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Supplemental Statistical Analysis Plan (sSAP)

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1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides 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.

2 SUMMARY OF CHANGES

These changes are being made:

- Imputations of missing recovery time are clarified to be done by actual body weight (ABW) and ideal body weight (IBW) for sugammadex group and by pooling NMBA and depth of block across all participants. Refer to Section 3.4.4 for details.
- The All Subject Treated (AST) population in Protocol 8616-146-00 is renamed as Full Analysis Set (FAS) and remains as the population for efficacy analysis. The AST population is re-defined for treated subjects, i.e., the only requirement to be included in the AST population is to receive NMBA and reversal agent (study treatment). AST is used for reporting baseline characteristics. In addition, the criterion that will be utilized to identify subjects that were potentially cross treated on the basis of ABW versus IBW, is added to the safety analysis population. Refer to Section 3.5 for details.
- The stratification stratum used in the analysis is clarified in Section 3.6. All the analyses will be based on the real stratification stratum that a subject belongs to. The weighting scheme of the stratified Miettinen and Nurminen method is clarified in Section 3.6.
- More details are added about the assessment of the treatment effect on the endpoint – time to recovery to TOF ratio (i.e. T_4/T_1 ratio) ≥ 0.9 after sugammadex administration. Refer to Section 3.6.1 for details.
- More details are added for calculating the 95% confidence interval (CI) of the pairwise comparison between two treatment arms in geometric means. Refer to Section 3.6.1. To note, in the previously published sSAP, the pairwise comparison between two treatment arms in geometric means, were interpreted as the pairwise geometric mean *difference*. However, as the distribution of recovery time (in minutes) is highly skewed and as the recovery time (in minutes) could be short for both treatment arms in certain pairwise comparison, e.g. ABW versus IBW, the pairwise geometric mean *ratio* of the recovery time between two treatment arms (i.e. the exponential transformation of the pairwise geometric mean difference in the logarithmic scale) is deemed by the sponsor as more interpretable or meaningful than the pairwise geometric mean *difference*. Therefore, the pairwise geometric mean ratio

is implemented in the corresponding key secondary analyses within this sSAP version.

- One exploratory analysis (i.e. a sensitivity analysis for key secondary analysis) is added for conservatively assessing the recovery time of subjects who received sugammadex ABW as compared to subjects who received sugammadex IBW. Refer to Section 3.6.1 for details.
- To provide the comparable overall incidences with the label-based preferred terms of adverse events (AEs) used in the prior submission, the summary of the grouped AE preferred terms is added to the safety analysis. It is clarified that 95% confidence interval by treatment groups using Clopper-Pearson method will be provided to the estimates of Tier 1 endpoints and Tier 2 events of clinical interest. Refer to Section 3.6.2 for details.
- Section 3.13 is added for describing how to execute time synchronization in the analysis.
- Due to Health Insurance Portability and Accountability Act (HIPPA) regulations, the trial collects partial birthday (year and month). This could make some participants (who are not less than 18 years old) have calculated age < 18 years. To include these eligible participants in the analyses, the youngest age group is updated to < 65 years in this analysis plan and these participants will be discussed in the clinical study report.
- Corrections are made to ensure that the sSAP is consistent with the analysis plan in Protocol NO. 146-1.

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2-3.12.

Study Design Overview	A randomized, active comparator-controlled trial evaluating the efficacy and safety of sugammadex when used to reverse neuromuscular blockade induced by either rocuronium or vecuronium in morbidly obese subjects.
Treatment Assignment	Subjects will be stratified by NMBA and randomized to depth of NMB (moderate or deep) and reversal agent in a 1:1:1:1:1 ratio as follows: <ol style="list-style-type: none"> 1. Moderate block and reversal with sugammadex 2 mg/kg, based on ABW 2. Moderate block and reversal with sugammadex 2 mg/kg, based on IBW 3. Moderate block and reversal with neostigmine(0.05 mg/kg up to 5 mg) + glycopyrrolate (10 µg/kg up to 1 mg maximum dose) based on ABW 4. Deep block and reversal with sugammadex 4 mg/kg, based on

	ABW 5. Deep block and reversal with sugammadex 4 mg/kg, based on IBW
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	The time to recovery to a TOF ratio of ≥ 0.9 for a comparison of ABW and IBW dosing of sugammadex pooled across depth of block and NMBA
Key Secondary Endpoint(s)	Distribution of time to recovery to a TOF ratio of ≥ 0.7 , ≥ 0.8 and ≥ 0.9 as well as the proportions of subjects with prolonged recovery (>10 minutes) pooled across depth of block and NMBA.
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will evaluate the efficacy of sugammadex when dosed according to ABW as compared with IBW on time to recovery to a TOF ratio of ≥ 0.9 using a stratified log-rank test (adjusted for the depth of block and NMBA). Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	A tiered approach will be used to safety analyses. Tier 1 parameters will be subject to inferential testing for statistical significance with 95% confidence intervals for between-group comparisons. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.
Interim Analyses	A pharmacokinetic (PK) only interim analyses (IA) will be conducted in this study when approximately 64 evaluable subjects treated with sugammadex (approximately 16 subjects per treatment dose [2 mg/kg and 4 mg/kg] and weight-based dosing [ABW and IBW] categories) have been enrolled, in order to examine the PK profile of sugammadex in the setting of morbid obesity. No unblinding of safety or efficacy will occur in support of this PK-only IA.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The total planned sample size is approximately 200 subjects. If subjects are equally allocated in each NMBA strata, there would be ~100 subjects per NMBA with ~20 subjects in each of the 5 treatment arms. However, if approximately 30% of the total subjects (i.e., 60 subjects) are enrolled in the vecuronium stratum, there would be ~12 subjects in each of the 5 treatment groups in the vecuronium stratum. Assuming the difference of median time-to-recovery in ABW and IBW groups is one minute based on the simulated data, a sample size of N ~80 per group (across both NMBA and depth of block) provides estimated power of > 99% to detect a shift in time-to-recovery.

3.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

Sponsor study team personnel will be blinded to study medication assignments for randomized subjects, with the exception of designated Sponsor personnel (e.g., unblinded Clinical Research Associates [CRAs], the pharmacokineticist, statistician(s) not associated with the study who will complete the PK IA and provide the data to the siDMC, and other designated individuals as required). The official final database will not be unblinded until

medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented using an IVRS.

3.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 of the protocol.

3.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

3.4.1 Efficacy Endpoints

The primary efficacy endpoint is the time to recovery to a TOF ratio of ≥ 0.9 for a comparison of ABW and IBW based dosing of sugammadex. See Section 4.2.3.1 of the protocol for more details.

Secondary efficacy endpoints are:

- Summary statistics for the recovery times to TOFs of ≥ 0.7 , ≥ 0.8 and ≥ 0.9 for ABW and IBW dosing groups pooled across both the depth of block and NMBA
- The proportions of subjects with prolonged recovery (>10 minutes) for ABW and IBW dosing groups pooled across both the depth of block and NMBA

Exploratory efficacy endpoints are:

- Summary statistics for the recovery times for sugammadex and neostigmine in the setting of moderate block pooled across NMBA
- Summary statistics for the recovery times to TOFs of ≥ 0.7 , ≥ 0.8 and ≥ 0.9 for ABW and IBW dosing groups separately by the depth of block and by NMBA
- The proportions of subjects with prolonged recovery (>10 minutes) for ABW and IBW dosing groups by the depth of block and by NMBA.

3.4.2 Safety Endpoints

Safety endpoints that will be evaluated in each dosing group are listed below. For safety analyses other than the primary safety endpoint (which includes events up to 30 minutes post administration of study medication), the primary approach to the summary of AEs will include all events that occur up to 7 days post administration of study medication. A

supplemental summary of all AEs occurring up to 14 days post administration of study medication will also be included.

The primary safety endpoints are:

- Proportion of subjects with treatment emergent sinus bradycardia defined as a heart rate <60 bpm that has also decreased more than 20%, compared to the subject's baseline heart rate value, sustained for at least 1 minute after administration of study medication
- Proportion of subjects with treatment emergent sinus tachycardia defined as a heart rate ≥ 100 bpm that has also increased more than 20%, compared to the subject's baseline heart rate value, sustained for at least 1 minute after administration of study medication
- Proportion of subjects with other treatment emergent cardiac arrhythmias defined as new or worsening arrhythmias (e.g., atrial fibrillation, atrial tachycardia, ventricular fibrillation, or ventricular tachycardia), sustained for at least 1 minute after administration of study medication

The baseline heart rate for the primary safety endpoints will be recorded approximately five minutes before administration of study medication (sugammadex or neostigmine) to determine events of treatment emergent sinus bradycardia, treatment emergent sinus tachycardia, or other treatment emergent cardiac arrhythmias. In addition to the primary safety endpoints,

Some supportive safety endpoints considered as Tier 2 endpoints are listed below:

- Proportion of subjects with adjudicated hypersensitivity
- Proportion of subjects with adjudicated anaphylaxis
- Proportion of subjects with at least one clinically relevant sinus bradycardia event defined as any bradycardia event necessitating intervention, as determined by investigator judgment
- Proportion of subjects with at least one clinically relevant sinus tachycardia event defined as any tachycardia event necessitating intervention, as determined by investigator judgment
- Proportion of subjects with a least one other clinically relevant cardiac arrhythmia defined as any other cardiac arrhythmia event necessitating intervention, as determined by investigator judgment

In addition, proportion of subjects with any AE, serious AE, drug-related AE, serious and drug-related AE, discontinuation due to AE and specific AEs, SOCs, or PDLCs (incidence ≥ 4 of subjects in one of the treatment group) will be considered as Tier 2 safety endpoints.

3.4.3 Pharmacokinetic Endpoints

The pharmacokinetics of sugammadex will be evaluated in obese participants when dosed according to ABW and IBW.

Actual elapsed plasma sampling times relative to the time of dose will be used to estimate the pharmacokinetic parameters for each treatment in each subject. Sugammadex pharmacokinetic parameters will be calculated using noncompartmental methods. The apparent terminal rate constant (λ) will be estimated by regression of the terminal log-linear portion of the plasma concentration time profile; apparent terminal $t_{1/2}$ will be calculated as the quotient of $\ln(2)$ and λ . AUC to the last time point with a quantifiable plasma concentration (AUC_{0-last}) will be 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}) will be estimated as the sum of AUC_{0-last} and the extrapolated area given by the quotient of the last quantifiable concentration and λ . The maximum observed concentration (C_{max}) will be obtained by inspection of the plasma concentration data. Mean residence time (MRT) of sugammadex in the systemic circulation following IV administration will be estimated. Total clearance (CL=Dose/ AUC_{0-inf}) and volume of distribution (V_d), defined as volume of distribution estimated at steady-state following a single IV dose administration (V_{ss}=MRT x CL) and V_d during the terminal elimination phase (i.e. Dose/(AUC_{0-inf} x λ z)) will be calculated. No value for AUC_{0-∞}, CL, λ z, $t_{1/2}$, V_z, MRT, V_{ss} will be reported for concentration-time profiles where the terminal linear phase is not clearly defined.

Additional pharmacokinetic analyses may be conducted if deemed appropriate.

3.4.4 Derivations of Efficacy /Pharmacokinetics Endpoints

For imputation of missing times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8 and 0.9, a worst case scenario for sugammadex and a best case scenario for neostigmine will be applied, consistent with the approach used in the adult program. For each of the two NMBAs, separately, the following explicit imputation procedure (i.e. the primary imputation method) will be used:

If the time from the start of administration of study drug to recovery of the TOF ratio to 0.9 is missing, there are three cases of particular importance for imputation purposes:

1. Time to TOF ratio to 0.8 is available:

- Sugammadex group: first, for all subjects randomized to receive sugammadex and with times to recovery of the TOF ratio to 0.8 and 0.9 available, the difference between these two recovery times will be calculated. Next, the 95th percentile (P95) of these differences will be added to the time to recovery of the TOF ratio to 0.8 of the subjects with missing times to recovery of the TOF ratio to 0.9. This will be used as the imputed missing time to recovery of the TOF ratio to 0.9.

- Neostigmine group: same as for the sugammadex group but now only subjects randomized to receive neostigmine will be used, and the 5th percentile (P5) of the differences in time to recovery of the TOF ratio to 0.8 and 0.9 will be calculated.

2. Time to TOF ratio to 0.7 is available, but the time to TOF ratio to 0.8 is missing:

- Sugammadex group: first for all subjects randomized to sugammadex and with times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference in time between these two recovery times will be calculated. Next, the P95 of these differences will be added to the time to recovery of the TOF ratio to 0.7. This will be used as imputation of the missing time to recovery of the TOF ratio to 0.9.
- Neostigmine group: same as for sugammadex group but now only subjects randomized to receive neostigmine will be used and the P5 of the differences in time to recovery of the TOF ratio to 0.7 and 0.9 will be calculated.

3. Times to TOF ratio to 0.7 and to 0.8 are both missing:

- Sugammadex group: the P95 of the time to recovery in all subjects randomized to sugammadex with an observed recovery time of the TOF ratio to 0.9 will be imputed.
- Neostigmine group: the P5 of the time to recovery in all subjects randomized to neostigmine with an observed recovery time of the TOF ratio to 0.9 will be imputed.

A corresponding procedure will be followed for imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8 (secondary efficacy variable). For imputation of missing times, P95 (sugammadex) or P5 (neostigmine) of the differences in time between recovery of the TOF ratio to 0.7 and 0.8 will be used.

For imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.7 (secondary efficacy variable), the P95 observed time for the subjects randomized to the sugammadex group will be imputed. For subjects randomized to the neostigmine group the P5 observed time will be imputed. Imputation of missing times of the primary and secondary efficacy variables, however, should always result in a non-descending sequence of times to recovery of the TOF ratios to 0.7, 0.8, and 0.9.

Note that,

- the imputation will be across NMBA and depth of blocks,
- the imputation will be by ABW and IBW for the sugammadex group,
- the imputation of missing time generated from the above procedures will be calibrated with the time of last reliable TOF ratio time as:

maximum of: 1) the imputed time from the above procedures and 2) the time to the last reliable ratio

This will be used in the analysis with “Explicit Imputation”. Refer to Section 3.6.1.

In addition, the exploratory sensitivity analyses will be conducted for the key secondary efficacy analyses using an imputation method that is conservative for evaluating the recovery time of participants dosed with sugammadex according to ABW as compared to participants dosed with sugammadex according to IBW. The “conservative” imputation method is similar to the imputation described in this section, but uses the P5 (instead of P95 as described in the explicit imputation) for imputing the missing recovery time for participants who received sugammadex IBW and is for the analysis with “Conservative Imputation” in Section 3.6.1:

- If the time from the start of administration of study drug to recovery of the TOF ratio to 0.9 is missing but the time to TOF ratio to 0.8 is available:

First, for all subjects randomized to receive sugammadex IBW with times to recovery of the TOF ratio to 0.8 and 0.9 available, the difference between these two recovery times will be calculated. Next, the P5 of these differences will be added to the time to recovery of the TOF ratio to 0.8 of the subjects with missing times to recovery of the TOF ratio to 0.9. This will be used as the conservatively imputed missing time to recovery of the TOF ratio to 0.9.

- If the time from the start of administration of study drug to recovery of the TOF ratio to 0.9 is missing, the time to TOF ratio to 0.7 is available, but the time to TOF ratio to 0.8 is missing:

First, for all subjects randomized to sugammadex IBW with times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference in time between these two recovery times will be calculated. Next, the P5 of these differences will be added to the time to recovery of the TOF ratio to 0.7. This will be used as conservative imputation of the missing time to recovery of the TOF ratio to 0.9.

- If the time from the start of administration of study drug to recovery of the TOF ratio to 0.9 is missing, and the times to TOF ratio to 0.8 and to 0.7 are also missing: the P5 of the time to recovery in all subjects randomized to sugammadex IBW with an observed recovery time of the TOF ratio to 0.9 will be imputed.
- A corresponding procedure will be followed for imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8 and to 0.7.

3.5 Analysis Populations

3.5.1 Efficacy Analysis Population

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized subjects who:

- are dosed with both an NMBA and reversal agent (study treatment),
- have at least one post-randomization efficacy assessment.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population. Details on the approach to handling missing data are provided in Section 3.6.1 Statistical Methods.

3.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects, this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Percentage of the assigned dose criterion will be utilized to identify subjects that were potentially cross treated on the basis of ABW versus IBW. The criterion is as follows:

- <70% of the assigned dose would be utilized to reclassify subjects randomized to ABW as IBW subjects.
- >143% of the assigned dose would be utilized to reclassify subjects randomized to IBW as ABW subjects.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 3.6.2 Statistical Methods.

3.5.3 All Subjects Treated Population

The All Subjects Treated (AST) population consists of all randomized subjects who are dosed with both an NMBA and reversal agent (study treatment). Subjects will be included in the treatment group to which they are randomized for the analysis using the AST population. The AST population is used for reporting baseline characteristics.

3.5.4 Pharmacokinetic Population

Subjects with evaluable sugammadex concentrations at approximately 2, 5, 15, 60 min and 4-6 hr post-dose will be included for pharmacokinetic analysis.

3.6 Statistical Methods

Statistical testing and inference for efficacy and safety analyses are described in Section 3.6.1 and 3.6.2 respectively. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.8, Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution, due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at the $\alpha=0.05$ (2-sided) level. All the

analyses will be based on the real stratification stratum (i.e. rocuronium or vecuronium) that a subject actually received.

3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

All efficacy analyses will be based on the Full Analysis Set.

The primary efficacy endpoint is the time to recovery, defined as a TOF ratio (i.e. T_4/T_1 ratio) ≥ 0.9 after sugammadex administration. The primary efficacy analysis is the stratified log-rank test adjusted for the depth of block and NMBA. Formal tests for efficacy, in comparison of sugammadex dosed according to ABW versus IBW, will be conducted across NMBA. A stratified [stratification factors are depth of block and NMBA] Cox proportional hazards model, with Efron method of tie handling, will be used to assess the magnitude of the treatment difference between treatment arms. For the treatment effect, the hazard ratio and its 95% confidence interval will be reported from the same Cox model. Furthermore, to understand the impact of the depth of block and NMBA on the time to recovery to TOF ratio ≥ 0.9 after sugammadex administration, the efficacy analyses on the time to recovery to TOF ratio ≥ 0.9 stratified by depth of block and NMBA, are repeated separately by depth of block and by NMBA.

Secondary efficacy endpoints and some exploratory efficacy endpoints are summaries of time to recovery, including cumulative distribution plots, boxplots, and summary statistics (mean, standard deviation, median, geometric mean and its 95% CI) will be provided, as well as the proportions of subjects with prolonged time to recovery (>10 minutes) by treatment groups ABW versus IBW (pooled and separately by depth of block and by NMBA). In addition, the 95% confidence intervals for pairwise comparisons will be provided for time to recovery and proportions (both overall and separately by depth of block and by NMBA).

Table 1 summarizes the key efficacy analyses. For other exploratory efficacy endpoints, the summary statistics (mean standard deviation, median, geometric mean and its 95% CI) will be provided for the comparison of time to recovery for each sugammadex dose group and neostigmine in the setting of moderate block across NMBA. To note, the pairwise comparisons between two treatment arms in geometric means for time to recovery, is through the pairwise geometric mean ratio of the recovery time between two treatment arms and its 95% CI, which can be obtained from following:

- Take the logarithm of the recovery time and calculate the mean of the recovery time in the logarithmic scale for each treatment arm.
- Calculate the mean difference between the two treatment arms and its 95% CI based on t-distribution.
- Take the exponential transformation of the pairwise geometric mean difference in the logarithmic scale and its 95% CI.

Additional exploratory sensitivity analyses will be conducted for the key secondary efficacy analyses. These analyses are the same as the ones for the key secondary endpoints in Table 1, but with an imputation method that is conservative for evaluating the recovery time of participants dosed with sugammadex according to ABW as compared to participants dosed with sugammadex according to IBW. The “conservative” imputation method used in the sensitivity analyses is described in Section 3.4.4.

Table 1
Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach [†]	Statistical Method [‡]	Analysis Population	Missing Data Approach
Primary Endpoint/Hypothesis				
Time to recovery to a TOF ratio ≥ 0.9 for ABW and IBW dosing groups pooled across depth of block and NMBA	P	Stratified Log-rank test	FAS	Censored
Secondary Endpoints				
Time to recovery to a TOF ratio ≥ 0.9 for ABW and IBW dosing groups, separately by depth of block and by NMBA	S	Stratified Log-rank test	FAS	Censored
Distribution of time to recovery of TOFs of ≥ 0.7 , ≥ 0.8 and ≥ 0.9	S	Descriptive statistics (cumulative distribution plots, boxplots, mean, standard deviation, median, geometric mean and its 95% CI)	FAS	Explicit Imputation, Conservative Imputation [%]
Distribution of time to recovery of TOFs of ≥ 0.7 , ≥ 0.8 and ≥ 0.9 for ABW and IBW dosing groups, pooled across depth of block and NMBA	S	Pairwise comparison via the ratio of geometric mean and 95% CI	FAS	Explicit Imputation, Conservative Imputation [%]
Proportion of subjects with prolonged time to recovery (> 10 minutes) for ABW and IBW dosing groups, pooled across depth of block and NMBA	S	Pairwise difference in proportion and 95% CI using the stratified Miettinen and Nurminen method	FAS	Explicit Imputation, Conservative Imputation [%]
Distribution of time to recovery of TOFs of ≥ 0.7 , ≥ 0.8 and ≥ 0.9 for ABW and IBW dosing groups, separately by depth of block and by NMBA	S	Pairwise comparison via the ratio of geometric mean and 95% CI	FAS	Explicit Imputation, Conservative Imputation [%]
Proportion of subjects with prolonged time to recovery (> 10 minutes) for ABW and IBW dosing groups, separately by depth of block and by NMBA	S	Pairwise difference in proportion and 95% CI using the stratified Miettinen and Nurminen method	FAS	Explicit Imputation, Conservative Imputation [%]
[†] P=Primary approach; S=Supportive approach. [%] Imputation approaches described in Section 3.4.4. [‡] Statistical models are described in Section 3.6.1. The stratified Miettinen and Nurminen method uses the sample-size weighting scheme.				

3.6.2 Statistical Methods for Safety Analyses

All safety analyses will be based on the All Subjects as Treated population.

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and ECG measurements. To provide the comparable overall incidences with the label-based preferred terms of adverse events (AEs) used in the prior submission, the AE preferred terms are grouped based on BRIDION label for the United States:

- Nausea includes preferred terms nausea and procedural nausea
- Vomiting includes preferred terms vomiting and procedural vomiting
- Abdominal pain includes preferred terms abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, and epigastric discomfort
- Pain includes preferred terms pain and procedural pain
- Red blood cell count decreased includes preferred terms red blood cell count decreased, hemoglobin decreased, and hematocrit decreased
- Electrocardiogram QT interval abnormal includes preferred terms electrocardiogram QT interval abnormal and electrocardiogram QT interval prolonged
- Hypertension includes preferred terms hypertension, procedural hypertension, and blood pressure increased
- Hypotension includes preferred terms hypotension, procedural hypotension, and blood pressure decreased
- Tachycardia includes preferred terms tachycardia and heart rate increased
- Bradycardia includes preferred terms bradycardia and heart rate decreased

The analysis of safety results will follow a tiered approach (Table 2). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

The incidence of safety parameters will be summarized by treatment group and preferred term across all 5 dosing groups. Between-group comparisons will be made for each ABW and IBW dosing group of sugammadex and neostigmine pooled across NMBA, as well as separately by NMBA. The primary safety endpoints, as well as other supportive safety

endpoints are considered Tier 1 events. Both Tier 1 endpoints and Tier 2 events of clinical interest (i.e. adjudicated hypersensitivity, adjudicated anaphylaxis, clinically relevant sinus bradycardia, clinically relevant sinus tachycardia, other clinically relevant cardiac arrhythmia) will be estimated with 95% confidence interval by treatment groups using Clopper-Pearson method [1]. P-values (Tier 1 only) and 95% confidence interval (Tier 1 and Tier 2) will be provided for between-treatment differences using the stratified Miettinen and Nurminen method [2] with NMBA as a stratification factor. The sample-size weighting scheme is used for the stratified Miettinen and Nurminen method.

Adverse experiences (specific terms as well as System Organ Class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as Tier 1 endpoints will be classified as belonging to Tier 2 or Tier 3, based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have fewer than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AE and predefined limits of change.

Continuous measures, such as changes from baseline in laboratory and vital signs that are not pre-specified as Tier 1 endpoints, will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, blood pressure will be evaluated in participants with Tier 1 safety events.

Table 2 summarizes the safety tier and level of analysis for the safety endpoints.

Table 2 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint ^a	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Treatment emergent sinus bradycardia	X	X	X
	Treatment emergent sinus tachycardia	X	X	X
	Other treatment emergent cardiac arrhythmias	X	X	X
Tier 2	Adjudicated hypersensitivity		X	X
	Adjudicated anaphylaxis		X	X
	Clinically relevant sinus bradycardia		X	X
	Clinically relevant sinus tachycardia		X	X
	Other clinically relevant cardiac arrhythmia		X	X
	Any AE		X	X
	Any serious AE		X	X
	Any drug-related AE		X	X
	Any serious and drug-related AE		X	X

	Discontinuation due to AE		X	X
	Grouped AE		X	X
	Specific AEs, SOCs, or PDLCS ^b (incidence ≥ 4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCS ^b (incidence < 4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X
<p>a Adverse Experience references refer to both Clinical and Laboratory AEs. b Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier 2 endpoints. Abbreviations: CI = Confidence interval; SOC=System Organ Class; PDLCS=Pre-Defined Limit of Change; X = results will be provided.</p>				

3.6.3 Statistical Methods for Pharmacokinetic Analysis

For the following analysis all the subjects that have evaluable sugammadex concentrations will be included.

Individual dose normalized (dn) AUC_{0-inf} and dnC_{max} values for each of the sugammadex treatments (4mg/kg, 2mg/kg) will be natural log-transformed and evaluated with a linear fixed effect model having fixed terms for treatment and mode (IBW, ABW) and an interaction term for mode x treatment. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Both interaction term (mode x treatment) and mode will be tested for statistical significance at alpha=0.05 for each of the pharmacokinetic parameters. If either one or both of these terms for any or both of the pharmacokinetic parameters (dnAUC_{0-inf} and dnC_{max}) are statistically significant, then appropriate contrasts will be used to construct 90% confidence intervals (CIs) for the difference in least-squares (LS) means on the log scale for dnAUC_{0-inf} and dnC_{max} for each of the modes of administration. These CIs will then be exponentiated to obtain a 90% CIs for the true dnAUC_{0-inf} geometric mean ratio, GMR (4mg/kg versus 2mg/kg) and true dnC_{max} GMR (4mg/kg versus 2mg/kg) for each of the modes of administration.

If both interaction (mode x treatment) and mode terms of the model for both dnAUC_{0-∞} and dnC_{max} are not statistically significant at alpha=0.05, then the data for both modes of administration will be pooled and the final model will include treatment as fixed effect. Ninety percent (90%) CIs for the true dnAUC_{0-inf} GMR (4mg/kg versus 2mg/kg) and true dnC_{max} GMR (4mg/kg versus 2mg/kg) will be obtained from the model. For each mode of administration LS means and corresponding 95% CI obtained from the model will also be reported for dnAUC_{0-inf} and dnC_{max} by treatment.

Additionally, individual CL and V_d will be natural log-transformed and analyzed separately using linear effects model as previously described. For each mode of administration, LS means and corresponding 95% CIs for CL and V_d will be provided for each treatment.

For each mode of administration, individual values will be listed for each PK parameter (AUC_{0-inf}, AUC_{0-last}, C_{max}, dnAUC_{0-inf}, dnC_{max}, CL, V_{ss}, V_d, MRT, and t_{1/2}) by treatment and the following (non-model-based) descriptive statistics will be provided: N

(number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as $100 \times \text{standard deviation}/\text{arithmetic mean}$), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as $100 \times \sqrt{\exp(s^2) - 1}$), where s^2 is the observed variance on the natural log-scale).

Mean (standard error) and median (interquartile range) concentration-time plots for each treatment and mode of administration will be provided. Additionally for each mode of administration, individual ratios overlaid with GMR and corresponding 90% CI for each treatment for dnAUC0-inf and dnCmax will be provided. Plots of dnAUC0-inf versus ABW, dnAUC0-inf versus IBW, dnCmax versus ABW, dnCmax versus IBW will also be provided.

3.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

3.6.4.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender, BMI, race, ethnicity), baseline characteristics, surgical procedures, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

3.6.4.2 Population PK Analyses

Population-based methods of analysis may be explored at the completion of the study to further characterize the PK profiles within morbidly obese subjects and/or permit comparisons to historical data.

3.7 Interim Analyses

An interim pharmacokineticist and an interim statistician separate from the sugammadex development team, both of whom will be unblinded during the interim analysis, will perform the interim analysis. Only the available data from the subjects (approximately 64 subjects total treated with sugammadex [~ 16 per combination of dose (2mg/kg, 4mg/kg) and weight-based dosing ([ABW, IBW]), Table 3) for whom evaluable sugammadex PK samples are available will be included in the interim analysis.

Table 3 Sample Size for Interim Analysis

Approximate Number of subjects that will trigger Interim analysis			
2 mg/kg (ABW)	4 mg/kg (ABW)	2 mg/kg (IBW)	4 mg/kg (IBW)
16	16	16	16

The interim analysis of the pharmacokinetic parameters will be performed as previously described in Section 3.6.3. In addition to the model-based analysis, the interim unblinded statistician will also provide descriptive statistics for the pharmacokinetic parameters as

previously specified in Section 3.6.3. No individual listings for the PK parameters will be provided from the interim analysis for decision making.

The siDMC will review the results of the planned IA to make recommendations regarding the need to study the 16 mg/kg sugammadex dose. The decision about a 16 mg/kg dose will be based upon the evaluation of the 90% confidence intervals of the geometric mean ratio for both the Area Under the Curve_{0-inf} (AUC_{0-inf}) and Maximum Concentration (C_{max}) from the IBW and ABW data.

3.8 Multiplicity

In this study, the primary hypothesis is a single comparison of sugammadex dosed with ABW and IBW using one endpoint in the primary hypothesis; therefore, no corrections of multiplicity are required. Sample Size and Power Calculations.

3.9 Sample Size and Power Calculations

3.9.1 Sample Size and Power for Efficacy Analyses

This study will enroll approximately 200 subjects in total. If subjects are equally enrolled in each NMBA strata, there would be ~20 subjects in each of the five treatment groups within NMBA. However, due to enrollment kinetics, an effort will be made to enroll approximately 30% of vecuronium-treated subjects. Therefore, ~12 subjects will be randomized to each of the 5 treatment groups in the vecuronium stratum. The primary approach to the assessment of sample size is via simulation using the primary efficacy model to compare time to recovery for sugammadex dosed to ABW versus IBW. Time-to-recovery data are simulated using distributional assumptions derived from dose-ranging efficacy data within the sugammadex clinical program, assuming that dosing according to IBW would result in weight-based dosing approximately half of that from dosing according to ABW for either depth of block. In addition, the general conclusion in phase 2 studies shows that participants administered 1 mg/kg in moderate block and 2 mg/kg in deep block would have time to recovery increased by roughly 1 minute comparing to 2 mg/kg and 4 mg/kg, respectively. Based on that assumption, subjects in the ABW group have a median time-to-recovery of ~2.2 minutes with a standard deviation of ~1.3, while subjects in the IBW have median time to recovery of ~3.3 minutes with a standard deviation of ~2.3. [Figure 1](#) illustrates data simulated from the above assumption.

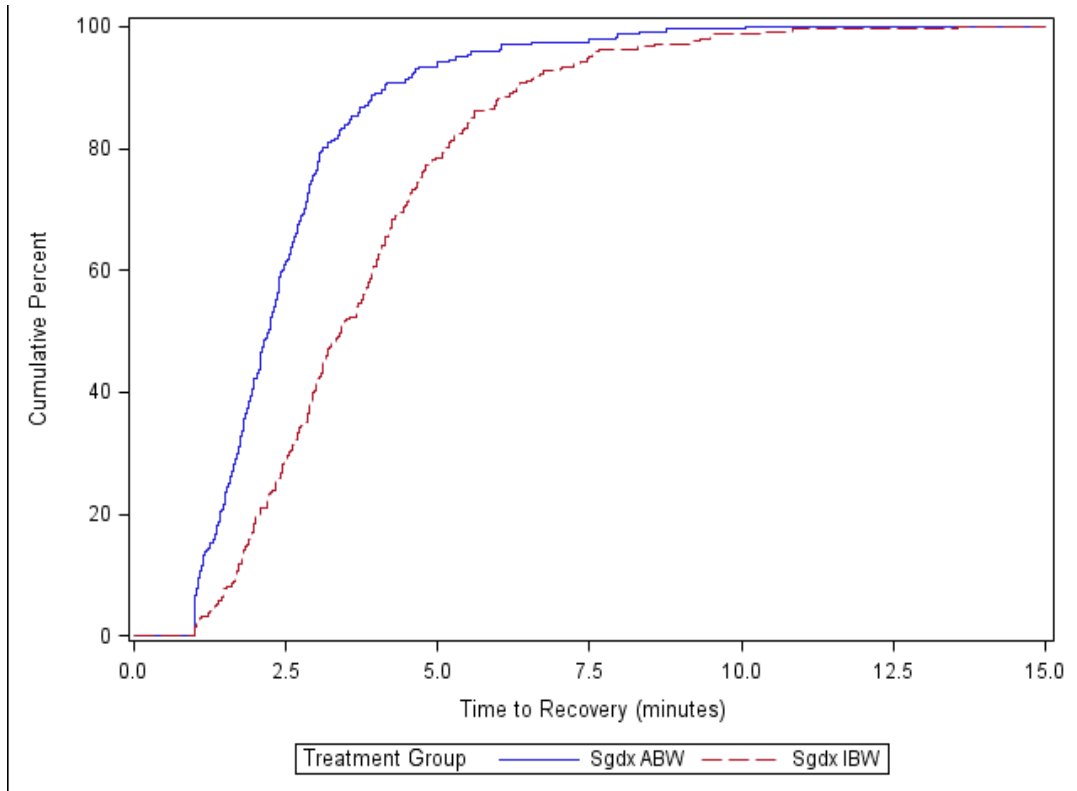


Figure 1: Illustrative Scenario of Time-to-Recovery to TOF ratio of 0.9 for ABW vs. IBW

The power calculation is based on a log-rank test, with an alpha level of 0.05 based on 1000 simulated samples and a function of sample size per group expected to be included in the analysis, and is carried out using [SAS v9.3]. Simulated power levels for the primary comparison as a function of sample size are shown in [Table 4](#).

Table 4: Simulated power levels for the primary comparison and related subgroup analyses as a function of sample size

N/arm	15	30	40	50	60	70	80
Power	51%	81%	89%	95%	98%	99%	>99%

Assuming the difference of median time-to-recovery in ABW and IBW groups is one minute based on the simulated data, a sample size of N~80 per group (across both NMBA and depth of block) provides estimated power of > 99% to detect a shift in time-to-recovery, as well as sufficient subject exposure to characterize safety and tolerability profiles of the distinct dosing paradigms. Although this study is well-powered for an efficacy comparison of sugammadex ABW and IBW, the subgroup analyses by NMBA and depth of block are likely underpowered, given the range of simulated power levels in [Table 4](#).

3.9.2 Sample Size for Safety Analyses

The probability of observing at least one event of any treatment emergent arrhythmia in this study depends on the number of subjects treated and the underlying percentage of subjects with an AE in the study population. If no events are observed among the 20 subjects in a treatment group, an upper bound of 95% CI for subjects with treatment emergent sinus bradycardia/tachycardia is ~16.8% (1 in every 6 subjects) in a treatment group. If no events are observed in an arm with 12 subjects, an upper bound of the 95% CI would change to ~26.5%.

The estimate of incidence and the upper bound of the 95% CI for the underlying percentage of subjects with any treatment emergent arrhythmia within a treatment group are provided in [Table 5](#). These calculations are based on the exact binomial method proposed by Clopper and Pearson (1934) [1]. The 95% CIs are provided in [Table 6](#) for the difference in incidence in any treatment emergent arrhythmia between the sugammadex and neostigmine groups although neostigmine is primarily an active control in this study as opposed to an active comparator and the main interest in this study is an estimation of the absolute incidence of AEs in the sugammadex arms.

Table 5
Estimate of Incidence of Any Treatment Emergent Arrhythmia and 95% Upper Confidence Bound
Based on Hypothetical Number of Subjects with Any Treatment Emergent Arrhythmia
Among 20 Subjects in a Treatment Group

Hypothetical Number of Subjects With Any Treatment Emergent Arrhythmia	Estimate of Incidence	95% Upper Confidence Bound [†]
1	5%	24.9%
2	10%	31.7%
3	15%	37.9%
4	20%	43.7%
5	25%	49.1%
[†] Based on the two-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934) [7].		

Table 6
Differences in Incidence in Any Treatment Emergent Arrhythmia between the Sugammadex and Neostigmine Groups Assuming Two-Sided 5% alpha level with 20 Subjects in a Treatment Group

Incidence of Adverse Event		Risk Difference	
Sugammadex (%)	Neostigmine (%)	Percentage Points	95% CI ^a
5%	10%	5	(-26%, 15.2%)
10%	20%	10	(-33.7%, 13.7%)
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group.			
^a Based on an asymptotic method (Farrington and Manning (1990)).			

3.9.3 Precision Estimates for Pharmacokinetic Parameters (AUC0-inf, Cmax)

The precision of the estimated ratios of geometric means (4 mg/kg versus 2 mg/kg) of pharmacokinetic parameters obtained from this study can be assessed by calculating the half-width of the 90% confidence intervals expected for the given sample size and assumed variability. The between-subject geometric coefficient of variation (GCV) for sugammadex AUC0-inf obtained from the population analysis is approximately 23%. Assuming a sample

size of 16 subjects per treatment and observed pooled between-subject standard deviation of 0.23 for AUC_{0-inf} on the natural log scale, then the half width of the 90% confidence intervals of GMRs for AUC_{0-inf} on the log scale will be 0.138. The lower and upper 90% confidence limits for the true GMRs will be given by OBS/1.148 and OBS*1.148 for AUC_{0-inf}, respectively, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC_{0-inf} was 1.00, then the 90% CIs for the GMR would be 0.87 to 1.15. These calculations also apply to the precision of the estimated geometric mean ratios for C_{max} as the between-subject GCV for C_{max} was assumed to be similar to that of AUC_{0-inf}.

3.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated pooled across depth of block and NMBA within each category of each subgroup. The following are classification variables:

- Age category (<65, 65-74, >74 years)
- Sex (female, male)
- Race (white, other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Region (United States, Non-United States)

Subgroup analyses/summaries will only be performed for those classification variables with ≥10% participants in each subgroup.

3.11 Compliance (Medication Adherence)

Compliance with dosage (in mg/kg) will be assessed based on the actual dosage (mg) of study medication administered and the reported body weight, per dosing occasion. Any dosage that differs by more than 10% from the planned dosage will be listed. No statistical tests will be performed with respect to treatment compliance.

3.12 Extent of Exposure

The extent of exposure to study medication will be summarized in a table presenting per treatment group the number of subjects who were randomized and received the study medication (i.e. were treated). If information on actual dose of study medication is available, summary statistics will be provided on the actual dose of study medication received (mg/kg).

3.13 Time Synchronization

During the course of the trial, there were two sources that might be used to reflect time of day. One source of time is from the laptop used for recording the TOF monitoring trace, and the other is the wall clock used for collecting other information. All the efficacy endpoints (recovery times to TOF ratios of 0.9, 0.8, 0.7, etc.), and the treatment start and stop times are

from the laptop, and all the other times (e.g. AE start time, start and stop times of cardiac arrhythmia events etc.) are collected based upon the wall clock.

Sites are instructed to synchronize the time on the laptop and the time on the wall clock before conducting TOF monitoring. The wall clock time at a reference moment and the corresponding laptop time are collected during the surgery for capturing any time difference between the laptop and the wall clock at the reference moment. If the sites synchronize the laptop time and the reference wall clock time as instructed, the reference wall clock time and the corresponding laptop time should be the same, and no time adjustment is needed. If the sites do not synchronize the two times correctly, the reference wall clock time and the laptop time are not the same and their difference could be used for adjusting the time points as follows:

- Compare the reference wall clock time collected through eCRFs and the corresponding laptop time collected on the TOF monitoring trace. Obtain the difference between the two times. We expect all data to be collected at least to the level of minutes. If the reference wall clock time has missing seconds, we will impute 00 for the seconds, which is the most conservative imputation. The reason imputing 00 for the seconds of reference wall clock time is considered the most conservative is because:
 - Adjusted start time of treatment = Collected start time of treatment + Reference wall clock time – corresponding laptop time
 - To make the adjusted start time of treatment as early as possible means imputing 00 which is the smallest value for seconds of reference wall clock time.
 - The reason to impute in a manner that creates the earliest adjusted start time is to attribute any safety findings that may occur during this unknown (and imputed) time frame to the treatment period.
- Use the time difference between the reference wall clock time and the corresponding laptop time to adjust all the time points from the laptop (including all the efficacy TOF time points, and the treatment start and stop times) to the wall clock time.
- All the other times collected directly through the wall clock remain unchanged.

Through this adjustment, all the analyses are consistently based on the wall clock time. The adjustment will be incorporated into the SDTM datasets, so that the SDTM variables (e.g. EPOCH) based on these timing variables are derived properly and provide linear traceability from SDTM to ADaM to TLFs.

4 REFERENCES

[1] Clopper C, and Pearson ES. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika* 26: 404–413

[2] Miettinen OS, and Nurminen M. (1985). "Comparative analysis of two rates", *Statistics in Medicine* 4: 213—226