# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | 22225 S-014 |
| **Link to EDR** | \\CDSESUB1\evsprod\NDA022225\0632 |
| **Submission Date** | June 12, 2024 |
| **Submission Type** | *[Priority review]* |
| **Brand Name** | Bridion |
| **Generic Name** | Sugammadex |
| **Dosage Form and Strength** | 200 mg/2 mL 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 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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| **Clinical Pharmacology Secondary Review (Division Director)** | *Mehul U. Mehta, 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 P169 to establish efficacy in pediatric patients Birth – 2 years old. Safety and pharmacokinetics of sugammadex in patients Birth – 2 years old provide support for the efficacy of proposed dosing regimen established in clinical study P169. |
| General dosing instructions | • A dose of 4 mg/kg BRIDION 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 following rocuronium- or vecuronium-induced neuromuscular blockade [see Warnings and Precautions (5.8)].<br>• A dose of 2 mg/kg BRIDION is recommended if spontaneous recovery has reached the reappearance of the second twitch (T2) in response to TOF stimulation following rocuronium- or vecuronium-induced neuromuscular blockade [see Warnings and Precautions (5.8)].<br>For rocuronium only:<br>• 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:<br>• 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.<br>• 2 mg/kg is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation. |
| Labeling | (b) (4) |
| 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

A clinical trial (Study 2 or P169) was conducted as part of post marketing requirement (PMR 3003-09) comparing sugammadex to placebo and/or drug approved for the management of the reversal of the effects of neuromuscular blockade induced by rocuronium or vecuronium in pediatric patients' birth to less than 2 years of age. The Division of Anesthesiology, Addiction Medicine and Pain Medicine opined that, "Given the immaturity of multiple organ systems in patients < 2 years old including neonates, and in particular the neuromuscular system, the appropriate dose for efficacy, in addition to safety, must be established in the < 2 year old patient population. Therefore, efficacy in patients ages 0 to < 2 years old cannot be extrapolated and will be determined by the separate study outlined in the Written Request (WR).". Hence, Part A of Study 2 or P169 was conducted to assess safety and pharmacokinetics of sugammadex followed by Part B to assess safety and efficacy.

Study 2/P169 - Part A Assessed PK and identified the doses (2mg/kg and 4 mg/kg) to be used in Part B of the study. Part A was subdivided into Panel 1 and Panel 2, as subjects were randomized to one of two groups in a 1:1 ratio, to evaluate two doses of sugammadex, to reverse moderate block. Panel 1 received sugammadex 2mg/kg to reverse moderate neuromuscular blockade, and Panel 2 received sugammadex 4 mg/kg to reverse deep neuromuscular blockade. Pharmacokinetic samples were required for only Part A of the study. Samples were collected at 2-, 15-, 30-, and 60- minutes, and 4 to 6 hours following sugammadex administered by IV bolus. An additional sample between 10 to 12 hours after sugammadex administration was optional. For all participants in Part A, PK blood samples were to be drawn from a separate IV line other than what the site used for study treatment administration to reduce the potential for PK sample contamination from IV administration of study treatment. The adequacy of the pharmacokinetic analysis plan and bioanalytical assay used for sample analysis in Study 2 (P169) were addressed by means of protocol related correspondence dated May 16, 2019, and review of bioanalytical report submitted to NDA 22225 S008 submission for Study 1 (P089). Part A of Study 2 assessed PK and identified the doses to be used in Part B of the study. Interim analyses and PK analyses were performed in a stepwise approach before proceeding to next age cohorts. No dose adjustments were required in Part B of the study. Based on our review of the interim PK data as of May 2023, it appeared that the Sponsor had acquired enough PK data in all age cohorts, and for both doses (i.e., 2 mg/kg and 4 mg/kg), to be able to describe clearance and volume of distribution with the precision required in the PWR. Since the interim analysis from Part A of Study 2 indicated adequate PK data were acquired, additional PK sampling in pediatric patients in Part B were not required.

In the NDA 022225/S-014 submission, the PK data in terms of Cmax, AUC, Clearance and Volume of distribution are precise. Non-compartmental analysis of plasma concentration profiles by the reviewer agreed with the sponsor's analysis, with or without dose-normalization. PK parameters without dose-normalization are presented in the review. Minimum enrollment expectations for P169 Part A were specified in the protocol, including at least 3 participants in Panel 1 of each age cohort and 6 participants in Panel 2 of each age cohort. A total sample size of 6 in each age cohort was estimated to result in approximately 91% likelihood that the 95% CI of the Geometric mean (GM) of CL in that age cohort will be within 60% and 140% of the GM estimates of sugammadex CL. The PK analysis dataset included 47 subjects enrolled in Part A of Study P169 distributed across age categories and sugammadex treatments, contributing a total of 249 evaluable PK sample with >9 participants included in each age cohort meeting the enrollment expectations for Part A of the trial (Table 1). No samples were excluded from the PK dataset.

Table 1: Summary of Treatment Age Cohorts in Study P169.

| Interim | Age Category | 2 mg/kg Sugammadex (N) | 4 mg/kg Sugammadex (N) | Total |
|---|---|---|---|---|
| IA01 | 6 months to < 2 years | 6 | 7 | 13 |
| IA02 | 3 months to < 6 months | 3 | 10 | 13 |
| IA03 | 28 days to < 3 months | 3 | 8 | 11 |
| IA04 | Birth to 27 days | 4 | 6 | 10 |
| | Total | 16 | 31 | 47 |
| Abbreviations: IA= Interim analysis; N=Number of subjects | | | | |

Source: [P169MK8616: adam-adsl]

All plasma PK parameter calculations were performed using the actual administered dose that each participant received and actual times in hours relative to the time of study treatment administration. The PK parameters were determined using non-compartmental methods based on individual sugammadex plasma concentration vs time data.

Individual values of PK parameters (AUC0-inf, AUC0-1hr, AUC0-4hr, Cmax, CL, Vd, Vss) were calculated using Phoenix® WinNonlin®. The following descriptive statistics: arithmetic mean (AM), standard deviation (SD), arithmetic coefficient of variation (ACV), median (Med), minimum (Min), maximum (Max), GM, and geometric coefficient of variation (GCV) were provided for all plasma sugammadex PK parameters (i.e., AUC0-inf, AUC0-1hr, AUC0-4hr, Cmax, Tmax, t½, CL, MRT, Vd, and Vss presented in Table 2) by treatment (2 mg/kg and 4 mg/kg) groups). They were natural log-transformed and evaluated with a fixed effects model containing treatment (2 mg/kg and 4 mg/kg), age cohort (birth to 27 days, 28 days to < 3 months, 3 months to <6 months, 6 months to <2 years from P169, and adults ≥17 years from P034), and treatment by age cohort interaction term as fixed effects.

Summary descriptive statistics of the PK parameter estimates by treatment group are presented in (Table 2). Figure 1 presents the PK profiles of sugammadex and Figure 2 presents individual values overlaid with GMs and corresponding 95% CIs for Cmax.

Figure 1: Plasma concentration profiles of sugammadex following a single IV dose of 2 or 4 mg/kg administered in pediatric patients (Grouped by dose level and age).

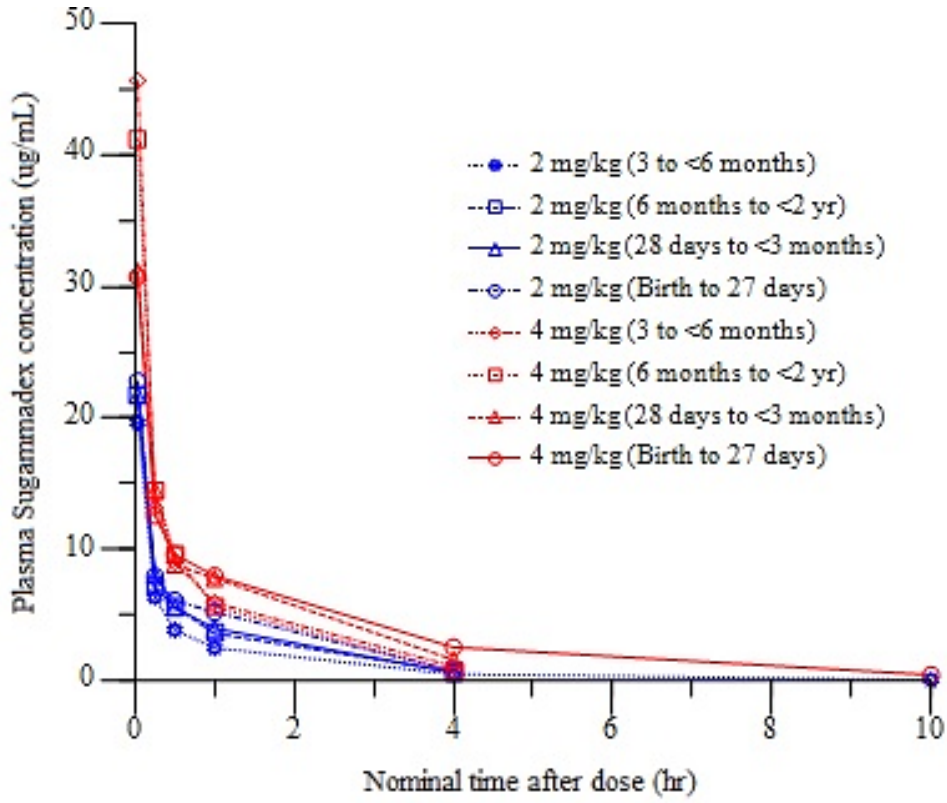
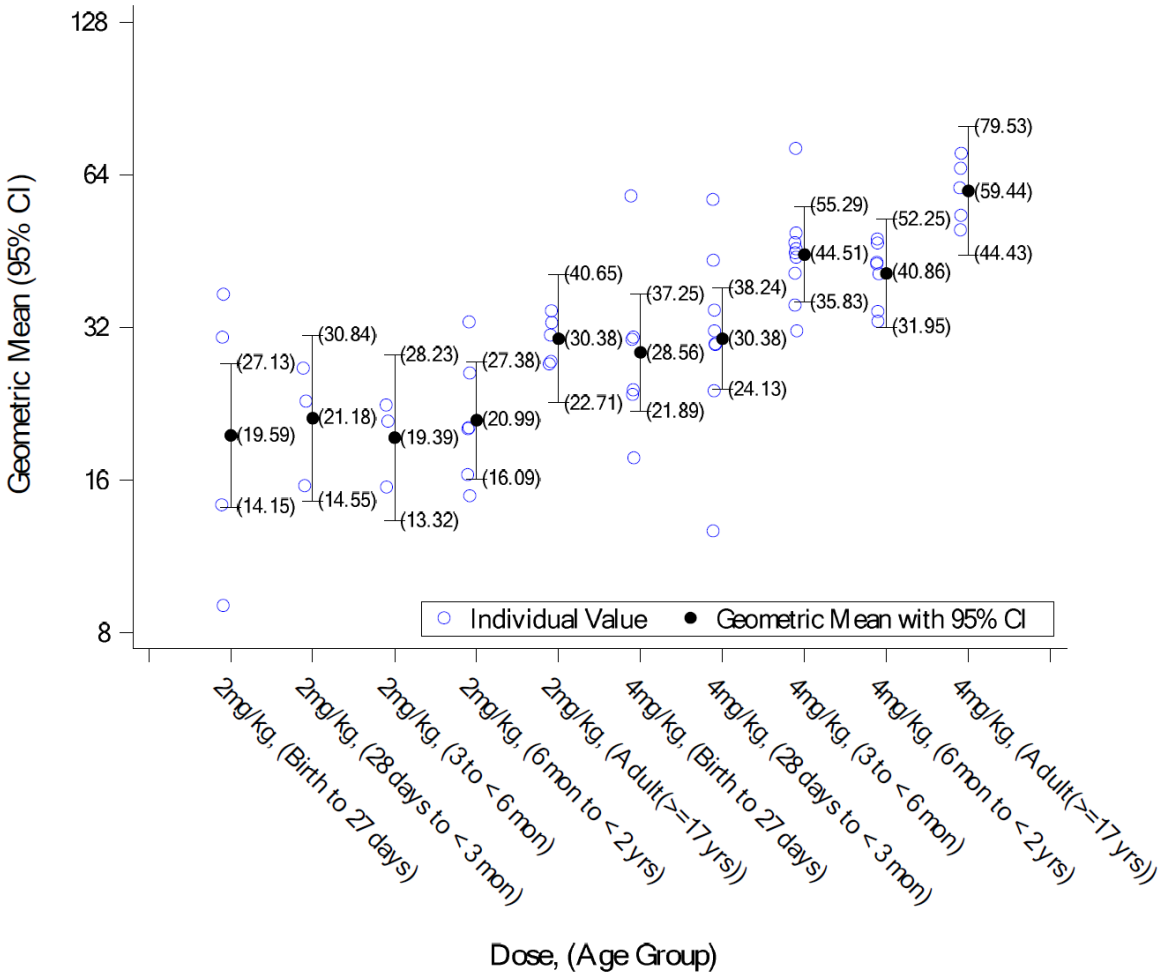


Figure 2: Sugammadex Cmax (µg/mL) following a single IV dose of 2 or 4 mg/kg administered in pediatric patients from Study P169 (Grouped by dose level and age cohorts (Birth to 27 days, 28 days to <3 months, 3 months to < 6 months, and 6 months to < 2 years). Adult PK data from Study P034, previously reviewed, were used for comparison/context.




y-axis values are logarithmically spaced.
CI=confidence interval; Cmax=maximum concentration; PK=pharmacokinetic; IV=intravenous.
Note: All PK parameters except for Cmax for one participant in 2mg/kg dose group (birth to 27 days) with an atypical concentration profile were excluded.

While the PK parameters in the pediatric patients were precise, it can be noted that Cmax and AUC are lower in these groups compared to adults (cross study). As indicated above, extrapolation of efficacy and the need to dose adjust to match adult plasma levels was not required. Hence, review of safety and efficacy data from Part A of the Study 2/P169 revealed that 2 mg/kg and 4 mg/kg doses can be evaluated in Part B. The primary efficacy endpoint for Part B of Study 2 will be "time to neuromuscular recovery," defined as the interval from administration of reversal agent to time to neuromuscular recovery (See Dr. Lee Anne Connell-Templin's review).

Table 2: Summary Statistics of Plasma Pharmacokinetic Parameters of Sugammadex Following a Single IV Dose of 2 mg/kg or 4 mg/kg Sugammadex in Pediatric patients (P169, Part A: Birth to 27 days, 28 days to <3 months, 3 months to <6 months, and 6 months to <2 years).

| Parameters | 2 mg/ kg | | | 4 mg/ kg | | |
|---|---|---|---|---|---|---|
| | N | GM | 95% CI | N | GM | 95% CI |
| **Birth to 27 days** | | | | | | |
| AUC0-inf (hr*µg/mL)[a] | 2 | 13.40 | | 6 | 39.09 | (31.85, 47.98) |
| AUC0-1hr (hr*µg/mL)[a] | 3 | 6.95 | (5.38, 8.99) | 6 | 12.38 | (10.33, 14.85) |
| AUC0-4hr (hr*µg/mL)[a] | 2 | 10.68 | | 6 | 27.79 | (22.95, 33.64) |
| Cmax (µg/mL)[a] | 4 | 19.59 | (14.15, 27.13) | 6 | 28.56 | (21.89, 37.25) |
| CL (L/hr)[a] | 2 | 0.43 | | 6 | 0.35 | (0.28, 0.45) |
| Vd (L)[a] | 2 | 1.14 | | 6 | 1.22 | (0.98, 1.52) |
| Vss (L)[a] | 2 | 1.04 | | 6 | 1.11 | (0.92, 1.34) |
| Tlast (hr)[b] | 3 | 4.54 | (1.62, 10.00) | 6 | 10.20 | (4.16, 11.74) |
| MRT (hr)[c] | 2 | 2.43 | | 6 | 3.13 | 28.62 |
| t1/2 (hr)[c] | 2 | 1.84 | | 6 | 2.39 | 27.34 |
| **28 days to <3 months** | | | | | | |
| AUC0-inf (hr*µg/mL)[a] | 3 | 16.22 | (12.14, 21.67) | 6 | 31.90 | (25.99, 39.16) |
| AUC0-1hr (hr*µg/mL)[a] | 3 | 7.63 | (5.90, 9.87) | 7 | 14.39 | (12.16, 17.02) |
| AUC0-4hr (hr*µg/mL)[a] | 3 | 13.99 | (10.67, 18.33) | 6 | 27.16 | (22.43, 32.89) |
| Cmax (µg/mL)[a] | 3 | 21.18 | (14.55, 30.84) | 8 | 30.38 | (24.13, 38.24) |
| CL (L/hr)[a] | 3 | 0.66 | (0.47, 0.92) | 6 | 0.61 | (0.48, 0.78) |
| Vd (L)[a] | 3 | 1.45 | (1.06, 1.98) | 6 | 1.35 | (1.08, 1.68) |
| Vss (L)[a] | 3 | 1.23 | (0.94, 1.60) | 6 | 1.18 | (0.98, 1.43) |
| Tlast (hr)[b] | 3 | 5.23 | (4.00, 10.91) | 7 | 4.30 | (1.00, 5.60) |
| MRT (hr)[c] | 3 | 1.86 | 22.30 | 6 | 1.94 | 20.83 |
| t1/2 (hr)[c] | 3 | 1.52 | 20.21 | 6 | 1.53 | 16.42 |
| **3 to <6 months** | | | | | | |
| AUC0-inf (hr*µg/mL)[a] | 3 | 11.50 | (8.61, 15.37) | 8 | 24.75 | (20.73, 29.56) |
| AUC0-1hr (hr*µg/mL)[a] | 3 | 6.10 | (4.72, 7.88) | 9 | 13.46 | (11.61, 15.61) |
| AUC0-4hr (hr*µg/mL)[a] | 3 | 10.13 | (7.73, 13.27) | 8 | 21.51 | (18.23, 25.39) |
| Cmax (µg/mL)[a] | 3 | 19.39 | (13.32, 28.23) | 9 | 44.51 | (35.83, 55.29) |
| CL (L/hr)[a] | 3 | 1.28 | (0.91, 1.80) | 8 | 0.97 | (0.79, 1.19) |
| Vd (L)[a] | 3 | 2.68 | (1.96, 3.67) | 8 | 2.16 | (1.78, 2.62) |
| Vss (L)[a] | 3 | 2.07 | (1.59, 2.70) | 8 | 1.69 | (1.43, 1.98) |
| Tlast (hr)[b] | 3 | 4.10 | (4.05, 9.99) | 10 | 4.50 | (1.01, 11.12) |
| MRT (hr)[c] | 3 | 1.62 | 31.73 | 8 | 1.74 | 27.64 |
| t1/2 (hr)[c] | 3 | 1.45 | 28.57 | 9 | 1.51 | 28.79 |
| **6 months to <2 years** | | | | | | |
| AUC0-inf (hr*µg/mL)[a] | 5 | 14.07 | (11.24, 17.61) | 5 | 27.75 | (22.17, 34.74) |
| AUC0-1hr (hr*µg/mL)[a] | 6 | 7.31 | (6.09, 8.76) | 7 | 13.92 | (11.76, 16.46) |
| AUC0-4hr (hr*µg/mL)[a] | 5 | 12.57 | (10.19, 15.50) | 6 | 22.43 | (18.52, 27.15) |
| Cmax (µg/mL)[a] | 6 | 20.99 | (16.09, 27.38) | 7 | 40.86 | (31.95, 52.25) |
| CL (L/hr)[a] | 5 | 1.34 | (1.03, 1.74) | 5 | 1.27 | (0.98, 1.65) |
| Vd (L)[a] | 5 | 2.70 | (2.11, 3.44) | 5 | 2.77 | (2.17, 3.53) |
| Vss (L)[a] | 5 | 2.14 | (1.74, 2.63) | 5 | 2.18 | (1.77, 2.68) |
| Tlast (hr)[b] | 6 | 4.54 | (1.03, 9.98) | 7 | 5.19 | (1.15, 10.00) |
| MRT (hr)[c] | 5 | 1.60 | 17.99 | 5 | 1.71 | 23.47 |
| t1/2 (hr)[c] | 5 | 1.40 | 24.25 | 5 | 1.51 | 19.46 |

AUC0-1hr=area under the concentration-time curve from 0 to 1 hour; AUC0-4hr=area under the concentration-time curve from 0 to 4 hours; AUC0-inf=area under the concentration-time curve from 0 to infinity; CI=Confidence interval; CL=clearance ; Cmax=maximum concentration; GM=Geometric least-squares mean; MRT=Mean residence time ; Tlast= time of last measurable concentration; t1/2=half-life; Vd=apparent volume of distribution at terminal elimination phase; Vss=apparent volume of distribution at steady state.

Note: AUC0-inf and AUC0-1hr are model based in P034. AUC0-inf and AUC0-1hr are based on NCA for P169. Cmax is based on NCA for both P034 and P169.

N represents the number of participants with at least 4 evaluable PK samples per participant (as per protocol).

[a]Back-transformed least squares mean and CI from linear fixed effects model performed on natural log-transformed values.

[b]Median and range are provided.

[c]Geometric mean and geometric percent coefficient of variation are provided.

Note: All PK parameters except for Cmax for one participant in 2mg/kg dose group (Birth to 27 days) with an atypical concentration profile were excluded.

Based on the PK results from this study, the following PK conclusions can be made:

- Sugammadex PK data collected from pediatric participants birth to <2 years old in Part A of P169 permitted acceptable characterization of sugammadex PK parameter values when used for reversal of moderate or deep NMB. No dose dependent-trends or relevant deviations from dose linearity were observed. Additionally, sugammadex PK along with efficacy (See Dr. Lee Anne Connell-Templin's review) confirmed that no further PK data were required in Part B of P169.
- Sugammadex exposures (Cmax, AUC0-1hr) were broadly comparable for the age cohorts birth to 27 days, 28 days to <3 months, 3 months to <6 months and 6 months to <2 years in comparison to next older age cohorts receiving equivalent sugammadex doses (2 mg/kg and 4 mg/kg).
- Based on both PK considerations evaluated in Part A, treatment with 2 or 4 mg/kg for reversal of moderate or deep block, respectively, in pediatric participants birth to <2 years old was supported in Part B of the study.
- PREA PMR 3003-09 is adequately addressed from a clinical pharmacology perspective.
- Sponsor has adequately addressed clinical pharmacology requirements specified in PWR in Part A of Study P169.

## 2.1 Labeling

Additions and deletions are indicated as Bold text and ~~Strikethrough~~ text respectively. The sponsor revised the existing pediatric PK information in section 12.3 with the following:

Pediatric Patients

~~Sugammadex pharmacokinetic parameters were estimated in pediatric patients 2 to <17 years of age with patients enrolled into 3 age groups (2 to <6, 6 to <12 and 12 to <17 years of age) and intravenous doses of 2 or 4 mg/kg sugammadex administered for reversal of moderate or deep neuromuscular blockade, respectively. Both clearance and volume of distribution increase with increasing age in pediatric patients. Sugammadex exposure (AUC 0-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 [see Clinical Studies (14.1)].~~

~~The observed steady-state volume of distribution of sugammadex is approximately 3 to 10 liters and clearance is approximately 38 to 95 mL/min resulting in a half-life of approximately 1-2 hours in pediatric patients 2 to <17 years of age.~~

The pharmacokinetics of sugammadex in pediatric patients have been evaluated in 2 clinical studies following administration of intravenous doses of 2 or 4 mg/kg sugammadex administered for reversal of moderate or deep neuromuscular blockade, respectively. In one study, sugammadex pharmacokinetic parameters were estimated in pediatric patients 2 to <17 years of age with patients enrolled into 3 age groups (2 to <6, 6 to <12 and 12 to <17 years of age). In a second study, sugammadex pharmacokinetic parameters were estimated in pediatric patients birth to <2 years of age with patients enrolled into 4 age groups (birth to 27 days, 28 days to <3 months, 3 months to <6 months and 6 months to < 2 years).

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

Both clearance and volume of distribution increase with increasing age in pediatric patients, whereas elimination half-life is generally similar across pediatric patients. As a result, the observed steady-state volume of distribution of sugammadex is approximately 3 to 10 liters and clearance is approximately 38 to 95 mL/min resulting in a half-life of approximately 1-2 hours in pediatric patients 2 to <17 years of age. By comparison, observed steady-state volume of distribution of sugammadex is approximately 1 to 3 liters and clearance is approximately 38 to 95 mL/min with a half-life of approximately 1-2 hours in pediatric patients age birth to 2 years.

## 2.2 Bioanalytical:

A total of 249 human plasma study samples stored at -20 °C before bioanalysis. The analytical method is based on a sample protein precipitation extraction (96-well format) of MK-8616 from human plasma using acetonitrile with 0.3% HCl. The analyte MK-8616 and its internal standard, Org 26265, were chromatographed using reversed phase LC and detected with tandem mass spectrometric detection employing a turbo ion spray (TIS) interface in the negative ion mode. The selected reaction monitoring (SRM) transitions were (±0.2 for each mass) m/z 999.5 → 963.4 for MK-8616 and m/z 1055.5 → 467.2 for Org 26265. The lower limit of quantitation (LLOQ) for this method was 100 ng/mL with a quadratic calibration range from 100 to 40000 ng/mL. The bioanalytical method and the $Q^2$ Solutions partial validation report, which contains the Merck Validation report, were previously reviewed and found acceptable. The accuracy, precision, dilution, matrix effect, selectivity, sensitivity, long term stability (304 days at -20 °C for QC standards and 87 days for samples) were acceptable.

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