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ARTICLE

Pharmacokinetics of Sugammadex Dosed by Actual and Ideal Body Weight in Patients With Morbid Obesity Undergoing Surgery

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This analysis of a published study (NCT03346070) evaluated the pharmacokinetics (PKs) of sugammadex dosed by actual body weight (ABW) or ideal body weight (IBW) for reversal of moderate or deep neuromuscular block (M-NMB or D-NMB) in adults with morbid obesity. Adults with body mass index ≥ 40 kg/m^2, ABW ≥ 100 kg, and American Society of Anesthesiologists (ASA) Class 3 were stratified by NMB agent (rocuronium or vecuronium) and randomized 1:1:1:1:1 to (i) M-NMB, sugammadex 2 mg/kg ABW; (ii) M-NMB, sugammadex 2 mg/kg IBW; (iii) M-NMB, neostigmine 5 mg + glycopyrrolate 1 mg; (iv) D-NMB, sugammadex 4 mg/kg ABW; and (v) D-NMB, sugammadex 4 mg/kg IBW. Plasma samples for sugammadex quantification were collected predose, 2, 5, 15, 60, and 120 minutes, and 4, 6 hours postdose. Natural log PK parameters were analyzed using linear fixed effect model with treatment, mode (ABW and IBW), and mode by treatment interaction as fixed terms. The sugammadex PK profile showed rapid distribution followed by monophasic decline consistent with a two-compartment model examined by dose and mode. Absolute sugammadex exposures were ~ 50% higher in the ABW vs. IBW group; dose-independent parameters (clearance and volume of distribution) and terminal half-life remained constant. Sugammadex PK parameter values increased in dose-dependent, linear manner following dosing by ABW or IBW, such that PK continues to be predictive across the clinical dose range. In conjunction with previously published results showing faster recovery with ABW vs. IBW dosing across NMB agent and depth of NMB, these PK findings continue to support dosing by ABW in patients with morbid obesity irrespective of depth of NMB.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Sugammadex reverses neuromuscular blockade (NMB) induced by the NMB agents (NMBAs) rocuronium and vecuronium. The development program for sugammadex utilized dosing by actual body weight (ABW) to mirror dosing of rocuronium/vecuronium. As with many drugs, the appropriate weight-based correction scheme remains unexplored in patients with morbid obesity and therefore this population may not be optimally dosed.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This analysis of a multicenter, randomized, double blind trial evaluated the pharmacokinetics (PKs) of single dose sugammadex (2 or 4 mg/kg) dosed by either ABW or ideal body weight for the reversal of rocuronium-induced or vecuronium-induced moderate or deep NMB in adults with morbid obesity.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ No clinically relevant differences in PK parameters were observed between patients with obesity and the general population when dosed by ABW.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ The current PK analysis and efficacy/safety results (reported elsewhere) continues to support ABW-based sugammadex dosing in adults with morbid obesity irrespective of the depth of NMB (moderate or deep) and NMBA used (rocuronium or vecuronium).

Neuromuscular blocking agents (NMBAs) are potent muscle relaxants frequently used during anesthesia to facilitate tracheal intubation, artificial ventilation, and other surgical procedures. Sugammadex (Bridion; Merck, Kenilworth, NJ) is a modified gamma-cyclodextrin administered at the end of surgical procedures to reverse paralysis induced by the steroidal NMBAs rocuronium and vecuronium.[1] Sugammadex achieves reversal of neuromuscular blocking (NMB) by tightly encapsulating unbound rocuronium or vecuronium molecules, thereby preventing their biological

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action at the neuromuscular junction (NMJ) and restoring muscle function.[1,2] Use of sugammadex for NMB reversal circumvents the undesired side effects of anticholinesterases and their accompanying antimuscarinic reversal drugs.[3–6] When used for routine reversal, doses of 2 and 4 mg/kg are recommended for the reversal of moderate and deep NMB (M-NMB and D-NMB), respectively.[7] In previous studies, sugammadex pharmacokinetics (PKs) were demonstrated to be linear over doses of 0.1 to 96 mg/kg.[8–10] The majority of an intravenously administered dose of sugammadex is renally eliminated unchanged with a clearance approximating the glomerular filtration rate.[11] Renal function is the single most important predictor of sugammadex PK; no clinically relevant effects of age, sex, race, and body mass index (BMI) have been observed.[12,13]

Obesity rates are increasing, with > 13% of the adult population worldwide currently classified as obese.[14] A patient with a BMI of 20–25 kg/m^2 is considered normal weight; 26–29 kg/m^2 overweight; 30–39 kg/m^2 obese, and ≥ 40 mg/m^2 morbidly obese.[15] The global rise in the incidence of obesity has significantly impacted the practice of medicine, including management of anesthesia in surgical patients.[16,17] Specific concerns associated with patients who are overweight and obese range from airway management difficulties, alterations in respiratory physiology, accidental awareness or delayed reversal during general anesthesia, and heightened peri-operative and post-operative risks due to comorbid diseases.[18,19] Due to obesity, changes in regional blood flow and the movement of drugs between body compartments also may impact the PKs and pharmacodynamics (PDs) of anesthetic agents.[20,21]

Clinically severe or morbid obesity creates additional challenges for anesthesia management.[22,23] The physiological and anthropometric changes associated with morbid obesity result not only in increased anatomic difficulties of access for both the surgeon and anesthesiologist but also have the potential to alter the PK and PD properties of drugs. Excess neck and pharyngeal adipose mass can further negatively affect both airway patency and lung function during surgical procedures as well as increase the risk of respiratory conditions postoperatively. Individuals with morbid obesity also have an increase in fat and lean body weight (LBW) when compared with normal weight individuals of similar age, height, and sex, which may account for as much as 20–40% of the excess total body weight and therefore markedly affect the apparent volume of distribution of some drugs in patients with morbid obesity.[24,25] Furthermore, obesity is associated with increased cardiac output and drug clearance, and changes in regional blood flow or plasma protein binding can affect peak plasma concentration, clearance, and elimination half-life of many anesthetic agents, with alterations in PD properties potentially exaggerating side effects of anesthetics or the onset and/or duration anesthesia or muscle relaxation.[24–27] For many drugs, optimal dosing in patients with morbid obesity remains unclear as appropriate weight-based correction schemes remain unexplored. As a result, patients with morbid obesity may be at higher risk of toxicity, undesirable effects, or reduced therapeutic effectiveness due to inappropriate dosing. Weight-based dosing scalars other than actual body weight (ABW) have been considered (e.g., ideal body weight (IBW), body surface area, BMI, and LBW). IBW is defined as the body weight associated with maximum life-expectancy for an individual's given height. Administration of drugs based on IBW can result in a subtherapeutic dose in patients with morbid obesity because IBW does not account for changes in body composition associated with obesity; namely, the calculated IBW of a patient with morbid obesity is less than their actual LBW.[28] Importantly, dosing of NMB reversal agents in patients with morbid obesity solely based upon IBW can result in a subtherapeutic dose because it does not account for changes in cardiac output, total blood volume, and changes in regional blood flow; underdosing may result in prolonged recovery, residual NMB, or recurrence of block. Incomplete reversal of NMB is accompanied by risks, including impaired pharyngeal function, aspiration, weakness of airway muscles, impaired ventilation, airway obstruction, hypoxemia, endotracheal re-intubation and mechanical ventilation, and prolonged recovery; incomplete reversal of NMB can greatly increase anesthesia-related morbidity and mortality.[29,30] Conversely, ABW-based dosing may be excessive for some reversal agents and exhibit a less favorable side effect profile.

The clinical development program for sugammadex used an ABW-based dosing scheme, consistent with rocuronium and vecuronium prescribing information, to ensure an adequate and consistent molar ratio of sugammadex:NMBA. No meaningful differences in the efficacy or safety of sugammadex were observed in a pooled analysis of patients with obesity (BMI ≥ 30 m^2/kg) across clinical registration studies, indicating no dosage adjustment is necessary in the setting of obesity; however, data informing the use of sugammadex in adults with morbid obesity to date is limited. A multicenter, randomized, double-blind trial (Clinicaltrials.gov: NCT03346070) was undertaken to compare the efficacy and safety of ABW-based vs. IBW-based dosing of sugammadex in adults with morbid obesity (BMI ≥ 40 kg/m^2) following M-NMB or D-NMB with either rocuronium or vecuronium. The primary efficacy and safety results of this study are reported elsewhere.[31] Briefly, ABW-based dosing of sugammadex resulted in significantly faster recovery times compared with IBW-based dosing with no additional safety risks in adults with morbid obesity. Taken together, these findings support routine dosing of sugammadex by ABW irrespective of the depth of NMB and NMBA used. An additional end point in this study included characterization of the full PK profile of sugammadex, including confirmation of PK linearity, to supplement the efficacy and safety findings. This paper documents the characterization of sugammadex PKs dosed by either IBW or ABW in adults with morbid obesity undergoing surgery.

METHODS

Study design

This phase IV, randomized, active comparator-controlled, parallel-group, double-blind study (Protocol 146; NCT03346070) conducted at 25 sites in 5 countries from January 1, 2018, to January 29, 2019, was approved by the institutional review board at each study center. All patients provided written informed consent before the initiation of

any study procedures. The details of the study design have been described previously. Briefly, treatment assignment determined the depth of NMB and study medication for reversal of NMB. Eligible patients were randomized equally to 1 of 5 maintenance/reversal combinations, and stratified by choice of NMBA: (i) M-NMB maintenance and reversal with sugammadex 2 mg/kg dosed by ABW; (ii) M-NMB maintenance and reversal with sugammadex 2 mg/kg dosed by IBW; (iii) M-NMB maintenance and reversal with neostigmine 5 mg + glycopyrrolate 1 mg; (iv) D-NMB maintenance and reversal with sugammadex 4 mg/kg dosed by ABW; and (v) D-NMB maintenance and reversal with sugammadex 4 mg/kg dosed by IBW. The IBW was calculated according to Kammerer MR *et al*.[32] A follow-up query was made 14 days after the procedure to collect adverse events and events of clinical interest. Only patients randomized to sugammadex (i.e., treatments 1, 2, 4, and 5) were included in the PK analysis reported herein.

Patients

Eligible patients included men and women ≥ 18 years with BMI ≥ 40 m^2/kg and American Society of Anesthesiologists (ASA) Physical Status class 3 undergoing a planned surgical procedure involving NMB with either rocuronium or vecuronium. Key exclusion criteria included: ABW < 100 kg; pacemaker or implantable cardioverter-defibrillator that precluded assessment of bradycardia or arrhythmias; condition or procedure dictating no reversal of NMB at the end of the procedure; neuromuscular disorder affecting NMB or assessments; severe renal insufficiency or dialysis dependence (defined as calculated creatinine clearance < 30 mL/minute by Cockcroft-Gault); history or family history of malignant hyperthermia; known or suspected allergy to medications used during anesthesia; and toremifene application 24 hours before or within 24 hours after study drug administration.

PK sample analysis

PK samples for determination of sugammadex concentrations were collected predose (i.e., prior to NMBA administration) and at prespecified timepoints following the administration of reversal agent (i.e., 2, 5, 15, 60, and 120 minutes; 4 to 6 hours). Depending on the length of hospital stay, a final PK sample may have been obtained postdose between 10 and 12 hours; however, this was considered optional and did not inform criteria for a PK evaluable population. Plasma samples were stored at –20°C until analysis. The sugammadex plasma concentrations were determined by Q^2 Solutions (Ithaca, NY) using a validated high-performance liquid chromatographic tandem mass spectrometric assay.[33] The assay lower limit of quantitation was 100 ng/mL with calibration range from 100 to 40,000 ng/mL. Incurred sample reproducibility was conducted on 114 study samples to confirm assay reproducibility. One hundred nine (109) samples selected for the incurred sample reproducibility test (95.6%) met acceptance criteria, exceeding the acceptance criteria of 67%; therefore, the bioanalytical data are considered reliable and reproducible to support evaluation of sugammadex plasma concentration values in patients with morbid obesity.

PK data analysis

The objective of the PK analyses was to characterize sugammadex PK profiles and parameter values in patients with morbid obesity following single-dose administration of sugammadex dosed according to ABW or IBW across depth of block (2 and 4 mg/kg). The PK end points included area under the concentration-time curve from zero to infinity (AUC_{0-inf}), AUC from zero to the last quantifiable concentration (AUC_{0-last}), maximum plasma concentration (C_{max}), total clearance (CL), volume of distribution during the terminal elimination phase after i.v. administration (V_d), apparent first-order terminal elimination half-life ($t_{1/2}$), and PK linearity of the aforementioned parameters. PK end points also included individual dose normalized (dn) AUC_{0-inf} and dnC_{max} values for each sugammadex dose (2 or 4 mg/kg).

Actual elapsed plasma sampling times relative to time of dose were used to estimate the PK parameters for each treatment in each patient. Sugammadex PK parameters were calculated using noncompartmental methods.[34] The apparent terminal rate constant (λ) was estimated by regression of the terminal log-linear portion of the plasma concentration time profile; apparent terminal $t_{1/2}$ was calculated as the quotient of ln(2) and λ. AUC_{0-last} was calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations up to the last quantifiable plasma concentration. Total exposure (AUC_{0-inf}) was estimated as the sum of AUC_{0-last} and the extrapolated area given by the quotient of the last quantifiable concentration and λ. C_{max} was obtained by inspection of the plasma concentration data. Mean residence time (MRT) of sugammadex in the systemic circulation following i.v. administration was estimated. CL was calculated as dose/AUC_{0-inf}. V_d was defined as volume of distribution estimated at steady-state following a single i.v. dose administration (V_{ss} = MRT × CL). V_d during the terminal elimination phase (i.e., dose/(AUC_{0-inf} × λz) was calculated. No values for AUC_{0-inf}, CL, λz, $t_{1/2}$, Vz, MRT, and V_{ss} were reported for concentration-time profiles where the terminal linear phase was not clearly defined.

Statistical analyses

Individual $dnAUC_{0-inf}$ and dnC_{max} values for each sugammadex dose (2 or 4 mg/kg) were natural log-transformed and were initially evaluated with a linear fixed effect model using fixed terms for treatment and mode of body weight calculation (IBW and ABW) and an interaction term for mode of body weight calculation-by-treatment. Because both interaction (mode of body weight calculation-by-treatment) and mode of body weight calculation terms of the model were found to be statistically nonsignificant at alpha = 0.05 for both $dnAUC_{0-inf}$ and dnC_{max}, these 2 terms were dropped from the model. The data from both modes of administration were pooled and analyzed using the model that included only treatment as a fixed effect. Ninety percent (90%) confidence intervals (CIs) for the difference in least-squares (LS) means on the log scale for $dnAUC_{0-inf}$ and dnC_{max} were obtained from the model. These CIs were exponentiated to obtain a 90% CIs for the true $dnAUC_{0-inf}$ geometric mean ratio (GMR; 2 vs. 4 mg/kg) and true dnC_{max} GMR (2 vs. 4 mg/kg). For

each mode of body weight calculation (IBW and ABW), LS means and corresponding 95% CIs obtained from the model also were calculated for $dnAUC_{0-inf}$ and dnC_{max} by treatment. Additionally, individual CL and V_d were natural log-transformed and analyzed separately using linear fixed effects model, as previously described. For each mode of body weight calculation (IBW and ABW), LS means and corresponding 95% CIs for CL and V_d were provided for each treatment.

RESULTS

In total, 21 sites in 5 countries screened 229 patients for inclusion in this study; 20 sites randomized 207 eligible patients, of which 150 were treated with sugammadex (i.e., either 2 or 4 mg/kg dosed by ABW or IBW). Two patients randomized to sugammadex treatment with fewer than two quantifiable samples were excluded from the PK analysis. The evaluable PK population therefore included 148 patients distributed across 4 treatment groups (**Table 1**). Patients randomized to the neostigmine control group (*N* = 38) did not receive sugammadex and therefore were not included in any PK analyses. Patient demographics and baseline characteristics were generally well balanced across the four treatment groups except for a slight imbalance in baseline ABW that tended to be lower in the sugammadex 2 mg/kg group, and a moderately greater proportion of male patients in the sugammadex 4 mg/kg ABW group (**Table 2**).

Table 1 Number of randomized patients contributing to the PK analyses presented by sugammadex dose and mode of body weight calculation

Category	2 mg/kg	4 mg/kg	Total
ABW	38	38	76
IBW	36	36	72
Total	74	74	148

ABW, actual body weight; IBW, ideal body weight; PK, pharmacokinetic.

Figure 1 shows the mean plasma concentration data from 148 patients with morbid obesity administered a single i.v. sugammadex dose (2 or 4 mg/kg) calculated by ABW or IBW across the full PK sampling time scale (up to 10–12 hours postdose). Following a single i.v. dose of 2 or 4 mg/kg, the mean sugammadex plasma concentration profiles demonstrated a rapid distribution phase followed by a monophasic decline consistent with a two-compartmental PK model. In general, dose-dependent trends were seen across the treatment groups with higher plasma concentrations seen with the administration of 4 mg/kg vs. 2 mg/kg. When these data were inspected within equivalent treatments (i.e., within the 2 or 4 mg/kg dose groups), sugammadex plasma concentrations were modestly lower when dosed according to IBW vs. ABW. This was expected because the overall dose of sugammadex is less when it is dosed according to IBW vs. ABW. Irrespective of the mode of dose (i.e., ABW and IBW), sugammadex plasma concentrations demonstrated the same monophasic decay from nadir.

Based on inspection of the concentration-time profiles, the sampling timepoints used in this study supported robust characterization of sugammadex PK parameter values. **Table 3** shows the results of the statistical comparisons between the 2 and 4 mg/kg dose groups, pooled across mode of body weight calculation (ABW and IBW). Dose-independent parameters, CL and V_d, showed overlapping distributions; apparent terminal $t_{1/2}$ (~ 2 hours) also was largely similar between the 4 and 2-mg/kg dose levels. For the 4 vs. 2 mg/kg comparison, the GMR (90% CI) were 0.90 (0.78–1.04) and 1.01 (0.84–1.21) for $dnAUC_{0-inf}$ and dnC_{max}, respectively. The 90% CI for the GMR included 1.00 for both $dnAUC_{0-inf}$ and dnC_{max}. There was no statistically significant interaction between dose and mode of body weight calculation (IBW and ABW) for either PK parameter (*P*value 0.611 and 0.328 for $dnAUC_{0-inf}$ and dnC_{max}, respectively); neither was there a statistically significant difference between the two modes

Table 2 Demographics and baseline characteristics of patients contributing to the PK analyses

Characteristics	Sugammadex 2 mg/kg ABW *N* = 38	Sugammadex 2 mg/kg IBW *N* = 36	Sugammadex 4 mg/kg ABW *N* = 38	Sugammadex 4 mg/kg IBW *N* = 36
Age, years	48 ± 14	48 ± 15	47 ± 11	49 ± 12
Female sex	32 (84)	25 (69)	22 (58)	29 (81)
White race	36 (95)	32 (89)	36 (95)	33 (92)
CrCl, mL/minute[a]	194 ± 66	216 ± 78	209 ± 59	217 ± 73
NMBA				
Rocuronium	27 (71)	23 (64)	26 (68)	27 (75)
Vecuronium	11 (29)	13 (36)	12 (32)	9 (25)
BMI (kg/m^2)	45.8 ± 4.5	46.9 ± 5.6	45.4 ± 5.0	46.5 ± 5.7
ABW (kg)	127 ± 21	135 ± 17	131 ± 20	131 ± 21
IBW (kg)	63 ± 7	65 ± 8	66 ± 7	63 ± 6
Sugammadex total dose, mg	254 ± 43	131 ± 15	525 ± 81	254 ± 24

Patient's ideal body weight is based on the gender category recorded at the time of randomization. Data entries are either *n* (%) or mean ± SD.
ABW, actual body weight; BMI, body mass index; CrCl, creatinine clearance; IBW, ideal body weight; NMBA, neuromuscular blocking agent; PK, pharmacokinetic.
[a]Sample sizes for CrCl: 2 mg/kg ABW *N* = 36; 2 mg/kg IBW *N* = 35; 4 mg/kg ABW *N* = 35; and 4 mg/kg IBW *N* = 33.

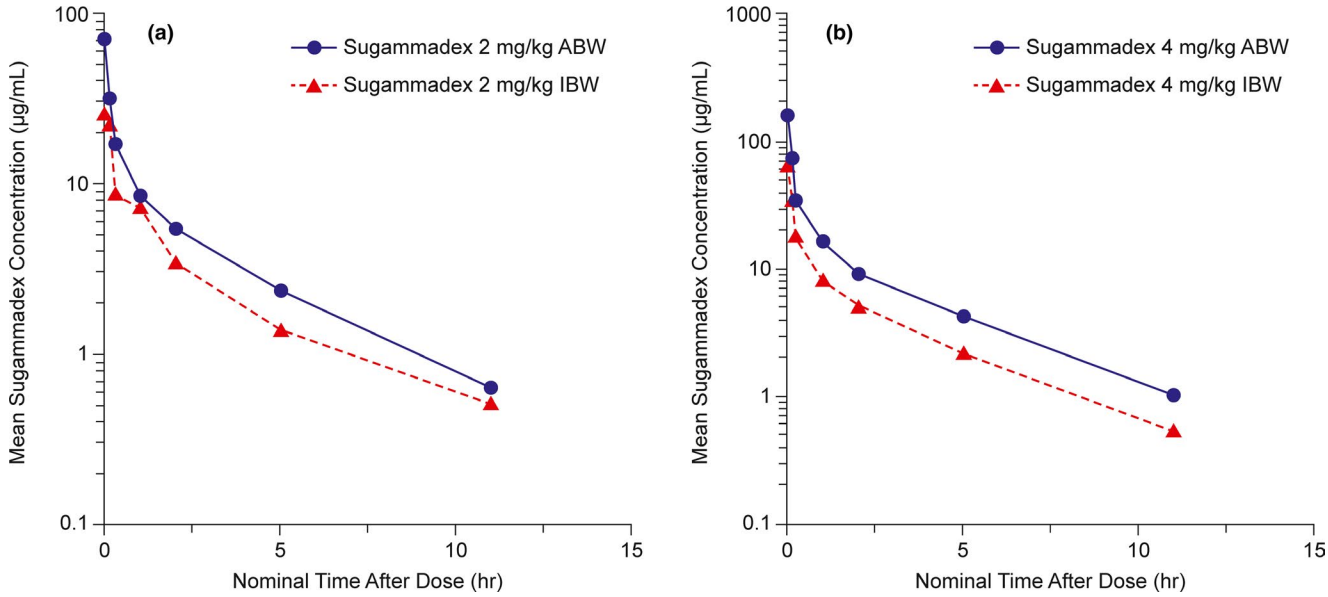

Figure 1 Mean sugammadex plasma concentration-time profiles following the administration of a single i.v. dose of sugammadex. We administered 2 mg/kg (**a**) or 4 mg/kg (**b**) in patients with morbid obesity. The blue and red lines represent the observed plasma concentrations for patients in the actual body weight (ABW) and ideal body weight (IBW) groups, respectively.

Table 3 Summary of PK parameters for sugammadex 2 and 4 mg/kg pooled across mode of body weight calculation and statistical comparisons

	2 mg/kg (pooled ABW and IBW)			4 mg/kg (pooled ABW and IBW)			4 mg/kg vs. 2 mg/kg	
PK parameter	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
$dnAUC_{0-inf}$, hour*µg/mL/mg[a]	74	0.161	(0.142–0.182)	74	0.145	(0.128–0.164)	0.90	(0.78–1.04)
dnC_{max}, µg/mL/mg[a]	74	0.197	(0.169–0.230)	74	0.199	(0.170–0.232)	1.01	(0.84–1.21)
$dnAUC_{0-5\ hrs}$, hour*µg/mL/mg[a]	74	0.130	(0.118–0.142)	74	0.120	(0.110–0.132)	--	--
CL, L/hour[a]	74	6.21	(5.50–7.03)	74	6.91	(6.11–7.81)	--	--
V_d, mL[a]	74	19,300	(17,500–21,200)	74	22,200	(20,200–24,400)	--	--
Apparent $t_{1/2}$, hours[b]	74	2.15	62.4	74	2.23	35.2	--	--

ABW, actual body weight; AUC_{0-inf}, area under the concentration-time curve from zero to infinity; CI, confidence interval; CL, total clearance; C_{max}, peak plasma concentration; dn, dose normalized; GM, geometric least-squares mean; GMR, geometric least-squares mean ratio; IBW, ideal body weight; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_d, terminal volume of distribution based.
[a]Back-transformed least squares mean and CI from fixed effects model performed on natural log-transformed values.
[b]Geometric mean and percent geometric coefficient of variation.

of body weight calculation (IBW and ABW; *P*value 0.378 and 0.381 for $dnAUC_{0-inf}$ and dnC_{max}, respectively).

The PK results for the between-dose comparisons are presented separately by mode of body weight calculation (IBW and ABW) in **Table 4**. The results were consistent with the pooled analysis establishing linearity across the dose range evaluated. The dn parameters ($dnAUC_{0-inf}$ and dnC_{max}) and the dose-independent parameters (CL, V_d, and $t_{1/2}$) were consistent between the 4 and 2-mg/kg groups when examined both within and between mode of body weight calculation (IBW and ABW). For the between-dose comparisons of $dnAUC_{0-inf}$ and dnC_{max}, the 90% CIs for the GMRs contained 1.00 when calculated separately by IBW and ABW. The individual dose-normalized mean plasma concentration-time profiles presented by individual treatment group are illustrated in **Figure 2**. The individual dose-normalized profiles overlapped and indicated similar PK properties across mode of body weight calculation (IBW and ABW) and dose groups, complementing the primary statistical analysis of dose linearity between 2 and 4 mg/kg pooled across mode of body weight calculation (IBW and ABW).

DISCUSSION

Sugammadex is administered postoperatively at doses of 2 or 4 mg/kg to reverse M-NMB or D-NMB, respectively, induced by the NMBAs rocuronium and vecuronium. The clinical development program for sugammadex utilized ABW-based dosing to mirror the recommended dosing of rocuronium and vecuronium, which also are dosed by ABW. The current multicenter, randomized, double-blind trial was conducted in adults with morbid

Table 4 Summary and statistical comparisons of PK parameters for sugammadex 2 and 4 mg/kg presented by mode of body weight calculation

	2 mg/kg (IBW)			4 mg/kg (IBW)			4 mg/kg vs. 2 mg/kg (IBW)	
PK parameter	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
$dnAUC_{0-inf}$, hour*µg/mL/mg[a]	36	0.171	(0.144–0.205)	36	0.147	(0.123–0.176)	0.86	(0.70–1.06)
dnC_{max}, µg/mL/mg[a]	36	0.198	(0.159–0.247)	36	0.179	(0.143–0.223)	0.90	(0.69–1.17)
$dnAUC_{0-5\ hrs}$, hour*µg/mL/mg[a]	36	0.134	(0.118–0.153)	36	0.121	(0.106–0.138)	--	--
CL, L/hour[a]	36	5.83	(4.89–6.96)	36	6.79	(5.69–8.11)	--	--
V_d, mL[a]	36	18,400	(16,000–21,100)	36	22,200	(19,300–25,500)	--	--
Apparent $t_{1/2}$, hours[b]	36	2.18	81.0	36	2.27	39.7	--	--
	2 mg/kg (ABW)			**4 mg/kg (ABW)**			**4 mg/kg vs. 2 mg/kg (ABW)**	
PK parameter	***N***	**GM**	**95% CI**	***N***	**GM**	**95% CI**	**GMR**	**90% CI**
$dnAUC_{0-inf}$, hour*µg/mL/mg[a]	38	0.152	(0.128–0.180)	38	0.142	(0.120–0.169)	0.94	(0.77–1.15)
dnC_{max}, µg/mL/mg[a]	38	0.196	(0.158–0.243)	38	0.219	(0.177–0.272)	1.12	(0.87–1.44)
$dnAUC_{0-5\ hrs}$, hour*µg/mL/mg[a]	38	0.125	(0.110–0.142)	38	0.120	(0.105–0.136)	--	--
CL, L/hour[a]	38	6.60	(5.55–7.83)	38	7.02	(5.91–8.34)	--	--
V_d, mL[a]	38	20,200	(17,600–23,100)	38	22,200	(19,400–25,400)	--	--
Apparent $t_{1/2}$, hour[b]	38	2.12	43.2	38	2.19	30.9	--	--

ABW, actual body weight; AUC_{0-inf}, area under the concentration-time curve from zero to infinity; CI, confidence interval; CL, total clearance; C_{max}, maximum plasma concentration; dn, dose normalized; GM, geometric least-squares mean; GMR, geometric least-squares mean ratio; IBW, ideal body weight; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; V_d, terminal volume of distribution based.
[a]Back-transformed least squares mean and CI from fixed effects model performed on natural log-transformed values.
[b]Geometric mean and percent geometric coefficient of variation.

obesity (BMI ≥ 40 kg/m^2; ABW ≥ 100 kg, and ASA class 3) to evaluate the efficacy and safety profile of sugammadex (2 or 4 mg/kg) dosed by ABW or IBW for the reversal of rocuronium-induced or vecuronium-induced M-NMB or D-NMB. In this study, rocuronium and vecuronium were dosed based on ABW according to product labeling

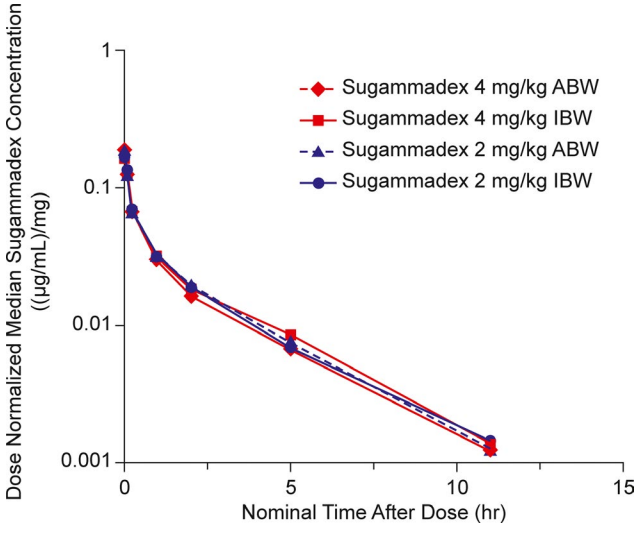

Figure 2 Dose normalized median sugammadex plasma concentration-time profiles following the administration of a single i.v. dose of sugammadex 2 mg/kg (blue lines) or 4 mg/kg (red lines) in patients with morbid obesity (log-linear scale). ABW, actual body weight; IBW, ideal body weight.

recommendations, irrespective of the subsequent mode of dosing sugammadex. The primary efficacy and safety results of this study are presented elsewhere.[31] Briefly, the primary findings of this study revealed a statistically significant delay in recovery of neuromuscular function with IBW vs. ABW dosing of sugammadex. Time to clinical recovery (train-of-four ratio ≥ 0.9) with sugammadex treatment was 1.5 min faster with ABW vs. IBW dosing, pooled across NMBA and depth of block ($P < 0.001$). The proportion of patients with prolonged recovery did not differ between ABW and IBW for either moderate block or deep block. Further, no clinically meaningful differences were seen in the safety and tolerability profiles across the sugammadex and neostigmine treatment groups confirming ABW-based sugammadex dosing is appropriate in adults with morbid obesity. An additional end point in this study was to characterize the full PK profile of sugammadex, including confirmation of PK linearity, to supplement the efficacy and safety findings.

The current paper documents the characterization of sugammadex PK dosed by either IBW or ABW in adults with morbid obesity undergoing surgery. The blood sampling schedule used in this study enabled a robust characterization of sugammadex PK parameters following the administration of single i.v. doses of sugammadex 2 or 4 mg/kg as calculated by ABW or IBW. The PK profiles and parameter values increased in a dose-dependent, linear fashion following i.v. administration when examined by mode of body weight calculation (ABW or IBW) and across depth of NMB. The plasma concentration profile in this population of adults

with morbid obesity showed the characteristic pattern of a two-compartment PK profile with an initial rapid distribution phase and a subsequent monophasic decline phase in both dose groups and across both body weight modes. The dose-normalized plasma concentration time curves were nearly superimposable across both dose groups and body weight modes. Taken together, these findings indicate that the PK properties of sugammadex remains consistent, even for the highest 4 mg/kg dose and the ABW dosing regimen, which tends to overdose relative to IBW.

The individual PK parameter values for sugammadex showed dose-dependent trends across the treatment groups in this population of adults with morbid obesity. Systemic exposure of sugammadex was ~ 50% lower with IBW dosing compared with ABW dosing. As expected, higher plasma concentration was seen following the administration 4 vs. 2 mg/kg and when dosed according to ABW vs. IBW. Regarding dose-independent parameters, CL and V_d, overlapping distributions were seen irrespective of dose level and mode of body weight calculation. The apparent terminal $t_{1/2}$ (~ 2 hours) also was similar across all treatment groups. The PK parameter values seen in this study of obese adults are similar to those observed previously in studies of healthy adults. In those studies, a dose-dependent linear relationship over the dose range of 0.1–8 mg/kg was seen with an elimination half-life of ~ 1.8 hour.[9,35,36] In healthy adults, sugammadex has a clearance rate of 88 mL/min and distribution volume of 11 to 14 L comparable to that seen here in patients with obesity irrespective of whether they were dosed according to ABW or IBW.[9]

The molar ratios of sugammadex to NMBA and resultant concentration gradients are important considerations to contextualize the dosing of sugammadex across different patient populations. At the recommended sugammadex doses based upon ABW (2 mg/kg at reappearance of the second twitch in response to train-of-four stimulation (T2), 4 mg/kg at 1–2 post-tetanic counts, and 16 mg/kg at 3 minutes after 1.2 mg/kg rocuronium), the molar ratio excesses of sugammadex over rocuronium, at 2 minutes post sugammadex dosing range from 5 to 8. Within these 2 minutes, enough rocuronium has flowed from the NMJ to the adjacent extracellular fluid (where the concentration of sugammadex is still increasing) and to the plasma (where sugammadex has encapsulated free rocuronium first) to achieve recovery. This creates a concentration gradient favoring the movement of the remaining rocuronium molecules from the NMJ back into the plasma, where they are encapsulated by free sugammadex molecules. The complexed NMBAs cannot bind to nicotinic receptors in the NMJ leading to a reversal of NMB; this complex is then eliminated by the kidneys. Based on the mode of body weight calculation alone, sugammadex exposures following administration based on ABW would be anticipated to be higher than those following administration based on IBW across both 2 and 4 mg/kg dose levels.

Prior studies showed linearity of sugammadex PK over a dose range of 0.1 to 96 mg/kg based on ABW,[8–10] such that sugammadex PKs and therefore the resultant molar ratios to NMBA at each of the doses (2, 4, and 16 mg/kg) were predictable in healthy subjects and the general adult patient population. The present study both confirms and extends these conclusions to patients with morbid obesity based on the observation that both PK linearity and exposure (AUC and C_{max}) increased in a dose-proportional manner with other PK parameter values (dnAUC, dnC_{max}, CL, V_d, and $t_{1/2}$) remaining stationary across the 2 and 4 mg/kg dose groups. Thus, there was no evidence of an impact of mode of body weight calculation on the assumptions of linearity in this population of otherwise healthy patients with morbid obesity. Furthermore, given that linearity is maintained and PK at lower doses is predictive of that at higher doses, it is reasonable to assume that results presented herein following administration of 2 and 4 mg/kg sugammadex would be applicable to a 16 mg/kg dose of sugammadex for immediate reversal of NMB.

In conclusion, this study demonstrated that the PK of sugammadex in patients with morbid obesity are dose-linear over the 2–4 mg/kg range when administered according to ABW and IBW across depth of NMB. Based on confirmation of dose linearity, combined with efficacy and safety data (reported separately), patients with morbid obesity undergoing surgery with NMB via rocuronium or vecuronium should receive reversal with sugammadex dosed by ABW.

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1. Bom, A. *et al.* A novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrin-based synthetic host. *Angew. Chem. Int. Ed. Engl.* **41**, 266–270 (2002).
2. Epemolu, O., Bom, A., Hope, F. & Mason, R. Reversal of neuromuscular blockade and simultaneous increase in plasma rocuronium concentration after the intravenous infusion of the novel reversal agent Org 25969. *Anesthesiology* **99**, 632–637 (2003), discussion 636A.
3. Blobner, M. *et al.* Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur. J. Anaesthesiol.* **27**, 874–881 (2010).
4. Jones, R.K., Caldwell, J.E., Brull, S.J. & Soto, R.G. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology* **109**, 816–824 (2008).
5. Khuenl-Brady, K.S. *et al.* Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. *Anesth. Analg.* **110**, 64–73 (2010).
6. Lemmens, H.J., El-Orbany, M.I., Berry, J., Morte, J.B. Jr & Martin, G. Reversal of profound vecuronium-induced neuromuscular block under sevoflurane anesthesia: sugammadex versus neostigmine. *BMC Anesthesiol.* **10**, 15 (2010).

7. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA. Information for Health Professionals. Data sheet Bridion. Website <https://www.merckconnect.com/bridion/dosing-administration/> (2019). Accessed August 4, 2020.
8. Peeters, P.A. *et al*. Safety, tolerability and pharmacokinetics of sugammadex using single high doses (up to 96 mg/kg) in healthy adult subjects: a randomized, double-blind, crossover, placebo-controlled, single-centre study. *Clin. Drug Investig.* **30**, 867–874 (2010).
9. Gijsenbergh, F., Ramael, S., Houwing, N. & van Iersel, T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *Anesthesiology* **103**, 695–703 (2005).
10. Mitchell, C. & Lobaz, S. An Overview of Sugammadex. Anaesthesia Tutorial of the Week <https://www.wfsahq.org/components/com_virtual_library/media/f5eb49b34e301681400b3d1d9489d37b-332-An-Overview-of-Sugammadex.pdf> (2006) Accessed October 27, 2020.
11. Peeters, P. Sugammadex is cleared rapidly and primarily in an unchanged form via renal excretion. *Clin. Pharmacol. Ther.* **85**, S83 (Abstract PIII-50) (2009).
12. Kleijn, H.J., Zollinger, D.P., van den Heuvel, M.W. & Kerbusch, T. Population pharmacokinetic-pharmacodynamic analysis for sugammadex-mediated reversal of rocuronium-induced neuromuscular blockade. *Br. J. Clin. Pharmacol.* **72**, 415–433 (2011).
13. McDonagh, D.L. *et al*. Efficacy, safety, and pharmacokinetics of sugammadex for the reversal of rocuronium-induced neuromuscular blockade in elderly patients. *Anesthesiology* **114**, 318–329 (2011).
14. World Health Organization. Obesity and overweight. Website <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> (2020). Accessed August 3, 2020.
15. MacLean, L.D., Rhode, B.M. & Nohr, C.W. Late outcome of isolated gastric bypass. *Ann. Surg.* **231**, 524–528 (2000).
16. Casati, A. & Putzu, M. Anesthesia in the obese patient: pharmacokinetic considerations. *J. Clin. Anesth.* **17**, 134–145 (2005).
17. Palmer, J. *et al.* Underestimating the size of the problem? UK anaesthesia for patients with obesity. *Obes. Res. Clin. Pract.* **11**, 703–708 (2017).
18. Cook, T.M., Woodall, N., Harper, J. Benger, J. & Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *Br. J. Anaesth.* **106**, 632–642 (2011).
19. Pandit, J.J. *et al*. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. *Br. J. Anaesth.* **113**, 549–559 (2014).
20. Hanley, M.J., Abernethy, D.R. & Greenblatt, D.J. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin. Pharmacokinet.* **49**, 71–87 (2010).
21. Lee, J.B., Winstead, P.S. & Cook, A.M. Pharmacokinetic alterations in obesity. *Orthopedics* **29**, 984–988 (2006).
22. Dong, D. *et al*. Morbid obesity alters both pharmacokinetics and pharmacodynamics of propofol: dosing recommendation for anesthesia induction. *Drug Metab. Dispos.* **44**, 1579–1583 (2016).
23. Smit, C. *et al*. A prospective clinical study characterizing the influence of morbid obesity on the pharmacokinetics of gentamicin: towards individualized dosing in obese patients. *Clin. Pharmacokinet.* **58**, 1333–1343 (2019).
24. Cheymol, G. Effects of obesity on pharmacokinetics implications for drug therapy. *Clin. Pharmacokinet.* **39**, 215–231 (2000).
25. Forbes, G.B. & Welle, S.L. Lean body mass in obesity. *Int. J. Obes.* **7**, 99–107 (1983).
26. Collis, T. *et al*. Relations of stroke volume and cardiac output to body composition: the strong heart study. *Circulation* **103**, 820–825 (2001).
27. Stokholm, K.H., Brochner-Mortensen, J. & Hoilund-Carlsen, P.F. Increased glomerular filtration rate and adrenocortical function in obese women. *Int. J. Obes.* **4**, 57–63 (1980).
28. Ingrande, J. & Lemmens, H.J. Dose adjustment of anaesthetics in the morbidly obese. *Br. J. Anaesth.* **105**(suppl. 1), i16–i23 (2010).
29. Llaurado, S., Sabate, A., Ferreres, E., Camprubi, I. & Cabrera, A. Sugammadex ideal body weight dose adjusted by level of neuromuscular blockade in laparoscopic bariatric surgery. *Anesthesiology* **117**, 93–98 (2012).
30. Jahr, J.S. *et al*. Sugammadex: a scientific review including safety and efficacy, update on regulatory issues, and clinical use in Europe. *Am. J. Ther.* **22**, 288–297 (2015).
31. Horrow, J. *et al*. Actual body weight vs ideal body weight dosing of Sugammadex in the morbidly Obese. American Society of Anesthesiologists [Abstract Archive] <http://www.asaabstracts.com/strands/asaabstracts/abstractArchive.htm> (2019). Accessed August 4, 2020.
32. Kammerer, M.R., Porter, M.M., Beekley, A.C. & Tichansky, D.S. Ideal body weight calculation in the bariatric surgical population. *J. Gastrointest. Surg.* **19**, 1758–1762 (2015).
33. Zeng, W., Xu, Y., Constanzer, M.L., Goykhman, D. & Woolf, E.J. Determination of sugammadex in human plasma using protein precipitation and ultra high performance liquid chromotography / tandem mass spectrometry. *SF J. Pharmaceut. Analyt. Chem.* **1**, 1007 (2018).
34. Certara. Phoenix WinNonlin. Software. Version 8.1.0.3530 <https://www.certara.com/software/phoenix-winnonlin/>. Accessed August 4, 2020.
35. Sorgenfrei, I.F. *et al*. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. *Anesthesiology* **104**, 667–674 (2006).
36. Sparr, H.J. *et al*. Early reversal of profound rocuronium-induced neuromuscular blockade by sugammadex in a randomized multicenter study: efficacy, safety, and pharmacokinetics. *Anesthesiology* **106**, 935–943 (2007).