Office of Clinical Pharmacology Review

NDA or BLA Number	22225 S008
Link to EDR	\\CDSESUB1\evsprod\NDA022225\0290
Submission Date	08/26/2021
Submission Type	*[Standard review]*
Brand Name	Bridion
Generic Name	Sugammadex
Dosage Form and Strength	200 mg/2mL or 500 mg/5 mL in a single-dose vial for bolus injection
Route of Administration	Intravenous Injection
Proposed Indication	Reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.
Applicant	Organon USA Inc., a Subsidiary of Merck and Co. Inc.
Associated IND	*IND 68,029*
OCP Division:	*Division of Neuropsychiatric Pharmacology*
OND Division:	*Division of Anesthesiology, Addiction Medicine, and Pain Medicine*
Clinical Pharmacology Reviewer	*Srikanth C. Nallani, Ph.D.*
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1. EXECUTIVE SUMMARY

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The Sponsor conducted clinical efficacy trial P089MK8616 (P089) to establish efficacy in pediatric patients 2 – 17 years old. Safety and pharmacokinetics of sugammadex in patients 2 – 17 years old provide support for the efficacy of proposed dosing regimen established in clinical study P089MK8616 (P089).
General dosing instructions	For rocuronium and vecuronium: • 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation. • 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation. For rocuronium only: • 16 mg/kg is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Pediatrics: For rocuronium and vecuronium: • 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation. • 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation.
Labeling	Pharmacokinetics of sugammadex in pediatric patients 2 – 17 years old have been determined. See section 2.4 for details.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable
Other (specify)	Not applicable

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

BRIDION (Sugammadex), a modified gamma cyclodextrin, forms a complex with the neuromuscular blocking agents (NMBA) reducing their binding to nicotinic cholinergic receptors in the neuromuscular junction thus resulting in the reversal of neuromuscular blockade (NMB) by rocuronium and vecuronium. Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg following IV bolus administration. In adult anesthetized patients with normal renal function, the elimination half-life ($t_{1/2}$) of sugammadex is about 2 hours and the estimated plasma clearance is about 88 mL/min (based on compartmental pharmacokinetic analysis). Sugammadex is known to be substantially excreted by the kidney. The half-life of sugammadex in patients with mild, moderate and severe renal impairment is 4, 6, and 19 hours, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For rocuronium and vecuronium:

- 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation.
- 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation.

For rocuronium only:

- 16 mg/kg is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium.

2.2.2 Therapeutic individualization

For pediatric patients 2 – 17 years old to reverse neuromuscular block induced by rocuronium and vecuronium:

- 4 mg/kg is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts (PTC) and there are no twitch responses to train-of-four (TOF) stimulation.
- 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation.

Safety, efficacy and pharmacokinetics of 16 mg/kg dose of sugammadex have not been evaluated in pediatric patients.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

(b) (4)

[redacted] Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant [see Clinical Studies (14.1)].

The observed steady-state volume of distribution of sugammadex is approximately 3 to [redacted] liters and clearance is approximately [redacted] – 95 mL/min in pediatric patients 2 to <17 years of age.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

At the time of approval of NDA 22225 (Bridion), PMR 3003-1 was issued specifying conduct of a "A randomized, controlled trial evaluating the efficacy, safety, and pharmacokinetics of sugammadex injection when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium must be conducted in pediatric patients ages birth to 17 years old." The sponsor conducted Study P089MK8616 (P089) to fulfill requirements for establishing efficacy, safety and PK of sugammadex in 2 – 17 years old pediatric patients. Another study P169 investigating efficacy, safety and PK in birth – 2 years old pediatric patients is ongoing. In addition to the PREA PMR 3003-1, a pediatric written request (PWR) was issued specifying pharmacokinetic and clinical efficacy objectives in two pediatric studies (birth to 2 years, and 2 -17 years age). The clinical pharmacology review shows that the sponsor has met the objectives and requirements specified in the PWR with regard to pharmacokinetic endpoints in pediatric patients 2 – 17 years of age (Study P089).

Previously, the sponsor had conducted a pediatric study "Trial 19.4.306" or Study P034 (Reviewed under IND 68,029 SDN690). This trial was designed as a Study 034 was a multicenter, randomized, parallel dose-finding, safety-assessor blinded study designed to investigate 4 doses of sugammadex (0.5, 1.0., 2.0 and 4.0 mg/kg) and placebo for the reversal of rocuronium induced moderate NMB ("at the reappearance of T2") at different age groups of pediatric subjects. The trial also investigated a cohort of adult subjects. However, limited number (four to five subjects per dose group) of pediatric subjects recruited per age group were evaluated in this pediatric study.

3.2 General Pharmacology and Pharmacokinetic Characteristics

BRIDION (Sugammadex) is a modified gamma cyclodextrin. It forms a complex with the neuromuscular blocking agents rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to nicotinic cholinergic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium and vecuronium. Reversal of drug-induced NMB for surgical intervention is used to accelerate recovery from the effects of NMBAs. The molar ratios of sugammadex to NMBA and resultant concentration gradient are important considerations for the dosing of sugammadex across populations. At the recommended sugammadex doses in adults (2 mg/kg for reversal of [redacted] NMB, 4 mg/kg for reversal of [redacted] NMB), the molar ratio excesses of sugammadex over rocuronium, at 2 minutes after sugammadex dosing, range from 5 to

8. Within these 2 minutes, enough rocuronium has flowed from the NMJ to the adjacent extracellular fluid (where the concentration of sugammadex is still increasing) and to the plasma (where sugammadex has encapsulated free rocuronium first) to achieve recovery.

Sugammadex pharmacokinetic parameters were calculated from the total sum of non-complex-bound and complex-bound concentrations of sugammadex. Pharmacokinetic parameters as clearance and volume of distribution are assumed to be the same for non-complex-bound and complex-bound sugammadex in anesthetized patients. The observed steady-state volume of distribution of sugammadex is approximately 11 to 14 liters in adult patients with normal renal function (based on conventional, non-compartmental pharmacokinetic analysis). Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose. In adult anesthetized patients with normal renal function, the elimination half-life ($t_{1/2}$) of sugammadex is about 2 hours and the estimated plasma clearance is about 88 mL/min (based on compartmental pharmacokinetic analysis). Sugammadex is known to be substantially excreted by the kidney. The half-life of sugammadex in patients with mild, moderate and severe renal impairment is 4, 6, and 19 hours, respectively.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The Sponsor conducted clinical efficacy trial P089MK8616 (P089) to establish efficacy in pediatric patients 2 – 17 years old. Safety and description of pharmacokinetics of sugammadex in patients 2 – 17 years provide support for the proposed dosing regimen established in clinical study P089MK8616 (P089).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Clinical trials, described in product label, support the 2 mg/kg, 4 mg/kg and 16 mg/kg of IV sugammadex in adults.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Because the sugammadex dosing is based on bodyweight, it is not necessary to alter dosing regimen of sugammadex in pediatric patients 2 – 17 years of age.

Pharmacokinetic parameters from Study P089 after single-dose administration of 2 or 4 mg/kg sugammadex in pediatric patients 2 to <17 years of age are shown in Table 1. Patients were enrolled into 3 age groups and intravenous doses of 2 or 4 mg/kg sugammadex were administered for reversal of moderate or deep neuromuscular blockade, respectively.

Sugammadex exposure ($AUC_{0\text{-}inf}$ and C_{max}) increased in a dose-dependent, linear manner following administration of 2 and 4 mg/kg across patients 2 to <17 years of age. Sugammadex exposure was approximately 40% lower in patients 2 to <6 years of age following administration of 2 or 4 mg/kg

sugammadex compared to older pediatric patients (6 to <17 years) and adults; however, this difference was not clinically relevant.

Table 2 and Figure 1 summarize the molar ratio of sugammadex and rocuronium concentrations at 2 minutes with different sugammadex doses ([Table 2]) and at different times after dose for the 2- and 4-mg/kg dose levels ([Figure 1]) across adult and pediatric age categories in P034.

Table 1: Geometric Mean (% GCV) Pharmacokinetic Parameters in Pediatric Participants After Single-Dose Administration of Sugammadex.

Age Group (years)	Dose (mg/kg)	Pharmacokinetic Parameters						
		$AUC_{0\text{-}inf}$ (h*µg/mL)	C_{max} (µg/mL)	CL (L/hr)	wnCL ((L/hr)/kg)	Vss (L)	wnVss (L)	t1/2 (hr)
2 to <6	2	14.1 (19.4)	17.5 (33.1)	2.30 (21.4)	0.142 (19.4)	3.58 (21.3)	0.221 (22.5)	1.23 (17.4)
	4	26.9 (18.5)	47.1 (22.1)	2.26 (29.4)	0.149 (18.5)	3.10 (27.7)	0.204 (7.95)	1.23 (25.2)
6 to <12	2	18.8 (27.4)	32.2 (15.6)	3.58 (26.2)	0.107 (27.4)	5.16 (31.4)	0.154 (6.27)	1.29 (25.1)
	4	38.2 (73.0)	51.6 (69.2)	3.43 (105)	0.105 (73.0)	6.24 (73.9)	0.190 (38.4)	1.66 (32.5)
12 to <17	2	27.6 (58.0)	41.3 (85.8)	4.68 (52.5)	0.0726 (58.0)	7.20 (32.8)	0.112 (38.7)	1.49 (23.2)
	4	49.2 (20.1)	61.9 (13.5)	5.69 (24.1)	0.0812 (20.1)	9.88 (27.7)	0.141 (17.4)	1.49 (19.2)

$AUC_{0\text{-}inf}$=area under the concentration-time curve from time zero to infinity; CL=clearance; C_{max}=maximum concentration; GCV=geometric coefficient of variation; t1/2=half-life; Vss=apparent volume of distribution at steady state; wnCL=weight-normalized clearance; wnVss=weight normalized apparent volume of distribution at steady state.

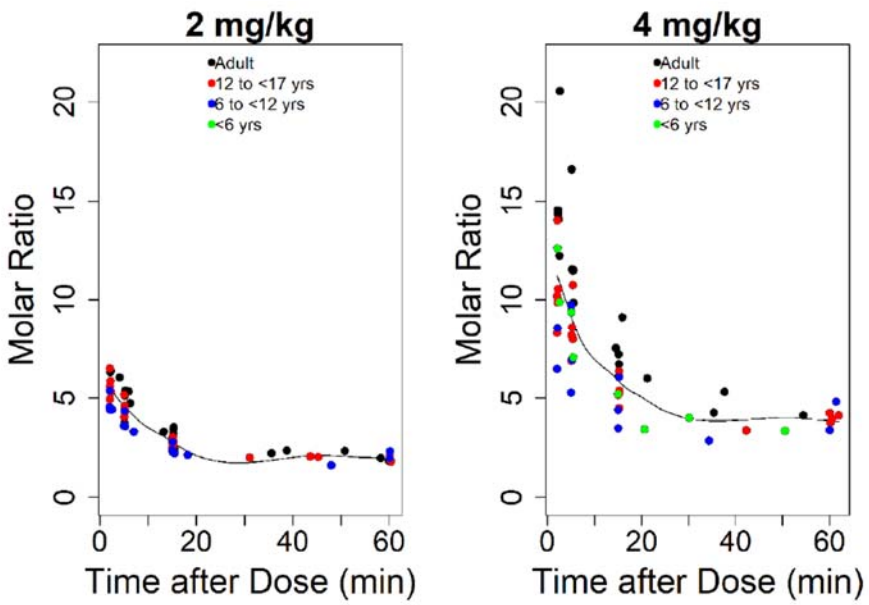
Table 2: Molar Ratio of Sugammadex/Rocuronium at 2 Minutes After Sugammadex Administration in Pediatric (6<12 years and 12 – 17 years) and Adult Participants (17+) (P034).

Age Category	Dose (mg/kg)	N	Mean	Median	Min	Max
6 to <12	0.5	4	1.29	1.22	0.99	1.71
	1	4	2.26	2.30	1.86	2.60
	2	4	4.68	4.48	4.41	5.38
	4	3	8.25	8.54	6.46	9.74
12 to <17	0.5	4	1.44	1.36	0.98	2.08
	1	5	2.62	2.64	2.15	3.24
	2	5	5.63	5.56	4.93	6.49
	4	6	10.5	10.1	8.28	14.01
17+	0.5	5	1.50	1.38	1.01	2.11
	1	6	2.94	3.03	2.05	3.84
	2	5	5.92	6.30	4.50	6.40
	4	6	14.7	14.2	12.2	20.5

Abbreviations: max=maximum; min=minimum; N=number of participants
Data for age class 2 to <6 not shown due to limited data, only 1 participant for 0.5 mg/kg and 1 participant for 4-mg/kg dose group were available.

Source: [Ref. 5.3.5.3: 05HVRV: Table 10]

Figure 1: Molar Ratio of Sugammadex/Rocuronium Over Time After Sugammadex Administration in Pediatric and Adult Participants (P034).



Source: [Ref. 5.3.5.3: 05HVRV: Figure 12]

For the single participant 2 to <6 years of age administered sugammadex 4 mg/kg, a molar excess of 9.88 was estimated. These results confirm the molar excess of sugammadex versus rocuronium being consistently >4 in the different age categories at the initial 2-minute timepoint for both 2- and 4-mg/kg doses. At later timepoints through 60-minutes post-dose, this molar excess is maintained at a level >2 for the 2-mg/kg dose and >4 for the 4-mg/kg dose in all included age categories. Overall, sugammadex doses of 2 and 4 mg/kg can be assumed to provide a minimum molar excess of >2 and continue to ensure encapsulation of NMBA, reducing the risk of recurrence of NMB.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

None.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical method used was a validated high-performance liquid chromatographic tandem mass spectrometric (LC/MS/MS) method developed to quantitate sugammadex in human plasma. The development and validation of the bioanalytical method, as well as the analysis of plasma samples, was performed by (b) (4) The assay was validated over the concentration range of 0.100 to 40.0 µg/mL in human plasma. Accuracy of quality control samples ranged from -3.3 to 1.0% and precision ranged from 3.9 to 8.4%. Blood sample collection procedures and the bioanalytical assay method were consistent with procedures and methods employed in recent sugammadex clinical trials in adult participants, and therefore, support integration with and comparison to historical pediatric and/or adult data. To confirm assay reproducibility, 43 (20.3%) of 212 samples were selected for incurred sample reanalysis (ISR). All 43 samples selected for the ISR test (100%) met acceptance criteria, exceeding the acceptance criteria of 67%; therefore, the bioanalytical data are considered reliable to support evaluation of sugammadex plasma concentration values in pediatric participants aged 2 to <17 years.

4.2 Clinical PK Assessments

Study P089MK8616 (P089): 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 induced by rocuronium or vecuronium.

The study design consisted of 2 parts, Part A and B. 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
Upon completion of Part A of the study, an interim analysis was performed to evaluate pharmacokinetic (PK) and safety data prior to enrollment in Part B, results of which were reviewed by a standing internal data monitoring committee (siDMC). The safety data was also reviewed by an external DMC (eDMC). 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 sugammadex in Part B. Of note, PK was only collected and evaluated in Part A.

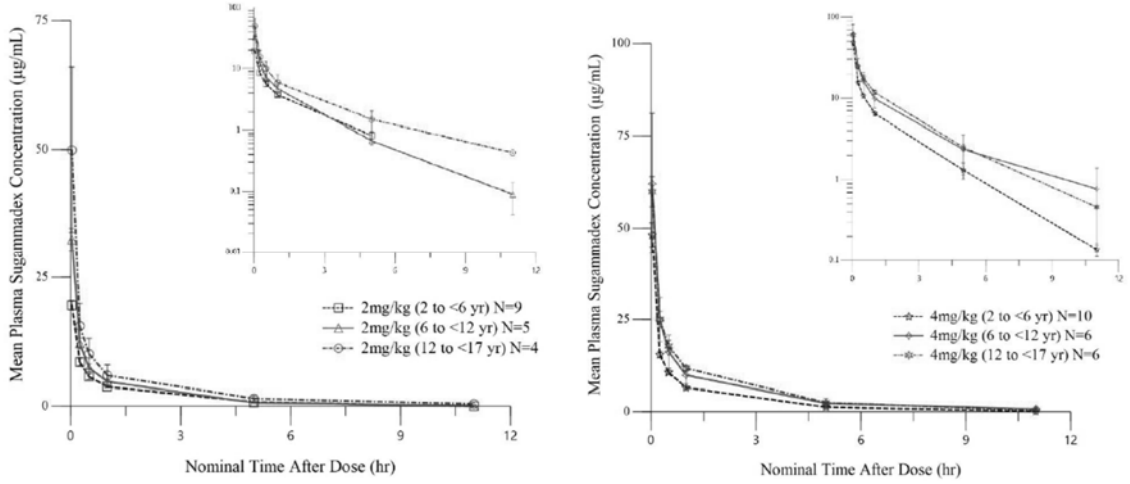
In Part B, participants were randomized to 1 of 3 intervention groups in an overall 1:1:5 ratio to:
• moderate block and reversal with 2 mg/kg sugammadex; or
• moderate block and reversal with neostigmine + glycopyrrolate or atropine sulfate (hereafter, referred to as neostigmine) [active control]; or
• 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 neuromuscular blocking agent (NMBA) (rocuronium or vecuronium). Study interventions used in the study are provided in the below table.

Intervention	Unit Dose	Route of Administration	Treatment Period	Use
Sugammadex, 2 or 4 mg/kg	100 mg/mL	IV	Perianesthetic	Investigational
Neostigmine methylsulfate, 50 mcg/kg	0.5 mg/mL	IV	Perianesthetic	Comparator
Glycopyrrolate, 5 to 15 mcg/kg	0.2 mg/mL	IV	Perianesthetic	Required to be used with comparator
Atropine Sulfate, 10 to 30 mcg/kg	0.4 mg/mL	IV	Perianesthetic	Required to be used with comparator

The objectives of the PK analyses were to (1) characterize PK parameter values following administration of 2- and 4-mg/kg sugammadex in pediatric participants; and (2) confirm the appropriateness of the 2- and 4-mg/kg doses for subsequent evaluation of sugammadex safety and efficacy for reversal of (b) (4) NMB, respectively, in pediatric participants. In each treatment group (2 and 4 mg/kg) and across each of the age categories (2 to <6 , 6 to <12 and 12 to <17 years of age), at least 4 participants were eligible for inclusion in the PK analyses, with at least 8 pediatric participants 2 to <6 years of age in each treatment group, exceeding the minimum enrollment expectations for Part A of the study. The mean (± SE) plasma sugammadex concentration-time profiles after a single IV dose of 2- or 4-mg/kg sugammadex were examined for apparent trends (Figures 2 and 3).

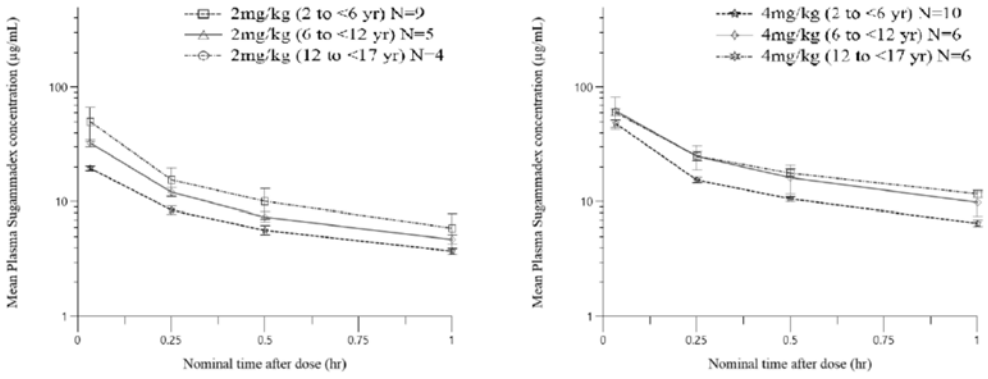
Figure 2: Arithmetic Mean (±SE) Plasma Concentration-Time Profiles of Sugammadex Following a Single IV Dose of 2 mg/kg (Left Panel) or 4 mg/kg (Right Panel) Sugammadex Administered in Pediatric Participants (2 yr to <6 yr, 6 yr to <12 yr, 12 yr to <17 yr) (Inset: Semi-Log Scale).



Source: [Ref. 5.3.5.1: P089MK8616: 16.2.5.7: Figure 3-1]

Given the critical interval over which efficacy is expected, a truncated post-dose duration of 0 to 60 minutes was also evaluated.

Figure 3: 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).



Source: [PK089MK8616: adam-adpc]

Pharmacokinetic characteristics of sugammadex following 2 mg/kg and 4 mg/kg IV dose in different pediatric age groups are described in Tables 4, 5, and 6. The mean plasma sugammadex AUC0-1hr in participants 2 to <6 years of age administered 2 mg/kg were 31% and 54% lower, than those in participants 6 to <12 years of age and 12 to <17 years of age, respectively, with largely similar differences after administration of 4 mg/kg. Mean Cmax in participants 2 to <6 years of age administered 2 mg/kg were 45% and 57% lower than those in participants 6 to <12 years of age and 12 to <17 years of age, respectively. By comparison, any mean differences between participants 2 to <6 years of age and those 6 to <17 years of age following 4 mg/kg were modest (<20%) suggesting largely comparable and overlapping sugammadex peak (Cmax) concentrations between these age categories.

Table 4: Summary Statistics for Sugammadex Plasma Pharmacokinetic Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (P089 Part A: 2 to <6 yr).

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)

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

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

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

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

Source: [Ref. 5.3.5.1: P089MK8616: 16.2.5.7: Table 3-1]

CL and volume of distribution (Vz and Vss) relationships indicate that CL increased with age, with a similar trend for volume of distribution (Tables 4, 5, and 6). Body weight-normalized CL and volume of distribution in children (6 to <12 years of age) was higher than those in adolescents and increased with decreasing age. The elimination $t_{1/2}$ was generally comparable across all age cohorts. Body weight-normalized CL and volume of distribution as well as elimination $t_{1/2}$ of sugammadex for each age category were largely similar at both sugammadex doses, confirming dose linearity.

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)

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

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

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

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

Source: [Ref. 5.3.5.1: P089MK8616: 16.2.5.7: Table 3-3]

Table 5: Summary Statistics for Sugammadex Plasma Pharmacokinetic Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (P089 Part A: 6 to <12 yr).

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)

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

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

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

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

Source: [Ref. 5.3.5.1: P089MK8616: 16.2.5.7: Table 3-2]

Table 6: Summary Statistics for Sugammadex Plasma Pharmacokinetic Parameters Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric Participants (P089 Part A: 12 to <17 yr).

The sponsor was asked to provide an explanation, particularly any experimental considerations with regard to sample collection and assay procedures, regarding lower exposure in 2 – 6-year old patients. In response to the information request the sponsor indicated blood sample collection procedures and the bioanalytical assay method were consistent with procedures and methods employed in recent sugammadex clinical studies in adult participants and the historical pediatric study P034, and therefore, support integration with and comparison to historical pediatric and/or adult data. Any differences in the observed PK are not expected to be attributable to sample collection or assay procedures.

Overall, based upon the concentration-time profiles alone, the age cohorts and the selected PK sampling time points applied in P089 Part A permitted acceptable characterization of sugammadex PK parameter values. Importantly, the sugammadex PK profiles in pediatric participants 2 to <6 years of age (Table 4) suggest that the weight-based regimen minimizes excursions beyond the observational data in older children (6 to <12 years of age, Table 5) and adolescents (12 to <17 years of age, Table 6) such that based upon PK alone, safety and tolerability in the youngest children would be anticipated to be similar to that in older children.

4.3 Annotated Responses by Sponsor to Pediatric Written Request (PK Endpoints)

Clinical studies Study 1: This study will be a 2-part, randomized, assessor-blinded, multicenter study evaluating pharmacokinetics (PK) and safety of sugammadex used for reversal of neuromuscular blockade in pediatric patients 2 to < 17 years old. Part A will be a randomized, multicenter study evaluating PK of sugammadex used for reversal of neuromuscular blockade in pediatric patients 2 to < 17 years old. Part A will evaluate initial doses of 2 mg/kg sugammadex for moderate block (spontaneous return of T2) and 4 mg/kg sugammadex for deep block (1-2 post-tetanic twitches). Part B will be a randomized, assessor-blinded, active-controlled, multicenter study evaluating the safety of sugammadex for reversal of neuromuscular blockade induced by rocuronium and vecuronium in pediatric patients 2 to < 17 years old who have moderate (spontaneous return of T2 in a train-of-four) and deep block (at least 1 to 2 post-tetanic counts and no twitch responses to a train-of-four). The dosing for each depth of block in this study will be based on the results from Part A. In Part B, for patients with spontaneous recovery of T2, sugammadex will be compared to neostigmine.	Protocol Amendment 089-01: Section 5.4 Scientific Rationale for Study Design and Section 7.4 Blinding [Ref. 5.3.5.1: P089MK8616: 16.1.1.2] P089 CSR: Section 9.1 Study Design [Ref. 5.3.5.1: P089MK8616: 9.1]
Part A of this study must assess PK and identify a dose to be used in Part B. Results of Part A must be reported to and the dose agreed upon by the Agency prior to the initiation of Part B. Pharmacokinetics in the targeted pediatric population must be accurately evaluated and estimated in Part A of Study 1. Otherwise, additional PK samples may need to be collected in Part B of the study. Also, the study protocol must include stopping criteria for adverse events of interest (i.e., bradycardia and anaphylaxis). If greater than predicted cardiovascular adverse events (e.g., bradycardia) or unexpected severe adverse events in Study 1, Part A are observed, you will need to submit your safety data to the Agency for review prior to initiation of Study 2 enrollment. Finally, since the lower age sub-cohort (2 to < 6 years) is potentially at greater risk of adverse events, in particular bradycardia, you must ensure that at least N=2 for each level of block (moderate and deep) are between 2 to <3 years of age in Part A of the study.	Protocol Amendment 089-01: Section 5.4 Scientific Rationale for Study Design and Section 10.7 Interim Analyses [Ref. 5.3.5.1: P089MK8616: 16.1.1.2] P089 CSR: Section 16.2.5.7 P089 Sugammadex Pharmacokinetic Analysis Report, Section 2 Methods [Ref. 5.3.5.1: P089MK8616: 16.2.5.7]
Objective of each study: Study 1 Part A: Part A of this study must assess PK and identify a dose to be used in Part B in patients 2 to < 17 years of age.	

Part B: To evaluate the safety and tolerability of sugammadex in pediatric patients 2 to < 17 years old. Descriptive efficacy findings should also be recorded. Efficacy findings, while not required to be statistically significant, should favor sugammadex.	
Patients to be Studied. Age group in which studies will be performed. Study 1 will evaluate patients from 2 to < 17 years old. In each study, the number of patients must be approximately evenly distributed between genders and within each age cohort being studied.	P089 CSR: Section 10.4.1 Demography and Baseline Disease Characteristics [Ref. 5.3.5.1: P089MK8616: 10.4.1]
Number of patients to be studied: Study 1, Part A: The sample size must be sufficient to estimate the PK parameters (clearance and volume of distribution) by employing a scientifically justified PK approach. In addition, the study needs to be adequately powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution with 80% power for a drug in each age group to be studied.	Protocol Amendment 089-01: Section 10.9.3 Sample Size and Power Calculations for Pharmacokinetic Analyses [Ref. 5.3.5.1: P089MK8616: 16.1.1.2]
Statistical information, including power of studies and statistical assessments: Part A of Study 1: Sample size for all studies must prospectively target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for the drug in each pediatric subgroup with at least 80% power. Population PK modeling analysis based on sparse PK sampling, or other scientifically justified methods can be applied to achieve this precision standard [Wang Y. et al., Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies (J Clin Pharmacol. 2012 Oct; 52(10):1601-6)].	Protocol Amendment 089-01: Section 10.9 Sample Size and Power Calculations [Ref. 5.3.5.1: P089MK8616: 16.1.1.2] P089 CSR: Section 9.7 Statistical Analysis Plan [Ref. 5.3.5.1: P089MK8616: 9.7] P089 CSR: Section 16.2.5.7 P089 Sugammadex Pharmacokinetic Analysis Report, Section 2.2 Statistical Analysis Plan [Ref. 5.3.5.1: P089MK8616: 16.2.5.7]

The clinical pharmacology review shows that the sponsor has met the objectives and requirements specified in the PWR with regard to pharmacokinetic endpoints in pediatric patients 2 – 17 years of age (Study P089).

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/s/

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