EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2024
EMA/CHMP/23106/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bridion

International non-proprietary name: Sugammadex

Procedure No. EMEA/H/C/000885/II/0047

Note

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

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List of abbreviations

AChE	Acetylcholinesterase
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APaT	All participants as treated
APT	All participants treated
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BSA	Blinded safety assessor
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration
CSR	Clinical study report
DILI	Drug-induced liver injury
ECI	Events of clinical interest
eDMC	External data monitoring committee
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
ERA	Extubation readiness assessment
ERC	Ethical review committee
FDA	Food and Drug Administration
GCP	Good clinical practice
GPvP	Good pharmacovigilance practice
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
IV	Intravenous(ly)
IIV	Inter-individual variability
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
MAH	Marketing authorisation holder
MK-8616	Sugammadex
NMB	Neuromuscular block
NMBA	Neuromuscular blocking agent
NMR	Neuromuscular recovery
NMTM	Neuromuscular transmission monitoring
OR	Operating room
PACU	Post-anaesthesia care unit
PDLC	Predefined limits of change
PH	Proportional hazards
PK	Pharmacokinetic(s)
PNS	Peripheral nerve stimulator
PPK	Population pharmacokinetic(s)
Q	Intercompartmental clearance
QA	Quality assurance
QTL	Quality tolerance limits
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
sSAP	Supplemental statistical analysis plan
t½	Half-life
TOF	Train-of-four stimulation
TTNMR	Time to neuromuscular recovery
ULN	Upper limit of normal
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
V_{SS}	Volume of distribution (at steady state)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency on 27 June 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from birth to less than 2 years of age for Bridion based on final results from paediatric study PN169 (MK-8616-P169); this is a Phase 4 double-blinded, randomized, active comparator-controlled clinical trial to study the efficacy, safety, and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in pediatric participants aged birth to <2 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 8.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to implement minor editorial corrections and to update the information intended for healthcare professionals (HCPs) at the end of the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	27 June 2024
Start of procedure:	20 July 2024
CHMP Rapporteur Assessment Report	10 September 2024
PRAC Rapporteur Assessment Report	10 September 2024
PRAC Outcome	3 October 2024
CHMP members comments	7 October 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 October 2024
Request for supplementary information (RSI)	17 October 2024
PRAC Rapporteur Assessment Report	15 November 2024
PRAC members comments	n/a
CHMP Rapporteur Assessment Report	15 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	5 December 2024
Opinion	12 December 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Drug-induced neuromuscular blockade is commonly required for e.g. intubation and surgery. Bridion (sugammadex) is used to accelerate recovery from the effects of neuromuscular blocking agents rocuronium and vecuronium.

For adults, the approved therapeutic indication of Bridion (sugammadex) is "*reversal of neuromuscular blockade induced by rocuronium or vecuronium*". For the paediatric population, the approved therapeutic indication is "*sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years*".

The scope of the current variation application is to extend the paediatric indication to include treatment of paediatric patients from birth to less than 2 years of age. The proposed new indication for the paediatric population is as follows: "*sugammadex is only recommended for routine reversal of rocuronium induced blockade in paediatric patients from birth to 17 years*.".

2.1.2. About the product

Sugammadex is a modified γ cyclodextrin and a selective relaxant binding agent that reverses neuromuscular blockade (NMB) induced by neuromuscular blocking agents (NMBAs) rocuronium and

vecuronium. Dose-response studies evaluated in the initial MAA suggested that the affinity of sugammadex for rocuronium is slightly higher compared with vecuronium.

Sugammadex is administered intravenously (IV) as a single bolus injection.

Sugammadex is a ready-for-use, clear, colourless to slightly yellow or yellow-brown solution for injection filled in 2 ml or 5 ml glass vials. Sugammadex 100 mg/mL may be diluted to a concentration of 10 mg/mL, using sodium chloride 9 mg/mL (0.9%), to increase the accuracy of dosing in the paediatric population. There are no changes to the formulation or manufacturing processes reflected in this current application. It is intended that the currently available commercial formulation of sugammadex supports administration to paediatric patients aged from birth to <2 years.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Prior studies in the paediatric population

Sugammadex was evaluated in a randomized placebo-controlled dose-response study 19.4.306 (P034) that evaluated reversal of rocuronium-induced moderate NMB. Study P034 was submitted and assessed in the initial marketing authorisation application (MAA). Sugammadex reversed rocuronium-induced NMB in adult and paediatric patients with similar recovery times to train-of-four (TOF) 0.9 when sugammadex doses of at least 2.0 mg/kg were administered at reappearance of T2, supporting similar weight-based doses in paediatric and adult populations. The results of Study P034 supported the initially approved paediatric indication for routine reversal of rocuronium induced blockade in children and adolescents (from 2 to <17 years of age) and the dose of 2 mg/kg sugammadex at reappearance of T2.

More recently, a study in paediatric participants 2 to <17 years of age (Study P089) was submitted and assessed by the CHMP in variation application II/42. Study P089 was a postmarketing requirement by the FDA and evaluated the use of sugammadex versus neostigmine administered to paediatric participants from 2 to <17 years of age for the reversal of NMB induced by either rocuronium or vecuronium. Results of Study P089 showed that the time to recovery was significantly faster in participants dosed with sugammadex 2 mg/kg compared to neostigmine. The results also indicated that the efficacy of sugammadex 4 mg/kg for reversal of deep NMB in paediatric patients was comparable to that reported for adults. The relevant change in the SmPC approved in the variation was to add the recommended posology (4 mg/kg) for children and adolescents 2 to <17 years of age for routine reversal of rocuronium induced blockade at 1-2 post-tetanic count (PTC), i.e. deep NMB. The MAH did not propose in variation application II/42 to extend the paediatric indication for reversal of vecuronium induced blockade.

2.1.4. General comments on compliance with GCP

Study P169 was performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

In the current variation application Type II, a justification for not to submit an updated ERA dossier was included. The MAH does not consider that extending the indication to 0 to less than 2 years of age patients will significantly increase the extent of use of sugammadex. This is agreed and in line with the EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data was submitted in this type II variation application. A justification for not submitting the updated ERA assessment was included and was deemed acceptable. No change in SmPC section 5.3 is needed.

Assessment of paediatric data on non-clinical aspects

This type II variation considers a change of therapeutic indication to include paediatric patients from birth to less than 2 years of age. The nonclinical data from previously conducted juvenile toxicity studies in rats with sugammadex are valid for the proposed indication extension. Based on these data, the risk for adverse effects on bone growth and development in the paediatric population was considered to be low and is communicated in the SmPC section 5.3; preclinical safety data state that sugammadex does not adversely affect tooth colour or bone quality, bone structure, or bone metabolism, or has no effects on fracture repair and remodelling of bone.

2.2.3. Conclusion on the non-clinical aspects

Based on the information submitted in this application, the extended indication to 0-2 years of age paediatric patients does not lead to a significant increase in environmental exposure further to the use of sugammadex and is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application provides the results from one clinical study: Study P169 (MK-8616-169), a Phase 4, active comparator-controlled clinical study that evaluated the use of sugammadex in paediatric participants from birth to <2 years of age for the reversal of NMB induced by either rocuronium or vecuronium. This study was conducted as an FDA postmarketing requirement. The first aim of this study (Part A) was to confirm the doses of sugammadex that produce similar exposures in neonates and children from birth to <2 years of age when compared with systemic exposure noted in adults after administration of the 2 mg/kg and 4 mg/kg doses. In Part B, the safety and efficacy of sugammadex 2 mg/kg and 4 mg/kg were assessed.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Phase	Country/ Region	Study Title	Study Design	Dosing Regimen	Study Population	Participant Exposure
8616-169 [Ref. 5.3.5.1: P169MK8616]	4	Australia Belgium Brazil Denmark Finland France Hungary Malaysia Mexico Netherlandss Russian Federation US	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 Aged Birth to <2 Years	Randomized, double-blind, parallel-group, active controlled	Sugammadex: 2- or 4 mg/kg; IV, single dose Neostigmine: 50 mcg/kg + 5 to 15 mcg/kg glycopyrrolate or 10 to 30 mcg/kg of atropine sulfate dose; IV, single dose	Males/females Age: birth to <2 years Participants were of ASA Class 1, 2, or 3 undergoing a procedure requiring NMB	Sugammadex 2 mg/kg: 44 Sugammadex 4 mg/kg: 63 Neostigmine: 31

2.3.2. Pharmacokinetics

Absorption, distribution and elimination

Sugammadex is administered intravenously as a single bolus injection and bioavailability is therefore 100%. The volume of distribution of sugammadex is approximately 11 to 14 litres in adult patients with normal renal function (based on non-compartmental analysis). Neither sugammadex nor the complex of sugammadex and rocuronium binds to plasma proteins or erythrocytes. Sugammadex is not metabolized, but it is renally excreted with a clearance approximating the glomerular filtration rate (GFR). In adult anaesthetised patients with normal renal function the elimination half-life of sugammadex is about 2 hours.

Dose proportionality and time dependencies

Sugammadex exhibits linear kinetics in adults over the dose range of 1 to 16 mg/kg when administered as an IV bolus dose.

Sugammadex exposure immediately following the IV injection, which is reflected by C_{max}, is more relevant for efficacy than the overall exposure (AUC) because reversal of NMB takes place within a few minutes after the injection.

Study P169

See section 2.4.2 of this AR for detailed summary of Study P169.

Bioanalytical methods

The original validation of the method for plasma sugammadex concentrations was performed by partner (The Netherlands). A partial validation was conducted to transfer the method to partner (USA). This site also performed the analysis of the plasma samples. The validation report by Merck is also included.

The bioanalytical method is based on a sample protein precipitation extraction of sugammadex from human plasma using acetonitrile with 0.3% HCl which disrupts the complexes between sugammadex and vecuronium or rocuronium resulting in quantification of total sugammadex. Heparin was used as an anticoagulant. The analyte sugammadex (MK-8616) and the internal standard modified cyclodextrin

were chromatographed using reversed phase LC and detected with tandem mass spectrometric detection.

The selected reaction monitoring (SRM) transitions were (±0.2 for each mass) *m/z* 999.5 → 963.4 for sugammadex and *m/z* 1055.5 → 467.2 for Org 26265.

The lower limit of quantitation (LLOQ) for the method was 100 ng/mL with a quadratic calibration range from 100 to 40 000 ng/mL.

The method was also validated for accuracy, precision, dilution integrity, selectivity, matrix effects, and carryover. Stability of the stock solution and working solutions of the analyte, freeze and thaw stability of the analyte, short term stability of the analyte at room temperature and long term stability of the analyte stored in the freezer were also studied. The results met the requirements of EMA guideline on bioanalytical method validation. Additionally, interference testing has been conducted showing that rocuronium or vecuronium does not interfere with the total sugammadex assay.

Blood sample collection procedures and the bioanalytical assay method were consistent with procedures and methods employed in sugammadex clinical trials in paediatric and adult participants, and therefore, support integration with and comparison to historical paediatric and/or adult data.

The study samples were stored at -20 °C (max. 87 days) and analysed within the confirmed long-term stability of the analyte (304 days).

To confirm assay reproducibility, 42 (16.9%) of 249 samples were selected for incurred sample reproducibility (ISR) testing. Thirty-one samples (73.8%) met acceptance criteria, exceeding the acceptance criteria of 67%.

Pharmacokinetic analyses

Pharmacokinetic blood samples were collected in Part A at 2, 15, 30, and 60 minutes and 4 to 6 hours following sugammadex administration. An optional PK sample between 10 to 12 hours after sugammadex administration could be obtained, depending on the length of hospital stay. PK data were not collected in Part B of the study. PK and exposure parameters were calculated using non-compartmental analysis and validated software (Phoenix WinNonlin).

Separately for each of the PK parameters, individual values of parameters 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 a prior study P034), and treatment by age cohort interaction term as fixed effects. For each treatment, the least squares (LS) means and their 95% confidence intervals (CIs) were constructed on the natural log scale. Exponentiating the LS means and their 95% CIs yielded estimates for the population geometric means and 95% CIs about the geometric means on the original scale.

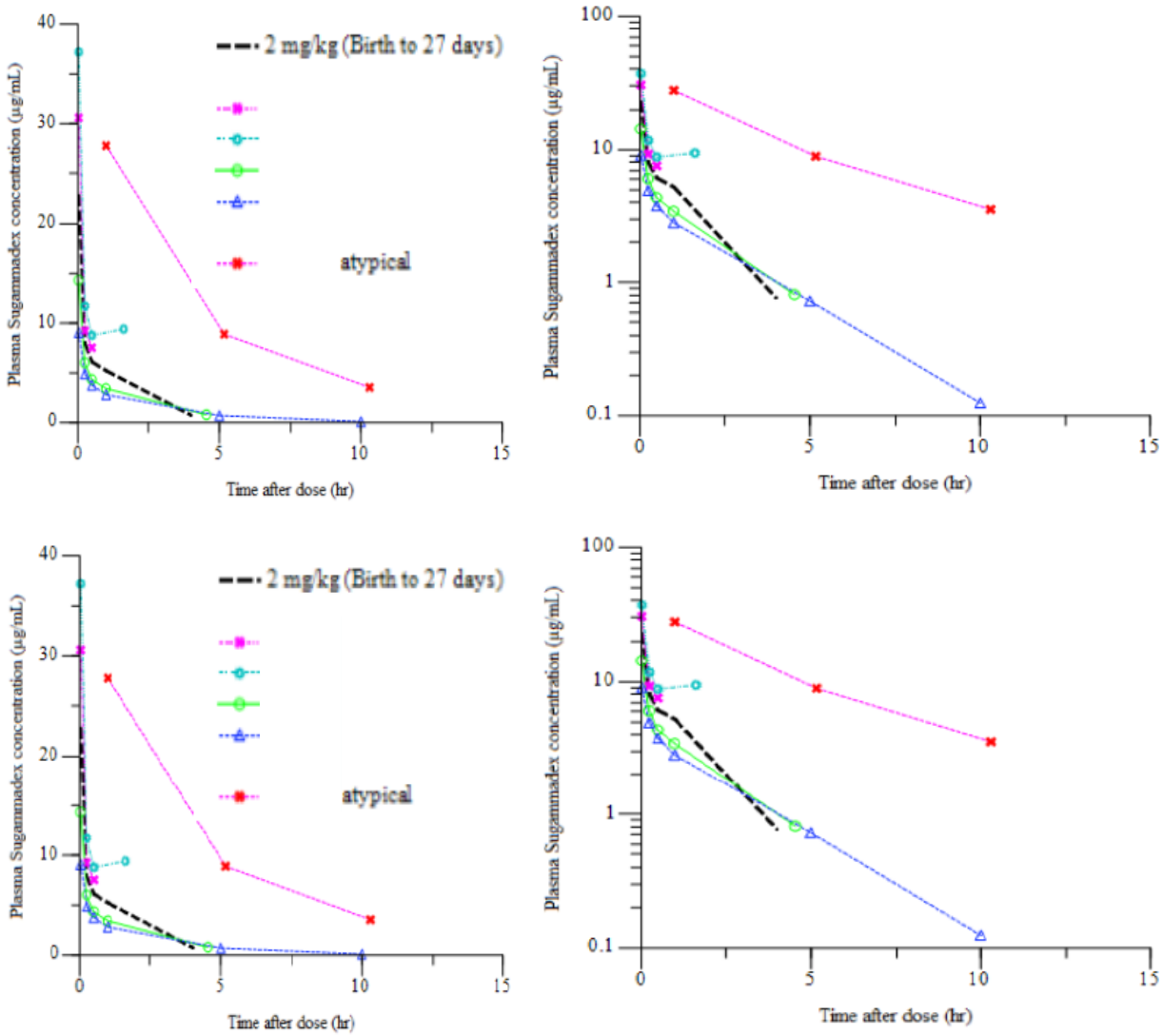
PK data imputations and exclusions

There was a single participant (one subject; age cohort 3 months to <6 months; assigned to 2 mg/kg sugammadex) where the administered dose was imputed because the volume of the drug administered was missing but where PK concentration data were collected and reported. For this participant the administered dose was calculated based upon the body weight and treatment assignment (2 mg/kg) and the data were included in the PK analyses. Inspection of data from this participant did not suggest any obvious deviation from other participants, which supported inclusion in the PK analyses.

Visual inspection of superimposed individual plasma sugammadex concentration-time profiles suggested a deviation from typical plasma concentration-time profiles for a single participant (one subject, birth to 27 days of age, assigned to 2 mg/kg sugammadex). Concentration-time data through 30 minutes post-

dose (at 2, 15 and 30 minutes) reported from this participant were comparable with other participants in this age and dose group. However, this participant had a major secondary peak at 60 minutes post-dose (Figure 1). The PK profile for this participant strongly suggested the potential for additional sugammadex administration followed by a typical pattern of a peak concentration with a rapid decline through 10 hours. A review of the bioanalytical methods and performance of the original analytical runs did not identify any analytical or process concerns leading to observations. Additional clinical investigation did not identify a plausible scientific rationale for the observations, including additional sugammadex administration based upon the clinical condition of the participant between 30 to 60 min post study treatment administration. Given the unreliable scientific plausibility of the reported concentration values for this participant and the absence of any similar patterns in this study or those reported across the sugammadex development program, PK analyses excluded concentration values beyond 30 minutes post-dose from this participant.

Figure 1. Superimposed concentration-time curves for subjects birth to 27 days (sugammadex 2 mg/kg)

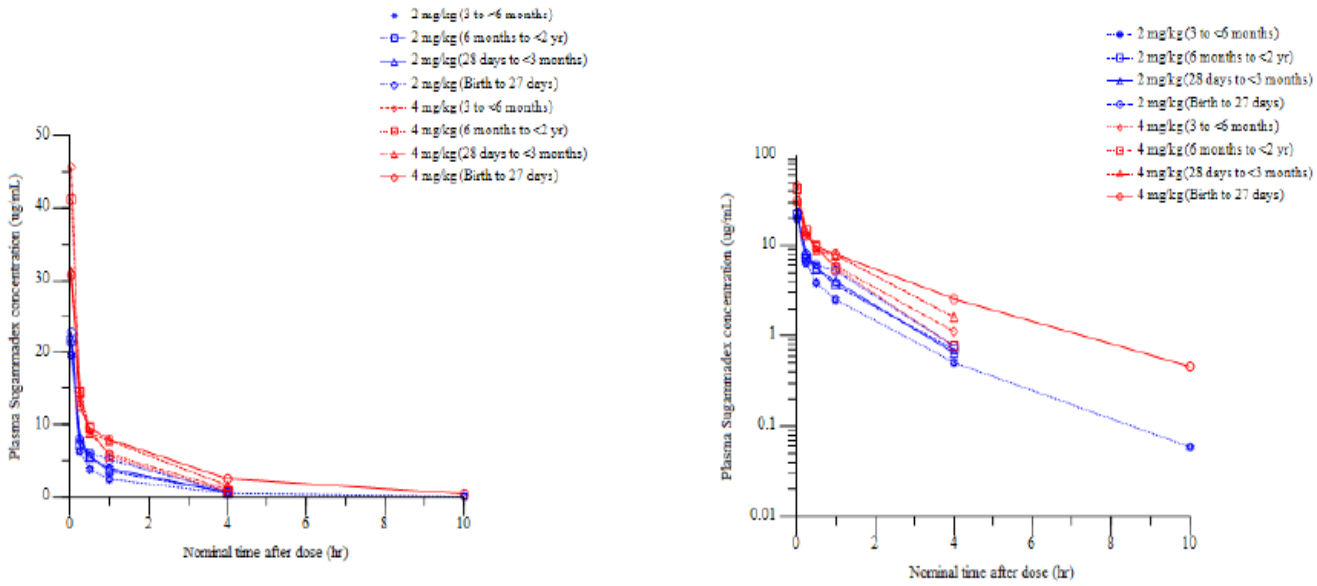


Observed pharmacokinetics

The PK analysis dataset included 47 subjects with at least one evaluable PK sample, contributing a total of 249 evaluable PK samples.

Mean plasma sugammadex concentration-time profiles are shown in Figure 2 by dose and age group. As expected, C_{max} was observed immediately after IV bolus injection and plasma sugammadex concentration decreased rapidly (approximately 70-80% over the first 30 minutes) after administration. No dose-dependent trends or deviations from dose-linearity based upon visual examination of the terminal elimination slopes were observed.

Figure 2. Arithmetic mean plasma concentration - time profiles of sugammadex following a single IV dose of 2 or 4 mg/kg by age group (Study Part A)



At the time point of 10 hours the mean value is not plotted where ≥ 50% of the participants do not have evaluable concentration values

PK parameters by age cohort were compared with historical adult PK parameters (Table 1). Weight normalized clearance and volume of distribution were higher in paediatric participants (birth to <2 years of age) than those in adults (Table 2). Consistent with higher weight normalized clearance and volume of distribution, sugammadex C_{max} and $AUC_{0\text{-}1h}$ were approximately 30% and 30-50% lower, respectively, in paediatric subjects from birth to <2 years of age compared with adults (Table 3).

Table 1. Summary statistics of plasma PK parameters of sugammadex following a single IV dose of 2 mg/kg or 4 mg/kg in paediatric (study P169, part A) and adult (study P034) participants

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)
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)
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)
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)
Adults (≥17 years)						
AUC0-inf (hr*µg/mL)[a]	5	31.54	(25.20, 39.48)	5	47.07	(37.61, 58.92)
AUC0-1hr (hr*µg/mL)[a]	5	13.97	(11.45, 17.05)	5	20.07	(16.45, 24.48)
Cmax (µg/mL)[a]	5	30.38	(22.71, 40.65)	5	59.44	(44.43, 79.53)
CL (L/hr)[a]	5	5.19	(3.99, 6.75)	5	6.28	(4.83, 8.17)
Vss (L)[a]	5	12.37	(10.07, 15.19)	5	11.06	(9.00, 13.58)

GM=Geometric least-squares mean; **CI**=Confidence interval

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.

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

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

Table 2. Summary statistics of weight normalized PK parameters of sugammadex following a single IV dose of 2 mg/kg or 4 mg/kg in paediatric (study P169, part A) and adult (study P034) participants

Parameters	2 mg/ kg			4 mg/ kg		
	N	GM	95% CI	N	GM	95% CI
Birth to 27 days						
wnCL ((L/hr)/kg)	2	0.15		6	0.10	(0.08, 0.13)
wnVd (L/kg)	2	0.40		6	0.35	(0.30, 0.41)
wnVss (L/kg)	2	0.36		6	0.32	(0.28, 0.37)
28 days to < 3 months						
wnCL ((L/hr)/kg)	3	0.12	(0.09, 0.16)	6	0.13	(0.10, 0.15)
wnVd (L/kg)	3	0.27	(0.22, 0.34)	6	0.28	(0.24, 0.33)
wnVss (L/kg)	3	0.23	(0.19, 0.28)	6	0.24	(0.21, 0.28)
3 to < 6 months						
wnCL ((L/hr)/kg)	3	0.17	(0.13, 0.23)	8	0.16	(0.14, 0.19)
wnVd (L/kg)	3	0.36	(0.29, 0.46)	8	0.36	(0.31, 0.41)
wnVss (L/kg)	3	0.28	(0.23, 0.34)	8	0.28	(0.25, 0.32)
6 months to < 2 years						
wnCL ((L/hr)/kg)	5	0.14	(0.11, 0.18)	5	0.14	(0.12, 0.18)
wnVd (L/kg)	5	0.29	(0.24, 0.34)	5	0.31	(0.26, 0.37)
wnVss (L/kg)	5	0.23	(0.20, 0.27)	5	0.25	(0.21, 0.29)
Adults (≥17 years)						
wnCL ((L/hr)/kg)	5	0.06	(0.05, 0.08)	5	0.08	(0.07, 0.11)
wnVss (L/kg)	5	0.15	(0.13, 0.18)	5	0.15	(0.13, 0.17)

CI=confidence interval; **GM** = geometric least-squares mean; **wn** = weight-normalized.
Back-transformed least squares mean and CI from linear fixed effects model performed on natural log-transformed values.

Table 3. Geometric mean ratio (90% CI) for sugammadex exposure parameters following a single IV dose of 2 mg/kg or 4 mg/kg sugammadex in paediatric (study P169, part A) and adult (study P034) participants

Dose	Parameter	GMR (90% CI)			
		Birth to 27 days vs Adults	28 days to < 3 months vs Adults	3 to < 6 months vs Adults	6 months to < 2 years vs Adults
2 mg/kg	AUC0-inf (hr*ug/mL)	0.42 (0.30, 0.60)	0.51 (0.38, 0.70)	0.36 (0.27, 0.49)	0.45 (0.34, 0.58)
	AUC0-1hr (hr*ug/mL)	0.50 (0.38, 0.65)	0.55 (0.42, 0.72)	0.44 (0.33, 0.57)	0.52 (0.42, 0.65)
	Cmax (ug/mL)	0.64 (0.45, 0.93)	0.70 (0.47, 1.04)	0.64 (0.43, 0.95)	0.69 (0.50, 0.96)
4 mg/kg	AUC0-inf (hr*ug/mL)	0.83 (0.64, 1.07)	0.68 (0.53, 0.87)	0.53 (0.41, 0.67)	0.59 (0.45, 0.77)
	AUC0-1hr (hr*ug/mL)	0.62 (0.49, 0.77)	0.72 (0.58, 0.89)	0.67 (0.55, 0.82)	0.69 (0.56, 0.86)
	Cmax (ug/mL)	0.48 (0.35, 0.67)	0.51 (0.38, 0.70)	0.75 (0.55, 1.01)	0.69 (0.50, 0.94)

CI=confidence interval; **GMR** = geometric mean ratio; **IV**=intravenous.
Note: AUC0-inf and AUC0-1hr are model based from P034. AUC0-inf and AUC0-1hr are based on NCA for P169. Cmax is based on observed data for both P034 and P169.
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.

2.3.3. Pharmacodynamics

Mechanism of action

Sugammadex is a modified gamma cyclodextrin which is a selective relaxant binding agent. It forms a complex with the neuromuscular blocking agents rocuronium or vecuronium in plasma and thereby reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade induced by rocuronium or vecuronium.

2.3.4. PK/PD modelling

The MAH submitted an updated population PK (PPK) model of sugammadex (report date 20-MAY-2024). The proposed changes in section 5.2 of the SmPC are based on this updated PPK model.

Introduction

The submitted PPK model ("pediatric-newborn update") is the fourth major version of the sugammadex PPK model (see Table 4).

The objectives of the current PPK modelling were as follows:

1. Re-evaluate the prior 2-compartment PPK model for its appropriateness to describe sugammadex with newly generated PK data from the paediatric population from birth to <2 years of age.
2. Refit and optimize the population PK model to describe the data for all age classes.
3. Re-estimate PK parameters of sugammadex in various populations based on the updated population PK model.

Table 4. Major versions and scope of the sugammadex PK-PD and PK models

Name	Year	Studies Included	Description
Original PK-PD	2009	194.101 (Part II only), 194.201, 194.202, 194.205, 194.208 A&B, 194.304, 194.305, P034 (194.306)	Model for PK interaction between sugammadex and rocuronium and resultant effect on neuromuscular blockade
Renal update	2014	All of the above + 194.333, P105	Model refit to describe effect of renal impairment on Sugammadex PK
Paediatric-child update	2020	All of the above + P089	Model refit to confirm sugammadex PK predictions in children (2 to <17 years of age)
Paediatric-newborn update	2024	All of the above + P169	Model re-evaluation to describe sugammadex PK predictions in newborn children and toddlers (birth to <2 years)

Methods

- Software: NONMEM (v. 7.5.1), PsN (v. 5.3.1), and R (v. 4.2.3).
- Estimation method: FOCE-I (on log-transformed data).
- Base model: The year 2020 2-compartment PPK model ("paediatric-child update"): A 2-compartment model with zero-order input and first-order elimination from the central compartment, previously developed manifesting in a short distribution phase followed by a mono-exponential elimination phase. Central and peripheral volume of distribution and intercompartmental clearance (but not clearance) were allometrically scaled on bodyweight using fixed theoretical exponents (1.0 and 0.75). Estimated covariates included creatinine clearance (power) and body weight (linear) on CL; body weight (linear) and race (categorical) on Vc; and creatinine clearance (exponential) on Vp. IIV was included on CL but not on other parameters, and the residual error model was additive on the log scale.

Creatinine clearance (CrCL) was calculated according to the Cockcroft-Gault formula for adults (≥18 years) and according to the Schwartz formula for the paediatric population (all participants <18 years). Further paediatric age- and size-dependent correction factors on renal function as specified by Rhodin were also tested in the current model update using the following equations.

A body size correction (Fsize) was calculated as shown in Equation 1:

$$F_{size} = \left(\frac{W_i}{70}\right)^{0.75} \qquad \textbf{Equation 1}$$

where 0.75 represents a commonly applied allometric scaling exponent, 70 kg represents a standard BW, and W_i is individual BW.

A postmenstrual age correction was calculated as shown in Equation 2:

$$F_{PMA} = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}} \qquad \textbf{Equation 2}$$

where PMA=age–40 weeks, the Hill coefficient used was 3.4, and TM_{50} was 47.7 weeks (0.917 years).

The collective corrections were applied as shown in Equation 3:

$$R_{eGFR} = CrCl_{Schwartz} \times F_{size} \times F_{PMA} \qquad \textbf{Equation 3}$$

Simulations

Two sets of simulations were performed to characterize the sugammadex PK and to support the product information using the updated PPK model:

1. Simulation of concentration-versus-time profiles in predefined typical Caucasian participants. Population PK parameter estimates were used. Variability (IIV or uncertainty) was not included in the simulation.
2. Prediction of PK parameters CL, volume of distribution at steady state (Vss), $t_{½,\alpha}$, and $t_{½,\beta}$ and associated AUC_{inf} and C_{max} in predefined typical participants (Table 5). The simulation using population PK model parameters included IIV.

Table 5. Characteristics of the typical caucasian participants used in simulations

Population	Age (years)	Weight (kg)	Height (cm)	CrCL (mL/min)
Age categories consistent with prior model evaluation and study P169 cohorts				
0 to <28 days (neonates)	0.04	3.8	52.3	12.9
28 days - <3 months	0.17	5.6	58.4	16.5
3 to <6 months	0.38	7.0	63.9	19.3
6 months <2 years	1.25	10.3	79.1	26.6
2 to <3 years	2.5	13.4	91.4	33.0
3 to <6 years	4.5	17.2	105.3	40.7
6 to <12 years (middle childhood)	9	28.5	133.5	59.9
12 to <18 years (adolescent)	15	56.2	170	95.3
≥18 years	40	75.0	NA	100
Elderly (≥65 years)	75	75	NA	80
Additional age categories consistent with current paediatric labeling for sugammadex				
Infant (28 days to 12 months)	0.54	7.9	67.6	21.2
Toddler (13 months to 2 years)	1.54	10.9	82.3	28
Early childhood (2 to 5 years)	3.5	15.3	99	37

Results

Demographics for the participants included in the analysis are provided by age category in Table 6. The paediatric participants were from studies P034/19.4.306, P089, and P169. For 1 participant from Study P169, CrCL was missing and imputed with the median value within the corresponding age category.

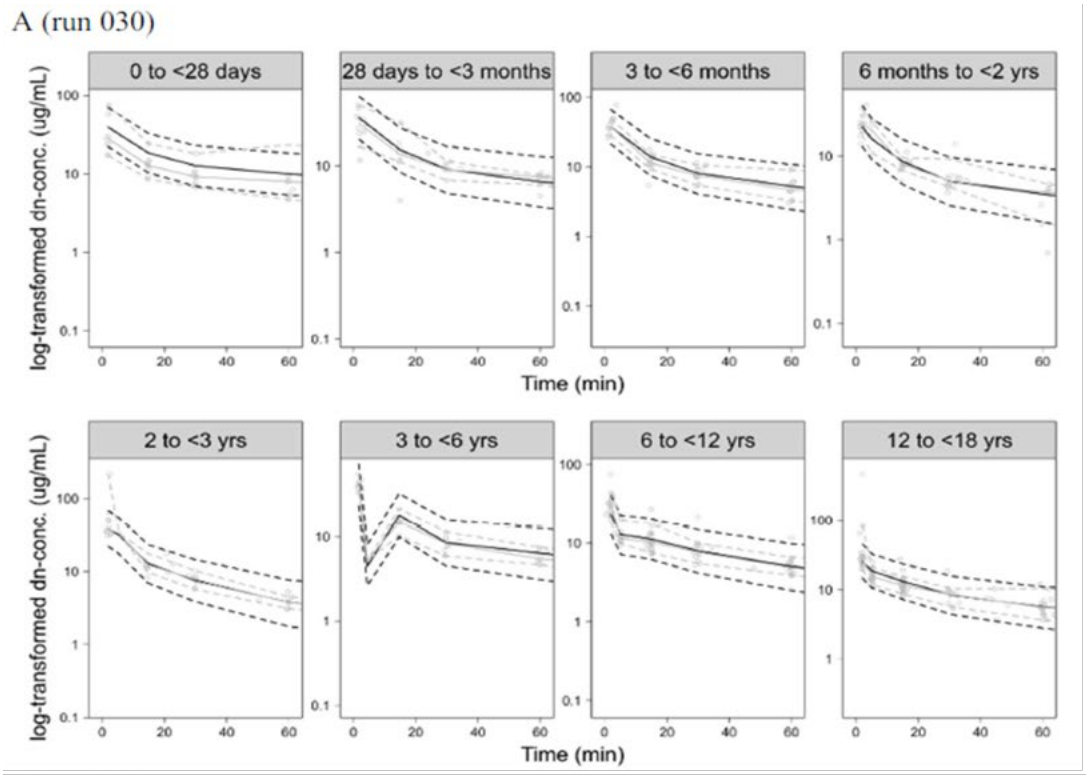
Table 6. Descriptive statistics of demographics across age categories

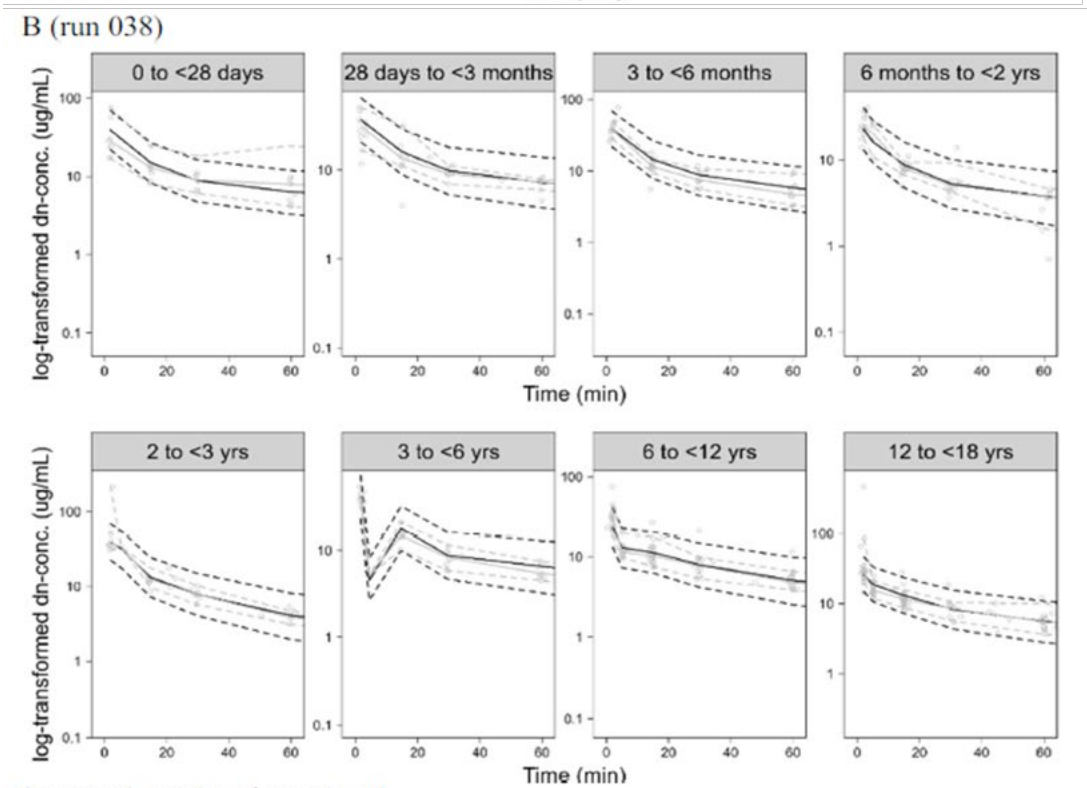
Covariate	Age Category	N	Mean	SD	Minimum	Median	Maximum
Weight (kg)	<28 days	10	3.27	0.729	2.28	3.34	4.3
	28 days - <3 mon	11	5.23	1.130	3.30	5.44	6.9
	3 - <6 mon	13	6.52	1.340	4.14	6.70	8.9
	6 mon - <2 yrs	15	9.62	1.370	8.17	9.40	13.4
	2 - <3 yrs	11	13.10	2.380	10.00	13.00	18.0
	3 - <6 yrs	10	18.40	3.860	14.00	16.50	24.0
	6 - <12 yrs	26	34.70	18.100	18.00	34.00	107.0
	12 - <18 yrs	31	62.20	17.300	36.00	61.00	130.0
	≥18 yrs	354	77.10	15.200	40.00	76.30	139.0
Creatinine clearance (CrCL) (mL/min)	<28 days	10	6.74	2.77	1.88	7.34	10.2
	28 days - <3 mon	11	19.40	6.85	10.50	20.80	27.9
	3 - <6 mon	13	34.30	12.00	18.10	31.90	63.6
	6 mon - <2 yrs	15	45.40	10.10	28.40	41.40	62.9
	2 - <3 yrs	11	55.80	9.96	38.00	55.30	68.7
	3 - <6 yrs	10	71.10	22.00	30.60	71.10	98.4
	6 - <12 yrs	26	105.00	32.10	60.80	100.00	209.0
	12 - <18 yrs	31	164.00	31.00	102.00	160.00	226.0
	≥18 yrs	354	112.00	41.00	4.30	116.00	213.0

The year 2020 model (run 030) was able to capture the median trend and variability of the data in most age categories. However, there was a tendency towards overprediction of concentrations in neonates (Figure 3A). Different strategies were tested to address this: Allometric scaling on CL and V (as a fixed or an estimated exponent), Rhodin formula correction of CrCL, and addition of age effects on CL and V were evaluated. Neither allometric scaling of CL nor the Rhodin maturation correction for CrCL improved the model fit. However, addition of neonatal age category effects on CL and V using empirical correction factors resulted in improved fit (run 038; ΔOFV= -39.969 points) and the

tendency for overprediction was reduced compared to the year 2020 model (Figure 3B). No further changes in model structure were made; the PK parameter estimates of the final model are presented in Table 7.

Figure 3. VPC (time: 0-60 minutes) for the 2020 model (A) and the current paediatric-newborn update model (B)





Source: mk-sgmdx-gof-vpc-v2.rmd

Solid black and dashed black lines show the mean and 95% confidence interval of model predictions, respectively. Solid gray and dashed gray lines show the mean and 95% confidence interval of observations, respectively. Gray symbols represent individual observations.

Table 7. Parameter estimates of the final sugammadex population PK model

Parameter	Estimate	RSE%	Shrinkage	Median Bootstrap	Bootstrap 95%CI
CL(L/min)	0.0876	2.16		0.0876	0.0852, 0.0907
V_c (L)	4.50	1.09		4.48	4.27, 4.70
Q (L/min)	0.204	2.90		0.205	0.190, 0.223
V_p (L)	7.06	1.47		7.04	6.76, 7.36
Covariate effects[a]					
CLCR on CL	1.27	2.70		1.27	1.15, 1.40
BW on CL	0.00660	5.77		0.00674	0.00553, 0.00774
BW on Vc	-0.00474	8.97		-0.00468	-0.00645, -0.00353
Race on V_c	-0.154	19.5		-0.153	-0.228, -0.0729
CrCL on V_p	-0.00400	6.18		-0.00407	-0.00495, -0.00340
Neonatal effect on CL	2.02	9.04		1.93	1.33, 3.05
Neonatal effect on V_c	1.34	12.0		1.34	1.06, 1.58
Between-subject variability					
CL	0.0727	8.02	24.7%	0.0713	0.0556, 0.0868
Residual error					
Proportional error	0.120	0.693	4.00%	0.120	0.0928, 0.155

Source: mk-sgmdx-gof-vpc-v2.rmd

[a] Overall covariate relations were defined as follows:

$$CL = 0.876 * \left(\frac{2 * CrCL}{CrCL + 115.2}\right)^{1.27} * \left(1 + 0.00660\ (BW - 72.9)\right) * \ (1 + \ (Category = Neonatal) \times 2.02)$$

$$V_c = 4.50 * \left(\frac{BW}{70}\right)^{1} * \left(1 - 0.00474\ (BW - 72.9)\right) * (1 - 0.154 * Race) * (1 + \ (Category = Neonatal) \times 1.34)$$

where Race=0 for Caucasian, Black, and Hispanic and Race=1 for Asian participants

$$V_p = 7.06 * \left(\frac{BW}{70}\right)^{1} * e^{-0.0400\ (CrCl - 115.2)}$$

$$Q = 0.204 * \left(\frac{BW}{70}\right)^{0.75}$$

Abbreviations: BW=body weight; CI=confidence interval; CL=clearance; CrCL=creatinine clearance; PK=pharmacokinetic; Q=inter-compartmental clearance between central and peripheral compartments; RSE%=percent residual standard error; V_c=central volume of distribution; V_p=peripheral volume of distribution

Goodness-of-fit plots by age category (Figure 4 and Figure 5) indicated good performance by the model for all paediatric age categories, especially for the first 4 hours after dosing.

Figure 4. Population-predicted vs observed (DV) log-transformed sugammadex concentrations for paediatric participants by age category

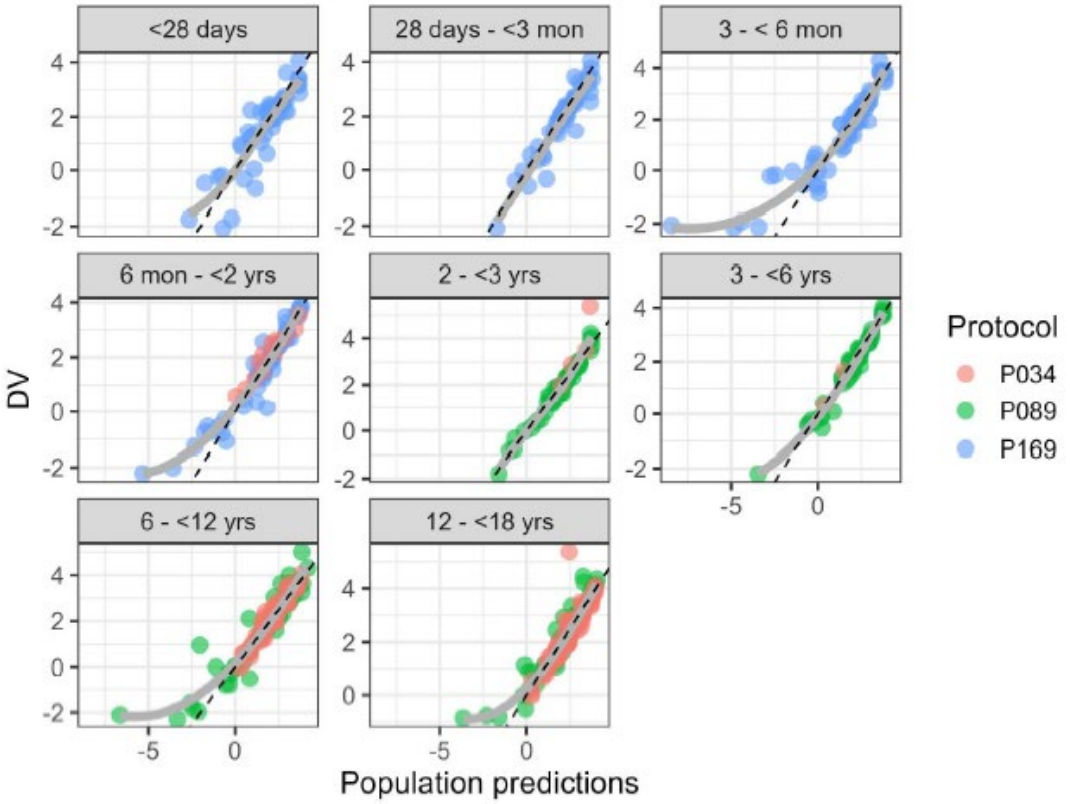
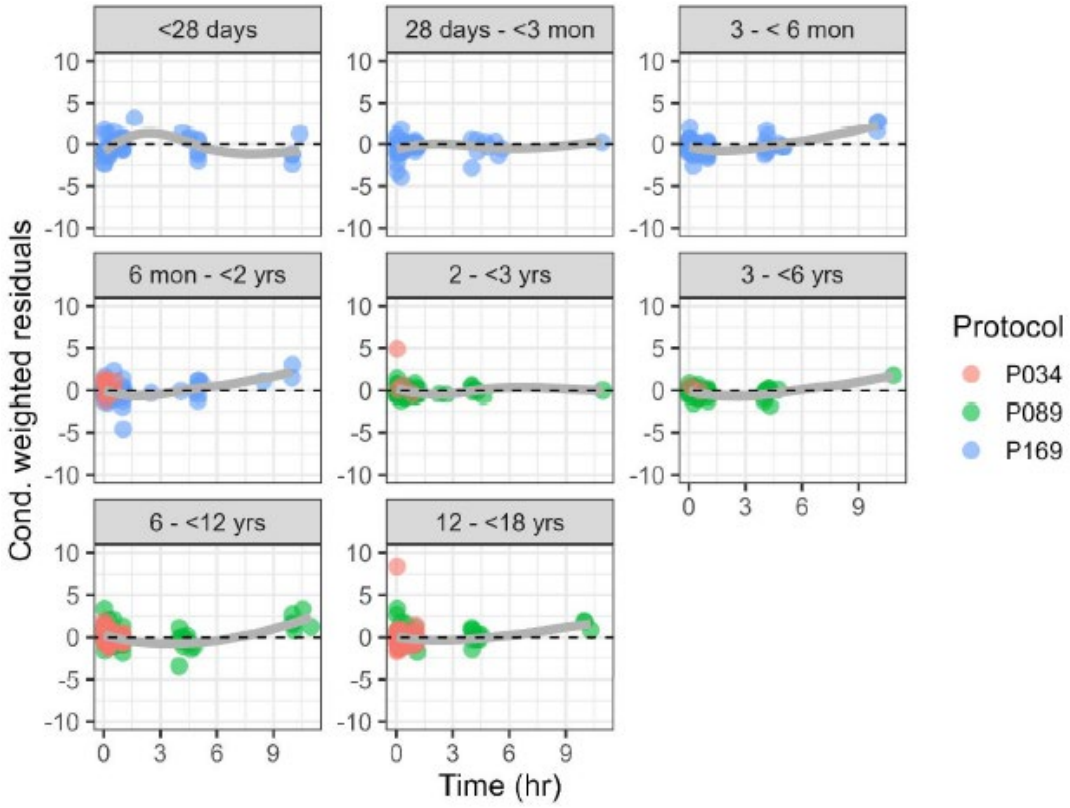


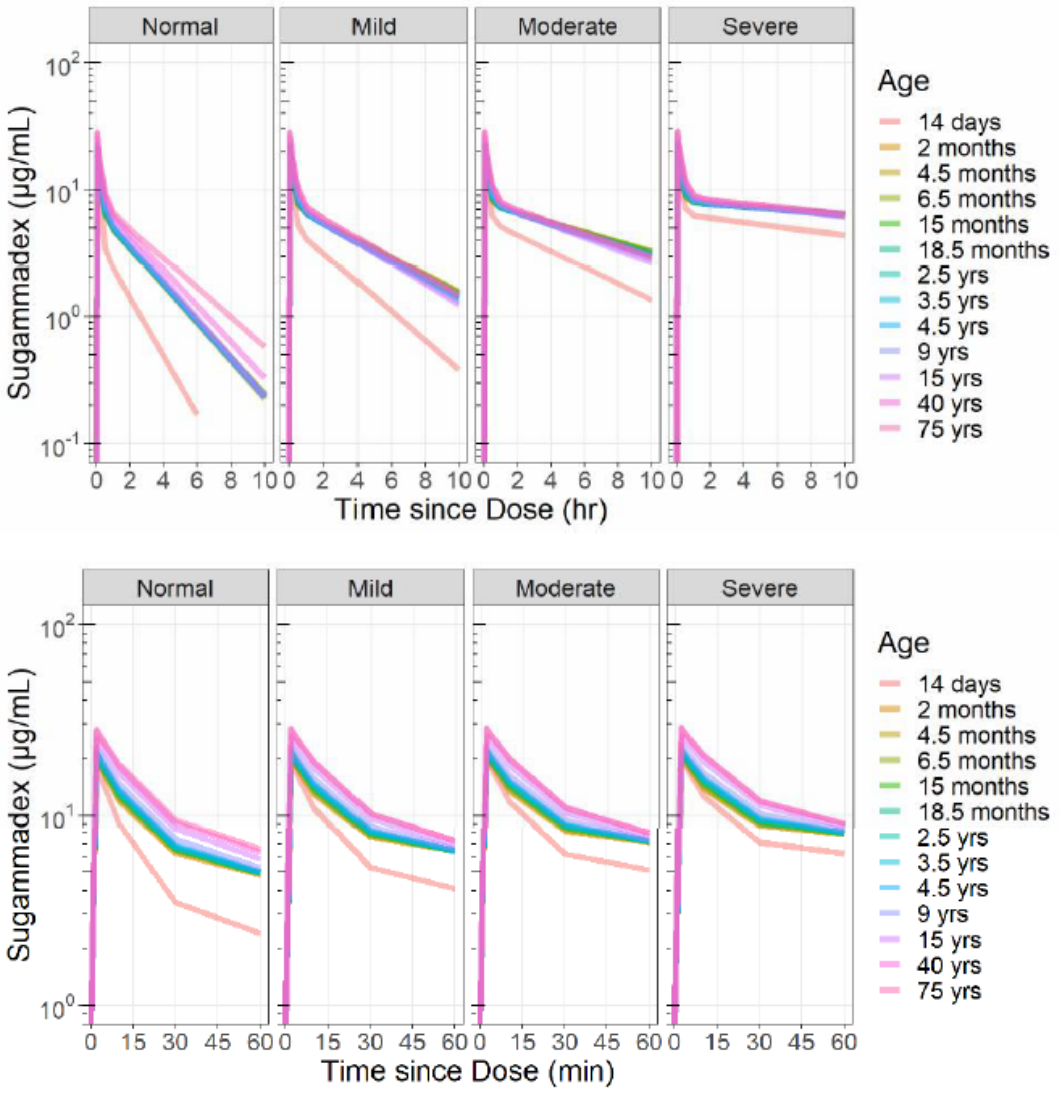
Figure 5. Conditional weighted residuals vs time for paediatric participants by age category



Simulations

Based on the final population PK model, a series of simulations was performed for different age categories treated with 2 mg/kg. Predicted concentration-time profiles for typical Caucasian participants are shown in Figure 6. Renal function strongly affects clearance, whereas volume of distribution and C_{max} are more affected by age. Overall, the simulations indicate lower exposure in neonates compared with older children and adults.

Figure 6. Sugammadex concentration-versus-time profile for typical participants of each age category, stratified by renal function



2.3.5. Discussion on clinical pharmacology

Bioanalytical methods

Plasma sugammadex concentrations were measured using adequately validated bioanalytical methods. Rocuronium and vecuronium concentrations were not measured.

Observed PK in Study P169

Study P169 Part A was adequately designed and conducted to characterize exposure to sugammadex following 2 mg/kg and 4 mg/kg IV injection in paediatric patients from birth to <2 years of age, although the value of formal statistical comparisons is limited because of small number of observations especially in the youngest age groups for the 2 mg/kg dose.

Descriptive summary statistics indicate that following a single dose of sugammadex 2 mg/kg or 4 mg/kg, the clinically most relevant exposure measures (C_{max} and AUC_{0-1hr}) were approximately 30% and 30-50% lower, respectively, in paediatric subjects from birth to <2 years of age compared with exposure in adults in a prior study. Weight normalized clearance and volume of distribution were higher in paediatric subjects from birth to <2 years of age compared with historical adult data.

Population PK modelling

The prior (year 2020) PPK model overpredicted the exposure in the neonatal (0 to <28 days) age category even though it performed reasonably well in older age categories (28 days to <3 months, 3 to <6 months, and 6 months to <2 years). Overprediction was seen immediately after the administration (at 2 minutes, i.e. the first time point with observed concentrations), which suggests challenges in modelling early distribution shortly after the administration.

Allometric scaling on CL and V, Rhodin formula correction of CrCL, and addition of age effects on CL and V were evaluated; addition of empirical age category (neonatal) effects on CL and Vc was selected based on model fit criteria and improved VPC plots. Details of the tested alternative models were not provided in the report, but this issue is not pursued. The updated PPK model adequately described the observed sugammadex concentrations in each paediatric age category (and adults).

The proposed extension of indication is supported by observed efficacy and safety in the target population with the proposed posology. Further refining of the PPK model is not expected to affect the outcome of the variation application and is not requested.

2.3.6. Conclusions on clinical pharmacology

Observed PK data indicate that following a single bolus injection, the exposure parameters C_{max} and AUC_{0-1hr} were approximately 30% and 30-50% lower, respectively, in paediatric subjects from birth to <2 years of age compared with exposure in adults in a prior study.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Not applicable.

2.4.2. Main study(ies)

Study P169: A Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics

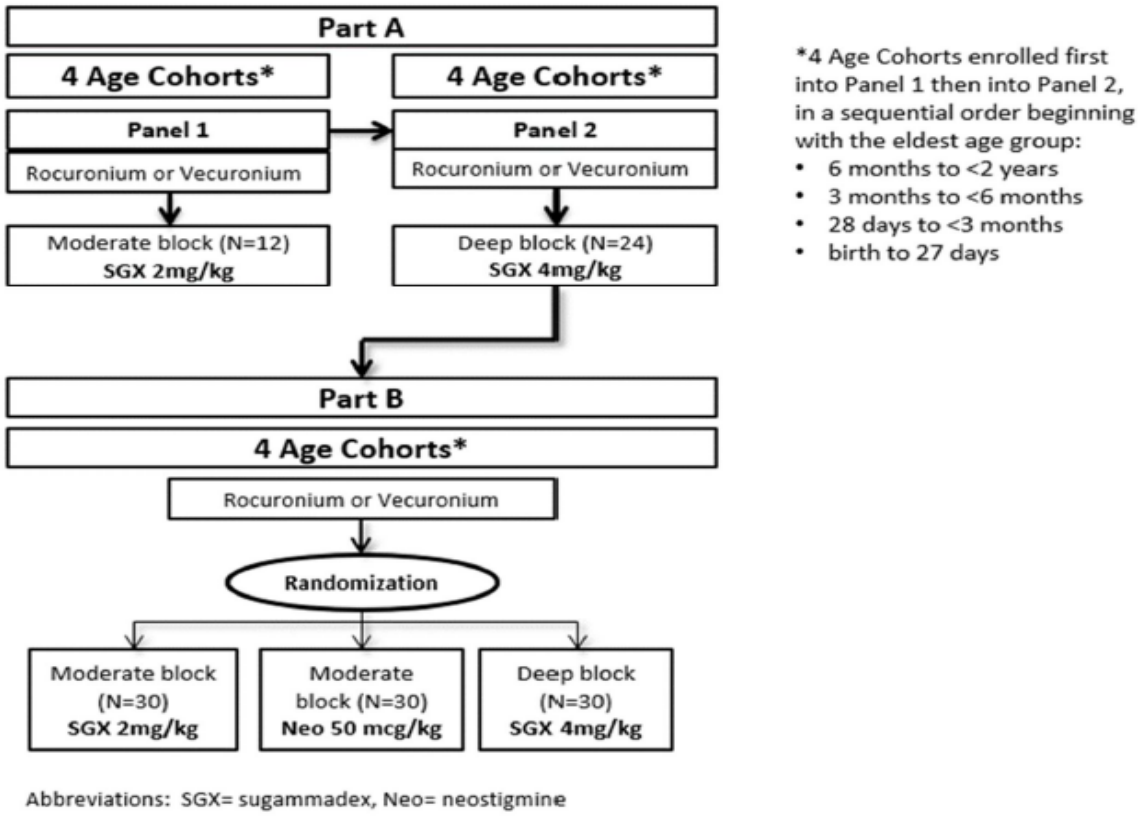
of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years

Methods

Study design is summarized in Figure 7. Study P169 consisted of 2 parts (Part A and Part B), and 4 age cohorts in each part (6 months to <2 years, 3 months to <6 months, 28 days to <3 months, and birth to 27 days).

- Part A that focused on PK and safety was open-label, not randomized, and there was no comparator arm. It was further divided into Panel 1 (sugammadex 2 mg/kg in the moderate block setting) and Panel 2 sugammadex 4 mg/kg in the deep block setting).
- Part B of the study assessed safety and efficacy parameters. Participants were randomized to sugammadex 2 mg/kg, neostigmine 50 µg/kg, or sugammadex 4 mg/kg.

Figure 7. Study P169 design



Abbreviations: SGX= sugammadex, Neo= neostigmine

Study visits are summarized in Table 8. After a screening period of up to 14 days, each participant received a single bolus dose of assigned study treatment at Visit 2. After the end of treatment, each participant had a posttreatment safety visit between 4 and 36 hours after administration of study treatment. A follow-up contact (phone call or visit) with the participant's parent/legally acceptable representative took place at approximately 14 days posttreatment.

Table 8. Study visits of study P169

Study Period	Screening	Treatment	Follow-up	
Visit Number and Title	**Visit 1** Screening	**Visit 2** Peri-anaesthetic period	**Visit 3** Post-anaesthetic period	**Visit 4** Follow-up contact
Scheduled Day	Day -1	Day 1	Day 1 to 2	Day 14
Scheduling Window Days	Day -14 to Day 1	± 0 days	Between 4 and 36 hours after administration of study treatment.	+2 days

Study participants

The study was conducted in 12 countries: Australia, Belgium, Brazil, Denmark, Finland, France, Hungary, Malaysia, Mexico, Netherlands, Russian Federation, and the US.

The inclusion criteria were as follows:

1. Was categorized as ASA Physical Status Class 1, 2, or 3 as determined by the investigator.
2. Had a planned nonemergent (not an acute life-threatening emergency) surgical procedure or clinical situation (e.g., intubation) that requires moderate or deep NMB with either rocuronium or vecuronium.
3. Had a surgical procedure or clinical situation that would allow neuromuscular monitoring techniques to be applied for neuromuscular transmission monitoring.
4. Was male or female, between birth and <2 years of age at Visit 2.
5. The participant's legally acceptable representative for the study participant provided documented informed consent/assent for the study.

An individual was excluded from the study if the individual met any of the following key exclusion criteria:

1. Was a preterm infant or neonate <36 weeks gestational age at birth.
2. Had any clinically significant condition or situation (e.g., anatomical malformation that complicates intubation) other than the condition requiring the use of NMBA that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study.
3. Had a neuromuscular disorder that may affect NMB and/or study assessments.
4. Was dialysis-dependent or has (or is suspected of having) severe renal insufficiency.
5. Had or was suspected of having a family or personal history of malignant hyperthermia.
6. Was expected to require mechanical ventilation after the procedure.
7. Had received or is 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

All investigational medicinal products were administered as IV bolus injection. Sugammadex for investigational use was provided centrally by the Sponsor, which was identical in formulation to commercially available sugammadex injection for intravenous use.

- Part A: Subjects in moderate and deep NMB setting were treated with sugammadex 2 mg/kg and sugammadex 4 mg/kg, respectively.
- Part B: Subjects in moderate NMB setting were randomized to sugammadex 2 mg/kg or neostigmine 50 µg/kg [plus glycopyrrolate (5 to 15 µg/kg) or atropine (10 to 30 µg/kg)]. Subjects in deep NMB setting were treated with sugammadex 4 mg/kg.

The administered dose (mg/kg) was within ±11% of the intended dose for each participant in each group.

Objectives

Study objectives and endpoints of Study P169 are summarized in Table 9.

Table 9. Objectives and endpoints of study P169 (Part A+B)

Primary Objectives	**Primary Endpoints**
Objective (PK): To describe the pharmacokinetic parameters of sugammadex when used for reversal of moderate NMB or deep NMB (Part A).	PK parameters: Area under the plasma concentration-time curve (AUC), clearance (CL), apparent volume of distribution (Vz and Vss), maximum plasma concentration (C_{max}), and half-life ($t_{½}$).
Objective (Efficacy): To evaluate the time to neuromuscular recovery of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B). Hypothesis: Sugammadex is superior to neostigmine in reversing moderate NMB as measured by time to neuromuscular recovery.	Time to neuromuscular recovery (TTNMR): Interval from administration of reversal agent to time to neuromuscular recovery.
Objective (Safety): To evaluate the safety and tolerability of sugammadex (data pooled across Part A and Part B).	Number of participants experiencing adverse events.
Secondary Objectives	**Secondary Endpoints**
Objective (Efficacy): To evaluate the time to extubation 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.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate the time to discharge, incidence of delayed recovery and proportion of participants with neuromuscular recovery after the first 5 minutes of administration of sugammadex in comparison to neostigmine for the reversal of moderate NMB (Part B).	Time to operating room (OR) discharge. Time to post-anaesthesia care unit (PACU) discharge. Time to hospital discharge. Incidence of delayed recovery (any observation that is >3 times the geometric mean recovery time of neuromuscular recovery using readiness for extubation assessment). Proportion of participants with neuromuscular recovery after the first 5 minutes of study medication administration.

Outcomes/endpoints

Neuromuscular Transmission Monitoring

Neuromuscular transmission monitoring (NMTM) was performed to maintain the target depth of block throughout the procedure and to ensure appropriate timing of dose administration of study medication occurred. Neuromuscular monitoring was performed using a locally available NMTM device (e.g., TOF-Watch®SX or PNS). Depth of block was assessed and recorded at depth appropriate intervals to ensure appropriate timing of dose administration.

Monitoring Neuromuscular Recovery

Time to neuromuscular recovery (TTNMR) was the primary efficacy endpoint. Due to the technical challenges involved with the use of quantitative TOF monitoring for this youngest paediatric age group and anticipated considerable interpatient variability of data collected, TTNMR was able to be assessed by 1 of 4 methods deemed appropriate for the participant and consistent with typical clinical practice for individual sites. These methods were inclusive of either clinical signs (head lift or hip flexion) or NMTM (using either a standard PNS or quantitative NMTM to TOF ratio ≥0.9), with adjustments for participants with endotracheal extubation under deep sedation, as stipulated in the protocol. If clinically necessary, the recovery assessment method could be adjusted mid-procedure, based on investigator judgment, as long as TTNMR was established by 1 of the 4 allowable methods. If the participant was not to be extubated, neuromuscular recovery was to be monitored every minute for at least 30 minutes after administration of study treatment. If neuromuscular recovery was not achieved, TTNMR was censored at the time of last assessment of neuromuscular recovery.

Monitoring Extubation Readiness

Time to extubation was a secondary efficacy endpoint. From the time of study treatment administration to 30 minutes after study treatment administration, extubation readiness was to be assessed every 60 seconds until time of extubation readiness was achieved. Beginning 30 minutes after study treatment administration, readiness for extubation was to be assessed at least every 5 minutes until time of extubation readiness was achieved. Extubation readiness was to be assessed until either the removal of the endotracheal tube, or the clinical decision was made to not extubate the participant as originally planned. Assessments and documentation of extubation readiness were to be monitored in all participants as specified in the protocol. Neuromuscular recovery was expected to be achieved before extubation. If extubation readiness was not achieved, time to extubation was censored at the time of last assessment of extubation readiness.

Sample size

The sample size of the study is in alignment with the number of participants required to obtain the relevant safety information for each level of block, as specified by the Sponsor's commitments. A 1:1:1 randomization ratio was used for sugammadex 2 mg/kg, neostigmine, and sugammadex 4 mg/kg in the enrolment of approximately 90 participants in Part B (30 in each treatment group). Along with 12 participants on sugammadex 2 mg/kg and 24 participants on sugammadex 4 mg/kg in Part A, the study was to enrol approximately 42 participants on sugammadex in moderate block, 54 participants on sugammadex in deep block, and 30 participants on neostigmine in moderate block.

Sample Size and Power Calculations for Efficacy Analyses

The sample size was estimated to have 85% or higher power to demonstrate difference in TTNMR between 2 mg/kg of sugammadex versus neostigmine for moderate block, when using Cox PH model and 2-sided 5% significance level (Table 10). The underlying assumptions of the relative effect size were based on adult data for recovery to a TOF ratio of ≥0.9 and its correlation with TTNMR. Due to expected additional sources of variability in the paediatric setting, the assumptions were made more conservative.

Table 10. Power estimates for detecting various differences in time to neuromuscular recovery (in minutes) between sugammadex and neostigmine in moderate block

Sugammadex Mean (SD)	Neostigmine Mean (SD)	Hazard Ratio	Power [a]
3 (2)	13 (15)	6.96	>99%
5 (3)	13 (15)	3.39	97%
6 (4)	13 (15)	2.55	85%

SD = standard deviation
[a] Based on N=27 for each treatment group to allow for 10% participants not treated with study medication using Cox PH model; 2-sided, 5%-level Chi-Square Test;
Data are simulated based on lognormal distribution.

Randomisation

Part A focused on pharmacokinetics. It was open-label, not randomized, and there was no comparator arm. In Part B, participants were randomized to one of three intervention arms in a 1:1:1 ratio:

- Moderate block and reversal with 2 mg/kg sugammadex; or
- Moderate block and reversal with neostigmine + glycopyrrolate or atropine sulfate (hereafter, called neostigmine); or
- Deep block and reversal with 4 mg/kg sugammadex

Randomization occurred centrally using interactive response technology. Randomization was stratified by age cohort, beginning with the oldest cohort (6 months to <2 years; 3 months to <6 months; 28 days to <3 months, birth to 27 days), and NMBA (rocuronium or vecuronium).

Blinding (masking)

Blinding was only applicable to Part B. An unblinded study site pharmacist prepared study treatments and provided them to site staff in the operating room (OR) in a masked syringe to ensure that the contents of the syringe will not be revealed. The anaesthesiologist and other OR staff were blinded to the reversal agent in the moderate block arms. Although sugammadex for the deep block arm was provided to the OR in a masked syringe, OR staff aware of the depth of block knew the study treatment (sugammadex 4 mg/kg) because neostigmine is not appropriate for reversal of deep block.

The blinded safety assessor (BSA) was blinded to study treatment assignment, the depth of NMB, and drug preparation records, and was not present during the operation. The BSA completed the post-anaesthetic safety visit at 4 to 36 hours after administration of study treatment and completed the causality assessment for all recorded AEs, including any perioperative AEs.

Statistical methods

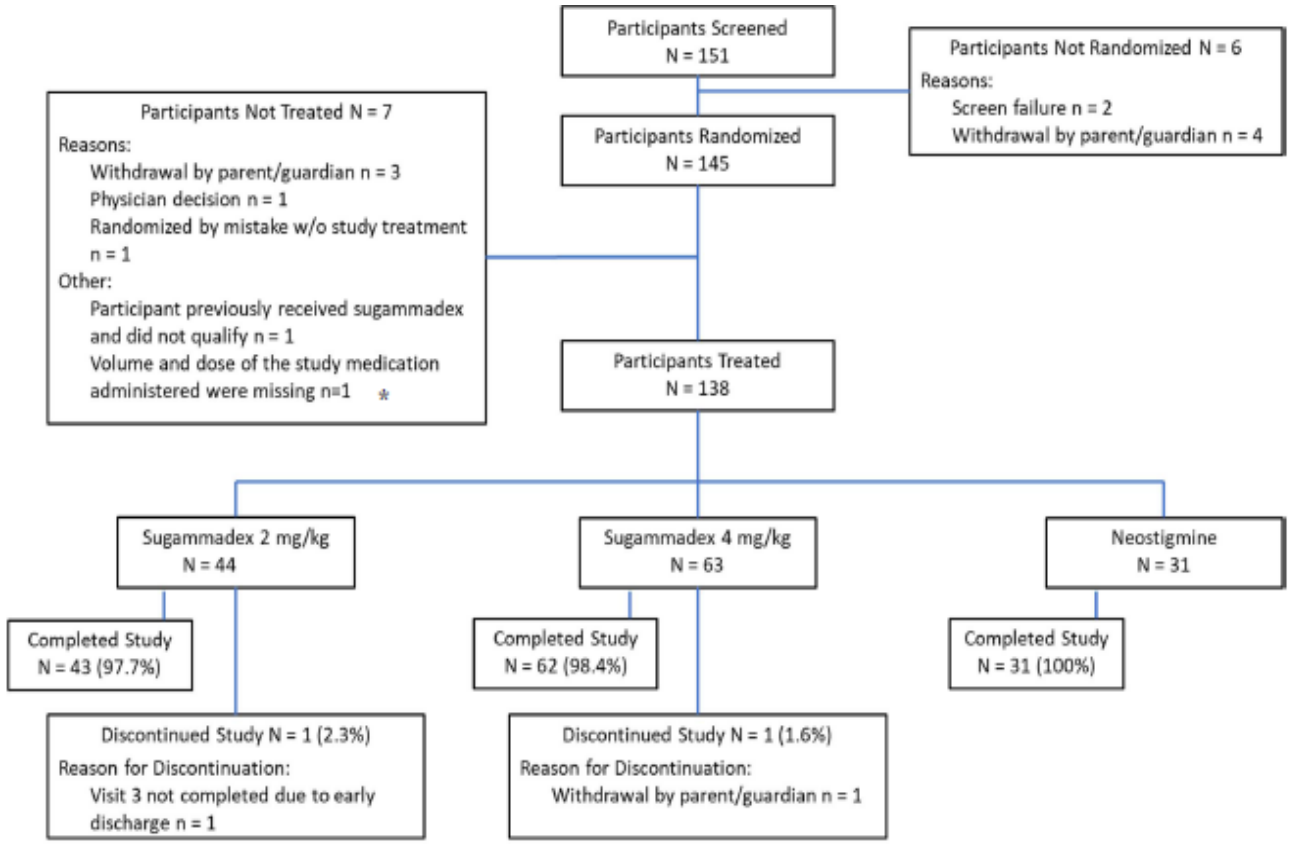
Efficacy: A formal test for efficacy in the comparison of sugammadex to neostigmine in the setting of moderate block was conducted with data from Part B. TTNMR and time to extubation were analysed by a Cox proportional hazard (PH) model, adjusting age (continuous) and stratified by NMBA (rocuronium and vecuronium). In addition, the Cox PH model for time to extubation included a covariate of endotracheal extubation type (deep and not deep, determined as "deep" if, in extubation readiness assessment, mental status question was marked as "yes" based on criterion "Other- extubation at deep sedation").

TTNMR was censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery was not achieved, and time to extubation was censored at the time of last assessment of extubation readiness if extubation readiness was not achieved.

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a 95% CI) for the primary and secondary efficacy endpoints was estimated within each subgroup of predefined classification variables based on the primary efficacy analysis model (Cox PH) in the setting of moderate block. In the subgroup analyses, no stratification by NMBA was done, and age was in the model for subgroup analysis by age.

Results

Participant flow



Recruitment

The study was conducted from 23-JUL-2019 (first patient first visit) to 21-SEP-2023 (last patient last visit).

A total of 151 participants were screened and 145 were assigned to treatment in Part A and Part B (not randomized in Part A; randomized in Part B) across 23 global study sites. A total of 7 participants assigned to treatment were not treated (see above). A total of 138 participants had reported treatment and primary efficacy data: 44 received sugammadex 2 mg/kg (15 from Part A, 29 from Part B), 63 received sugammadex 4 mg/kg (32 from Part A, 31 from Part B), and 31 received neostigmine (Part B). A total of 136 participants completed the study.

Of note, in Part A there was a single participant (one subject; age cohort 3 months to <6 months; assigned to 2 mg/kg sugammadex) where the administered dose was imputed because the volume of the drug administered was missing. This subject was classified as "Not treated" in efficacy and safety analyses, but for this participant the administered dose was calculated based upon the body weight and treatment assignment (2 mg/kg) and the data were included in the PK analyses.

Conduct of the study

The original protocol was dated 05-FEB-2019. One major amendment was implemented (Amendment 1, 17-MAR-2020) and included the following changes:

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

Another amendment was also implemented (Amendment 2, 27-OCT-2022): The Sponsor Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

The statistical analysis plan (SAP) was included in the protocol. A supplemental SAP (sSAP) was introduced on 17-OCT-2023. It provided additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

A total of 5 study sites were audited by the sponsor in investigator site audits and study-level audits: site in USA, site in Malaysia, site in Australia, site in Denmark, and site in Finland.

Important protocol deviations were reported for 17 randomized participants (11.7%). Fourteen (9.7%) participants had important protocol deviations that were considered to be clinically important (Table 11). Of these, 11 participants (7.6%) had deviations pertaining to IMP being administered at incorrect depth of block.

Table 11. Summary of important protocol deviations considered to be clinically important (all randomized participants, part A+B)

	Part A: Sugammadex 2 mg/kg		Part A: Sugammadex 4 mg/kg		Part B: Sugammadex 2 mg/kg		Part B: Sugammadex 4 mg/kg		Part B: Neostigmine		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	**16**		**34**		**31**		**32**		**32**		**145**	
with one or more clinically important protocol deviations	2	(12.5)	1	(2.9)	1	(3.2)	6	(18.8)	4	(12.5)	14	(9.7)
with no clinically important protocol deviations	14	(87.5)	33	(97.1)	30	(96.8)	26	(81.3)	28	(87.5)	131	(90.3)
Informed Consent	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.1)**	**0**	**(0.0)**	**1**	**(0.7)**
Participant had no documented initial consent to enter the trial.	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	0	(0.0)	1	(0.7)
Safety Reporting	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(0.7)**
Participant had a reportable Safety Event and/or follow up Safety Event information that was not reported per the timelines outlined in the protocol.	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)
Study Intervention	**2**	**(12.5)**	**1**	**(2.9)**	**1**	**(3.2)**	**5**	**(15.6)**	**3**	**(9.4)**	**12**	**(8.3)**
IMP administered at incorrect depth of block.	2	(12.5)	1	(2.9)	1	(3.2)	4	(12.5)	3	(9.4)	11	(7.6)
IMP not administered within protocol specified timing.	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(3.1)	2	(1.4)
Trial Procedures	**1**	**(6.3)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.1)**	**2**	**(1.4)**
Neuromuscular recovery was not performed in source using one of the 4 options stipulated by the protocol and according to required timepoints.	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.1)	1	(0.7)
No neuromuscular transmission monitoring (with TOF-Watch or other device) was performed.	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.7)

Every participant is counted a single time for each applicable row and column.
All Randomized participants include all enrolled participants in Part A and all randomized participants in Part B.
IMP = investigational medicinal product; **TOF** = train-of-four stimulation.

In addition, protocol deviations associated with the COVID-19 pandemic were reported for 8 participants (5.5%). None of the COVID-19 related protocol deviations were considered clinically important.

No participant's data were excluded from analysis due to a protocol deviation and no protocol deviations were classified as a serious GCP compliance issue.

Finally, there was 1 incident in the study involving 1 participant in which unblinding or biasing information was accidentally disclosed to the Sponsor's personnel who were blinded to the study intervention. The incident was not considered to be a significant quality issue impacting the overall validity of data or reliability of study results. Therefore, data from this participant were included in the analyses.

Baseline data

The baseline characteristics were generally comparable across intervention groups. Selected baseline characteristics are summarised in Table 12.

Table 12. Baseline characteristics (study P169, part A+B)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	44		63		31		138	
Sex								
Male	33	(75.0)	40	(63.5)	19	(61.3)	92	(66.7)
Female	11	(25.0)	23	(36.5)	12	(38.7)	46	(33.3)
Age (Days)								
Birth to 27 days	11	(25.0)	12	(19.0)	5	(16.1)	28	(20.3)
28 days to < 3 months	9	(20.5)	17	(27.0)	9	(29.0)	35	(25.4)
3 months to < 6 months	10	(22.7)	19	(30.2)	8	(25.8)	37	(26.8)
6 months to < 2 years	14	(31.8)	15	(23.8)	9	(29.0)	38	(27.5)
Mean	175.4		149.1		179.3		164.3	
SD	183.0		143.3		193.8		168.0	
Median	116.0		102.0		94.0		100.5	
Range	1 to 649		3 to 543		1 to 720		1 to 720	
ASA Class								
ASA Class 1	13	(29.5)	23	(36.5)	10	(32.3)	46	(33.3)
ASA Class 2	25	(56.8)	29	(46.0)	15	(48.4)	69	(50.0)
ASA Class 3	6	(13.6)	11	(17.5)	6	(19.4)	23	(16.7)
Type of Neuromuscular Blocking Agent (NMBA)								
Rocuronium	35	(79.5)	44	(69.8)	19	(61.3)	98	(71.0)
Vecuronium	9	(20.5)	19	(30.2)	12	(38.7)	40	(29.0)
Stratifications								
Rocuronium, Birth to 27 days	10	(22.7)	10	(15.9)	4	(12.9)	24	(17.4)
Rocuronium, 28 days to < 3 months	8	(18.2)	13	(20.6)	6	(19.4)	27	(19.6)
Rocuronium, 3 months to < 6 months	7	(15.9)	11	(17.5)	5	(16.1)	23	(16.7)
Rocuronium, 6 months to < 2 years	10	(22.7)	10	(15.9)	4	(12.9)	24	(17.4)
Vecuronium, Birth to 27 days	1	(2.3)	2	(3.2)	1	(3.2)	4	(2.9)
Vecuronium, 28 days to < 3 months	1	(2.3)	4	(6.3)	3	(9.7)	8	(5.8)
Vecuronium, 3 months to < 6 months	3	(6.8)	8	(12.7)	3	(9.7)	14	(10.1)
Vecuronium, 6 months to < 2 years	4	(9.1)	5	(7.9)	5	(16.1)	14	(10.1)

Numbers analysed

A total of 29 participants randomized to sugammadex 2 mg/kg and 31 participants randomized to neostigmine in Part B were included in primary and secondary efficacy analyses. Of these 60 participants, one participant randomized to neostigmine had censored TTNMR.

Outcomes and estimation

Primary outcome

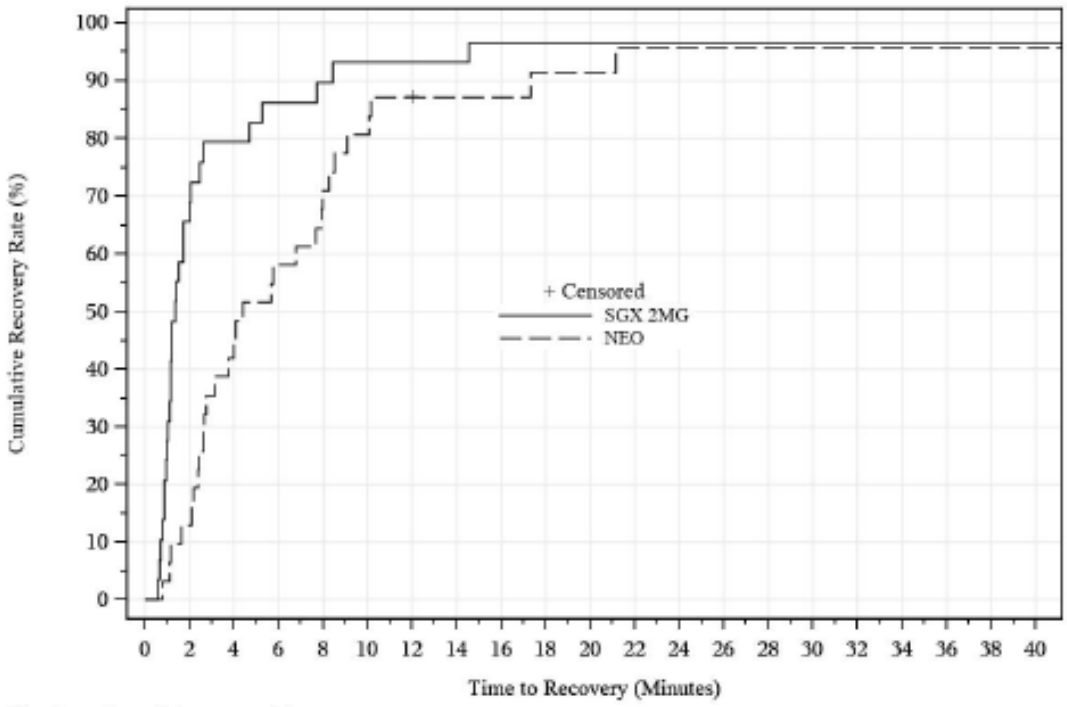
The primary efficacy endpoint, time to neuromuscular recovery (TTNMR) in study Part B, was significantly faster in participants dosed with sugammadex 2 mg/kg compared with neostigmine, as shown by Cox PH model and log-rank test (Table 13). Kaplan-Meier plot of TTNMR is shown in Figure 8. Approximately 79.3% (23/29) of participants treated with sugammadex 2 mg/kg reached neuromuscular recovery within 4 minutes compared with 41.9% (13/31) of participants treated with neostigmine.

Table 13. Analysis of time to neuromuscular recovery (all participants treated, part B)

Treatment	N	Number of Events (%)	TTNMR † (Minutes) Median (95% CI) [Q1, Q3]
Sugammadex 2 mg/kg	29	29 (100.0)	1.4 (1.1, 2.0) [1.0, 2.5]
Neostigmine + (Glycopyrrolate or Atropine)	31	30 (96.8)	4.4 (2.7, 7.9) [2.4, 8.5]
Pairwise Comparisons		Hazard Ratio‡ (95% CI)‡	p-Value §
Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)		2.40 (1.37, 4.18)	0.0002

†From product-limit (Kaplan-Meier) method for censored data.
‡Based on Cox regression model with Efron's method of tie handling with covariates of treatment, age (continuous) and stratified by neuromuscular blocking agent.
§Two-sided p-value based on log-rank test stratified by neuromuscular blocking agent and age groups.
Per analysis plan, TTNMR is censored at the time of last assessment of neuromuscular recovery if neuromuscular recovery is not achieved.
CI = confidence interval; Q1 = the first quartile; Q3 = the third quartile; TTNMR = time to neuromuscular recovery.

Figure 8. Kaplan-Meier plot of time to neuromuscular recovery (all participants treated, part B)



Number of participants at risk

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

Number of events inside period

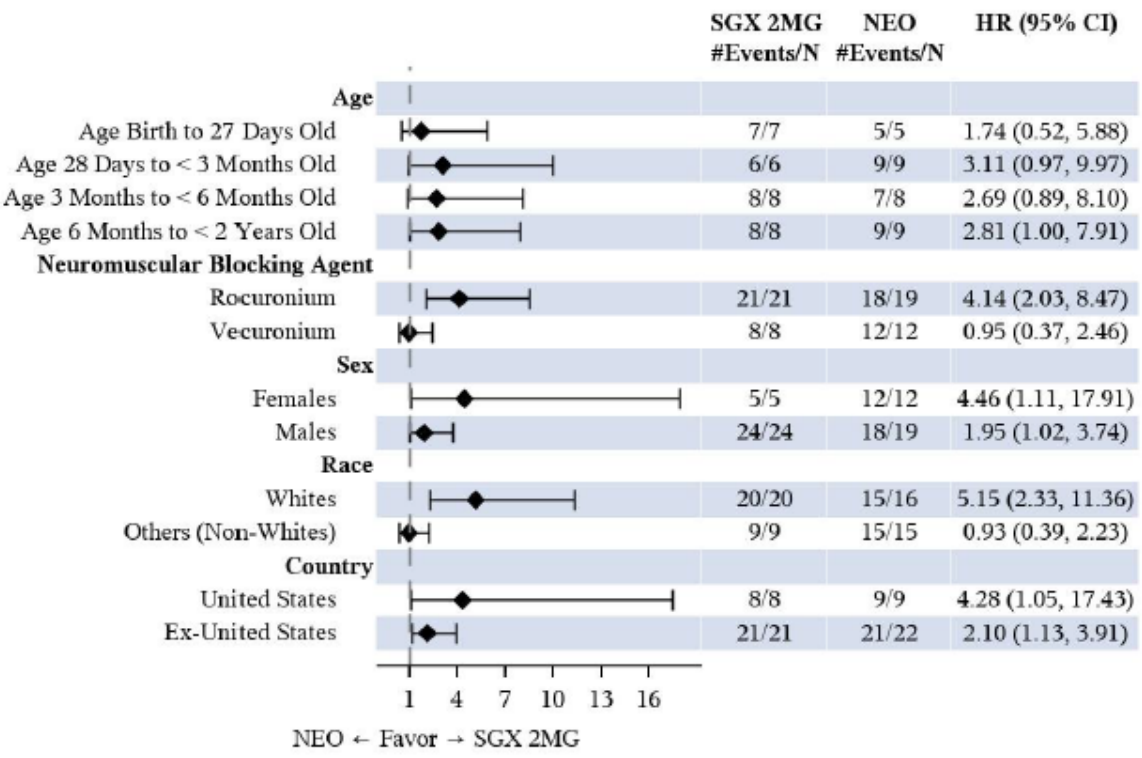
SGX 2MG	19	4	2	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1
NEO	4	9	5	4	3	2	0	0	1	0	1	0	0	0	0	0	0	0	0	1

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

Subgroup analyses showed that effect of treatments was generally consistent with the overall analysis result for TTNMR favouring sugammadex 2 mg/kg as compared with neostigmine in most subgroups

(Figure 9). However, analysis by neuromuscular blocking agent suggested that TTNMR was significantly shorter for sugammadex 2 mg/kg in NMB induced by rocuronium but not in NMB induced by vecuronium.

Figure 9. Analysis of time to neuromuscular recovery by subgroup. Hazard ratio and 95% confidence interval, sugammadex 2 mg/kg versus neostigmine (all participants treated, part B)

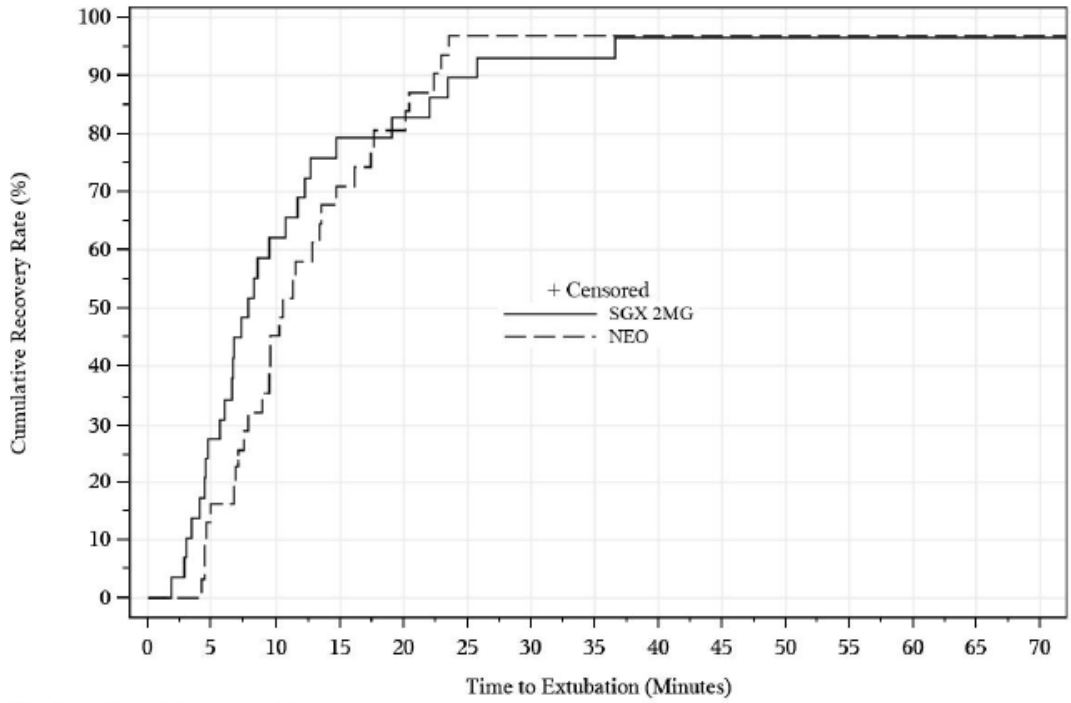


Note: Subgroup analyses are only performed for those classification variables with ≥5 participants in each subgroup.
SGX 2MG = sugammadex 2 mg/kg; NEO = neostigmine.

Secondary outcome

The secondary efficacy endpoint, time to extubation in Part B, was similar in participants dosed with sugammadex 2 mg/kg and neostigmine (hazard ratio = 1.30, 95% CI: 0.76, 2.21). Based on Kaplan-Meier estimates, 79.3% (23/29) of participants in the sugammadex 2 mg/kg group were extubated within 15 minutes from study intervention administration compared with 71.0% (22/31) of participants in the neostigmine group (Figure 10). Subgroup analyses results (age, NMBA, sex, race, country) were consistent with the overall analysis result for the time to extubation.

Figure 10. Kaplan-Meier plot of time to extubation (all participants treated, part B)



Number of participants at risk

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

Number of events inside period

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

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

Tertiary/exploratory outcomes

Tertiary/exploratory efficacy endpoints time to OR discharge, PACU discharge, and hospital discharge suggested no difference between participants dosed with sugammadex 2 mg/kg or neostigmine.

Tertiary/exploratory endpoint delayed recovery was defined as any observation that was >3 times the geometric mean of TTNMR within each intervention group across Part A and Part B. The number of delayed recovery events by this definition was low and generally similar across treatment groups, making assessment of comparative incidences inconclusive (Table 14). In reviewing the cases of delayed recovery, there were no differences across sex, age group, or site. Based on review of the data the most common potential reasons for delayed recovery were technical in nature, e.g., measurement anomaly due to suboptimal set-up or administration of IMP at incorrect depth of block.

Table 14. Participants with delayed recovery (all participants treated, part A+B)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Participants in population	44		63		31	
Delayed Recovery	5	(11.4)	2	(3.2)	3	(9.7)
Delayed recovery is any observation that is >3 times the geometric mean of time to neuromuscular recovery within each treatment group.						

Pooled analyses

When data were pooled across Part A and Part B, the results for TTNMR and time to extubation remained consistent with the analyses for Part B alone (Table 15). Although no comparator existed for the reversal of deep block, sugammadex 4 mg/kg achieved rapid neuromuscular recovery in this setting with a median of 1.1 minutes.

Table 15. Summary of time to neuromuscular recovery and time to extubation (all participants treated, part A+B)

Efficacy Endpoint	Treatment	N	Number of Events	Mean	(SD)	Median	Range	Geometric Mean	(95% CI)
Time to Neuromuscular Recovery	Sugammadex 2 mg/kg	44	43	5.0	(18.3)	1.2	(0.6, 121.0)	1.7	(1.3, 2.3)
	Sugammadex 4 mg/kg	63	63	1.9	(4.6)	1.1	(0.2, 36.9)	1.2	(0.9, 1.4)
	Neostigmine + (Glycopyrrolate or Atropine)	31	30	14.6	(48.4)	4.2	(0.8, 269.7)	4.9	(3.2, 7.4)
Time to Extubation	Sugammadex 2 mg/kg	44	43	15.6	(20.1)	8.4	(1.9, 122.1)	10.0	(7.7, 13.2)
	Sugammadex 4 mg/kg	63	63	12.2	(13.7)	6.3	(1.4, 65.6)	7.9	(6.3, 9.9)
	Neostigmine + (Glycopyrrolate or Atropine)	31	31	20.2	(46.9)	10.5	(4.2, 270.7)	11.6	(8.7, 15.4)
CI = confidence interval; SD = standard deviation.									

Ancillary analyses

Not applicable.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of efficacy for study P169

Title: 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 Aged Birth to < 2 Years

Study identifier	Protocol Number: P169 (MK-8618-169) IND: 68029 EudraCT: 2017-000693-11 NCT: 03909165		
Design	This was a randomized, active comparator-controlled, parallel-group, multisite, double-blinded study to evaluate the PK, safety, and efficacy of sugammadex in pediatric participants aged birth to <2 years for the reversal of moderate and deep neuromuscular blockade (NMB). In Part B, participants were randomized to 1 of 3 intervention arms in a 1:1:1 ratio: • Moderate NMB and reversal with 2 mg/kg sugammadex; or • Moderate NMB and reversal with neostigmine + glycopyrrolate or atropine sulfate (hereafter, called neostigmine); or • Deep NMB and reversal with 4 mg/kg sugammadex		
	Duration of main phase:		Approximately 48 months
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Sugammadex is superior to neostigmine in reversing moderate NMB as measured by time to neuromuscular recovery.		
Treatments groups	Sugammadex 2 mg/kg		Sugammadex 2 mg/kg IV, single dose, 29 participants treated in Part B
	Neostigmine + glycopyrrolate or atropine sulfate (neostigmine)		Neostigmine IV, single dose, 31 participants treated (Part B only)
Endpoints and definitions	Primary	Time to Neuromuscular Recovery (TTNMR) (Part B)	Interval from administration of reversal agent to time to neuromuscular recovery.
	Secondary	Time to Extubation (Part B)	Interval from administration of reversal agent to removal of the endotracheal tube.
Database lock	24-OCT-2023/17-NOV-2023		
Results and Analysis			
Analysis description	**Pre-specified Primary Efficacy Analyses**		
Analysis population and time point description	The efficacy analyses were based on the All Participants Treated (APT) population that includes all randomized participants who received at least 1 dose of study intervention. Primary efficacy analysis was based on the APT population from Part B in the moderate NMB.		
Descriptive statistics and estimate variability	Treatment group	Sugammadex 2 mg/kg	Neostigmine + (Glycopyrrolate or Atropine)
	Number of subjects	29	31
	Primary Endpoint		
	TTNMR (minutes) Median	1.4	4.4
	95% CI [Q1,Q3]	1.1, 2.0 [1.0, 2.5]	2.7, 7.9 [2.4, 8.5]
	Secondary Endpoint		
	Time to Extubation (minutes) Median	7.9	10.5

	95% CI [Q1,Q3]	5.7, 11.6 [4.7, 12.6]	7.9, 13.5 [7.1, 17.4]
Effect estimate per comparison	Primary Endpoint: TTNMR	Comparison groups	Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)
		Hazard Ratio	2.40
		95% CI	1.37, 4.18
		p-value	0.0002
	Secondary Endpoint: Time to Extubation	Comparison groups	Sugammadex 2 mg/kg vs. Neostigmine + (Glycopyrrolate or Atropine)
		Hazard Ratio	1.30
		95% CI	0.76, 2.21
		p-value	0.2107

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The overall study design was appropriate and the study report does not suggest misconduct or GCP deviations.

The primary efficacy endpoint was the time to neuromuscular recovery (TTNMR), which could be determined using either neuromuscular transmission monitoring or clinical signs. TTNMR was adequately defined in the protocol. The rationale for using TTNMR as the primary endpoint (instead of quantitative TOF ratio ≥0.9, which was used in a similar study in older paediatric patients) was that technical challenges were anticipated with the use of quantitative TOF monitoring in the current study population. The primary efficacy endpoint was appropriate.

The statistical methods applied in the evaluation of time-to-event data and comparing groups were conventional. For the formal comparison only data from subjects randomised of sugammadex 2 mg/kg or neostigmine in Part B were used. This is appropriate; use of data from nonrandomised participants of Part A would be a potential source of bias. In the stratified log-rank test the stratum-wise sample sizes as low as 2 (or even less when considering participants of Part B only) may challenge robustness of statistical inference, i.e., the p-value. In the Cox PH model, planned as the primary method for evaluation, a more parsimonious approach was taken: NMBA was taken as a stratification factor, while subjects' age was fitted as a continuous covariate. The model assumes that for every additional month of age there may be a fold-change in hazard rate of TTNMR. A model with the logarithm of age as a covariate would have been better aligned with the way participants were stratified for the randomisation. Nevertheless, consistency of conclusions from the fully stratified log-rank test compared with the less stratified Cox PH model will increase the level of trust to their shared conclusion. Despite the lack of randomisation of Part A subjects, consistency of data between Parts A and B will further reduce concerns about statistical uncertainty.

In the analysis of time to extubation, an adjustment for endotracheal extubation type was done. It is unclear whether such an adjustment affected the result; the frequencies of extubation types are not reported. Regardless, adjustment for endotracheal extubation type is not appropriate as it is a post-baseline covariate. This issue was not pursued further because time to extubation was a secondary endpoint only and the applicant does not propose the results to be included in SmPC.

Efficacy data and additional analyses

The formal comparison of efficacy was between sugammadex 2 mg/kg and neostigmine 50 microg/kg in patients with moderate block (n=29 and n=31, respectively) in study P169 Part B. The results for the primary efficacy endpoint demonstrated that the time to neuromuscular recovery was significantly faster in participants dosed with sugammadex 2 mg/kg (median time 1.4 minutes) compared to neostigmine (median time 4.4 minutes).

As shown in Figure 9, a trend favouring sugammadex was observed in most pre-specified subgroup analyses (age group, gender, race, country) but the 95% CIs were wide and often included 1.0. Due to the small number of participants (5 to 9) in many subgroups, the subgroup-specific estimates are uncertain. Subgroup analysis by NMBA suggested that sugammadex 2 mg/kg would be superior to neostigmine for reversal of NMB induced by rocuronium but not of NMB induced by vecuronium. When results from non-randomized open-label Part A were pooled with those from Part B, the TTNMR in participants dosed with sugammadex 2 mg/kg was essentially the same (median time 1.2 minutes), supporting the results of the primary analysis.

No comparator was used for sugammadex 4 mg/kg in the setting of deep block. Results for the pooled results of study P169 Part A+B demonstrated fast TTNMR following IV injection of sugammadex 4 mg/kg at deep block in paediatric subjects aged from birth to <2 years of age (median time 1.1 minutes).

No statistically significant or clinically meaningful differences were identified in analyses for secondary efficacy endpoint time to extubation and in tertiary/exploratory endpoints (time to operating room discharge, time to post-anaesthesia care unit discharge, time to hospital discharge, incidence of delayed recovery, and proportion of participants with neuromuscular recovery after the first 5 minutes of study medication administration).

2.4.4. Conclusions on the clinical efficacy

Efficacy results of study P169 support the extension of indication as proposed by the MAH to "*For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in paediatric patients from birth to 17 years.*".

2.5. Clinical safety

Introduction

Sugammadex is administered concomitantly with neuromuscular blocking agents and anaesthetics in surgical patients. The causality of adverse events is therefore difficult to assess. According to the SmPC, the most commonly reported adverse reactions in surgical patients were cough, airway complication of anaesthesia, anaesthetic complications (e.g., movement or coughing during the anaesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube), procedural hypotension and procedural complication (e.g., coughing, tachycardia, bradycardia, movement, and increase in heart rate).

Hypersensitivity reactions, including anaphylaxis, have occurred in some patients and volunteers. Cases of marked bradycardia have been observed within minutes after the administration of sugammadex in post marketing experience.

The safety profile of sugammadex in dedicated studies in paediatric patients 2-17 years of age, morbidly obese patients, and patients with severe systemic disease (ASA class 3 or 4) has been generally similar to that observed in adults.

Patient exposure

In study P169 (Part A+B), 44 patients aged from birth to <2 years of age were treated with sugammadex 2 mg/kg and 63 with sugammadex 4 mg/kg. In addition, 31 patients were treated with neostigmine in study Part B. See section 5.4.2 of this AR for details.

Study subjects had a surgical procedure or clinical situation (e.g., intubation) that required moderate or deep NMB. More than 75% of the participants received concomitant treatment with anaesthetics (78.3%) and analgesics (90.6%). Beyond anaesthetics and analgesics, the most frequently reported medications were consistent with the procedural setting and included ibuprofen (14.5%), glucose + sodium chloride (13.0%), and cefazolin (12.3%).

Adverse events

Safety analysis was performed with combined data from Study P169 Part A and Part B. The overall incidence of adverse events (AEs) was similar across intervention groups (Table 17). The most frequently reported AE in all intervention groups was procedural pain, which is anticipated in participants undergoing surgery. Vomiting and procedural pain were the only AEs reported (up to 7 days posttreatment) with incidence ≥4 participants and were comparable between the sugammadex groups and the neostigmine group. Drug-related AEs were reported in 1 (2.3%), 0 (0.0%), and 3 (9.7%) participants treated with sugammadex 2 mg/kg, sugammadex 4 mg/kg, and neostigmine + glycopyrrolate/atropine, respectively (Table 18).

Table 17. Adverse event summary (study P169 part A+B, up to 7 days post-treatment)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Participants in population	44		63		31	
with one or more adverse events	30	(68.2)	43	(68.3)	19	(61.3)
with no adverse event	14	(31.8)	20	(31.7)	12	(38.7)
with drug-related[a] adverse events	1	(2.3)	0	(0.0)	3	(9.7)
with serious adverse events	3	(6.8)	1	(1.6)	0	(0.0)
with serious drug-related adverse events	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 adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

[a] Determined by the investigator to be related to the drug.

Table 18. Participants with drug-related adverse events (incidence >0% in one or more treatment groups) (study P169 part A+B, up to 7 days post-treatment)

	Sugammadex 2 mg/kg		Sugammadex 4 mg/kg		Neostigmine + (Glycopyrrolate or Atropine)	
	n	(%)	n	(%)	n	(%)
Participants in population	44		63		31	
with one or more drug-related adverse events	1	(2.3)	0	(0.0)	3	(9.7)
with no drug-related adverse events	43	(97.7)	63	(100.0)	28	(90.3)
Cardiac disorders	**1**	**(2.3)**	**0**	**(0.0)**	**2**	**(6.5)**
Bradycardia	1	(2.3)	0	(0.0)	2	(6.5)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(3.2)**
Blood pressure increased	0	(0.0)	0	(0.0)	1	(3.2)
Heart rate increased	0	(0.0)	0	(0.0)	1	(3.2)
Every participant is counted a single time for each applicable row and column.						

Events of clinical interest included adjudicated hypersensitivity and/or anaphylaxis (Tier 1 event), clinically relevant bradycardia (Tier 1 event), and drug-induced liver injury (Tier 3 event).

Hypersensitivity / anaphylaxis

In the timeframe up to 7 days posttreatment a total of 3 potential cases of hypersensitivity/anaphylaxis (Tier 1 event) were submitted for adjudication and reviewed by an independent external adjudication committee (2 cases in sugammadex 4 mg/kg [3.2%)] and 1 in neostigmine [3.2%]). No cases were adjudicated as hypersensitivity or anaphylaxis up to 7 days posttreatment.

Bradycardia

Clinically relevant bradycardia (Tier 1 event) was defined as any bradycardia event that occurred after administration of study treatment and required intervention, as determined by investigator judgment.

Treatment-emergent bradycardia (Tier 2 event) was defined as a heart rate generally below the first percentile for age that had also decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.

Treatment-emergent relative bradycardia (Tier 3 event) was defined as a heart rate that decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment.

Bradycardia events reported in the timeframe up to 30 minutes posttreatment are summarized in Table 19. A single event of clinically relevant bradycardia was reported for one participant in sugammadex 2 mg/kg group. Similar results were obtained up to 7-days post treatment.

Table 19. Analysis of bradycardia events (study P169 part A+B, up to 30 minutes post-treatment)

Treatment	n	(%)	Difference in % vs Neostigmine + (Glycopyrrolate or Atropine) Estimate (95% CI)†	p-value†
Participants in population				
Sugammadex 2 mg/kg	44			
Sugammadex 4 mg/kg	63			
Neostigmine + (Glycopyrrolate or Atropine)	31			
Clinically Relevant Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)	2.3 (-10.6, 13.5)	0.398
Sugammadex 4 mg/kg	0	(0.0)	0.0 (-12.3, 6.4)	>0.999
Neostigmine + (Glycopyrrolate or Atropine)	0	(0.0)		
Treatment-Emergent Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)	-8.0 (-25.5, 4.0)	
Sugammadex 4 mg/kg	2	(3.2)	-6.2 (-22.7, 3.6)	
Neostigmine + (Glycopyrrolate or Atropine)	3	(9.7)		
Treatment-Emergent Relative Bradycardia				
Sugammadex 2 mg/kg	1	(2.3)		
Sugammadex 4 mg/kg	2	(3.2)		
Neostigmine + (Glycopyrrolate or Atropine)	6	(19.4)		

† Based on Miettinen & Nurminen method stratified by neuromuscular blocking agent and age group; if no participants are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

Estimated differences, confidence intervals and p-values are provided in accordance with the statistical analysis plan.

CI = confidence interval.

Drug-induced liver injury

None of the participants met the Hy's Law criteria for drug-induced liver injury and there were no participants with postbaseline elevated ALT and AST (≥3 x ULN).

Elevated bilirubin (≥2 x ULN) was observed in 6 (15.0%), 7 (13.0%), and 2 (6.9%) participants treated with sugammadex 2 mg/kg, sugammadex 4 mg/kg, and neostigmine, respectively, and elevated alkaline phosphatase (ALP) (≥1.5 x ULN) was observed in 1 (2.6%), 2 (3.7%), and 2 (6.9%) participants treated with sugammadex 2 mg/kg, sugammadex 4 mg/kg, and neostigmine, respectively. These participants had elevated bilirubin and/or ALP already at screening and no trends for treatment-induced increase in bilirubin and/or ALP were observed.

Serious adverse event/deaths/other significant events

A total of 8 serious adverse events (SAEs) were reported across 4 unique participants up to 7-days posttreatment and two additional SAEs were reported up to 14 days posttreatment. No SAEs were considered related to study intervention by the investigator. No deaths were reported in the study. Other significant events (hypersensitivity/anaphylaxis; bradycardia; drug-induced liver injury) are summarised above.

Laboratory findings

No clinically meaningful changes from baseline in laboratory values were observed.

Discontinuation due to adverse events

No treated participants were reported to have an AE that led to discontinuation of study intervention.

Post marketing experience

The MAH provided a postmarketing summary of spontaneous and noninterventional study reports received for sugammadex worldwide in patients from birth to <17 years of age from the IBD of 31-JUL-2008 through 31-JAN-2024. A total of 706 paediatric cases (205 serious and 501 nonserious) containing a total of 1,196 events were retrieved (Table 20).

Table 20. Number of events by seriousness and paediatric age group in cases with age values

Age Group	# Serious Events	# Nonserious Events	Total # of Events
Neonates (Birth to 28 days)	14	37	51
Infants (29 days to <3 months)	12	39	51
Infants (3 months to <6 months)	15	42	57
Infants (6 months to 1 year)	20	93	113
Children (>1 year to <2 years)	1	40	41
Children (2 years to <17 years)	243	490	733
Total	**305**	**741**	**1046**[1]
[1] Total number of events listed is less than total number of events (1,196) involving all paediatric patients, as the total number of events for all paediatric patients included cases lacking age values.			

The most frequently reported AEs (≥2 events) in paediatric subjects are summarised in Table 21. In paediatric subjects <2 years of age (i.e., the scope of the current variation application), the most frequently reported AEs included off-label use, product administered to patients of inappropriate age, product use issue, and no adverse event. In the age group infants (6 months to 1 year), there were a total of 22 events of pyrexia reported in 4 cases from a Postapproval Safety Monitoring Program in China. Fifteen of the 22 events were from a single case, 2 cases contained 3 events each, and the remaining case contained a single event of pyrexia. All the cases lacked sufficient information for a meaningful clinical assessment.

Table 21. The most frequent adverse events (≥2) in cases with age values

Age group	Preferred terms (PT)	Total # of Events	#Serious events	#Nonserious events
Neonates (Birth to 28 days)	Off-label use	9	0	9
	No adverse event	6	0	6
	Recurrence of NMB	6	4	2
	Product administered to patients of inappropriate age	5	0	5
	Product use issue	4	1	3
	Exposure via breast milk	2	0	2
	Foetal exposure during pregnancy	2	1	1
Infants (29 days to <3 months)	Off-label use	12	3	9
	Product use issue	9	1	8
	Product administered to patients of inappropriate age	7	3	4
	Laryngospasm	3	3	0
	NMB prolonged	3	0	3
	No adverse event	2	0	3
Infants (3 months to <6 months)	Off-label use	16	0	16
	No adverse event	6	0	6
	Product administered to patients of inappropriate age	5	0	5
	Product use issue	4	0	4
	Bradycardia	2	2	0
	Erythema	2	0	2
	Recurrence of NMB	2	2	0
	Respiratory arrest	2	2	0
Infants (6 months to 1 year)	Off-label use	27	7	20
	Pyrexia	22	0	22
	Product administered to patients of inappropriate age	10	0	10
	No adverse event	6	0	6
	Product use issue	4	0	4
	Recurrence of NMB	4	2	2
	Accidental overdose	2	0	2
	Anaphylactic reaction	2	2	0
	Bradycardia	2	2	0
	Drug ineffective	2	1	1
	NMB prolonged	2	0	2
	Vomiting	2	0	2
Children (≥1 year to <2 years)	Off-label use	10	0	10
	Product administered to patient of inappropriate age	8	0	8
	No adverse event	5	0	5
	Product use issue	3	0	3
	Pyrexia	3	0	3
	Agitation postoperative	2	0	2
Children (≥ 2 years to <17 years)	Off-label use	172	0	172
	Anaphylactic reaction	49	45	4
	Procedural pain	32	0	32
	Pyrexia	26	0	26

As noted above, there were several cases and events where the actual patient age was not provided but the reports included mention of a specific paediatric age group (such as neonate, infant, child, or adolescent) only within the case narrative. There were 82 such cases (150 events) identified (Table 22). The most frequently reported AEs included off-label use, product administered to patients of inappropriate age, product use issue, and no adverse event (Table 23).

Table 22. Number of events by seriousness and paediatric age group in cases without age values

Age Group	# Serious Events	# Nonserious Events	Total # of Events
Neonate	4	28	32
Infant	2	34	36
Child	18	59	77
Adolescent	0	5	5
Total	**24**	**126**	**150**

Table 23. The most frequent adverse events (≥2) in cases without age values

Age Group	Preferred terms (PT)	Total # of Events	# Serious Events	# Nonserious Events
Neonate	Off-label use	9	0	9
	NMB prolonged	7	0	7
	Product administered to patients of inappropriate age	2	0	2
Infant	Off-label use	5	0	5
	Bronchospasm	4	0	4
	Product administered to patients of inappropriate age	4	0	4
	Recurrence of NMB	4	0	4
	Asthma	3	0	3
	Dyspnoea	3	0	3
	Respiration abnormal	3	0	3
	Muscle Spasms	2	0	2
Child	Off-label use	13	0	13
	Product use issue	8	0	8
	No adverse event	5	0	5
	Bradycardia	4	4	0
	Incorrect dose administered	4	0	4
	Muscle contracture	4	1	3
	Underdose	4	0	4
	Anaphylactic reaction	3	3	0
	Bronchospasm	2	1	1
	Post procedural haemorrhage	2	2	0
	Therapeutic response unexpected	2	0	2
Adolescent	Drug hypersensitivity	2	0	2

2.5.1. Discussion on clinical safety

A total of 107 participants aged from birth to <2 years of age were treated with a single dose of sugammadex (2 mg/kg, n=44; 4 mg/kg, n=63) in Study P169; most participants received concomitant treatment e.g. with anaesthetics and analgesics.

The approved SmPC of Bridion has a warning regarding marked bradycardia observed within minutes after the administration of sugammadex and bradycardia was a pre-specified event of clinical interest in study P169. Individual cases of clinically relevant bradycardia, treatment-emergent bradycardia, and treatment-emergent relative bradycardia were observed in participants treated with sugammadex (see Table 19).

The approved SmPC of Bridion has a warning regarding drug hypersensitivity reactions (including anaphylactic reactions) after the administration of sugammadex and adjudicated hypersensitivity and/or anaphylaxis was a pre-specified event of clinical interest in study P169. There were no cases of adjudicated hypersensitivity or anaphylaxis in the study.

The MAH also provided a postmarketing summary of spontaneous and noninterventional study reports received for sugammadex worldwide in patients from birth to <17 years of age from the IBD of 31-JUL-2008 through 31-JAN-2024. In paediatric subjects <2 years of age (i.e., the scope of the current variation application), the most frequently reported AEs included off-label use, product administered to patients of inappropriate age, product use issue, and no adverse event. The AEs of spontaneous and noninterventional study reports did not suggest unique safety concerns in paediatric subjects <2 years of age.

Overall, the limited observed safety results of study P169 and AEs of spontaneous and noninterventional study reports support the MAH's conclusion that in studies of paediatric patients from birth to <2 years of age, the safety profile of sugammadex (up to 4 mg/kg) was generally similar to the profile observed in older paediatric patients (≥2 years of age) and in adults.

2.5.2. Conclusions on clinical safety

The limited observed safety results of study P169 and AEs of spontaneous and noninterventional study reports support the MAH's conclusion that in studies of paediatric patients from birth to <2 years of age, the safety profile of sugammadex (up to 4 mg/kg) was generally similar to the profile observed in older paediatric patients (≥2 years of age) and in adults.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.0 is acceptable.

Safety concerns

No safety concerns are included in the safety specification. The summary of safety concerns remain unchanged. No changes were proposed relevant to the current process which is endorsed.

Pharmacovigilance plan

Routine Pharmacovigilance activities

A safety review of post marketing safety data in the paediatric population aged from birth will be included in the PSUR. No additional PhV activities were proposed. The MAH's proposed PhV plan is considered acceptable.

Risk minimisation measures

No changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s).

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes to the package leaflet are minimal; in particular the key messages for the safe use of the medicinal product are not impacted. The proposed revisions do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Drug-induced neuromuscular blockade is commonly required for e.g. intubation and surgery. Bridion (sugammadex) is used to accelerate recovery from the effects of NMBAs.

The proposed indication is as follows (changes to approved indication are highlighted with ~~strikethrough~~ and **bold** font):

Reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults.

For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in ~~children and adolescents aged 2 to 17 years~~ ***paediatric patients from birth to 17 years***.

3.1.2. Available therapies and unmet medical need

Before the availability of sugammadex, all clinically available NMB reversal agents were acetylcholinesterase (AChE) inhibitors such as neostigmine. These agents are appropriate for reversal of moderate NMB, a degree of block that requires partial spontaneous recovery of neuromuscular transmission, which limits their utility.

Additionally, AChE inhibitors cause nonselective potentiation of cholinergic neurotransmission, which may lead to undesirable effects caused by increased acetylcholine concentrations outside the neuromuscular junction (e.g., hypotension, bradycardia, cardiac arrhythmias, bronchial constriction, increased salivation). A muscarinic receptor antagonist, such as atropine or glycopyrrolate, must be coadministered with an AChE inhibitor to antagonize these muscarinic side effects. However, the muscarinic antagonists themselves can cause undesirable effects (e.g., tachycardia, dry mouth, cardiac arrhythmias, urinary retention).

3.1.3. Main clinical studies

One clinical study (P169) was conducted in the target population. The primary efficacy analysis is based on Part B of the study, in which paediatric participants from birth to <2 years of age were randomized to sugammadex 2 mg/kg, neostigmine, or sugammadex 4 mg/kg. Sugammadex 2 mg/kg and neostigmine were administered in moderate NMB setting whereas sugammadex 4 mg/kg was administered in deep NMB setting.

The anaesthesiologist and other operating room personnel were blinded to the reversal agent in the moderate block arms. In deep NMB setting those aware of the depth of block knew the study treatment (sugammadex 4 mg/kg) because there was no comparator for reversal of deep block.

The aim of the non-randomized open-label Part A of study P169 was to obtain PK data for sugammadex in the target population and to confirm that sugammadex dose in Part B was appropriate. Safety and supportive efficacy data were also collected in Part A.

3.2. Favourable effects

The primary efficacy endpoint, time to neuromuscular recovery (TTNMR) in Part B, was significantly faster in participants dosed with sugammadex 2 mg/kg (median 1.4 minutes; n=29) compared with neostigmine (median 4.4 minutes; n=31) (hazard ratio (HR): 2.40, 95% CI: 1.37, 4.18). Approximately 79.3% (23/29) of participants treated with sugammadex 2 mg/kg reached neuromuscular recovery within 4 minutes compared with 41.9% (13/31) of participants treated with neostigmine.

The secondary efficacy endpoint, time to extubation in Part B, was similar in participants dosed with sugammadex 2 mg/kg and neostigmine (HR: 1.30, 95% CI: 0.76, 2.21).

Sugammadex 4 mg/kg achieved rapid neuromuscular recovery in deep block setting with a median of 1.1 minutes (Part A+B results combined; total n=63).

3.3. Uncertainties and limitations about favourable effects

In Study P169, NMB was induced by rocuronium (n=40 in Part B) or vecuronium (n=20 in Part B) whereas the proposed new indication is for reversal of rocuronium induced blockade, in line with the indication approved for children and adolescents aged 2 to 17 years. Subgroup analysis by NMB (all participants treated, Part B) suggested that sugammadex 2 mg/kg would be superior to neostigmine for reversal of NMB induced by rocuronium (HR 4.14; 95% CI 2.03, 8.47) but not of NMB induced by vecuronium (HR 0.95; 95% CI 0.37, 2.46).

3.4. Unfavourable effects

A total of 107 participants aged from birth to <2 years of age were treated with a single dose of sugammadex (2 mg/kg, n=44; 4 mg/kg, n=63) in Study P169 (Part A+B combined). A total of 31 participants were treated with neostigmine (only in Part B).

Prespecified adverse events of interest (hypersensitivity/anaphylaxis; bradycardia; drug-induced liver injury) were based on safety profile of sugammadex in older paediatric and adult subjects. There were no cases of adjudicated hypersensitivity/anaphylaxis or drug-induced liver injury. Incidences of clinically relevant bradycardia and treatment-emergent bradycardia were low (0.0 to 3.2% for sugammadex 2 mg/kg and 4 mg/kg; 0.0 to 9.7% for neostigmine). The incidence of treatment-

emergent relative bradycardia appeared to be less frequent in the sugammadex groups (2.3 to 3.2 %) than in the neostigmine group (19.4%).

The most frequently reported adverse event in all intervention groups was procedural pain, which is anticipated in participants undergoing surgery.

The safety results of Study P169 suggest that the safety profile of sugammadex in paediatric subjects aged from birth to <2 years of age is comparable to that of older paediatric and adult subjects.

In addition, the MAH provided a postmarketing summary of spontaneous and noninterventional study reports received for sugammadex worldwide in patients from birth to <17 years of age from the IBD of 31-JUL-2008 through 31-JAN-2024. In subjects from birth to <2 years of age, the most frequently reported adverse events included off-label use, product administered to patients of inappropriate age, product use issue, and no adverse event.

3.5. Uncertainties and limitations about unfavourable effects

The number of subjects in Study P169 is too low to reliably evaluate the incidence of unfavourable effects. It is difficult to adjudicate the reported adverse events because of the underlying surgical procedure and concomitant treatment with anaesthetics and analgesics.

Incidence of unfavourable effects cannot be estimated using postmarketing data.

3.6. Effects Table

Table 24. Effects table for Bridion for routine reversal of neuromuscular blockade in subjects from birth to <2 years of age

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
TTNMR (Primary)	Interval from administration of reversal agent to time to neuromuscular recovery	minutes	1.4	4.4	HR 2.40 (1.37, 4.18) p-value: 0.0002 Consistent with prior adult and paediatric experience	P169 Study Report Table 11-1
Time to Extubation (Secondary)	Interval from administration of reversal agent to removal of the endotracheal tube	minutes	7.9	10.5	HR 1.30 (0.76, 2.21) p-value: 0.2107 Uncertainties: Time to extubation impacted in this youngest paediatric age group by the potential contribution of clinical practice factors not directly relevant to the agent used for reversal of neuromuscular blockade	P169 Study Report Table 11-2
Unfavourable Effects						
Adjudicated anaphylaxis and hypersensitivity	Incidence	%	0	0	3 potential cases (2 in sugammadex 4mg/kg [3.2%)] and 1 in neostigmine [3.2%]) were submitted for adjudication and reviewed by an independent external adjudication committee. None were confirmed cases of hypersensitivity/anaphylaxis	P169 Study Report Table 14.3-43 Table 14.3-44

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Clinically-relevant bradycardia[a]	Incidence	%	2.3 (2 mg/kg) 0 (4 mg/kg)	0	Comparable incidence among intervention groups (≤3 participants per group)	P169 Study Report Table 12-5
Treatment-emergent bradycardia[b]	Incidence	%	2.3 (2 mg/kg) 3.2 (4 mg/kg)	9.7	Comparable incidence among intervention groups (≤3 participants per group)	P169 Study Report Table 12-5
Treatment-emergent relative bradycardia[c]	Incidence	%	2.3 (2 mg/kg) 3.2 (4 mg/kg)	19.4	Occurred less frequently in the sugammadex groups (≤2 participants per group) than in the neostigmine group	P169 Study Report Table 12-5

Abbreviations: HR=Hazard Ratio

Notes:

[a] Defined as any bradycardia event that occurred after administration of study treatment and required intervention, as determined by investigator judgment

[b] Defined as a heart rate generally below the first percentile for age that had also decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment

[c] Defined as heart rate that decreased 20% or greater as compared with the participant's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Neostigmine, which was the comparator in Study P169, is approved nationally in EU countries for reversal of NMB caused by non-depolarising (competitive) agents such as rocuronium and vecuronium. Of note, neostigmine (and other AChE inhibitors) should only be administered at moderate NMB, a degree of block that requires partial spontaneous recovery of neuromuscular transmission.

Results of Study P169 in paediatric subjects from birth to <2 years of age demonstrated that:

- Moderate NMB induced by rocuronium or vecuronium was reversed faster by a single bolus injection of sugammadex 2 mg/kg compared with neostigmine. Time to recovery was comparable to that observed in paediatric subjects from 2 to <17 years of age and adults.
- Deep NMB induced by rocuronium or vecuronium was reversed by a single bolus injection of sugammadex 4 mg/kg with comparable time to recovery as observed in paediatric subjects from 2 to <17 years of age and adults.

The limited safety data from Study P169 and postmarketing safety data suggest that the safety profile of sugammadex in paediatric subjects aged from birth to <2 years of age is comparable to that of older paediatric and adult subjects.

3.7.2. Balance of benefits and risks

Efficacy of sugammadex in the proposed new indication in paediatric subjects from birth to <2 years of age is comparable to that in older children, adolescents, and adults.

No new safety concerns were found in paediatric subjects from birth to <2 years of age. Pharmacokinetic data indicate that exposure to sugammadex is slightly lower in paediatric subjects from birth to <2 years of age compared to adults. Sugammadex is administered intravenously as a single bolus injection, typically in operating room or similar environments under close medical supervision. Potential for delayed unfavourable effects is low, sugammadex is eliminated rapidly (typical t½ approximately 2 h).

3.7.3. Additional considerations on the benefit-risk balance

Bridion is approved for reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults, whereas it is only approved for routine reversal of rocuronium induced blockade in paediatric patients aged 2 to 17 years. The MAH now proposed to extend the paediatric indication to all paediatric age groups (from birth to 17 years).

The MAH could, in the future, consider applying for broadening the indication in all paediatric patients (from birth to 17 years) to include routine reversal of also vecuronium induced blockade, if they consider the benefit-risk balance to be positive in this population. In such case all supporting data (including safety and efficacy) should be submitted accordingly in a separate variation application. An extrapolation framework could be also used for further justifications (Reflection paper on the use of extrapolation in the development of medicines for paediatrics; EMA/189724/2018).

3.8. Conclusions

The overall B/R of Bridion is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of paediatric patients from birth to less than 2 years of age with Bridion based on final results from paediatric study PN169 (MK-8616-P169); this is a Phase 4 double-blinded, randomized, active comparator-controlled clinical trial to study the efficacy, safety, and pharmacokinetics of sugammadex (MK-8616) for reversal of neuromuscular blockade in paediatric participants aged birth to <2 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.0 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to implement minor editorial corrections and to update the information intended for healthcare professionals (HCPs) at the end of the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package

Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Bridion-H-C-000885-II-0047'