3381

N = the number of participants treated; CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile.
Hazard Ratio (95% CI) and two-sided p-value based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous), endotracheal extubation type (deep versus not deep) and stratified by neuromuscular blocking agent.

Source: Table 4 on the sponsor's RESPONSE TO FDA REGARDING PRIMARY AND SECONDARY ENDPOINT ANALYSIS received on Oct 16, 2024

Figure 3 Kaplan-Meier Plot of Time (in Minutes) to Extubation

Kaplan-Meier Plot of Time (in Minutes) to Extubation
(All Participants Treated, Part B)



Number of participants at risk

SGX 2MG	29	21	11	6	5	3	2	2	1	1	1	1	1	1	1
NEO	31	27	17	9	6	1	1	1	1	1	1	1	1	1	1

Number of events inside period

SGX 2MG	8	10	5	1	2	1	0	1	0	0	0	0	0	0	1
NEO	4	10	8	3	5	0	0	0	0	0	0	0	0	0	1

Per analysis plan, time to extubation is censored at the time of last assessment of extubation readiness if extubation readiness is not achieved.
SGX 2MG = sugammadex 2 mg/kg; NEO = neostigmine.

Source: Figure 11-1 in the Clinical Study Report for P169MK8616, page 61 out of 381

3.3 Evaluation of Safety

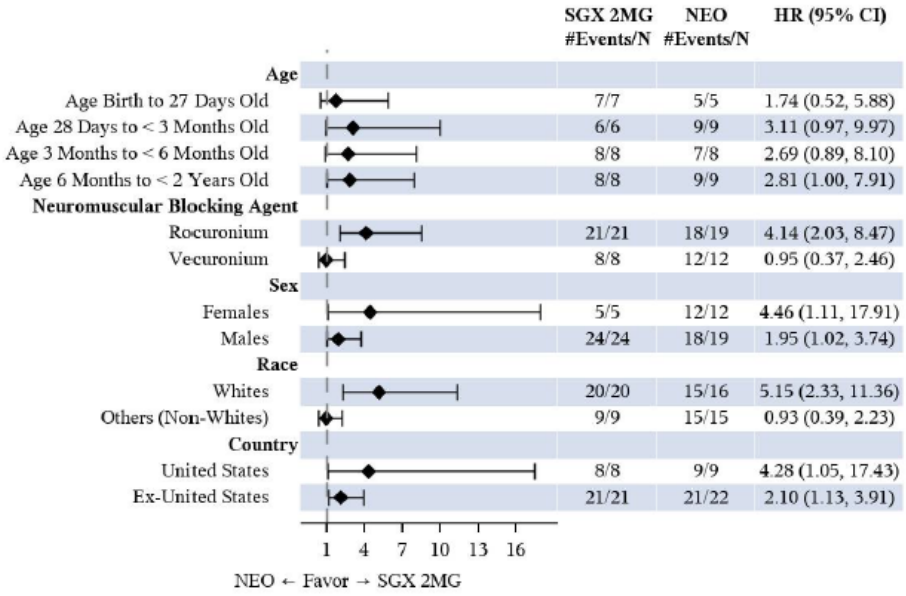
We defer to the clinical reviewer on the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Exploratory subgroup analyses were performed by age, gender, geographic region and neuromuscular blocking agent using the APT population. Figure 5 shows the hazard ratio and its 95% CI for each subgroup. The results from subgroup analyses were generally consistent with the overall analysis result for TTNMR. In the vecuronium and non-whites subgroups, the point estimates of the hazard ratio were less than but close to 1.

Figure 4 Forest Plot by Subgroup Factor



Note: Subgroup analyses are only performed for those classification variables with ≥5 participants in each subgroup.
SGX 2MG = sugammadex 2 mg/kg; NEO = neostigmine.

Source: Figure 11-1 in the Clinical Study Report for P169MK8616, page 59 out of 381

4.2 Other Special/Subgroup Populations

Subgroup analysis by stratification factor of neuromuscular blocking agent is described in Section 4.1.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The statistical team does not identify any major statistical issues that would impact the overall conclusions of Part B of Study 169.

5.2 Collective Evidence

There is only one study included in this sNDA submission.

5.3 Conclusions and Recommendations

In conclusion, the efficacy results from Part B of Study 169 showed that the TTNMR was significantly faster in participants in the sugammadex 2 mg/kg group compared with the neostigmine group. The findings from primary, sensitivity and supportive analyses of the primary efficacy endpoint are consistent. We agree that the efficacy results from Part B of Study

169 support the use of sugammadex for the reversal of moderate NMB in pediatric participants from birth to less than 2 years of age.

5.4 Labeling Recommendations (as applicable)

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

> "
> Time to neuromuscular recovery was significantly faster (b) (4) in participants dosed with BRIDION 2 mg/kg compared with neostigmine (median of 1.4 minutes for BRIDION 2 mg/kg and 4.4 minutes for neostigmine; hazard ratio=2.40, 95% CI: 1.37, 4.18). BRIDION 4 mg/kg achieved (b) (4) neuromuscular recovery with a median of 1.1 minutes. These effects were consistent across age cohorts studied (birth to 27 days, 28 days to <3 months, 3 months to <6 months, 6 months to <2 years of age) (b) (4)

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

- Include the number of participants in each treatment arm that were included in the analysis of TTNMR and remove the p-value from comparing BRIDION 2 mg/kg to neostigmine to be consistent with our previous practice.
- The observed effects by neuromuscular blocking agent may not be consistent: hazard ratio=4.14 (95% CI: 2.03, 8.47) for rocuronium and hazard ratio=0.95 (95% CI: 0.37, 2.46) for vecuronium, respectively.

6 REFERENCE

- ICH 'E3 Structure and Content of Clinical Study Reports' (1996) http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
- ICH E6 'E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)' (2018) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
- FDA Guidance for Industry 'Computerized Systems Used in Clinical Investigations' (2007) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computerized-systems-used-clinical-investigations
- Review templates including 'NDA/BLA Review Template' and 'NDA/BLA Filling Review Template' https://cderwiki.fda.gov/mw/index.php/Statistical_Review_Templates
- Link to keywords http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

- NDA022225 SDN497 (Supplement 14) \\CDSESUB1\evsprod\NDA022225\0632
- NDA022225 (Bridion®) approval letter https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022225Orig1s000ltr.pdf
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