Amsterdam, 17 September 2020
EMA/CHMP/520724/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Bridion

sugammadex

Procedure no: EMEA/H/C/000885/P46/025

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 03-Jul-2020, the MAH submitted a completed paediatric study for Bridion in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "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" - MK-8616-089 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in study MK-8616-089 was 100 mg/mL solution for injection (route of administration: intravenous).

The 100 mg/mL solution for injection formulation has been approved in the EU for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years. The recommended dose is 2 mg/kg. According to the approved product information, Bridion 100 mg/mL may be diluted to 10 mg/mL to increase the accuracy of dosing in the paediatric population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study MK-8616-089: "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"

2.3.2. Clinical study

Study MK-8616-089: 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

Description

This was a randomized, active comparator-controlled, parallel group, multisite, double-blinded trial of sugammadex in pediatric participants from 2 to <17 years of age for the reversal of neuromuscular blockade (NMB) induced by rocuronium or vecuronium.

The study design consisted of 2 parts. Part A of the trial identified the doses of sugammadex that would be tested in Part B, and Part B of the trial assessed safety and efficacy parameters.

In Part A, participants were randomized to 1 of 2 intervention groups in a 1:1 ratio to:

- moderate block and reversal with 2 mg/kg sugammadex; or
- deep block and reversal with 4 mg/kg sugammadex

In Part B, participants were randomized to 1 of 3 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 [active control]; or
- deep block and reversal with 4 mg/kg sugammadex

Randomization was stratified by age (2 to <6 years, 6 to <12 years, and 12 to <17 years) and neuromuscular blocking agent (NMBA) (rocuronium or vecuronium).

Neuromuscular transmission was monitored using the TOF-Watch® SX device and accessories. Moderate NMB was defined as neuromuscular recovery up to at least the reappearance of the second twitch (T2) following the last dose of administered NMBA. Deep NMB was defined as neuromuscular recovery having reached at least 1 to 2 post-tetanic counts (PTC) following the last administered dose of NMBA.

Methods

Objectives and endpoints

Objective/Hypothesis	Endpoint
Primary	
To describe the pharmacokinetic (PK) parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	PK parameters: area under the concentration-time curve (AUC), clearance (CL), apparent volume of distribution at terminal elimination phase (Vz), maximum concentration (C_{max}), and half-life ($t_{½}$).
To evaluate safety and tolerability of sugammadex (data will be pooled across Part A and Part B of the study).	Number of participants experiencing adverse events (AE).
To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B). **Hypothesis**: Sugammadex is superior to neostigmine in reversing moderate neuromuscular blockade as measured by time to recovery to a train-of-four (TOF) ratio of ≥0.9.	Time to recovery to a TOF ratio of ≥0.9.
Secondary	
To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	• Time to recovery to a TOF ratio of ≥0.8. • Time to recovery to a TOF ratio of ≥0.7.
Tertiary/Exploratory	
To evaluate the efficacy of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	• Time to extubation: Interval from administration of reversal agent to removal of the endotracheal tube • Time to OR discharge • Time to PACU discharge • Time to hospital discharge • Incidence of delayed recovery

Study design

This was a randomized, active comparator-controlled, parallel group, multisite, double-blinded trial of sugammadex in pediatric participants from 2 to <17 years of age for the reversal of NMB.

The trial consisted of 2 parts, Part A and Part B. Part A identified the doses of sugammadex that would be investigated in Part B based upon an evaluation of PK, safety, and efficacy endpoints. Part B of the trial assessed safety and efficacy parameters. Part A was conducted in the United States and Part B in Austria, Belgium, Denmark, Finland, Germany, Spain, Turkey and the United States.

In Part A, participants were randomized to 1 of 2 intervention groups in a 1:1 ratio (moderate block and reversal with 2 mg/kg sugammadex or deep block and reversal with 4 mg/kg sugammadex). Once Part A of the study completed, an interim analysis (IA) was performed (prior to enrollment in Part B) to evaluate PK and safety data and was reviewed by a standing internal Data Monitoring Committee (siDMC). The safety data was also reviewed by an external data monitoring committee (DMC). Part A PK and efficacy data were also submitted to the FDA for review, upon which the FDA agreed with continued evaluation of 2 mg/kg and 4 mg/kg in Part B.

In Part B, participants were randomized to 1 of 3 intervention groups in a 1:1:5 ratio (moderate block and reversal with either 2 mg/kg sugammadex or 50 mcg/kg neostigmine [active control] or deep block and reversal with 4 mg/kg sugammadex); randomization was stratified by age (2 to <6 years, 6 to <12 years, and 12 to <17 years) and NMBA (rocuronium or vecuronium).

The study design and the study interventions randomization schema are shown in Figure 1 and Figure 2, respectively.

Figure 1: **Study Design.**

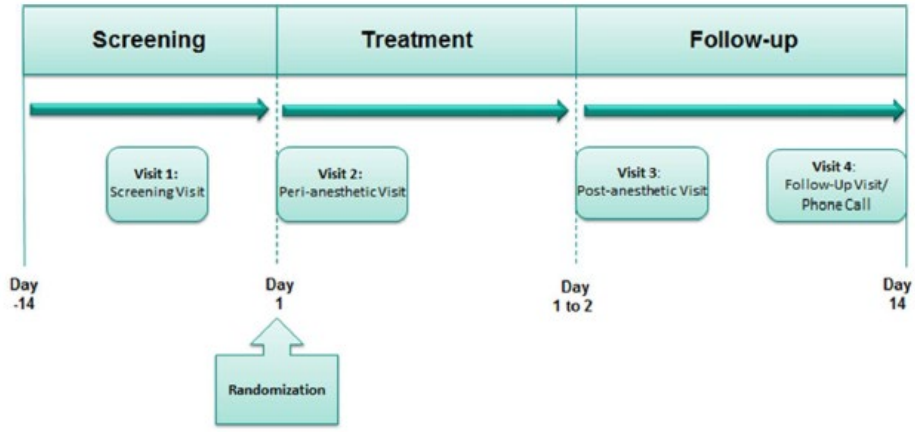
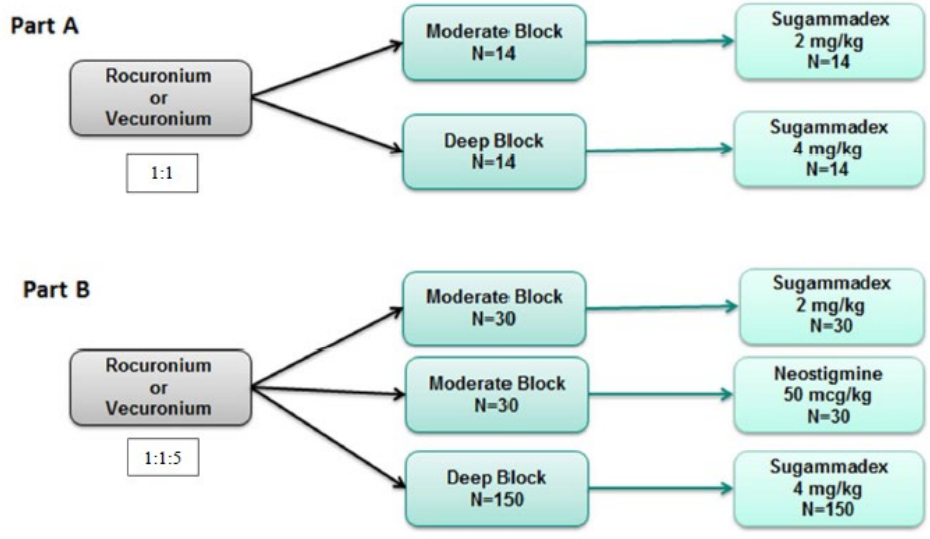


Figure 2: Study Intervention(s) Randomization



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

PK samples were only collected in Part A of the study. Samples were planned to be collected at 2, 15, 30, and 60 minutes and 4 to 6 hours following IV bolus administration of sugammadex. Depending on the length of hospital stay, an optional PK sample between 10 to 12 hours after sugammadex administration could be obtained. Sugammadex PK parameters were derived using a non-compartmental approach in Phoenix™ (WinNonlin® 6.4).

Study population /Sample size

Approximately 238 participants were to be enrolled in the study.

Main inclusion criteria were as follows:

Male/female participants between the ages of 2 and <17 years at Visit 2 who met the following key criteria were eligible to participate in the study:

1. Categorized as ASA physical status Class 1, 2, or 3, as determined by the investigator.
2. Had a planned non-emergent surgical procedure or clinical situation (e.g, intubation) that required moderate or deep NMB with either rocuronium or vecuronium.
3. Had a planned surgical procedure or clinical situation that would allow objective neuromuscular monitoring techniques to be applied with access to the arm for neuromuscular transmission monitoring.

Participants were excluded from the study if any of the following key criteria were met:

1. Had any clinically significant condition or situation (eg, anatomical malformation that complicates intubation) other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.
2. Had a neuromuscular disorder that could have affected NMB and/or trial assessments.
3. Dialysis-dependent or had (or was suspected of having) severe renal insufficiency.
4. Had or was suspected of having a family or personal history of malignant hyperthermia.
5. Had received or was planned to receive toremifene and/or fusidic acid via IV administration within 24 hours before or within 24 hours after administration of study treatment.

Treatments

Study treatments are summarised in Table 1.

Table 1: Study treatments

	Sugammadex (MK-8616)	**Neostigmine methylsulfate**	**Glycopyrrolate**	**Atropine sulfate**
Formulation	Solution for injection	Solution for injection	Solution for injection	Solution for injection
Unit Dose Strength(s)	100 mg/mL	0.5 mg/mL	0.2 mg/mL	0.4 mg/mL
Dosage Level(s)	2 mg/kg or 4 mg/kg	50 mcg/kg	5 to 15 mcg/kg	10 to 30 mcg/kg
Route of Administration	Intravenous	Intravenous	Intravenous	Intravenous
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Use	Investigational	Comparator	Required to be used with comparator	Required to be used with comparator

Statistical Methods

Key elements of the statistical methods and the statistical analysis plan are summarized in Table 2.

Table 2: Summary of statistical methods

Primary Endpoint(s)	**PK**: AUC, CL, V_Z, C_{max}, and $t_{½}$ **Safety**: AE reporting, laboratory and vital sign assessments. **Efficacy**: The time to recovery to a TOF ratio of ≥0.9
Secondary Endpoints	The time to recovery to a TOF ratio of ≥0.8 The time to recovery to a TOF ratio of ≥0.7
Statistical Methods for Key Efficacy/Immunogenicity/ PK Analyses	**PK**: Separately for each PK parameter, individual values of CL, AUC, C_{max}, and V_Z, will be natural log-transformed and evaluated with a fixed effects model containing terms dose and age group. At each dose, 95% confidence intervals (CIs) of geometric means for each parameter will be provided. Descriptive summary statistics will be provided for PK parameters including AUC, C_{max}, dnAUC, dnC_{max}, CL, V_Z and $t_{½}$. **Efficacy**: The efficacy hypothesis will be evaluated within Part B by comparing sugammadex to neostigmine in the setting of moderate block using log-transformed time-to-recovery values via Analysis of Variance (ANOVA), adjusting for neuromuscular blocking agent (NMBA) and age.
Statistical Methods for Key Safety Analyses	P-values (Tier 1 only) and 95% CI (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with NMBA and age group as stratification factors.
Interim Analyses	One interim analysis (IA) will be performed in this study to evaluate PK and safety data. PK and safety data will be reviewed by a standing internal Data Monitoring Committee (siDMC) and safety data will be reviewed by an external Data Monitoring Committee (eDMC). This interim analysis is summarized below • Timing: When Part A has been completed, prior to the commencement of enrollment of Part B. • Testing: IA will evaluate PK and safety data. No formal efficacy analyses are planned.
Multiplicity	No multiplicity adjustment is planned, as there is a single comparison of sugammadex versus neostigmine in the setting of moderate block using 1 endpoint in the primary efficacy hypothesis.
Sample Size and Power	The planned sample size is 238 participants, based on minimum safety database requirement. There will be 30 participants per treatment arm (sugammadex and neostigmine) in the setting of moderate block for efficacy analysis. For time to recovery to TOF ≥0.9, the trial has >99% power to demonstrate that sugammadex 2mg/kg is superior to neostigmine at an overall two-sided 5% alpha-level.

Results

Recruitment/ Number analysed

A total of 299 participants were screened and 288 were randomized across 28 global study sites. The main reasons for not randomizing participants were other and screen failure. Most (>90%) of the randomized participants received study intervention and completed the study as per protocol (Table 3).

One participant was randomized twice into the study. After initial enrollment, the participant was withdrawn from the study before receiving study intervention as efficacy assessments could not be performed. At a later date, this participant was randomized again, assigned a second allocation number, received study intervention, and completed the study intervention.

Of 276 treated participants, 51 received sugammadex 2 mg/kg (18 from Part A, 33 from Part B), 191 received sugammadex 4 mg/kg (22 from Part A, 169 from Part B), and 34 received neostigmine (Part B).

Table 3: Disposition of Subjects (All Randomized Subjects, Part A+B)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized							11	
Subjects in population	54		199		35		288	
Study Disposition								
Completed	50	(92.6)	189	(95.0)	33	(94.3)	272	(94.4)
Discontinued	4	(7.4)	10	(5.0)	2	(5.7)	16	(5.6)
Lost To Follow-Up	1	(1.9)	2	(1.0)	1	(2.9)	4	(1.4)
Physician Decision	1	(1.9)	2	(1.0)	1	(2.9)	4	(1.4)
Randomized By Mistake Without Study Treatment	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.3)
Withdrawal By Parent/Guardian	1	(1.9)	1	(0.5)	0	(0.0)	2	(0.7)
Other	1	(1.9)	4	(2.0)	0	(0.0)	5	(1.7)

Each subject is counted once for Study Disposition based on the latest corresponding disposition record.
One subject was enrolled twice. The first enrollment discontinued before treatment, while the second enrollment completed the study.

Baseline data

The intervention groups were comparably balanced for all baseline characteristics (Table 4). The percentage of male participants in the overall population was 55.4%. The mean (SD) [range] age of participants was 7.9 (4.4) [2 to 16], years. Most participants were white (89.5%), had an eGFR of >90 mL/min/1.73 m^2 (91.3%) computed using Schwartz formula, and were of ASA Class 1 (63.4%). Similar demographic and baseline characteristics were observed among the intervention groups in each part (A and B) of the study.

Table 4: Subject Characteristics (All Subjects Treated, Part A+B)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	51		191		34		276	
Gender								
Male	31	(60.8)	104	(54.5)	18	(52.9)	153	(55.4)
Female	20	(39.2)	87	(45.5)	16	(47.1)	123	(44.6)
Age (Years)								
2 to <6 years	22	(43.1)	80	(41.9)	12	(35.3)	114	(41.3)
6 to <12 years	15	(29.4)	64	(33.5)	13	(38.2)	92	(33.3)
12 to <17 years	14	(27.5)	47	(24.6)	9	(26.5)	70	(25.4)
Mean	7.7		7.8		8.5		7.9	
SD	4.6		4.4		4.3		4.4	
Median	7.0		7.0		8.0		7.0	
Range	2 to 16		2 to 16		2 to 16		2 to 16	
Race								
American Indian Or Alaska Native	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Asian	2	(3.9)	7	(3.7)	2	(5.9)	11	(4.0)
Black Or African American	2	(3.9)	4	(2.1)	0	(0.0)	6	(2.2)
Multiple	2	(3.9)	4	(2.1)	0	(0.0)	6	(2.2)
Black Or African American, White	2	(3.9)	0	(0.0)	0	(0.0)	2	(0.7)
White, Asian	0	(0.0)	4	(2.1)	0	(0.0)	4	(1.4)
Unknown	1	(2.0)	4	(2.1)	0	(0.0)	5	(1.8)
White	44	(86.3)	171	(89.5)	32	(94.1)	247	(89.5)
Body Mass Index (BMI) (kg/m^2)								
<15	8	(15.7)	40	(20.9)	7	(20.6)	55	(19.9)
≥15 to <25	37	(72.5)	134	(70.2)	24	(70.6)	195	(70.7)
≥25	6	(11.8)	17	(8.9)	3	(8.8)	26	(9.4)
Subjects with data	51		191		34		276	
Mean	18.5		18.3		18.7		18.4	
SD	4.2		4.9		4.4		4.7	
Median	17.1		16.6		17.8		16.8	
Range	13.6 to 32.4		11.3 to 46.3		12.7 to 31.2		11.3 to 46.3	
Weight (kg)								
Subjects with data	51		191		34		276	
Mean	34.1		33.7		35.4		34.0	
SD	21.4		21.6		21.8		21.6	
Median	24.0		24.0		29.0		25.0	
Range	11.0 to 85.0		10.0 to 130.0		11.0 to 99.0		10.0 to 130.0	
Estimated Glomerular Filtration Rate[5] (mL/min/1.73m^2)								
>30 to ≤60	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
>60 to ≤90	3	(5.9)	10	(5.2)	5	(14.7)	18	(6.5)
>90	46	(90.2)	177	(92.7)	29	(85.3)	252	(91.3)
Missing	2	(3.9)	3	(1.6)	0	(0.0)	5	(1.8)
Subjects with data	49		188		34		271	
Mean	128.2		126.8		118.5		126.0	
SD	22.6		29.1		21.0		27.2	
Median	129.0		121.9		117.8		123.0	
Range	83.0 to 184.5		57.3 to 264.9		81.1 to 170.8		57.3 to 264.9	
ASA Class								
ASA Class 1	30	(58.8)	121	(63.4)	24	(70.6)	175	(63.4)
ASA Class 2	13	(25.5)	52	(27.2)	9	(26.5)	74	(26.8)
ASA Class 3	8	(15.7)	18	(9.4)	1	(2.9)	27	(9.8)
Type of Neuromuscular Blocking Agent (NMBA)								
Rocuronium	37	(72.5)	123	(64.4)	20	(58.8)	180	(65.2)
Vecuronium	14	(27.5)	68	(35.6)	14	(41.2)	96	(34.8)

Efficacy results

Primary efficacy endpoint (Study Part B)

The time to recovery to a TOF ratio of ≥0.9 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). The supportive analysis results were consistent with the primary analysis results.

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 within 3 minutes compared with 8.8% (3/34) of participants in the

neostigmine group (Figure 3). Similar results were observed in the intervention groups with combined population from Parts A and B. The time to achieve full reversal was consistent (favouring sugammadex 2 mg/kg as compared to neostigmine) across the subgroups of age, NMBA, gender, and region; consistency across race subgroups could not be evaluated as the sample size for races other than White was too small (Figure 4).

Table 5: Time (minutes) to Recovery of the TOF Ratio ≥ 0.9 (All Subjects Treated)

Treatment	N	Mean (SD)	Median (Range)	Geometric Mean (95% CI)
Sugammadex 2 mg/kg	33	2.1 (2.4)	1.4 (0.7, 14.8)	1.6 (1.3, 2.0)
Neostigmine + (Glycopyrrolate or Atropine)	34	10.4 (9.3)	7.8 (1.1, 42.3)	7.5 (5.6, 10.0)
Pairwise Comparisons			***Ratio of Geometric Mean ǂ (95% CI)ǂ***	***p-Value ǂ***
Sugammadex 2 mg/kg versus Neostigmine + (Glycopyrrolate or Atropine)			0.22 (0.16, 0.32)	<0.0001

Per analysis plan, explicit imputation is used if the recovery time is missing.
ǂ Based on analysis of variance (ANOVA) for log-transformed time to recovery values, adjusting for neuromuscular blocking agent and age. P-value is two-sided.
SD: Standard Deviation. **CI**: confidence interval.

Figure 3: Time (minutes) to Recovery of the TOF Ratio ≥ 0.9 (All Subjects Treated)

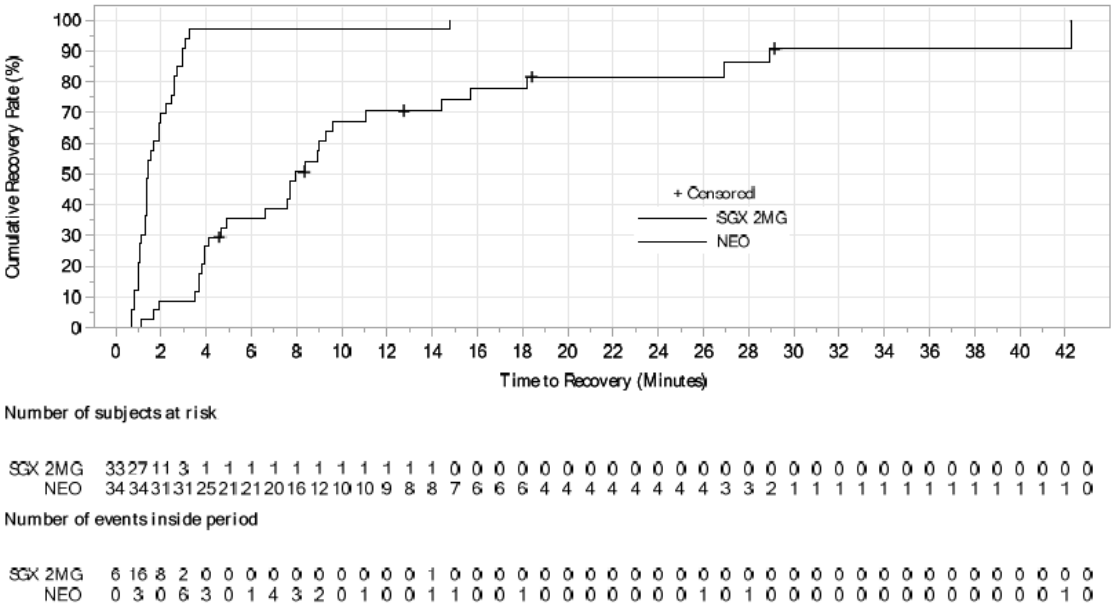
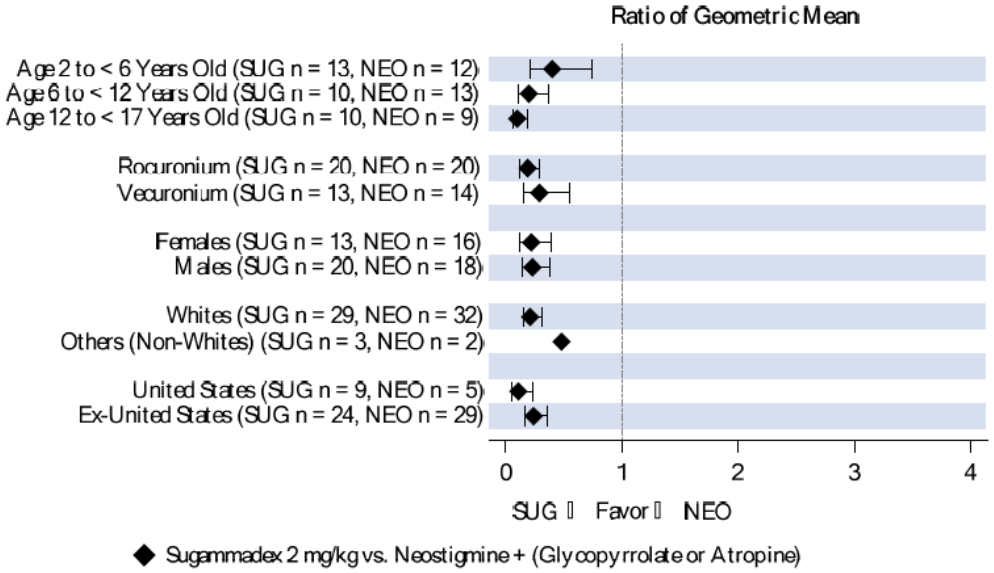


Figure 4: Time (minutes) to Recovery of the TOF Ratio ≥ 0.9 by Subgroup. Point Estimate and 95% Confidence Interval: Sugammadex 2 mg/kg versus Neostigmine + (Glycopyrrolate or Atropine) (All Subjects Treated).



Secondary efficacy endpoints (Study Part B)

The time to recovery to a TOF ratio of ≥0.8 was faster (nominal p value of <0.0001, not controlled for multiplicity) in participants dosed with sugammadex compared to neostigmine (ratio of geometric means = 0.26, 95% CI: 0.19, 0.37) (Table 6)

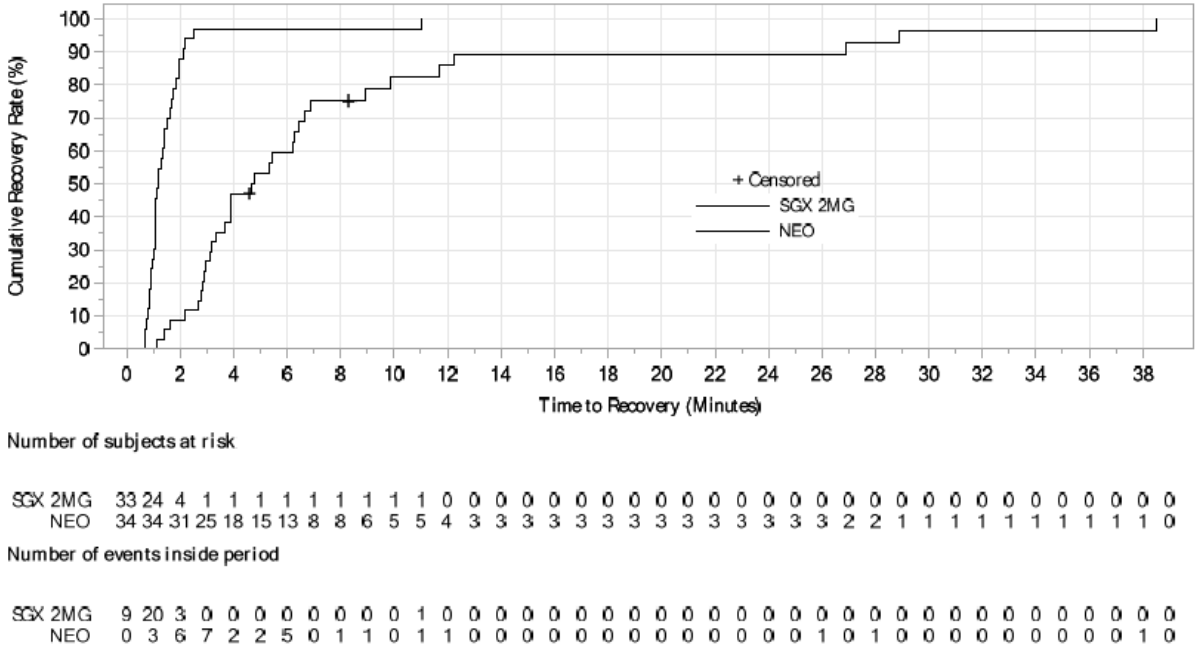
Based on Kaplan-Meier estimates, 97.0% (32/33) of participants dosed with sugammadex 2 mg/kg recovered to a TOF ratio of ≥0.8 within 3 minutes compared with 26.5% (9/34) of participants in the neostigmine group (Figure 5).

Table 6: Time (minutes) to Recovery of the TOF Ratio ≥ 0.8 (All Subjects Treated)

Treatment	**N**	**Mean (SD)**	**Median (Range)**	**Geometric Mean (95% CI)**
Sugammadex 2 mg/kg	33	1.6 (1.8)	1.2 (0.7, 11.1)	1.3 (1.1, 1.6)
Neostigmine + (Glycopyrrolate or Atropine)	34	7.3 (8.2)	4.6 (1.1, 38.5)	5.0 (3.8, 6.7)
Pairwise Comparisons			***Ratio of Geometric Mean ‡ (95% CI)‡***	***p-Value ‡***
Sugammadex 2 mg/kg versus Neostigmine + (Glycopyrrolate or Atropine)			0.26 (0.19, 0.37)	<0.0001

Per analysis plan, explicit imputation is used if the recovery time is missing.
‡ Based on analysis of variance (ANOVA) for log-transformed time to recovery values, adjusting for neuromuscular blocking agent and age. P-value is two-sided.
SD: Standard Deviation. **CI**: confidence interval.

Figure 5: Time (minutes) to Recovery of the TOF Ratio ≥ 0.8 (All Subjects Treated)



The time to recovery to a TOF ratio of ≥0.7 was faster (nominal p value of <0.0001, not controlled for multiplicity) in participants dosed with sugammadex compared to neostigmine (ratio of geometric means = 0.30, 95% CI: 0.22, 0.41) (Table 7).

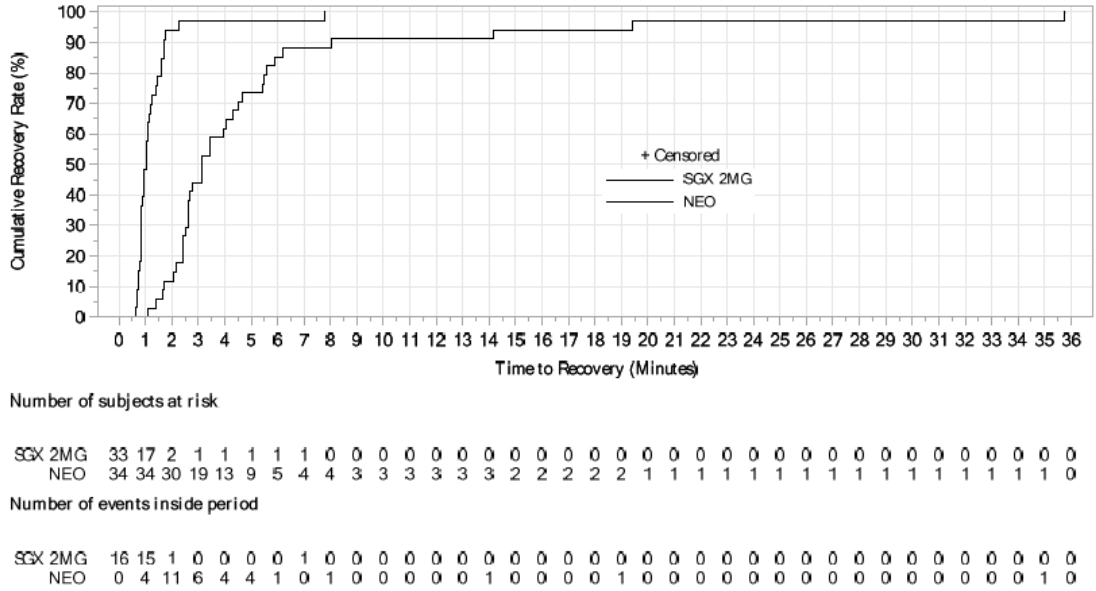
Based on Kaplan-Meier estimates, 97.0% (32/33) of participants dosed with sugammadex 2 mg/kg recovered to a TOF ratio of ≥0.7 within 3 minutes compared with 44.1% (15/34) of participants in the neostigmine group (Figure 6).

Table 7: Time (minutes) to Recovery of the TOF Ratio ≥ 0.7 (All Subjects Treated)

Treatment	**N**	**Mean (SD)**	**Median (Range)**	**Geometric Mean (95% CI)**
Sugammadex 2 mg/kg	33	1.3 (1.2)	1.1 (0.6, 7.8)	1.1 (0.9, 1.3)
Neostigmine + (Glycopyrrolate or Atropine)	34	5.2 (6.5)	3.2 (1.1, 35.8)	3.7 (2.9, 4.8)
Pairwise Comparisons			***Ratio of Geometric Mean ‡ (95% CI)‡***	***p-Value ‡***
Sugammadex 2 mg/kg versus Neostigmine + (Glycopyrrolate or Atropine)			0.30 (0.22, 0.41)	<0.0001

Per analysis plan, explicit imputation is used if the recovery time is missing.
‡ Based on analysis of variance (ANOVA) for log-transformed time to recovery values, adjusting for neuromuscular blocking agent and age. P-value is two-sided.
SD: Standard Deviation. **CI**: confidence interval.

Figure 6: **Time (minutes) to Recovery of the TOF Ratio ≥ 0.7 (All Subjects Treated)**



Tertiary/Exploratory Efficacy Endpoints

Delayed recovery was defined as any observation of the TOF ratio to ≥ 0.9 (in the original scale) that was > 3 times the geometric mean recovery time of the TOF ratio to ≥ 0.9 within each treatment group. In combined analysis of Study, Parts A and B, the incidence of delayed recovery was 2.0%, 7.3% and 8.8% in sugammadex 2 mg/kg, sugammadex 4 mg/kg and neostigmine + (glycopyrrolate or atropine) groups, respectively. The most common potential reasons for delayed recovery were potential measurement anomaly due to suboptimal set-up with high baseline T1 and potential slow drug administration.

When TOF data were pooled across Parts A and B, the results for time to recovery remained consistent with the primary analysis. Although no comparator existed for the reversal of deep block, sugammadex 4 mg/kg achieved rapid and complete reversal in this setting (Table 8).

Table 8: Time (minutes) to Recovery of the TOF Ratios (All Subjects Treated, Part A+B)

TOF Ratio	Treatment	N	Mean	(SD)	Median	Range	Geometric Mean	(95% CI)
TOF Ratio ≥ 0.9	Sugammadex 2 mg/kg	51	2.1	(2.2)	1.6	(0.7, 14.8)	1.6	(1.4, 1.9)
	Sugammadex 4 mg/kg	191	3.8	(10.0)	1.7	(0.4, 118.1)	2.0	(1.8, 2.3)
	Neostigmine + (Glycopyrrolate or Atropine)	34	10.4	(9.3)	7.8	(1.1, 42.3)	7.5	(5.6, 10.0)
TOF Ratio ≥ 0.8	Sugammadex 2 mg/kg	51	1.6	(1.6)	1.3	(0.4, 11.1)	1.3	(1.1, 1.5)
	Sugammadex 4 mg/kg	191	2.8	(8.8)	1.3	(0.4, 111.1)	1.5	(1.3, 1.7)
	Neostigmine + (Glycopyrrolate or Atropine)	34	7.3	(8.2)	4.6	(1.1, 38.5)	5.0	(3.8, 6.7)
TOF Ratio ≥ 0.7	Sugammadex 2 mg/kg	51	1.3	(1.1)	1.1	(0.4, 7.8)	1.1	(0.9, 1.3)
	Sugammadex 4 mg/kg	191	2.4	(8.2)	1.1	(0.4, 105.1)	1.3	(1.1, 1.4)
	Neostigmine + (Glycopyrrolate or Atropine)	34	5.2	(6.5)	3.2	(1.1, 35.8)	3.7	(2.9, 4.8)

SD: Standard Deviation. **CI**: confidence interval.
Per analysis plan, explicit imputation is used if the recovery time is missing.

Pharmacokinetic results

Pharmacokinetic data were only collected in Study Part A. The mean (± SE) plasma sugammadex concentration-time profiles following a single IV dose of 2 mg/kg or 4 mg/kg sugammadex are shown in Figure 7. Given the critical interval over which drug effect is expected, a truncated postdose duration of 0 to 60 minutes shown separately in Figure 8.

Figure 7: Arithmetic Mean (±SE) Plasma Concentration-Time Profiles of Sugammadex Following a Single IV Dose of 2 mg/kg (Left Panel) or 4 mg/kg (Right Panel) Sugammadex Administered in Pediatric Participants (2yr to <6 yr, 6yr to <12 yr, 12 yr to <17 yr) (Inset: Semi-Log Scale)

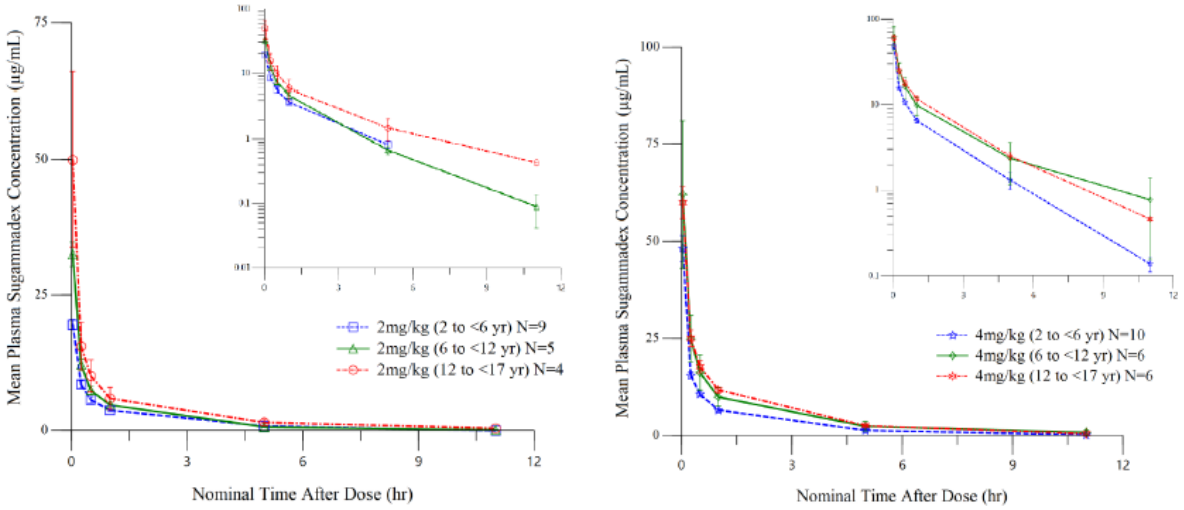
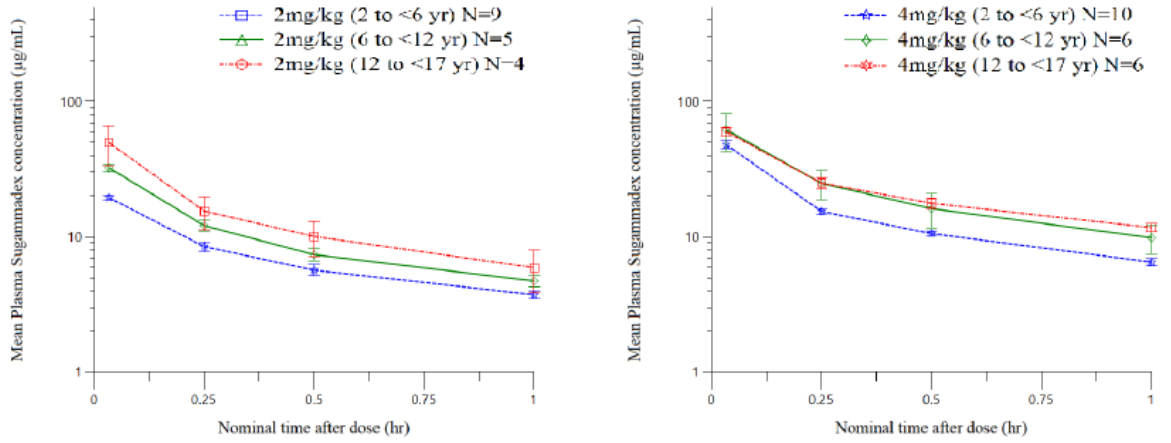


Figure 8: Arithmetic Mean Plasma Concentration-Time Profiles of Sugammadex Following a Single IV Dose of 2 mg/kg (Left Panel) or 4 mg/kg (Right Panel) Sugammadex Administered in Pediatric Participants (2yr to <6 yr, 6yr to <12 yr, 12 yr to <17 yr) – Time Scale 0 – 60 minutes (Semi-Log Scale)



In order to confirm the assumptions that dose-linearity and proportionality are conserved between the pediatric populations, the observed concentration-time data were dose-normalized with no appreciable differences identified in each of the age categories. CL and Vz and Vss relationships indicate that CL increased monotonically with age, with a similar trend for volume of distribution (Table 9, Table 10 and Table 11). Body weight-normalized CL and volume of distribution in children (<12 years of age) was higher than those in adolescents and increased with decreasing age. Consequently, the elimination half-life was generally comparable across all age cohorts. Body weight-normalized CL and volume of distribution as well as elimination half-life of sugammadex for each age category were largely similar at both sugammadex doses, confirming dose linearity.

Table 9: Summary Statistics for Sugammadex Plasma PK Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (Age 2 to <6 years)

Parameters	2 mg/ kg			4 mg/ kg		
	N	GM	95% CI	N	GM	95% CI
AUC0-inf (hr*ug/mL) †	9	14.08	(12.32, 16.10)	8	26.90	(23.35, 31.00)
AUC0-1hr (hr*ug/mL) †	9	7.24	(6.51, 8.06)	10	15.26	(13.79, 16.89)
AUC0-4hr (hr*ug/mL) †	9	12.73	(11.28, 14.36)	8	24.71	(21.75, 28.07)
Cmax (ug/mL) †	9	17.54	(14.48, 21.24)	10	47.11	(39.28, 56.49)
CL (L/hr) †	9	2.30	(1.93, 2.75)	8	2.26	(1.87, 2.72)
Vz (L) †	9	4.08	(3.29, 5.05)	8	4.00	(3.19, 5.02)
Vss (L) †	9	3.58	(3.01, 4.25)	8	3.10	(2.58, 3.71)
MRT (hr) §	9	1.55	16.00	8	1.37	21.32
t1/2 (hr) §	9	1.23	17.39	8	1.23	25.25
Dose-Normalized						
dnAUC0-inf (hr*ug/mL/mg) †	9	0.43	(0.36, 0.52)	8	0.44	(0.37, 0.54)
dnAUC0-1hr (hr*ug/mL/mg) †	9	0.22	(0.19, 0.26)	10	0.26	(0.23, 0.30)
dnCmax (ug/mL/mg) †	9	0.54	(0.44, 0.66)	10	0.80	(0.66, 0.97)
Weight-Normalized						
wnCL ((L/hr)/kg) †	9	0.14	(0.12, 0.16)	8	0.15	(0.13, 0.17)
wnVz (L/kg) †	9	0.25	(0.22, 0.29)	8	0.26	(0.23, 0.31)
wnVss (L/kg) †	9	0.22	(0.20, 0.25)	8	0.20	(0.18, 0.23)

dn=dose-normalized; **CI**=confidence interval; **GM**=geometric least-squares mean; **wn**=weight-normalized

Evaluable population for Cmax may be higher than the evaluable population for other PK parameters. N represents the number of subjects with at least 5 evaluable PK samples per subject

§ Geometric mean and percent geometric CV reported for t1/2 and MRT

† Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values

Table 10: Summary Statistics for Sugammadex Plasma PK Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (Age 6 to <12 years)

Parameters	2 mg/ kg			4 mg/ kg		
	N	GM	95% CI	N	GM	95% CI
AUC0-inf (hr*ug/mL) †	5	18.76	(11.10, 31.72)	6	38.25	(23.69, 61.77)
AUC0-1hr (hr*ug/mL) †	5	10.54	(6.96, 15.97)	6	19.48	(13.34, 28.45)
AUC0-4hr (hr*ug/mL) †	5	17.09	(10.92, 26.72)	6	32.76	(21.78, 49.29)
Cmax (ug/mL) †	5	32.17	(19.84, 52.16)	6	51.62	(33.21, 80.26)
CL (L/hr) †	5	3.58	(1.82, 7.02)	6	3.43	(1.86, 6.36)
Vz (L) †	5	6.65	(3.69, 11.97)	6	8.22	(4.80, 14.06)
Vss (L) †	5	5.16	(3.01, 8.85)	6	6.24	(3.82, 10.21)
MRT (hr) §	5	1.44	20.89	6	1.82	33.89
t1/2 (hr) §	5	1.29	25.10	6	1.66	32.51
Dose-Normalized						
dnAUC0-inf (hr*ug/mL/mg) †	5	0.28	(0.14, 0.55)	6	0.29	(0.16, 0.54)
dnAUC0-1hr (hr*ug/mL/mg) †	5	0.16	(0.09, 0.28)	6	0.15	(0.09, 0.25)
dnCmax (ug/mL/mg) †	5	0.48	(0.25, 0.91)	6	0.39	(0.22, 0.70)
Weight-Normalized						
wnCL ((L/hr)/kg) †	5	0.11	(0.06, 0.18)	6	0.10	(0.06, 0.17)
wnVz (L/kg) †	5	0.20	(0.14, 0.27)	6	0.25	(0.19, 0.33)
wnVss (L/kg) †	5	0.15	(0.12, 0.20)	6	0.19	(0.15, 0.25)

dn=dose-normalized; **CI**=confidence interval; **GM**=geometric least-squares mean; **wn**=weight-normalized

Evaluable population for Cmax may be higher than the evaluable population for other PK parameters. N represents the number of subjects with at least 5 evaluable PK samples per subject

§ Geometric mean and percent geometric CV reported for t1/2 and MRT

† Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values

Table 11: Summary Statistics for Sugammadex Plasma PK Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (Age 12 to <17 years)

Parameters	2 mg/ kg			4 mg/ kg		
	N	GM	95% CI	N	GM	95% CI
AUC0-inf (hr*ug/mL) †	4	27.55	(18.08, 41.99)	6	49.25	(34.91, 69.46)
AUC0-1hr (hr*ug/mL) †	4	15.70	(10.78, 22.85)	6	24.86	(18.30, 33.78)
AUC0-4hr (hr*ug/mL) †	4	24.38	(16.61, 35.79)	6	43.11	(31.50, 58.98)
Cmax (ug/mL) †	4	41.26	(23.93, 71.17)	6	59.21	(37.94, 92.41)
CL (L/hr) †	4	4.68	(3.11, 7.06)	6	5.69	(4.07, 7.96)
Vz (L) †	4	10.04	(6.75, 14.93)	6	12.26	(8.87, 16.96)
Vss (L) †	4	7.20	(5.15, 10.07)	6	9.88	(7.52, 12.99)
MRT (hr) §	4	1.54	24.79	6	1.74	15.61
t1/2 (hr) §	4	1.49	23.17	6	1.49	19.19
Dose-Normalized						
dnAUC0-inf (hr*ug/mL/mg) †	4	0.21	(0.14, 0.32)	6	0.18	(0.13, 0.25)
dnAUC0-1hr (hr*ug/mL/mg) †	4	0.12	(0.09, 0.17)	6	0.09	(0.07, 0.12)
dnCmax (ug/mL/mg) †	4	0.32	(0.16, 0.62)	6	0.21	(0.12, 0.36)
Weight-Normalized						
wnCL ((L/hr)/kg) †	4	0.07	(0.05, 0.11)	6	0.08	(0.06, 0.11)
wnVz (L/kg) †	4	0.16	(0.12, 0.20)	6	0.18	(0.14, 0.22)
wnVss (L/kg) †	4	0.11	(0.08, 0.15)	6	0.14	(0.11, 0.18)

dn=dose-normalized; **CI**=confidence interval; **GM**=geometric least-squares mean; **wn**=weight-normalized

Evaluable population for Cmax may be higher than the evaluable population for other PK parameters. N represents the number of subjects with at least 5 evaluable PK samples per subject

§ Geometric mean and percent geometric CV reported for t1/2 and MRT

† Back-transformed least squares mean and confidence interval from linear fixed effects model performed on natural log-transformed values

Safety results

An AE was reported for most participants in each intervention group (74.9% to 97.1% of participants; Table 12). The AE reported most frequently in all intervention groups was procedural pain. Other frequently reported AEs included bradycardia, nausea, and vomiting (Table 13).

Table 12: Adverse Event Summary (All Subjects as Treated, Part A+B, Up to 7 Days Post-Treatment)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Subjects in population	51		191		34	
with one or more AE	40	(78.4)	143	(74.9)	33	(97.1)
with no AE	11	(21.6)	48	(25.1)	1	(2.9)
with drug-related† AE	4	(7.8)	5	(2.6)	4	(11.8)
with serious AE	3	(5.9)	3	(1.6)	2	(5.9)
with serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who died due to a drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an AE	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)

AE=adverse event(s)

† Determined by the investigator to be related to the drug.

Table 13: Subjects with Specific Adverse Events (Incidence ≥ 5% in One or More Treatment Groups) (All Subjects as Treated, Part A+B, Up to 7 Days Post-Treatment)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Subjects in population	51		191		34	
with one or more specific adverse events	40	(78.4)	143	(74.9)	33	(97.1)
with no specific adverse events	11	(21.6)	48	(25.1)	1	(2.9)
Cardiac disorders	**5**	**(9.8)**	**16**	**(8.4)**	**5**	**(14.7)**
Bradycardia	3	(5.9)	12	(6.3)	3	(8.8)
Sinus bradycardia	2	(3.9)	1	(0.5)	2	(5.9)
Eye disorders	**3**	**(5.9)**	**1**	**(0.5)**	**1**	**(2.9)**
Gastrointestinal disorders	**8**	**(15.7)**	**35**	**(18.3)**	**4**	**(11.8)**
Nausea	1	(2.0)	12	(6.3)	2	(5.9)
Vomiting	4	(7.8)	20	(10.5)	2	(5.9)
General disorders and administration site conditions	**1**	**(2.0)**	**5**	**(2.6)**	**2**	**(5.9)**
Pyrexia	0	(0.0)	2	(1.0)	2	(5.9)
Infections and infestations	**1**	**(2.0)**	**3**	**(1.6)**	**3**	**(8.8)**
Injury, poisoning and procedural complications	**34**	**(66.7)**	**121**	**(63.4)**	**26**	**(76.5)**
Incision site pain	3	(5.9)	6	(3.1)	1	(2.9)
Procedural nausea	4	(7.8)	9	(4.7)	0	(0.0)
Procedural pain	30	(58.8)	111	(58.1)	24	(70.6)
Procedural vomiting	3	(5.9)	5	(2.6)	1	(2.9)
Investigations	**0**	**(0.0)**	**8**	**(4.2)**	**3**	**(8.8)**
Body temperature increased	0	(0.0)	1	(0.5)	2	(5.9)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**6**	**(3.1)**	**2**	**(5.9)**
Muscle spasms	0	(0.0)	0	(0.0)	2	(5.9)
Nervous system disorders	**2**	**(3.9)**	**4**	**(2.1)**	**3**	**(8.8)**
Respiratory, thoracic and mediastinal disorders	**1**	**(2.0)**	**3**	**(1.6)**	**3**	**(8.8)**

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

In all, 13 of 276 (4.7%) participants experienced an AE that was determined by the investigator to be related to the study drug (Table 14). Across all treatment groups, bradycardia was the most frequently reported AE considered to be drug-related (10 out of 13 participants). There were no serious drug-related AEs and no subject discontinued due to a drug-related AE.

Table 14: Subjects with Drug-Related Adverse Events (Incidence > 0% in One or More Treatment Groups) (All Subjects as Treated, Part A+B, Up to 7 Days Post-Treatment)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Subjects in population	51		191		34	
with one or more drug-related adverse events	4	(7.8)	5	(2.6)	4	(11.8)
with no drug-related adverse events	47	(92.2)	186	(97.4)	30	(88.2)
Cardiac disorders	**4**	**(7.8)**	**3**	**(1.6)**	**3**	**(8.8)**
Bradycardia	3	(5.9)	2	(1.0)	2	(5.9)
Sinus bradycardia	1	(2.0)	1	(0.5)	1	(2.9)
Gastrointestinal disorders	**0**	**(0.0)**	**1**	**(0.5)**	**1**	**(2.9)**
Vomiting	0	(0.0)	1	(0.5)	1	(2.9)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**
Tachypnoea	0	(0.0)	1	(0.5)	0	(0.0)

Every subject is counted a single time for each applicable row and column.

Events of clinical interest (ECI) for this trial included the following:

- hypersensitivity and/or anaphylaxis
- clinically relevant bradycardia defined as bradycardia necessitating intervention, as determined by investigator judgment
- drug-induced liver injury

Clinically relevant bradycardia within 7 days post-treatment was reported in 1 of 51 (2.0%), 3 of 191 (1.6%) and 2 of 34 (5.9%) participants in sugammadex 2 mg/kg, sugammadex 4 mg/kg and neostigmine + (glycopyrrolate or atropine) group, respectively. No cases of hypersensitivity, anaphylaxis or potential drug-induced liver injury was reported at any time point.

2.3.3. Discussion on clinical aspects

Bridion is approved for routine reversal of rocuronium-induced blockade in children and adolescents aged 2 to 17 years. The recommended dosing time in children and adolescents (2-17 years) is at reappearance of T2 and the recommended dose is 2 mg/kg. The recommended posology is based on one clinical study in the paediatric population. In adults, the recommended dose for routine NMB reversal is 4 mg/kg if recovery has reached at least 1-2 post-tetanic counts following rocuronium or vecuronium induced blockade or 2 mg/kg if spontaneous recovery has occurred up to at least the reappearance of T2 following rocuronium or vecuronium induced blockade. In addition, if there is a clinical need for immediate reversal following administration of rocuronium a dose of 16 mg/kg sugammadex is recommended in adults. Immediate reversal in children and adolescents has not been investigated and is therefore not recommended until further data become available.

In study MK-8616-089, the results for the primary efficacy endpoint (time to recovery to a TOF ratio of ≥0.9) indicate that the reversal of moderate NMB was faster following sugammadex 2 mg/kg (geometric mean: 1.6 minutes) compared with neostigmine (geometric mean: 7.5 minutes). The difference between the treatments was statistically significant and clinically meaningful. Pre-specified subgroup analyses and results for secondary and tertiary efficacy endpoints supported the primary analysis.

Efficacy data for sugammadex 4 mg/kg that were collected in 191 paediatric patients are relevant new information, although no comparator existed for reversal of deep block. In addition, data on the use for reversal of vecuronium-induced blockade in children and adolescents is valuable new information. The median time (range) to TOF ratio ≥0.9 was 1.7 (0.4; 118.1) minutes in patients with deep block. Delayed recovery was observed in 14 of 191 subjects (7.3%). Efficacy data for sugammadex 2 mg/kg (n = 33 in Part B) support the approved posology for reversal of moderate block in paediatric patients.

PK data were collected in 18 and 22 paediatric patients in sugammadex 2 mg/kg and 4 mg/kg groups, respectively. Two subjects in 4 mg/kg group had incomplete PK sampling and they were excluded from analysis of some PK parameters, which is acceptable. Overall, the PK data supported the conclusion of dose proportional increase in exposure over the dose range 2 to 4 mg/kg in paediatric subjects. This is in line with adult PK data.

AEs were reported in majority of patients, which is expected given the study population (patients with surgical procedure or clinical situation - e.g. intubation - that required moderate or deep NMB). The most common reported AE was procedural pain (reported in more than 50% of patients), followed by procedural or other nausea and vomiting. Of more interest are the drug-related AEs that were reported in 7.8%, 2.6% and 11.8% of patients in sugammadex 2 mg/kg, sugammadex 4 mg/kg and neostigmine + (glycopyrrolate or atropine) group, respectively, and cases of clinically relevant bradycardia (pre-specified event of clinical interest) that were reported in 2.0%, 1.6% and 5.9% of patients in sugammadex 2 mg/kg, sugammadex 4 mg/kg and neostigmine + (glycopyrrolate or atropine) group, respectively. Although the safety data are limited, they do not suggest dose-dependent or new safety

concerns in paediatric patients after a bolus IV dose of 4 mg/kg sugammadex for reversal of a deep NMB.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted a final clinical study report for study MK-8616-089 in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. The study report is written in accordance with the Note for guidance on structure and content of clinical study reports (CPMP/ICH/137/95) and it is acceptable.

☒ **Fulfilled:**

In view of the available data regarding Bridion, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions. It is noted that the MAH has already expressed their plan to submit a type II variation later this year (2020) to update the Product Information.