Received: 3 August 2021 | Revised: 15 November 2021 | Accepted: 19 November 2021

DOI: 10.1111/pan.14370

Pediatric Anesthesia WILEY

RESEARCH REPORT

Sugammadex for reversal of neuromuscular blockade in pediatric patients: Results from a phase IV randomized study

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Funding information
Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Editor: Brian Anderson

Abstract

Background: Few randomized studies have assessed recovery from rocuronium- or vecuronium-induced moderate or deep neuromuscular blockade with sugammadex in pediatric participants.

Aim: To assess sugammadex for reversal of neuromuscular blockade in pediatric participants.

Methods: This was a randomized, phase IV, active comparator-controlled, double-blind study. Participants aged 2 to <17 years, under moderate or deep neuromuscular blockade, were administered sugammadex (2 or 4 mg/kg) or neostigmine (50 μg/kg; for moderate neuromuscular blockade only). Predefined adverse events of clinical interest, including clinically relevant bradycardia, hypersensitivity, and anaphylaxis, were monitored. The primary efficacy endpoint was time to recovery to a train-of-four ratio of ≥0.9 in participants receiving sugammadex 2 mg/kg versus neostigmine for reversal of moderate neuromuscular blockade, analyzed by analysis of variance adjusted for neuromuscular blocking agent and age.

Results: Of 288 randomized participants, 272 completed the study and 276 were included in the analyses. Clinically relevant bradycardia was experienced by 2.0%, 1.6%, and 5.9% of participants in the sugammadex 2 mg/kg, sugammadex 4 mg/kg, and neostigmine groups, respectively. No hypersensitivity or anaphylaxis events were observed. Recovery to a train-of-four ratio of ≥0.9 with sugammadex 2 mg/kg was faster than neostigmine (1.6 min, 95% CI 1.3 to 2.0 vs. 7.5 min, 95% CI 5.6 to 10.0; $p < .0001$) and was comparable to sugammadex 4 mg/kg (2.0 min, 95% CI 1.8 to 2.3).

Conclusions: Pediatric participants recovered from rocuronium- or vecuronium-induced moderate neuromuscular blockade significantly faster with sugammadex 2 mg/kg than with neostigmine. Time to reversal of deep neuromuscular blockade with sugammadex 4 mg/kg was consistent with that of moderate neuromuscular blockade reversal. No meaningful differences in clinically relevant bradycardia, hypersensitivity, or anaphylaxis were seen with sugammadex vs neostigmine. These results support the use of sugammadex for reversal of moderate and deep rocuronium- and vecuronium-induced neuromuscular blockade in patients aged 2 to <17 years.

Clinical Trial Registration: NCT03351608/EudraCT 2017-000692-92.

KEYWORDS
anesthesia, neuromuscular blockade, pediatric, Sugammadex

1 | INTRODUCTION

Sugammadex (Bridion®, Merck & Co., Inc., Kenilworth, NJ, USA), a modified cyclodextrin, acts via encapsulation to reverse neuromuscular blockade (NMB) induced by the commonly used aminosteroidal NMB agents rocuronium or vecuronium.[1,2] In adults, sugammadex provides rapid and predictable reversal of rocuronium- and vecuronium-induced moderate and deep NMB,[2–6] without directly interacting with cholinergic systems and thereby circumventing the cholinergic adverse events associated with cholinergic NMB reversal agents such as neostigmine/glycopyrrolate.

Reversal of NMB with sugammadex in pediatric patients was examined in a phase IIIa trial.[7] This study provided evidence that the pharmacokinetics, efficacy, and safety of sugammadex at doses of at least 2 mg/kg in children and adolescents were comparable to those in adults.[7] A meta-analysis assessed the efficacy and safety of sugammadex in ten relatively small (<100 participants) pediatric studies.[8] Most studies assessed sugammadex in the moderate NMB setting with limited information in the deep NMB setting and only assessed reversal of rocuronium-induced NMB, with little information on reversal of vecuronium-induced NMB.

The aim of the present study was to evaluate the pharmacokinetics, safety (especially with regard to cardiac arrhythmias given that in rare cases marked bradycardia has been reported in association with sugammadex-mediated reversal of NMB[9,10]), and efficacy of sugammadex for the reversal of moderate or deep rocuronium- or vecuronium-induced NMB in pediatric participants aged 2 to <17 years. The study was conducted in accordance with the Sponsor's commitments under the Pediatric Research Equity Act of the USA. The primary hypothesis was that sugammadex is superior to neostigmine in reversing moderate neuromuscular blockade as measured by time to recovery to a train-of-four (TOF) ratio of ≥0.9.

What is already known about this topic?

Studies conducted to date have suggested benefit of sugammadex for reversing neuromuscular blockade in children/adolescents, but the sample sizes have been relatively small. Furthermore, most studies assessed sugammadex in the moderate neuromuscular blockade setting and only assessed reversal of rocuronium-induced blockade.

What new information does this study adds

This study randomized a total of 288 pediatric participants aged 2 to <17 years to sugammadex 2 mg/kg, sugammadex 4 mg/kg, or neostigmine 50 μg/kg. Pediatric participants recovered from rocuronium- or vecuronium-induced moderate neuromuscular blockade faster with sugammadex 2 mg/kg than with neostigmine. Reversal of deep neuromuscular blockade with sugammadex 4 mg/kg was consistent with that of moderate neuromuscular blockade reversal.

2 | METHODS

2.1 | Participants

Participants included males and females aged 2 to <17 years (at study Visit 2) with an American Society of Anesthesiologists physical status of 1, 2, or 3 and with a planned procedure requiring moderate or deep NMB with rocuronium or vecuronium. Those with neuromuscular disorders that could have affected NMB or severe renal disease were not eligible. All participants and/or a parent or legal guardian provided written, informed consent/assent for the trial. Participant confidentiality was maintained throughout the study. The study was conducted in accordance with principles of Good Clinical Practice in neuromuscular research[11] and was approved by the appropriate institutional review boards and regulatory agencies.

2.2 | Study design

This was a phase IV, double-blind, randomized, multicenter, in-clinic, study (MK-8616-089; NCT03351608) conducted in eight countries from February 2018 to January 2020. The study comprised four visits: screening, preanesthetic visit, postanesthetic visit, and follow-up visit (14 days poststudy drug treatment administration).

The study was conducted in two parts:

Part A evaluated the pharmacokinetics, safety, and tolerability of sugammadex 2 mg/kg and 4 mg/kg for reversal of moderate or deep NMB, respectively, induced by rocuronium or vecuronium, to confirm that these doses (ie, the recommended doses in adults) would be appropriate for evaluation in Part B.

Part B was active comparator-controlled and evaluated the safety and efficacy of sugammadex for reversal of moderate or deep NMB. For Part B, which was performed after an interim analysis of Part A, participants were randomized in a 1:1:5 ratio (overall) to one of three intervention groups: 1) moderate blockade and reversal with sugammadex 2 mg/kg, 2) moderate blockade and reversal with neostigmine methylsulfate 50 μg/kg plus either glycopyrrolate 5–15 μg/kg or atropine sulfate 10–30 μg/kg (active control), or 3) deep blockade and reversal with sugammadex 4 mg/kg. Enrollment was enriched in the

sugammadex 4 mg/kg group to address whether the highest routine sugammadex dose was associated with bradycardia. Randomization in Part B was also stratified by age group (2 to <6 years, 6 to <12 years, and 12 to <17 years) and by NMB with either rocuronium or vecuronium. Neostigmine is not indicated for the reversal of deep NMB, and no other comparator exists for sugammadex 4 mg/kg in the reversal of deep NMB. Rocuronium or vecuronium was dosed per prescribing information. Additional doses of the assigned NMB agent could be administered as clinically necessary for the duration of the surgery to target maintenance at the assigned depth of block. Participants were assigned treatment using computer-generated randomized allocation schedules. The site pharmacist (or delegate) was unblinded to study treatment assignments to prepare study treatment. Other site staff involved in the study were blinded to treatment. Study treatment was provided to site staff in the operating room in masked syringe(s) to ensure that the contents were not revealed.

Quantitative neuromuscular transmission monitoring (NMTM) was performed for all participants. After induction of anesthesia, NMTM was started before administration of the NMB agent and continued until either the participant reached the endpoint of recovery to TOF ratio ≥0.9, or for at least 30 min following study drug administration. Neuromuscular monitoring was performed with the TOF-watch SX® (Organon Ireland Ltd., Dublin, Ireland) at the adductor pollicis muscle using calibrated acceleromyography (CAL II method) with supramaximal electrical stimulation of the ulnar nerve in line with guidance for pharmacodynamic studies of NMB agents.[11] After the last dose of NMB agent, sugammadex or neostigmine was administered as a single bolus IV injection over 10 s within 2 min of the detection of reappearance of second twitch (T_2) for participants randomized to moderate blockade or at least 1–2 post-tetanic counts for participants randomized to deep blockade. All relevant study staff were trained on the NMTM protocol to reduce inter-assessor variability.

2.3 | Pharmacokinetics

In Part A, blood samples were collected, via an intravenous catheter not used for study drug administration, at ~2, 15, 30, 60, 300, and 600 min following sugammadex administration to support characterization of pharmacokinetic parameters. Sugammadex pharmacokinetic parameters including area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), volume of distribution at steady state (V_{ss}), clearance (Cl), and half-life ($t_{½}$) were derived in 3 age subgroups (2 to <6 years, 6 to <12 years, and 12 to <17 years) using a noncompartmental approach in Phoenix™ (WinNonlin® 6.4).

2.4 | Safety

Safety assessments were undertaken in parts A and B of the study and involved routine hematology and laboratory findings, vital signs, and monitoring of adverse events, including recurrence of NMB. Continuous electrocardiographic monitoring was initiated 5 min before the start of study drug administration and continued until at least 30 min after study drug administration. A directed physical examination was conducted by a blinded safety assessor at the postanesthetic visit. Safety data were periodically reviewed by an external Data Monitoring Committee.

Two main categories of safety events were considered to be of special interest in this population: hypersensitivity/anaphylaxis and clinically relevant bradycardia. Potential events of hypersensitivity and anaphylaxis were identified and referred to an external independent committee for adjudication. Events were adjudicated according to the Sampson criteria, including acute onset of an illness involving the skin/mucosal tissue and airway compromise, reduced blood pressure or associated signs, or hypotension after exposure to a known allergen.[12] Bradycardia was defined in three ways. Clinically relevant bradycardia was defined as bradycardia necessitating intervention as judged by the site investigator. Treatment-emergent bradycardia was defined as heart rate below the 1st percentile for age[13,14] and ≥20% less than the patient's predose baseline heart rate value, sustained for at least 30 seconds, and occurring after the administration of study treatment. Finally, treatment-emergent relative bradycardia was defined as any reduction of ≥20% below the participant's predose baseline heart rate value.

2.5 | Efficacy

In Part B, the primary efficacy endpoint was time from the start of administration of study drug to recovery to a TOF ratio of ≥0.9. Secondary endpoints were time to recovery to a TOF ratio of ≥0.8 and time to recovery to a TOF ratio of ≥0.7. Non-normalized TOF ratios were reported. Delayed recovery was also assessed as an exploratory endpoint and was defined as any observation of the time to recovery to TOF ratio to ≥0.9 (original scale) that was >3 times the geometric mean recovery time of the TOF ratio to ≥0.9 within each treatment group.

2.6 | Statistical analysis

Safety analyses were performed in the all-participants-as-treated population, defined as all randomized participants who received ≥1 dose of study drug in Parts A and B. Participants were included in the treatment group corresponding to the study treatment they received. Safety was analyzed using a tiered approach. Tier 1 safety endpoints (adjudicated hypersensitivity and/or anaphylaxis and clinically relevant bradycardia) were subject to inferential testing for statistical significance. For between-group comparisons for Tier 1 events, *p* values and 95% confidence intervals (CIs) were calculated. Point estimates and 95% CIs were assessed for Tier 2 parameters, defined as drug-induced liver injury, events with at least 4 participants in any treatment group that exhibited the event, treatment-emergent bradycardia, and summary clinical and laboratory adverse event categories. Tier 3 parameters (all other adverse events and predefined

limits of change) were evaluated by point estimates only. Analyses for Tier 1 and Tier 2 endpoints were performed using the Miettinen and Nurminen method,[15] stratified by NMB agent and age group.

Efficacy analyses were carried out for the all-patients-treated population, defined as all randomized participants who received ≥1 dose of study drug. Participants were included in the treatment group to which they were randomized (in practice, this was the same as the treatment to which they were randomized for all participants). Efficacy was evaluated by comparing sugammadex to neostigmine in the setting of moderate NMB, using log-transformed time-to-recovery values via analysis of variance (ANOVA) with SAS software Version 9.4, adjusting for NMB agent and age. Time to recovery was also assessed in participants reversed at deep NMB.

2.7 | Power

The planned sample size of 238 participants was based on the number of participants required to obtain safety information for each level of NMB, as specified by the Sponsor's commitments under the Pediatric Research Equity Act of the USA. For the efficacy analysis, the planned sample size was 30 participants per treatment arm (sugammadex 2mg/kg and neostigmine) in the setting of moderate NMB. For the primary efficacy endpoint of time to recovery to TOF ≥0.9, the trial had >99% power to demonstrate that sugammadex 2mg/kg is superior to neostigmine at an overall two-sided 5% alpha-level, based on the assumption of similar efficacy in the pediatric population to the previously studied adult population and assuming 10% of participants with nonevaluable data. An interim analysis was conducted prior to Part B enrollment to confirm the doses that would be used in Part B.

3 | RESULTS

3.1 | Participant Flow

Twenty-eight sites across eight countries screened a total of 299 participants and of these 288 were randomized (Figure 1). Of those randomized, 276 received treatment and 272 completed the study. Four participants who received treatment were lost to follow-up and did not complete the final study visit. Overall, 51 participants received sugammadex 2 mg/kg (18 from Part A, 33 from Part B), 191 received sugammadex 4 mg/kg (22 from Part A, 169 from Part B), and 34 received neostigmine 50 μg/kg +glycopyrrolate (mean dose = 10 μg/kg) or atropine (mean dose = 20 μg/kg) (Figure 1). In the 276 participants who were treated, the NMB agent was rocuronium in 180 (65.2%) and vecuronium in 96 (34.8%).

3.2 | Baseline characteristics

Participant baseline characteristics are shown in Table 1. The mean (SD) age of treated participants was 7.9 (4.4) years. Most were white (89.5%) and male (55.4%). Baseline characteristics were similar among the intervention groups in each study part.

3.3 | Pharmacokinetics (Part A)

A total of 40 participants were included in the pharmacokinetic analysis. Pharmacokinetic parameters in each of the 3 age groups are shown in Table 2. Sugammadex pharmacokinetics for ages 6 to <17 years were comparable to adults receiving equivalent

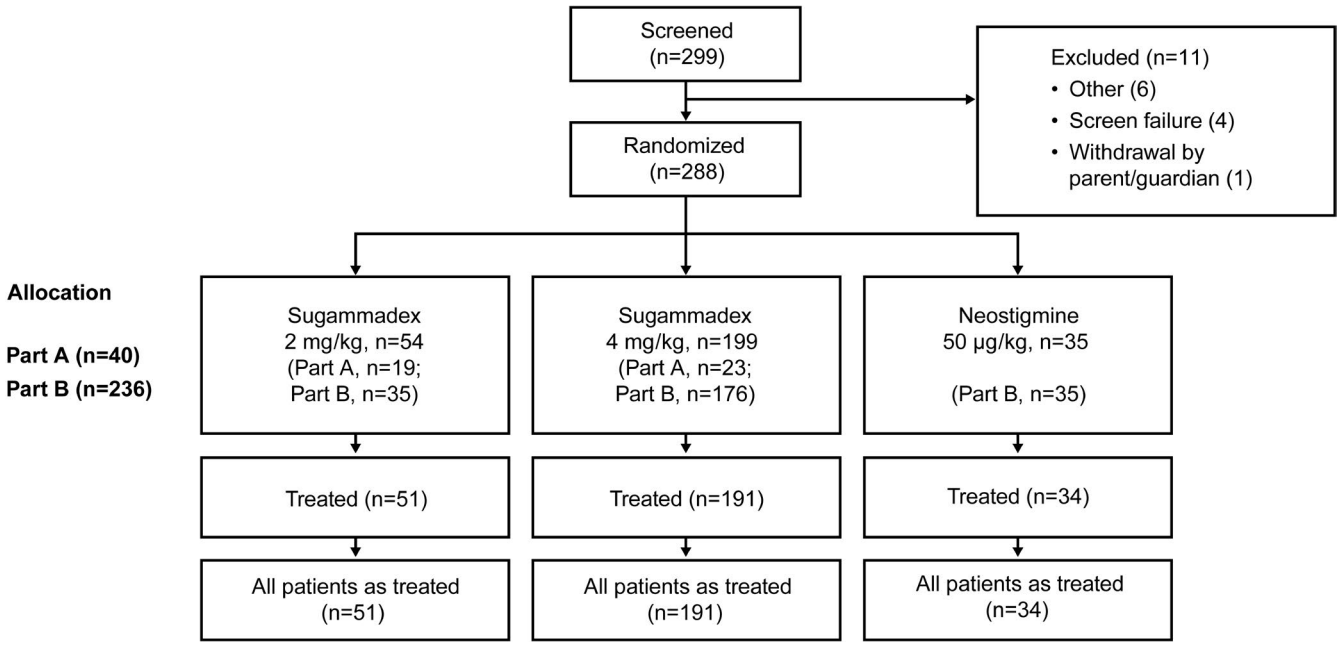

FIGURE 1 Disposition of participants

sugammadex doses (comparison based on data on file). Exposures (C_{max} and AUC) were 25–40% lower in the 2 to <6 years age group; however, the differences in the youngest children, taking into account also the tolerability and efficacy of sugammadex in this age group, were not considered clinically relevant. Based on the pharmacokinetic, safety, and efficacy profile of sugammadex in Part A, doses of 2 and 4 mg/kg, for reversal of moderate and deep blockade, respectively, were considered appropriate for evaluation in all pediatric age groups from 2 to <17 years in Part B.

3.4 | Safety (Parts A and B)

Overall, sugammadex was well tolerated, regardless of the depth of NMB. There were no deaths and no serious adverse events considered by the investigators to be related to the study drug. Most adverse events were rated as mild or moderate in intensity by the investigator or participant and ≤6% of participants in each group reported serious adverse events (Table 3). The most frequently reported adverse events were procedural pain (58.1%–70.6%) and vomiting (5.9%–10.5%) with no clinically meaningful differences across treatment groups. Drug-related adverse events in the sugammadex 2 mg/kg group were comparable to the neostigmine group. The most frequently reported drug-related adverse event was bradycardia (experienced by three (3/51; 5.9%), two (2/191; 1.0%), and two (2/34; 5.9%) participants in the sugammadex 2 mg/kg, 4 mg/kg, and neostigmine groups, respectively). Across age groups, the incidence of events of special interest was low and no adjudicated hypersensitivity, anaphylaxis, or drug-induced liver injury events were reported. One (1/51; 2.0%), three (3/191; 1.6%), and two (2/34; 5.9%) participants had a clinically relevant bradycardia in the sugammadex 2 mg/kg, 4 mg/kg, and neostigmine groups, respectively; the differences in percentages between sugammadex groups and neostigmine were not significant (2 mg/kg difference = −3.9, 95% CI −18.4 to 4.8, $p = .346$; 4 mg/kg difference = −3.9, 95% CI −17.5 to 1.3, $p = .152$). Treatment-emergent bradycardia was lowest in participants on sugammadex 2 mg/kg (2/51; 3.9%), followed by sugammadex 4 mg/kg (10/191; 5.2%), and neostigmine (4/34; 11.8%).

3.5 | Efficacy (Part B)

Geometric mean time to recovery to a TOF ratio of ≥0.9 was significantly faster ($p < .0001$) with sugammadex 2 mg/kg (1.6 min, 95% CI 1.3 to 2.0) than with neostigmine (7.5 min, 95% CI 5.6 to 10.0) in the setting of moderate NMB in Part B (Table 4). The ratio

TABLE 1 Baseline characteristics by treatment group (parts A and B)

Characteristic	Sugammadex 2 mg/kg *N* = 51	Sugammadex 4 mg/kg *N* = 191	Neostigmine + (Glycopyrrolate or Atropine) *N* = 34
Age, years, mean (SD)	7.7 (4.6)	7.8 (4.4)	8.5 (4.3)
2 to <6 years, *n* (%)	22 (43.1)	80 (41.9)	12 (35.3)
6 to <12 years, *n* (%)	15 (29.4)	64 (33.5)	13 (38.2)
12 to <17 years, n (%)	14 (27.5)	47 (24.6)	9 (26.5)
Sex, male, *n* (%)	31 (60.8)	104 (54.5)	18 (52.9)
BMI, kg/m^2, mean (SD)	18.5 (4.2)	18.3 (4.9)	18.7 (4.4)
Weight, kg, mean (SD)	34.1 (21.4)	33.7 (21.6)	35.4 (21.8)

Abbreviations: BMI, body mass index (not age adjusted); SD, standard deviation.

TABLE 2 Geometric mean (% geometric coefficient of variation) sugammadex pharmacokinetic parameters in pediatric participants (part A)

Age Group (years)	Dose (mg/kg)	N	$AUC_{0\text{-inf}}$ (h*µg/ml)	C_{max} (µg/ml)	CL (L/hr)	V_{ss} (L)	$t_{1/2}$ (hr)
2 to <6	2	9	14.1 (19.4)	17.5 (33.1)	2.30 (21.4)	3.58 (21.3)	1.23 (17.4)
	4	10[a]	26.9 (18.5)	47.1 (22.1)	2.26 (29.4)	3.10 (27.7)	1.23 (25.2)
6 to <12	2	5	18.8 (27.4)	32.2 (15.6)	3.58 (26.2)	5.16 (31.4)	1.29 (25.1)
	4	6	38.2 (73.0)	51.6 (69.2)	3.43 (105)	6.24 (73.9)	1.66 (32.5)
12 to <17	2	4	27.6 (58.0)	41.3 (85.8)	4.68 (52.5)	7.20 (32.8)	1.49 (23.2)
	4	6	49.2 (20.1)	61.9 (13.5)	5.69 (24.1)	9.88 (27.7)	1.49 (19.2)

Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum concentration; $t_{1/2}$, half-life; V_{ss}, apparent volume of distribution at steady state.

[a]$N = 10$ for C_{max}, $N = 8$ for other parameters.

TABLE 3 Summary of adverse events (parts A and B, up to 7 days post-treatment)

Participants with adverse events	Sugammadex 2 mg/kg *N* = 51	Sugammadex 4 mg/kg *N* = 191	Neostigmine + (Glycopyrrolate or Atropine) *N* = 34
One or more events	40 (78.4)	143 (74.9)	33 (97.1)
One or more study drug-related events	4 (7.8)	5 (2.6)	4 (11.8)
One or more serious events	3 (5.9)	3 (1.6)	2 (5.9)
One or more drug-related serious events	0	0	0
Deaths	0	0	0
Selected events of special interest			
Treatment-emergent relative bradycardia[a]	8 (15.7)	29 (15.2)	14 (41.2)
Treatment-emergent bradycardia[a]	2 (3.9)	10 (5.2)	4 (11.8)
Clinically relevant bradycardia[a]	1 (2.0)	3 (1.6)	2 (5.9)
Hypersensitivity	0	0	0
Anaphylaxis	0	0	0
Drug-induced liver injury	0	0	0
Events occurring in ≥5% of any treatment group			
Procedural pain	30 (58.8)	111 (58.1)	24 (70.6)
Vomiting	4 (7.8)	20 (10.5)	2 (5.9)
Bradycardia	3 (5.9)	12 (6.3)	3 (8.8)
Procedural nausea	4 (7.8)	9 (4.7)	0
Nausea	1 (2.0)	12 (6.3)	2 (5.9)
Incision site pain	3 (5.9)	6 (3.1)	1 (2.9)
Procedural vomiting	3 (5.9)	5 (2.6)	1 (2.9)
Sinus bradycardia	2 (3.9)	1 (0.5)	2 (5.9)
Pyrexia	0	2 (1.0)	2 (5.9)
Body temperature increased	0	1 (0.5)	2 (5.9)
Muscle spasms	0	0	2 (5.9)

[a]Up to 45 min post-treatment. Other adverse events are up to 7 days post-treatment.

of geometric means was 0.22 (95% CI 0.16 to 0.32). Geometric mean time to recovery of the TOF ratio to ≥0.9 following administration of sugammadex 2 mg/kg was 1.5 min (95% CI 1.1 to 2.1) for rocuronium-induced NMB and 1.8 min (95% CI 1.4–2.4) for vecuronium-induced NMB. Kaplan-Meier estimates demonstrated 90.9% (30/33) of participants receiving sugammadex 2 mg/kg for reversal of moderate rocuronium- or vecuronium-induced NMB recovered to a TOF ratio of ≥0.9 within 3 min of administration compared with 8.8% (3/34) of participants in the neostigmine group (Figure 2). Geometric mean times to recovery of the TOF ratios to ≥0.7 and ≥0.8 were also faster with sugammadex compared with neostigmine (Table 4; ratios of the geometric means were 0.3, 95% CI 0.22 to 0.41 and 0.26, 95% CI 0.19 to 0.37, respectively, both nominal $p < .001$ vs neostigmine, not controlled for multiplicity). Results were similar across all age groups and across both NMB agents, as well as various other subgroups (Figure 3). In those receiving sugammadex 4 mg/kg for reversal of deep rocuronium- or vecuronium-induced NMB, geometric mean time from start of sugammadex administration to recovery to TOF ratio of ≥0.9 was 2.0 min (95% CI 1.8 to 2.3; Table 4). The proportion of participants with delayed recovery was <9% (experienced by 1/51 [2.0%], 14/191 [7.3%], and 3/34 [8.8%] in the sugammadex 2 mg/kg, 4 mg/kg, and neostigmine groups, respectively). Recovery times in these patients were not affected by age group, sex, or site. There was no evidence of recurrence of NMB in pediatric participants in this study.

4 | DISCUSSION

In this study, we evaluated sugammadex for reversing rocuronium- or vecuronium-induced moderate or deep NMB in pediatric participants aged 2 to <17 years. Part A of the study determined that sugammadex doses of 2 and 4 mg/kg (ie, the doses recommended in adults) were appropriate for further evaluation in Part B. Sugammadex doses of 2 mg/kg and 4 mg/kg were well tolerated in pediatric participants in this study. No hypersensitivity or anaphylaxis was observed. The percentages of participants with

TABLE 4 Summary of the geometric mean time in min (95% CI) from start of administration of sugammadex or neostigmine to recovery of the TOF ratio (by age group and dose group for TOF ratio ≥0.9), and number of participants with delayed recovery

	Sugammadex 2 mg/kg *N* = 51	Neostigmine + (Glycopyrrolate or Atropine) *N* = 34	Ratio of geometric mean, *p* Value[a]	Sugammadex 4 mg/kg (Part A and B) *N* = 191
TOF ratio ≥ 0.9	1.6 (1.3, 2.0)[a] *n* = 33	7.5 (5.6, 10.0)[a] *n* = 34	0.22 (0.16, 0.32), *p* < .0001	2.0 (1.8, 2.3)
2 to <6 years	2.0 (1.3, 3.2)[a] *n* = 13	5.0 (3.2, 7.8)[a] *n* = 12	0.40 (0.21, 0.74), *p* < .0053	–
6 to <12 years	1.4 (1.0, 2.0)[a] *n* = 10	7.0 (4.3, 11.2)[a] *n* = 13	0.20 (0.11, 0.37), *p* < .0001	–
12 to <17 years	1.5 (1.1, 1.9)[a] *n* = 10	14.1 (7.7, 26.0)[a] *n* = 9	0.10 (0.06, 0.19), *p* < .0001	–
TOF ratio ≥0.8	1.3 (1.1, 1.6)[a] *n* = 33	5.0 (3.8, 6.7)[a] *n* = 34	0.26 (0.19, 0.37), *p* < .0001	1.5 (1.3, 1.7)
TOF ratio ≥0.7	1.1 (0.9, 1.3)[a] *n* = 33	3.7 (2.9, 4.8)[a] *n* = 34	0.30 (0.22, 0.41), *p* < .0001	1.3 (1.1, 1.4)
Delayed recovery[b]	1 (2.0)	3 (8.8)	–	14 (7.3)

Abbreviations: CI, confidence interval; TOF, train of four.

[a]Pairwise comparisons are between sugammadex 2 mg/kg and neostigmine. No comparator for sugammadex 4 mg/kg.

[b]Part B. *n* = number of participants in each group.

[c]Values are number (%) of participants. Delayed recovery = any observation of the TOF ratio to ≥0.9 (in the original scale) that is >3 times the geometric mean recovery time of the TOF ratio to ≥0.9 within each treatment group.

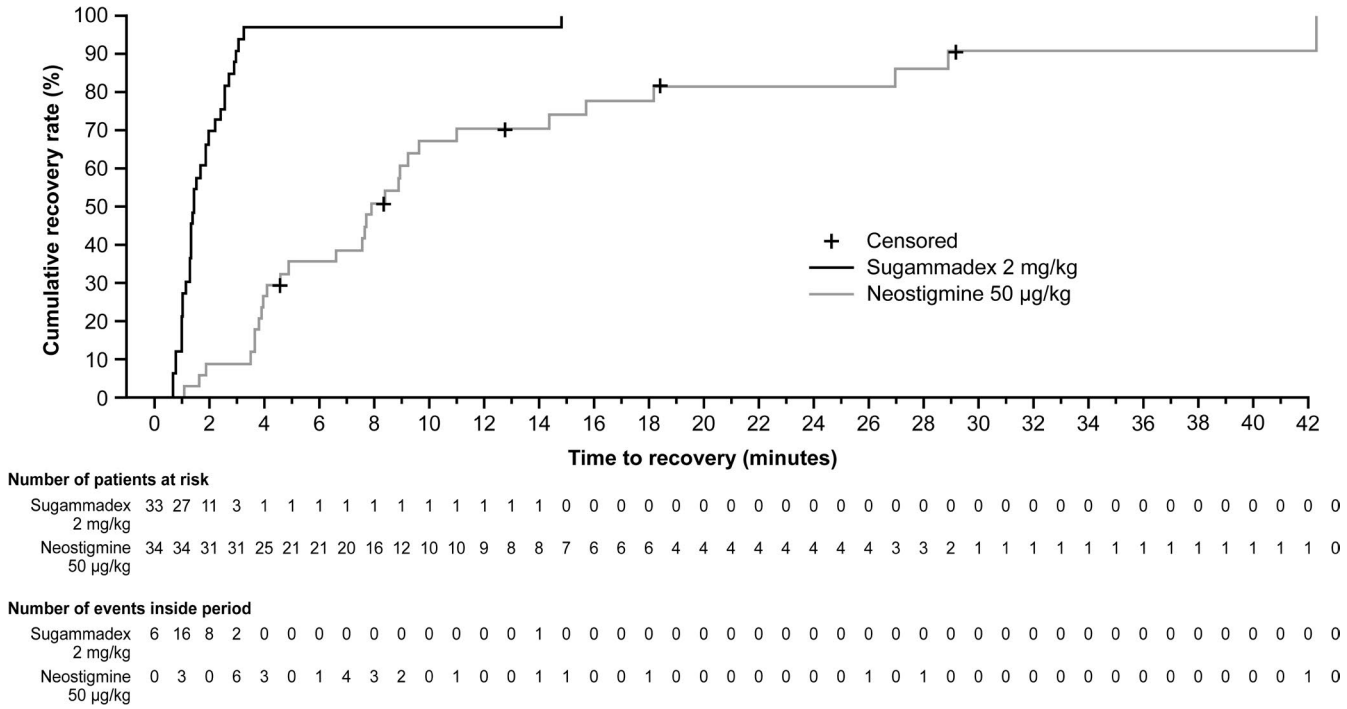

FIGURE 2 Cumulative percentage of participants achieving TOF ratio ≥0.9 versus time. A given participant's results were censored if monitoring terminated or data became unreliable. TOF, train of four

clinically relevant bradycardia, serious adverse events, or events of clinical interest were generally balanced across all treatment groups. No sugammadex dose-dependent effects on the rates of bradycardia were observed, despite enrichment of participant allocation to the sugammadex 4 mg/kg treatment group by a factor of five to facilitate detection of any potential safety concerns and to provide adequate data in the deep block setting. Incidence rates of bradycardia in the sugammadex groups were comparable to or numerically lower than those observed in the neostigmine group.

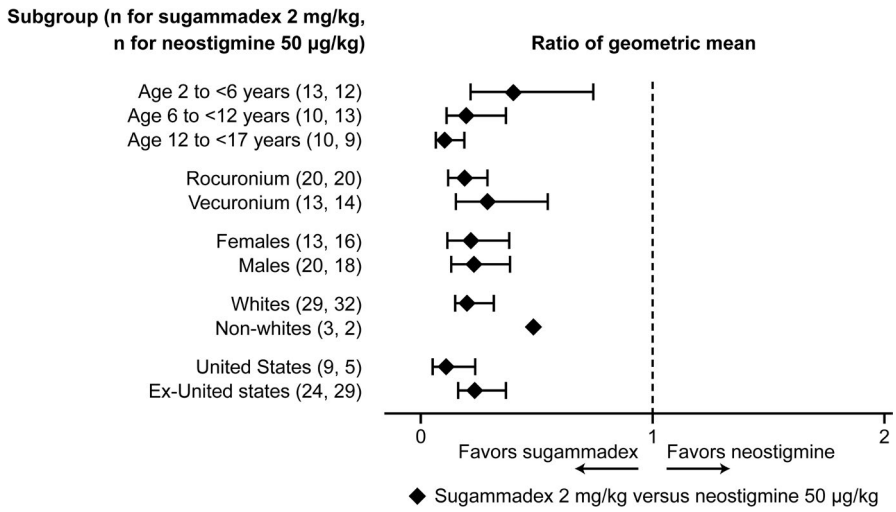

FIGURE 3 Recovery time to TOF ratio ≥0.9 for subgroups. Point estimates and 95% CI of the ratio of geometric mean for sugammadex versus neostigmine are presented for the subgroups (n [sugammadex, neostigmine]). CI, confidence interval; TOF, train of four

These safety findings are consistent with previous studies in pediatric patients.[7,8] A recent study by Alsuhebani et al.[16] reported a bradycardia incidence of 8% at a median of 2 min following the administration of sugammadex in a pediatric patient population (<18 years old). Alsuhebani et al. attributed their bradycardia rate at least partially to the presence of cardiac comorbidities in their cohort and also an association with male sex. A retrospective analysis of pediatric patient charts demonstrated fewer bradycardia events occurred with sugammadex than with neostigmine.[17] Similarly, the incidences of treatment-emergent bradycardia and relative bradycardia in this study were numerically lower for both sugammadex treatment groups versus neostigmine. The findings in pediatric patients are also generally consistent with results from a meta-analysis of over 4000 adult patients that found a significantly reduced risk of bradycardia with sugammadex compared with neostigmine.[18]

With regard to efficacy, sugammadex 2 mg/kg rapidly reversed moderate rocuronium- and vecuronium-induced NMB in pediatric participants with rates of reversal significantly faster than with neostigmine and comparable to those seen in adults.[2] Within 3 min, over 90% of the pediatric population dosed with sugammadex 2 mg/kg recovered to a TOF ratio of ≥0.9. In comparison, over 85% of sugammadex-treated adults for reversal of moderate NMB recovered to a TOF ratio of 0.9 within 5 min.[2] Moreover, time to reversal of deep rocuronium- or vecuronium-induced NMB with sugammadex 4 mg/kg was consistent with that observed for moderate NMB reversal in these pediatric participants with rates of recovery comparable to those seen in adults.[2] Despite the lack of a comparator for sugammadex 4 mg/kg, our study provides valuable new information on the clinical profile of this dose in the reversal of deep rocuronium- and vecuronium-induced NMB in pediatric patients.

Potential limitations of this study include that non-normalized TOF ratios were reported; however, a rigorous setup regimen consistent with Fuchs-Buder et al. (2007)[11] was implemented, such that normalizing to baseline before NMB was considered unnecessary in order for the TOF results to be reliable and comparable to other studies supporting sugammadex marketing applications. In addition, while the number of participants receiving sugammadex in this study (n = 202) was deemed sufficient for detection of an unanticipated increase in risk for hypersensitivity/anaphylaxis events in this population, the study was not powered for, nor intended to, definitively characterize the incidence, unlike other studies specifically designed to address this risk.[19] Of note, hypersensitivity/anaphylaxis event rates suggested by the overall pooled clinical trial experience and in postmarketing pharmacovigilance suggest it would not be feasible to prospectively address this question in a randomized clinical trial setting.[20]

Overall, the current findings support the use of sugammadex in reversing both moderate and deep levels of NMB in pediatric patients age 2 to <17 years. The time to recovery from NMB from either rocuronium or vecuronium was rapid and complete, unlike the distribution of recovery seen with comparator neostigmine, and consistent with efficacy results from previous trials in adults.[2] In addition, the safety profile observed was comparable to that of adults. Our findings are potentially important considering the possible risks associated with delayed recovery following administration of NMB agents, and subsequent risk of postoperative pulmonary events. In adult patients, sugammadex has been associated with a 30% reduced risk of postoperative pulmonary complications such as pneumonia and respiratory failure compared with neostigmine.[21] Further studies are necessary to determine the frequency of postoperative pulmonary complications in children and whether sugammadex might reduce their risk in this age group.

5 | CONCLUSIONS

Pediatric participants recovered from rocuronium- or vecuronium-induced moderate NMB significantly faster with sugammadex 2 mg/kg than with neostigmine. Sugammadex 2 mg/kg and 4 mg/kg were well tolerated by pediatric participants aged 2 to <17 years when used to reverse moderate or deep levels of rocuronium- or vecuronium-induced NMB. The rates of adverse events were generally similar across treatment groups, and there were no meaningful differences in clinically relevant bradycardia, hypersensitivity,

or anaphylaxis with sugammadex versus neostigmine. These results support the use of sugammadex for reversing rocuronium- or vecuronium-induced moderate and deep NMB in pediatric patients aged 2 to <17 years. Additional studies are being performed to evaluate the clinical profile of sugammadex for reversing NMB in infants under 2 years [ClinicalTrials.gov NCT03909165, NCT03728543].

ACKNOWLEDGMENTS

The authors thank the participants and their families. The following investigators took part in this study: Erica Sivak; Daniela Damian (Pittsburgh, PA), Gregory B. Hammer (Stanford, CA), Richard F. Kaplan (Washington, DC), Scott Siegel (New Brunswick, NJ), Shobha Malviya (Ann Arbor, MI), Francis X. McGowan (Philadelphia, PA), Brad Taicher (Durham, NC), Abhishek Karnwal (Los Angeles, CA), Alyssa Brzenski (San Diego, CA), Maria Elisabeth Matuszczak (Houston, TX), Pavithra Ranganathan Ellison (Morgantown, WV), all of the USA, and Walter Klimscha (Vienna, Austria), Vera Saldien (Antwerp, Belgium), An Teunkens (Leuven, Beligum), Torsten Lauritsen (Copenhagen, Denmark), Manfred Blobner (Munich, Germany), Friedrich Puehringer (Reutlingen, Germany), Ulrich Goebel (Munich, Germany), Alexander Reich (Warendorf, Germany), Michael Przemeck (Hannover, Germany), Hinnerk Wulf (Marburg, Germany), Javier Pueyo Villoslada (Pamplona, Spain), Gloria Veiga Ruiz (Cartegena, Spain), Ana Belen Ortega Floria (Madrid, Spain), Ernesto Martinez Garcia (Ankara, Turkey), Ozlem Selvi Can (Ankara, Turkey), Fatis Altindas (Istanbul, Turkey), Hulya Bilgin (Bursa, Turkey), Kamil Darcin (Istanbul, Turkey), Tomi Taivainen (Helsinki, Finland). We would also like to thank Liliane Noble, John Lombard, Angela Gee, Molly Watkins, Monica Martinho, and Lata Maganti of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, for their contributions to the study. Medical writing support, including assisting authors with development of the draft, was provided by Laila Guzadhur, PhD and editorial support was provided by Valerie Moss, PhD, CMPP both of Scion, London, UK. This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Additional editorial support was provided by Christopher Lines, PhD of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. The Sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors. At the time this trial was conducted, pediatric use of sugammadex for reversal of moderate block induced by rocuronium was approved in regions outside of the USA.

CONFLICTS OF INTEREST

TV, AW, MS, RW, and WJH are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Kenilworth, NJ, USA. MDeA was an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA at the time the study was conducted. VS and GH declare no competing interests.

AUTHOR CONTRIBUTIONS

TV, AW, MDeA, MS, RW, and WJH substantially contributed to the conception, design, or planning of the study. TV, AW, VS, and GH substantially contributed to the acquisition of data. TV, AW, MDeA, MS, RW, and GH substantially contributed to the analysis of the data. TV, AW, MDeA, MS, VS, GH, RW, and WJH substantially contributed to interpretation of the results. TV, VS, and GH substantially contributed to drafting of the manuscript. All authors reviewed the manuscript for important intellectual content and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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How to cite this article: Voss T, Wang A, DeAngelis M, et al. Sugammadex for reversal of neuromuscular blockade in pediatric patients: Results from a phase IV randomized study. *Pediatr Anesth*. 2022;32:436–445. doi:10.1111/pan.14370