



Schering-Plough

FDA Anesthetic and Life Support Advisory Committee Meeting

**Sugammadex Sodium Injection
(NDA 22-225)**

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Briefing Document (Background Package)

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**Organon USA,
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Table of contents

| | | |
|-------|--|----|
| 1. | EXECUTIVE SUMMARY | 12 |
| 2. | INTRODUCTION..... | 18 |
| 2.1 | Background for development | 18 |
| 2.2 | Proposed Indications and dosing recommendations..... | 19 |
| 2.3 | Clinical development program..... | 20 |
| 2.3.1 | Overview of clinical trials..... | 20 |
| 2.3.2 | Trial design..... | 22 |
| 2.3.3 | Organization of trials for proposed indications | 27 |
| 2.4 | Regulatory guidance and advice | 29 |
| 3. | UNMET MEDICAL NEED: HOW SUGAMMADEX FULFILLS UNMET NEED...31 | |
| 3.1 | Role of neuromuscular blocking drugs in general anesthesia..... | 31 |
| 3.2 | Current pharmacologic reversal of a nondepolarizing neuromuscular blockade | 32 |
| 3.3 | Sugammadex | 33 |
| 3.4 | Differences between sugammadex and acetylcholinesterase inhibitors | 34 |
| 3.5 | Potential role of sugammadex in neuromuscular blockade..... | 34 |
| 3.5.1 | Reversal of profound neuromuscular blockade..... | 34 |
| 3.5.2 | Residual Paralysis..... | 35 |
| 3.5.3 | Special patient populations | 38 |
| 3.5.4 | Cannot intubate/cannot ventilate (CICV) scenarios | 39 |
| 3.5.5 | Alternative to succinylcholine | 41 |
| 4. | CLINICAL PHARMACOLOGY OF SUGAMMADEX | 42 |
| 4.1 | Introduction and trial design | 42 |
| 4.2 | PK-PD modelling | 44 |
| 4.3 | Interpretation of results from clinical pharmacology trials | 45 |
| 4.3.1 | In vitro human biomaterials | 45 |
| 4.3.2 | Human pharmacokinetics..... | 46 |
| 4.3.3 | Human pharmacodynamics..... | 49 |
| 4.3.4 | Dose-response and dose selection | 49 |
| 4.3.5 | Population PK-PD model..... | 57 |
| 5. | SUMMARY OF EFFICACY | 61 |
| 5.1 | Description of trials supporting clinical efficacy | 61 |
| 5.2 | Summary of trial designs..... | 64 |
| 5.3 | Statistical analyses..... | 66 |

| | | |
|-------|---|-----|
| 5.4 | Demographics and baseline characteristics..... | 67 |
| 5.4.1 | Routine reversal: reversal at reappearance of T ₂ (Shallow NMB)..... | 67 |
| 5.4.2 | Routine reversal: reversal at 1-2 PTCs (Profound NMB)..... | 69 |
| 5.4.3 | Immediate reversal: reversal at 3 minutes after rocuronium..... | 70 |
| 5.5 | Efficacy results..... | 71 |
| 5.5.1 | Routine reversal: reversal at reappearance of T ₂ (Shallow NMB)..... | 71 |
| 5.5.2 | Routine reversal: reversal at 1-2 PTCs (Profound NMB)..... | 81 |
| 5.5.3 | Immediate reversal: reversal at 3 minutes after rocuronium..... | 89 |
| 5.5.4 | Other trials..... | 90 |
| 5.6 | Efficacy in subgroups..... | 91 |
| 5.6.1 | Drug-demographic interactions..... | 91 |
| 5.6.2 | Drug-drug interactions..... | 94 |
| 5.6.3 | Drug-disease interactions..... | 94 |
| 5.7 | Doses recommended for the proposed indication..... | 95 |
| 6. | SUMMARY OF SAFETY (INCLUDING TOXICOLOGY)..... | 96 |
| 6.1 | Safety monitoring methodology..... | 96 |
| 6.2 | Nonclinical data relevant to human safety..... | 101 |
| 6.3 | Extent of exposure and characteristics of subject population..... | 102 |
| 6.3.1 | Sugammadex vs. neostigmine..... | 102 |
| 6.3.2 | Sugammadex vs. placebo..... | 104 |
| 6.3.3 | Pooled Phase 1 - 3..... | 106 |
| 6.4 | Most common adverse events..... | 111 |
| 6.4.1 | Sugammadex vs. neostigmine..... | 111 |
| 6.4.2 | Sugammadex vs. placebo..... | 114 |
| 6.4.3 | Pooled Phase 1 – 3..... | 116 |
| 6.5 | Adverse events at least possibly trial-drug related..... | 122 |
| 6.5.1 | Sugammadex vs. neostigmine..... | 122 |
| 6.5.2 | Sugammadex vs. placebo..... | 122 |
| 6.6 | Deaths..... | 122 |
| 6.7 | Serious adverse events..... | 123 |
| 6.8 | Discontinuations due to an adverse event..... | 124 |
| 6.9 | Adverse events by subgroups..... | 124 |
| 6.9.1 | Demographic characteristics using the integrated dataset..... | 124 |
| 6.9.2 | Concomitant medication usage using the integrated dataset.. | 125 |
| 6.9.3 | Geriatric and pediatric subjects..... | 125 |
| 6.9.4 | Renal function..... | 125 |
| 6.9.5 | Pulmonary and cardiac function..... | 126 |
| 6.10 | Additional safety findings..... | 126 |

| | | |
|------------|--|-----|
| 6.10.1 | Reoccurrence of blockade/residual blockade..... | 127 |
| 6.10.2 | Anesthetic complications..... | 128 |
| 6.10.3 | Adverse events related to ventilation | 129 |
| 6.10.4 | Allergic reactions..... | 130 |
| 6.11 | Relationship of adverse events to treatment duration or dose | 130 |
| 6.12 | Adverse drug reactions | 132 |
| 6.13 | Clinical laboratory evaluations..... | 133 |
| 6.14 | Vital signs, ECGs and other physical findings..... | 134 |
| 6.14.1 | Vital signs..... | 134 |
| 6.14.2 | Electrocardiograms | 135 |
| 7. | BENEFIT RISK ASSESSMENT | 136 |
| 8. | REFERENCES..... | 148 |
| Appendix 1 | Tabular Listing of Clinical Trials | 143 |

| LIST OF TABLES | | Page |
|-----------------------|--|-------------|
| Table 1 | Sugammadex administered at reappearance of T ₂ following rocuronium administration: summary of the time to recovery of T ₄ /T ₁ to 0.9 (min) by dose, within and across trials (PP group) | 51 |
| Table 2 | Tolerance intervals for 2.0 mg/kg sugammadex administered at reappearance of T ₂ after rocuronium, 97.5% confidence (PP group) | 52 |
| Table 3 | Sugammadex administered at reappearance of T ₂ following vecuronium administration: summary of the time to recovery of T ₄ /T ₁ to 0.9 (min) by dose group, within and across trials (PP group) | 53 |
| Table 4 | Tolerance intervals for 2.0 mg/kg sugammadex administered at reappearance of T ₂ after vecuronium, 97.5% confidence (PP group) | 53 |
| Table 5 | Sugammadex administered at 1–2 PTC after rocuronium administration or 15 min after 0.6 mg/kg rocuronium: summary of the time to recovery of T ₄ /T ₁ to 0.9 (min) by dose, within and across trials (PP group) | 54 |
| Table 6 | Tolerance intervals for 4.0 mg/kg sugammadex administered at 1–2 PTC after rocuronium administration or 15 min after 0.6 mg/kg rocuronium, 97.5% confidence (PP group) | 55 |
| Table 7 | Sugammadex administered at 1–2 PTC following vecuronium administration: summary of the time to recovery of T ₄ /T ₁ to 0.9 (min) by dose, within and across trials (PP group) | 56 |
| Table 8 | Sugammadex administered at 3 or 5 minutes after 1.2 mg/kg rocuronium: summary of the time to recovery of T ₄ /T ₁ to 0.9 (min) by dose, within and across trials (PP group) | 57 |
| Table 9 | Recommended waiting times for re-administration with rocuronium or vecuronium after reversal with sugammadex | 59 |
| Table 10 | Demographics and baseline characteristics, IP administered at reappearance of T ₂ (ITT group) | 68 |
| Table 11 | Demographics and baseline characteristics, IP administered at 1-2 PTC (ITT group) | 69 |
| Table 12 | Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T ₂ following rocuronium to recovery of the T ₄ /T ₁ ratio to 0.9 (ITT group) | 71 |
| Table 13 | Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T ₂ following rocuronium or cisatracurium, respectively, to recovery of the T ₄ /T ₁ ratio to 0.9 (ITT group) | 72 |

| LIST OF TABLES (Continued) | | Page |
|-----------------------------------|---|-------------|
| Table 14 | Times (min.) from start of administration of IP, administered at reappearance of T ₂ after rocuronium/cisatracurium, to recovery of the T ₄ /T ₁ ratio to 0.9, 0.8 and 0.7 (ITT group)..... | 74 |
| Table 15 | Time (min.) from start of administration of 2.0 mg/kg sugammadex, administered at reappearance of T ₂ , to recovery of the T ₄ /T ₁ ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of rocuronium alone and those who received an intubating dose and at least one maintenance dose of rocuronium (ITT group)..... | 75 |
| Table 16 | Clinical signs of recovery, 2.0 mg/kg sugammadex, neostigmine and placebo administered at reappearance of T ₂ , rocuronium (ITT group)..... | 76 |
| Table 17 | Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T ₂ following vecuronium to recovery of the T ₄ /T ₁ ratio to 0.9 (ITT group)..... | 77 |
| Table 18 | Times (min.) from start of administration of IP, administered at reappearance of T ₂ after vecuronium, to recovery of the T ₄ /T ₁ ratio to 0.9, to 0.8 and to 0.7 (ITT group)..... | 79 |
| Table 19 | Time (min.) from start of administration of 2.0 mg/kg sugammadex, administered at reappearance of T ₂ , to recovery of the T ₄ /T ₁ ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of vecuronium alone and those who received an intubating dose and at least one maintenance dose of vecuronium (ITT group) | 80 |
| Table 20 | Clinical signs of recovery, 2.0 mg/kg sugammadex and neostigmine administered at reappearance of T ₂ , vecuronium (ITT group)..... | 81 |
| Table 21 | Summary of the time (min) from start of administration of sugammadex or neostigmine administered at 1-2 PTCs following rocuronium to recovery of the T ₄ /T ₁ ratio to 0.9 (ITT group) | 82 |
| Table 22 | Times (min.) from start of administration of IP, administered at 1-2 PTC after rocuronium, to recovery of the T ₄ /T ₁ ratio to 0.9, 0.8 and 0.7 (ITT group)..... | 84 |
| Table 23 | Time (min.) from start of administration of 4.0 mg/kg sugammadex at 1-2 PTC to recovery of the T ₄ /T ₁ ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of rocuronium alone and those who received an intubating dose and at least one maintenance dose of rocuronium (ITT group)..... | 85 |
| Table 24 | Summary of the time (min) from start of administration of sugammadex or neostigmine administered at 1-2 PTCs following vecuronium to recovery of the T ₄ /T ₁ ratio to 0.9 (ITT group) | 86 |

| LIST OF TABLES (Continued) | | Page |
|-----------------------------------|---|-------------|
| Table 25 | Times (min.) from start of administration of IP, at 1-2 PTC after vecuronium, to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 (ITT group) | 87 |
| Table 26 | Time (min.) from start of administration of 4.0 mg/kg sugammadex at 1-2 PTC to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of vecuronium alone and those who received an intubating dose and at least one maintenance dose of vecuronium (ITT group) | 88 |
| Table 27 | Summary of the time (min) from start of administration of rocuronium or succinylcholine to recovery of T_1 to 10% and to 90% (ITT group)..... | 90 |
| Table 28 | Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 controlled trials 19.4.301 and 19.4.302 | 103 |
| Table 29 | Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials with a placebo group..... | 105 |
| Table 30 | Number of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group | 106 |
| Table 31 | Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group | 108 |
| Table 32 | Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in Phase 3 controlled trials 19.4.301 and 19.4.302 | 112 |
| Table 33 | Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in pooled Phase 1-3 trials with a placebo group..... | 114 |
| Table 34 | Adverse events by MedDRA SOC and PT in at least 2.0% of the total sugammadex group or the placebo group in pooled Phase 1-3 trials | 118 |

| LIST OF FIGURES | | Page |
|------------------------|--|-------------|
| Figure 1 | Trials in the sugammadex clinical development program..... | 21 |
| Figure 2 | Recovery after sugammadex 2.0 mg/kg or neostigmine 50 mcg/kg at reappearance of T ₂ | 37 |
| Figure 3 | Recovery after sugammadex 4.0 mg/kg or neostigmine 70 mcg/kg at 1-2 PTCs..... | 38 |
| Figure 4 | Plot of geometric mean with corresponding 95% CI for the time from administration of 2.0 mg/kg sugammadex to recovery of the T ₄ /T ₁ ratio to 0.9 of all individual trials and pooled data, sugammadex administered at reappearance of T ₂ after administration of rocuronium (ITT group)..... | 73 |
| Figure 5 | Plot of geometric mean with corresponding 95% CI for the time from administration of 2.0 mg/kg sugammadex to recovery of the T ₄ /T ₁ ratio to 0.9 of all individual trials and pooled data, sugammadex administered at reappearance of T ₂ after administration of vecuronium (ITT group)..... | 78 |
| Figure 6 | Plot of geometric mean with corresponding 95% CI for the time from administration of 4.0 mg/kg sugammadex to recovery of the T ₄ /T ₁ ratio to 0.9 of all individual trials and pooled data, sugammadex administered at 1-2 PTC after administration of rocuronium (ITT group) | 83 |
| Figure 7 | Sugammadex safety datasets | 98 |

LIST OF ABBREVIATIONS

| | |
|------------------|--|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AIMS | Anesthetic Incident Monitoring Study |
| ALT | Alanine Aminotransferase |
| AMG | Acceleromyography |
| ANOVA | Analysis of Variance |
| aPTT | Activated Partial Thromboplastin Time |
| ASA | American Society of Anesthesiologists |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BUN | Blood Urea Nitrogen |
| CD | Cyclodextrin |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | Confidence Interval |
| CIAC | Central Independent Adjudication Committee |
| CICV | Cannot intubate, cannot ventilate |
| CK | Creatine Phosphokinase |
| CL _{CR} | Creatinine Clearance |
| CTR | Clinical Trial Report |
| CV | Coefficient of Variation |
| ECG | Electrocardiogram |
| EMG | Electromyography |
| FIV ₁ | Forced Inspiratory Volume in One Second |
| FDA | Food and Drug Administration |
| GGT | Gamma Glutamyl-transpeptidase |
| GI | Gastrointestinal |
| LDH | Lactate Dehydrogenase |
| ICH | International Conference on Harmonisation |
| IP | Investigational Product (sugammadex or comparator) |
| ITT | Intent-to-Treat |
| i.v. | Intravenous |
| MMG | Mechanomyography |
| NAG | N-acetyl Glucosaminidase |
| NOEL | No Observed Effect Levels |
| NMB | Neuromuscular Blockade |
| NMBA | Neuromuscular Blocking Agent |
| NYHA | New York Heart Association |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PT | Preferred Term |
| PT | Prothrombin Time |
| PTC | Post-tetanic Count |

| | |
|-----------------|--|
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SRBA | Selective Relaxant Binding Agent |
| $t_{1/2,\beta}$ | Terminal Elimination Half Life |
| TOF | Train of Four |
| V _{ss} | Volume of Distribution at Steady State |

DEFINITIONS

| | |
|--|---|
| ASA Class | Classification of physical status established by the American Society of Anesthesiologists: |
| ASA Class 1 | A normal healthy subject |
| ASA Class 2 | A subject with mild systemic disease |
| ASA Class 3 | A subject with a severe systemic disease that limits activity, but is not incapacitating |
| ASA Class 4 | A subject with an incapacitating systemic disease that is a constant threat to life |
| ASA Class 5 | A moribund subject not expected to survive 24 hours with or without operation |
| T ₁ | First twitch: amplitude of the first response to TOF stimulation, expressed as percentage of control T ₁ (%) |
| T ₂ | Second twitch: amplitude of the second response to TOF stimulation, expressed as percentage of control T ₁ (%) |
| T ₃ | Third twitch: amplitude of the third response to TOF stimulation, expressed as percentage of control T ₁ (%) |
| T ₄ | Fourth twitch: amplitude of the fourth response to TOF stimulation, expressed as percentage of control T ₁ (%) |
| TOF | Train of four; four consecutive square wave supra-maximal stimuli of 0.2 msec. duration delivered at a frequency of 2 Hz (repeated every 15 seconds) |
| T ₄ /T ₁ Ratio | Ratio of T ₄ over T ₁ (within one TOF stimulus) expressed in decimals; at complete recovery the T ₄ /T ₁ ratio is (approximately) 1.0 |
| Reappearance of T ₂ | First time point, from a sequence of three time points, that the T ₂ response is recorded |
| Re-occurrence of blockade | Re-occurrence of blockade based on the TOF-Watch SX [®] recording is defined as a decline in the T ₄ /T ₁ ratio from ≥ 0.9 to < 0.8 in at least three consecutive TOF values. |
| Residual blockade | Note: in the clinical trial reports and other documents issued prior to the CTD the term “residual recurarization” has been used instead of “residual blockade”. However, these are equivalent terms. |
| Time of recovery T ₁ to 10% | First time point from a sequence of three time points that the T ₁ response is ≥ 10% of the final T ₁ (all three consecutive T ₁ responses must be ≥ 10% of the final T ₁). For the time of recovery of T ₁ to 25%, 50%, 75% and 90%, the same principle applies as to the recovery of T ₁ to 10%. |

1. EXECUTIVE SUMMARY

Sugammadex is a modified γ -cyclodextrin and a novel Selective Relaxant Binding Agent (SRBA) which is able to reverse both shallow and profound aminosteroid-induced neuromuscular blockade (NMB), unlike currently available reversal agents such as neostigmine. Upon complexation with the neuromuscular blocking agents (NMBA), rocuronium or vecuronium bromide, sugammadex prevents the binding of the NMBAs to the nicotinic receptors in the neuromuscular junction and, hence, results in reversal of NMB. This unique mechanism of action distinguishes sugammadex from the class of anticholinesterase inhibitor reversal agents.

The advantage of using sugammadex as a NMB reversal agent is that sugammadex is very water soluble and does not possess intrinsic biological activity and therefore is unlikely to cause side-effects. Moreover, due to the high binding constant between sugammadex and rocuronium or vecuronium, residual blockade or re-occurrence of blockade is not expected if the recommended dose of sugammadex is administered.

Furthermore, select NMBAs (e.g., rocuronium) have been shown to have a higher affinity to sugammadex than to the nicotinic receptor, allowing the reversal of profound NMB. Due to its mechanism of action, there is no need for concomitant administration of antimuscarinic drugs, drugs that carry their own unfavorable side effect profile [20,21,22,23].

In situations requiring immediate reversal such as a Cannot Intubate, Cannot Ventilate (CICV) or even routine rapid sequence induction, current methods using succinylcholine have been shown to produce significant side effects including cardiovascular complications (e.g., sinus bradycardia, nodal rhythms, ventricular dysrhythmias, and cardiac arrest). Sugammadex would also provide an efficacious and safe alternative in this area of anesthesia with the ability to quickly reverse a rocuronium-induced NMB compared to succinylcholine alone.

Proposed Indications

The sponsor is seeking approval for routine reversal of shallow and profound rocuronium- or vecuronium-induced NMB and for immediate reversal of rocuronium-induced blockade at 3 minutes after administration of rocuronium.

Specifically the proposed dosing recommendations for sugammadex are:

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For routine reversal:

1. "A dose of 2.0 mg/kg sugammadex is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium- or vecuronium-induced blockade."
2. "A dose of 4.0 mg/kg sugammadex is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium- or vecuronium-induced blockade."

For immediate reversal:

3. "If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg sugammadex is recommended."

Number and Type of Trials

A total of 30 Phase 1-3 clinical trials were conducted and included in the sugammadex submission. There are a total of 7 Phase 1 trials and 23 Phase 2-3 trials. The Phase 2-3 trials include routine reversal at reappearance of T_2 , (shallow blockade), routine reversal at 1-2 PTCs or 15 min (profound blockade), immediate reversal, and other efficacy trials which assessed routine clinical usage and use after infusion of rocuronium. There are two pivotal trials (Trials 19.4.301 and 19.4.302) which compared the use of sugammadex in shallow and profound blockade, respectively, versus neostigmine. In addition, there are 5 Special Population trials which investigated the use of sugammadex in the renally impaired, geriatric, pediatric, pulmonary, and cardiac populations. In total, 2054 subjects have been exposed to sugammadex in Phase 1-3 trials and 1926 of those subjects have received sugammadex following administration of an NMBA (e.g. rocuronium).

Results**Primary Efficacy Parameter**

With the exception of one trial of the 23 Phase 2-3 Trials, efficacy was measured by the T_4/T_1 ratio to 0.9 as the primary endpoint since this has been shown to correlate well with a safe recovery from neuromuscular blockade. However, in Trial 19.4.303 (Immediate Reversal), the primary efficacy measured was T_1 10% since this was a comparative trial versus succinylcholine and T_4/T_1 ratios are not suitable to determine the degree of recovery of the depolarizing agent succinylcholine.

Efficacy Results

There are three trials that provide substantial evidence to support the use of the sugammadex in reversal of shallow (reappearance of T_2) and profound (1-2 PTC) neuromuscular blockade. One trial is used to support the indication for immediate reversal (reversal at 3 minutes after the administration of rocuronium). A short description of the efficacy results from these trials is presented below:

Routine Reversal

Trial 19.4.301 evaluated the efficacy of 2.0 mg/kg sugammadex vs. neostigmine in reversal (at the reappearance of T_2) of a NMB induced by rocuronium or vecuronium; Trial 19.4.310 evaluated the efficacy of sugammadex in reversal (at the reappearance of T_2) of a rocuronium-induced NMB vs. neostigmine in reversal (at the reappearance of T_2) of a cisatracurium-induced NMB. In both trials sugammadex resulted in statistically significant ($p < 0.0001$) and clinically relevant reductions in the (geometric) mean times to recovery of the T_4/T_1 ratio to 0.9 compared to neostigmine. In subjects who received a maintenance dose of the NMBA (compared with subjects who only received an intubating dose) or in subjects who received sevoflurane vs. subjects who received propofol, no clinically relevant increases in recovery times would require a sugammadex dose adjustment. Pooling results of all trials that assessed reversal (at the reappearance of T_2) of a rocuronium- or vecuronium-induced NMB provide supportive evidence to the individual results of Trials 19.4.301 and 19.4.310.

Trial 19.4.302 evaluated the efficacy of 4.0 mg/kg sugammadex vs. neostigmine in routine reversal of a profound block (i.e., at 1-2 PTCs) induced by either rocuronium or vecuronium. In this trial, sugammadex resulted in a statistically significant ($p < 0.0001$) and clinically relevant reduction in the (geometric) mean time to recovery of the T_4/T_1 ratio to 0.9 compared to neostigmine. Pooling results of all trials that assessed reversal of a profound rocuronium- or vecuronium-induced NMB support the individual results of Trial 19.4.302.

Immediate Reversal

Trial 19.4.303 directly evaluated the efficacy of 16.0 mg/kg sugammadex in an immediate reversal setting (3 minutes following a NMB induced by 1.2 mg/kg rocuronium) compared to spontaneous recovery from a NMB induced by 1.0 mg/kg succinylcholine. In this trial, sugammadex resulted in a statistically significant ($p < 0.0001$) and clinically relevant reduction in the (geometric) mean time to recovery of T_1 to 10% compared to spontaneous recovery from succinylcholine (2.7 minutes faster). In the 1.2 mg/kg rocuronium + sugammadex group, T_4/T_1 ratios were also determined. Relative to the time of administration of rocuronium, the mean recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 4.4, 4.6 and 5.4 minutes, respectively; relative to the time of administration of sugammadex, the mean recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 1.3, 1.5, and 2.2 minutes.

Safety Results

Safety data collected from all 30 trials conducted during the clinical development program demonstrate that sugammadex is safe and well tolerated. The most commonly reported AEs (all AEs and related AEs) in sugammadex-treated subjects were routinely managed events that are typically seen in a surgical/post-surgical population. Two deaths unrelated to sugammadex occurred in sugammadex-treated subjects. The pattern and incidence of SAEs did not appear to be notably different in sugammadex-treated subjects compared with placebo- and neostigmine-treated subjects. Only 4 out of 1926 subjects treated with sugammadex experienced re-occurrence of blockade (based on TOF Watch SX[®] measurements) at the proposed marketed doses (2 subjects treated with 2.0 mg/kg and 2 subjects treated with 16.0 mg/kg); all other cases occurred at sub-optimal doses (< 2.0 mg/kg) of sugammadex.

The overall incidence of AEs and SAEs did not appear to be related to the dose of sugammadex administered. The only individual AE (irrespective of relationship) that appeared to be dose-related was anesthetic complication. With regard to anesthetic complication, the fact that the 16 mg/kg sugammadex treatment group was the only dose group whose incidence was notably higher relative to placebo suggests that this AE may be related to the fast recovery associated with administering a high dose. Dysgeusia was the only related AE that appeared to be dose-related (among healthy non-anesthetized volunteers enrolled in the Phase 1 trials).

Although 3.0% of all subjects in the total sugammadex group experienced AEs (e.g., coughing, bucking) coded to “anesthetic complication”, these typically occurred

during trials in which sugammadex was administered early during the surgical procedure, thereby removing one of the components of balanced anesthesia. As a result, the level of anesthesia may not have been deep enough for the ongoing surgical procedure. Airway complications, delayed recovery from anesthesia, unwanted awareness during anesthesia, and cardiac-related anesthetic complications in sugammadex-treated subjects occurred at very low incidences and/or occurred at incidences that were comparable to or lower than incidences observed in neostigmine-treated subjects.

Few AEs (and SAEs) related to ventilation were reported. One subject (a healthy volunteer) had a probable allergic reaction following his first exposure to sugammadex that was self-limiting.

Although there were larger numbers of subjects in certain demographic subgroups, the incidences of AEs of special interest [anesthetic complications, dysgeusia, allergic reactions, and re-occurrence of blockade/residual blockade (i.e., the AEs that met the criteria established for an ADR) (Section 6.12) among subgroups who received sugammadex were similar with respect to age, gender, ethnicity, and race.

Subjects with impaired renal function (vs. subjects with normal renal function) were also studied because sugammadex is predominantly cleared via the kidneys; therefore, renal impairment would be expected to increase subjects exposure to sugammadex and the NMBA. In Trial 19.4.304, renally-impaired subjects had a prolonged and 17-fold higher exposure to sugammadex and a prolonged and 4-fold higher exposure to rocuronium compared to subjects with normal renal function. Nonetheless, the safety profiles between subjects with normal renal function vs. subjects with impaired renal function were not appreciably different. This is an important finding given that effective dialysis was not consistently demonstrated in Trial 19.4.304. Nonetheless, the use of sugammadex in severe renally-impaired subjects (creatinine clearance < 30 mL/min) will be strongly discouraged.

Extensive data collected from nonclinical trials and the population PK-PD simulations identified 3 specific drugs (toremifene, flucloxacillin and fusidic acid) and a class of compounds (hormonal contraceptives) that may potentially interact with sugammadex. However, because no formal clinical interaction trials have been conducted in adults with sugammadex and other drugs, anesthesiologists are recommended to monitor subjects for any potential drug interactions once sugammadex is used in clinical practice.

In subjects who received a NMBA in the pooled Phase 2 - 3 trials, observed changes in hematological parameters occurred as expected for surgical subjects; no dose

trends were observed for any of the hematology analytes, and the incidence of hematology-related AEs was very low overall. In addition, no dose related trends were observed for any of the biochemistry analytes, and the incidence of biochemistry-related AEs was very low overall. Laboratory data indicative of kidney function showed no evidence of renal damage in subjects after the administration of sugammadex. In addition, biochemistry results showed no clinically important effects of sugammadex on liver function.

No clinically important findings related to the administration of sugammadex were observed on vital signs that would limit its use. Based on two thorough QTc trials and pooled Phase 1-3 data, it was shown that sugammadex would not have a clinically important effect on an ECG.

Overall Conclusion

Sugammadex is an innovative compound in the field of anesthesia. It has the unique ability to reverse **both** shallow and profound NMB which is not possible with current reversal agents. Its mechanism of action has an advantage over the currently available agents such as neostigmine. Sugammadex does not affect the cholinergic nervous system and also excludes the use of concomitant anti-muscarinic drugs. Therefore, this unique action avoids the undesired autonomic nervous system and anti-muscarinic side effects which are usually associated with currently used compounds such as neostigmine and glycopyrrolate. In addition, the use of a combination of rocuronium and sugammadex will allow clinicians to achieve an immediate reversal in cases currently using succinylcholine, but without the negative side effect profile of succinylcholine.

Sugammadex has been shown to be efficacious and well tolerated and would provide clinicians with a predictable and reliable method to reverse NMB at the end of surgery.

2. INTRODUCTION

2.1 Background for development

Reversal of drug-induced NMB for surgical interventions is given to accelerate recovery from the effects of NMBAs. All of the currently available reversal agents, such as neostigmine and edrophonium, are acetylcholinesterase inhibitors. These drugs slow the rate of metabolism of acetylcholine and hence increase the amount of the neurotransmitter available to compete with the NMBA for occupancy of the nicotinic receptor at the neuromuscular junction. These reversal agents have no effect on the metabolism or elimination of the NMBAs themselves. As more acetylcholine molecules interact with nicotinic receptors, normal muscle function is restored. However, there is an upper limit to the effect of the current reversal agents; once maximum inhibition of the acetylcholinesterase activity has occurred; neural release of additional acetylcholine becomes the rate-limiting step in restoration of normal muscle function. Consequently, these agents are ineffective in reversing a profound NMB [1,2,3]. Additionally, the duration of action of some reversal agents may be shorter than the activity of the NMBAs themselves, leading to reappearance of the NMB, or residual paralysis [4]. There is a growing consensus that adequate recovery from a NMB is not achieved until a T_4/T_1 ratio of more than 0.8 to 0.9 is attained [5,6,7]. Unfortunately, several authors have also reported that an unsuspected and significant residual NMB, represented by T_4/T_1 ratios of 0.7 or below, is a common occurrence in the recovery room [8,9,10,11]. Incomplete recovery from NMB is associated with clinically relevant impairment of pulmonary function and obstruction of the upper airway [12,13,14]. It has also been demonstrated that this may result in an increased incidence of post-operative pulmonary disease such as pneumonia and/or atelectasis [15].

In addition to the limitations in efficacy, currently available reversal agents also have significant side effects due to increased acetylcholine concentrations. Due to activation of acetylcholine receptors, especially those in the heart and smooth muscle, neostigmine (and other acetylcholinesterase inhibitors) may cause hypotension, bradycardia, cardiac arrhythmias, abdominal cramps, bronchoconstriction, increased salivation, vomiting and diarrhea due to increased muscarinic receptor interaction [4,16,17,18,19]. In practice, a muscarinic receptor antagonist, such as atropine or glycopyrrolate, is administered with the acetylcholinesterase inhibitor to antagonize the muscarinic side effects. However, the muscarinic antagonists themselves cause a number of side effects, such as

tachycardia, dry mouth, cardiac arrhythmias, urinary retention and blurred vision [20,21,22,23].

In view of the safety and efficacy profile of currently available reversal agents, new reversal agents could offer room for marked improvement in the field of anesthesia. The criteria set for the development of a new reversal agent includes: (1) superior efficacy; (2) an onset of action not slower than neostigmine; (3) a long enough duration of action to prevent re-occurrence of blockade; (4) the capability of reversing a profound NMB; and (5) minimal side effects.

Cyclodextrins (CDs) are well-known for their capability to form inclusion complexes with various drug molecules [24]. The potential advantage of using CDs as reversal agents is that CDs are generally very water soluble, do not possess intrinsic biological activity and, therefore, are unlikely to result in the development of significant side effects. In addition, because potential CD-based reversal agents would form complexes with the NMBA, they may be useful for the reversal of a profound NMB for which the anticholinesterase inhibitor reversal agents (e.g., neostigmine) are not suitable [25].

Sugammadex is a modified γ -cyclodextrin, a novel Selective Relaxant Binding Agent (SRBA). Preclinical data also has distinguished this compound with the ability to reverse a profound aminosteroid-induced NMB. Upon complexation with the NMBAs rocuronium or vecuronium bromide, sugammadex prevents the binding of the NMBAs to the nicotinic receptors in the neuromuscular junction and, hence, results in reversal of NMB in vivo. This unique mechanism of action distinguishes sugammadex from the class of anticholinesterase inhibitor reversal agents. Furthermore, select NMBAs (e.g. rocuronium) have been shown to have a higher affinity to sugammadex than to the nicotinic receptor, allowing the reversal of profound NMB. The mechanism of action of sugammadex does not result in stimulation of the cholinergic nervous system, thereby avoiding the undesired autonomic nervous system side effects associated with neostigmine and other similar drugs [4,16,17,22]. Additionally, because of its mechanism of action, there is no need for concomitant administration of antimuscarinic drugs, drugs that carry their own unfavorable side effect profile [20,21,22,23].

2.2 Proposed Indications and dosing recommendations

The sponsor is seeking approval to market sugammadex for routine reversal of shallow or profound NMB induced by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium. Specifically, the sponsor is proposing the following dosing recommendations:

For routine reversal:

1. "A dose of 2.0 mg/kg sugammadex is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium- or vecuronium-induced blockade."
2. "A dose of 4.0 mg/kg sugammadex is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium- or vecuronium-induced blockade."

For immediate reversal:

3. "If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg sugammadex is recommended."

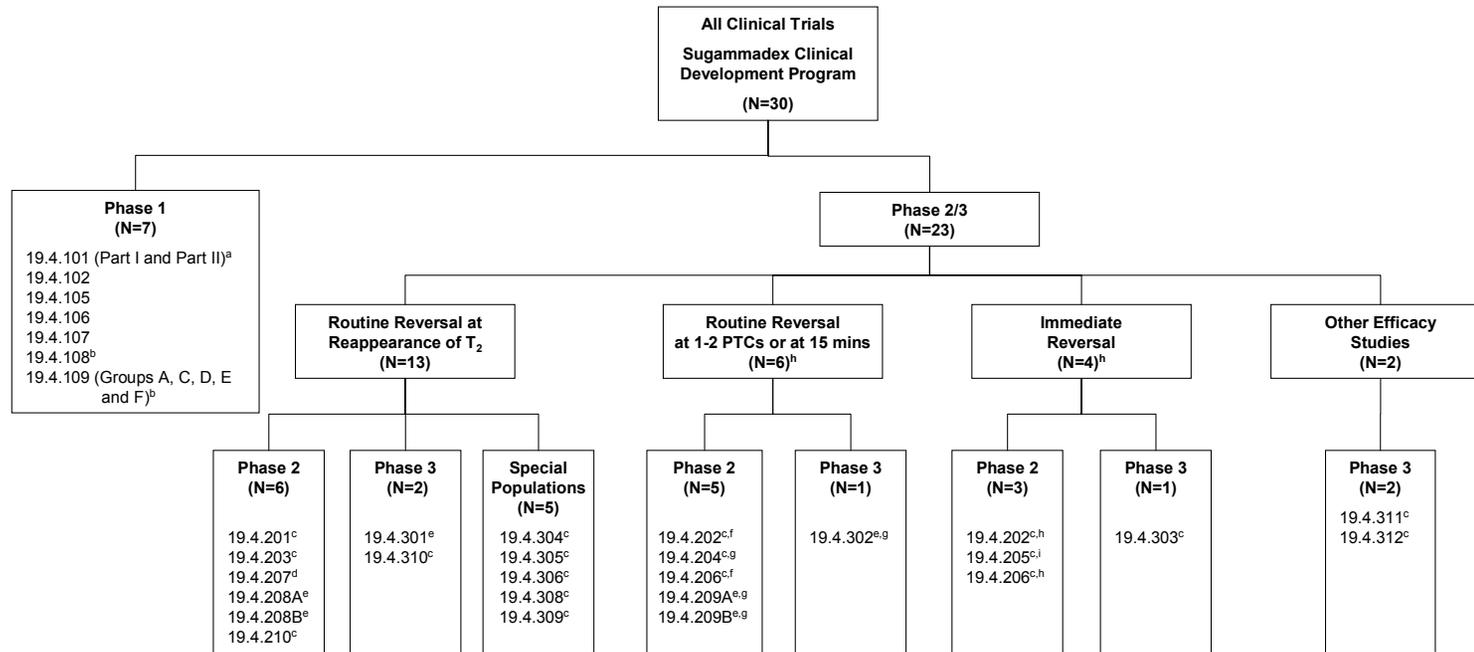
2.3 Clinical development program

2.3.1 Overview of clinical trials

The sugammadex clinical development program consisted of 30 clinical trials (Figure 1) (Appendix 1), including 7 Phase 1 trials (Trials 19.4.101, 19.4.102, 19.4.105, 19.4.106, 19.4.107, 19.4.108, and 19.4.109), 12 Phase 2 trials (Trials 19.4.201-19.4.207, Trials 19.4.208 A and B, Trials 19.4.209 A and B, and Trial 19.4.210), and 11 Phase 3 trials (Trials 19.4.301-19.4.306 and 19.4.308-19.4.312). [It should be noted that there were no trials with the designation "19.4.103", "19.4.104" or "19.4.307".] Sugammadex was administered following NMB (induced by rocuronium, vecuronium or pancuronium) in at least parts of 26 of the 30 trials, including all of the Phase 2 (n=12) and Phase 3 (n=11) trials and in 3 of the Phase 1 trials (Trials 19.4.101 [Part II only], 19.4.108 and 19.4.109 [Groups A and F only]). Sugammadex was administered to healthy volunteers with no concurrent anesthetic or NMBA in at least parts of 6 of the 7 Phase 1 trials (Trials 19.4.101 [Part I only], 19.4.102, 19.4.105, 19.4.106, 19.4.107 and 19.4.109 [Groups C, D and E only]).

These 30 trials provide adequate and sufficient safety and efficacy data to support the use of sugammadex for the proposed indication.

Figure 1 Trials in the sugammadex clinical development program



- a. sugammadex administered after rocuronium in Part II for Trial 19.4.101.
- b. sugammadex administered at the same time as rocuronium or vecuronium in Trial 19.4.108 and at the same time as rocuronium in Groups A and F for Trial 19.4.109.
- c. sugammadex administered after rocuronium.
- d. sugammadex administered after rocuronium, vecuronium, or pancuronium.
- e. sugammadex administered after rocuronium or vecuronium.
- f. Routine reversal at 15 minutes.
- g. Routine reversal at 1-2 PTCs.
- h. Studies 19.4.202 and 19.4.206 investigated immediate reversal at 3 minutes as well as routine reversal at 15 minutes; therefore, these studies are depicted twice in this figure.
- i. Immediate reversal at 5 minutes.

2.3.2 Trial design

Assessment of neuromuscular function

For efficacy, neuromuscular function was measured with a train-of-four (TOF) stimulus (i.e., using the TOF-Watch SX[®]; see discussion below) in all 23 efficacy trials conducted during the clinical development program. TOF stimulation consisted of four supramaximal stimuli delivered to the ulnar nerve (frequency of 2 Hz), which provoke four contractions (twitches) of the thumb. Typically the subsequent muscle contractions after a series of nerve stimulations diminished after administration of a non-depolarizing muscle relaxant like rocuronium or vecuronium ('fading'), which is caused by a lack of readily releasable acetylcholine in response to a higher rate of stimulation in the presence of the NMBA; the response of a muscle to electrical stimulation reaches maximum fading after four twitches. Counting the number of twitches in response to TOF stimulation (TOF count) or by comparing the height of the fourth twitch with the height of the first twitch (TOF ratio, T_4/T_1 ratio) are widely accepted methods of assessing the efficacy of NMBAs and reversal agents. A T_4/T_1 ratio of < 0.9 indicates impaired pharyngeal function with the risk of aspiration in the case of regurgitation, and a T_4/T_1 ratio of < 0.7 indicates subjects will additionally have an impaired hypoxic ventilatory response [26]. Recovery to a T_4/T_1 ratio of 0.9 or above has been shown to correlate well with adequate and safe recovery from a NMB [27]. Additionally, clinical signs of recovery from anesthesia were assessed in a subset of trials (i.e., level of consciousness, 5-second head lift, and a check for general muscle weakness, prior to the subject's transfer to the recovery room after extubation and prior to discharge from the recovery room) based upon a request made by the Food and Drug Administration (FDA) (Section 2.4). It should be noted that there is general agreement that assessments of clinical signs of recovery do not correlate very well with complete functional recovery from a NMB [5] and that objective monitoring should be used to monitor residual blockade with confidence [28,29]. Hence, clinical assessments were included as secondary endpoints in the Phase 3 trials only.

Objective monitoring of neuromuscular function (i.e., measurement of the TOF ratio) can either be performed by electromyography (EMG), mechanomyography (MMG) or acceleromyography (AMG). EMG has been shown to underestimate the neuromuscular block induced by non-depolarizing agents [30,31]. MMG, historically regarded as the gold standard for objective measurement of neuromuscular block, is not commercially available anymore and is not used in clinical practice. Its limited availability (only some very specialized research centers still have MMG available), its size and complex set-up and operation prevent the use of MMG in a clinical program of the magnitude conducted for sugammadex. In contrast, AMG is readily

available, validated, easy to set-up and compact enough to be used for all subjects; therefore, AMG was used for collecting neuromuscular data in the sugammadex clinical development program.

Justification for trial endpoints

The primary efficacy parameter during the clinical development of sugammadex was the recovery of neuromuscular blockade from the administration of Investigational Product (IP) to a T_4/T_1 ratio of 0.9. Secondary endpoints included the time from start of administration of IP to a T_4/T_1 ratio of 0.8 and to 0.7. These parameters signal that there is an index of satisfactory recovery; that the airway is protected and ventilation has recovered adequately.

In Trial 19.4.303 succinylcholine was compared to the combination of rocuronium and sugammadex. Since succinylcholine is a depolarizing NMBA the T_4/T_1 ratio cannot be used. Therefore in this trial the primary endpoint was defined as the time from start of administration of rocuronium or succinylcholine to recovery of T_1 to 10%. The secondary endpoint was the time from start of administration of rocuronium or succinylcholine to recovery of T_1 to 90%. At 3 minutes after a bolus dose of succinylcholine, T_1 is already starting to recover [26]. Thus, at 3 minutes post NMBA dose, recovery of succinylcholine is preceding recovery of rocuronium followed by sugammadex. However, clinical recovery, such as diaphragm movement and return of ventilation on the capnogram, is not observed before 4.5 minutes post dose for succinylcholine [27]. Therefore, a useful surrogate parameter for these signs of clinical recovery should reflect recovery after 4.5 minutes post administration of succinylcholine. After 0.6 and 1.0 mg/kg succinylcholine T_1 is recovered to 10% at 5.1 and 6.2 minutes respectively [32]. T_1 90% is not reached before approximately 9 to 10 minutes after a dose of 1.0 mg/kg succinylcholine [33,34,35,36,32]. According to the results of Trial 19.4.202, T_1 recovered to 10% already at about 4 minutes after administration of 0.6 mg/kg rocuronium (i.e. 1 minute after sugammadex) and at 5-6 minutes (i.e. 2-3 minutes after sugammadex) after rocuronium T_1 was 90%. So, when comparing these data it seemed that recovery of T_1 later than 4.5 minutes after rocuronium reversed by sugammadex is preceding recovery of T_1 after succinylcholine. Therefore, the primary efficacy parameter, for Trial 19.4.303 was chosen as time to recovery to T_1 of 10.

Clinical signs of recovery were assessed in most Phase 3 trials as secondary efficacy parameters (19.4.301-19.4.303, 19.4.305, and 19.4.308 -19.4.311).

Central Independent Adjudication Committee

A Central Independent Adjudication Committee (CIAC) was established for the following Phase 3 Trials: 19.4.301-19.4.305, and 19.4.308-19.4.312. The task of the CIAC was to assess objectively and independently, the acceptability of deviations from the neuromuscular transmission monitoring guidelines for clinical trials. The TOF-Watch® SX trace was submitted to the CIAC when there was a difference in the opinion on the evaluation of the trace between the investigator and the sponsor.

NMBA used in clinical trials

The effect of sugammadex was studied after administration of different types and doses of rocuronium and vecuronium.

Most trials were performed with rocuronium. The following trials were done with an intubating dose of rocuronium of:

- 0.6 mg/kg: 19.4.301, 19.4.302, 19.4.310, 19.4.201, 19.4.203, 19.4.204, 19.4.207, 19.4.210, 19.4.304, 19.4.305, 19.4.306, 19.4.308, 19.4.309, 19.4.311 and 19.4.312
- 0.9 mg/kg: 19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B
- 1.0 mg/kg: 19.4.206
- 1.2 mg/kg: 19.4.303, 19.4.204, 19.4.205, 19.4.206

In some trials administration of maintenance doses of rocuronium were allowed per protocol when needed according to the investigator: 0.1-0.2 mg/kg (19.4.208A, 19.4.208B, 19.4.209A, 19.4.209B and 19.4.301), 0.15 mg/kg (19.4.204, 19.4.302, 19.4.305, 19.4.308, 19.4.311). In one trial, maintenance doses were administered according to routine practice to maintain prolonged block (19.4.203). In one trial the bolus administration of rocuronium was followed by continuous infusion of rocuronium for maintenance, starting with an infusion rate of 7 µg/kg/min with subsequent adjustment by titration to maintain a depth of neuromuscular blockade of zero responses to TOF and PTC of ≤ 10 responses (19.4.312).

In the trials where NMB was induced with vecuronium the intubation dose was 0.1 mg/kg (19.4.301, 19.4.302, 19.4.207, 19.4.208A and B, 19.4.209A and B). In some trials maintenance doses were allowed per protocol: 0.015 mg/kg (19.4.302), 0.02-0.03 mg/kg (19.4.301, 19.4.208B, 19.4.209B) and 0.02-0.04 mg/kg (19.4.208A, 19.4.209A).

In Trial 19.4.303 rocuronium followed by sugammadex was compared with 1.0 mg/kg succinylcholine. A dose of 1.2 mg/kg rocuronium was used, which is 4 times the ED₉₀ for rocuronium and produces intubating conditions similar to succinylcholine.

In Trial 19.4.310 the combination rocuronium with sugammadex was compared to cisatracurium with neostigmine. For intubation with cisatracurium a dose of 0.15 mg/kg was administered. Maximally two maintenance doses of 0.1-0.2 mg/kg rocuronium or 0.03 mg/kg cisatracurium were allowed per protocol.

Time points of administration of sugammadex

Sugammadex was administered at:

- Reappearance of T₂ – shallow NMB (19.4.301, 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, 19.4.210, 19.4.304, 19.4.305, 19.4.306, 19.4.308, 19.4.309, 19.4.310)
- 1-2 PTC – profound NMB(19.4.302, 19.4.204, 19.4.209A and 19.4.209B)
- 3 minutes after administration of rocuronium (19.4.303, 19.4.202, 19.4.206)

These time points were used for pooled analysis (Section 5.5).

In Trial 19.4.311 sugammadex was administered at least 15 min after rocuronium. This situation mimics routine clinical practice for the use of sugammadex in a wide range of surgical procedures (including short cases). This time point was not used for pooled analysis.

In Trial 19.4.312 sugammadex was administered at a T₁ of 3-10% to trial the effect after infusion of rocuronium. This time point was not used for pooled analysis.

Assignment to treatment

Every trial was randomized to one or more of the following treatment groups:

- Dose of sugammadex or placebo or a comparator
- NMBA
- Dose of NMBA
- Anesthetic agent

Safety assessor blinding

Blinding for efficacy was not possible in these trials, since the results were available on the measuring device directly and rapid reversal was apparent to the staff in the

operating room by observing the patient. Therefore all trials were safety-assessor blinded for the subjective safety assessments, except for Trials 19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B. The safety assessor was not present during anesthesia. Only the person who prepared (and administered) the syringe with IP was unblinded. This person did not reveal the randomization code to other site personnel and he/she did not perform any subjective safety assessments after anesthesia.

Anesthetic technique

Phase 2 and 3 trials were performed in subjects receiving general anesthesia. In all Phase 2 trials, propofol was used for induction and maintenance of anesthesia. In Trials 19.4.210 and 19.4.312 however, a treatment arm was included in which maintenance of anesthesia was done using sevoflurane (comparison of effect of anesthetic regimen). In Trials 19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B propofol was used for induction and sevoflurane was used for maintenance. In Phase 3 the method of anesthesia was not specified in Trials 19.4.305, 19.4.308 and 19.4.311 to allow for routine anesthetic practices. In the other seven trials pre-specified anesthetics were used until clinical recovery was observed: induction with propofol and maintenance with sevoflurane in Trials 19.4.301 and 19.4.302, and propofol in Trials 19.4.303, 19.4.304, 19.4.306, 19.4.309, 19.4.310.

Subject selection

The following criteria were used for subject selection in Phase 2 and 3 trials (“xx” in the criteria differed per protocol). Per trial specific criteria were added if needed.

Inclusion criteria

- ASA class 1-xx (2,3 or 4)
- Above or equal to the age of xx (18 or 20 in Clinical Trials 19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B or 18-64 inclusive, etc)
- Scheduled for surgical procedure with general anesthesia with the use of rocuronium (or any other NMBA specified in the protocol) for endotracheal intubation (and maintenance of neuromuscular blockade)
- Scheduled for surgical procedures in the supine position
- Have given written informed consent

Exclusion criteria

- Known or suspected neuromuscular disorders impairing NMB and/or significant renal dysfunction (except for Clinical Trial 19.4.304)
- Known or suspected to have a (family) history of malignant hyperthermia

- Known or suspected to have an allergy to narcotics, muscle relaxants or other medication used during general anesthesia
- Receiving medication in a dose and/or at a time point known to interfere with the NMBA
- Contraindication for the comparator
- Pregnancy
- Childbearing potential not using any of the following methods of birth control: condom or diaphragm with spermicide, vasectomized partner (> 6 months), IUD, abstinence
- Breast-feeding
- Prior participation in the trial
- Participation in another clinical trial, not pre-approved by the sponsor, within 30 days (6 months in Clinical Trials 19.4.208A, 19.4.208B, 19.4.209A and 19.4.209B) of entering into the trial

Trial period

The trials began 7 days prior to surgery (screening) and ended 7 days after a single dose of sugammadex (follow-up), except for Trial 19.4.304. The follow-up period for Trial 19.4.304 ended 2-4 weeks after the operation.

2.3.3 Organization of trials for proposed indications

Efficacy data were collected in 23 of the 30 trials (all 12 Phase 2 trials and all 11 Phase 3 trials), 21 of which provide support for one of the three aforementioned proposed uses (Figure 1).

Routine Reversal at the Reappearance of T₂ – Shallow NMB

Following NMB, the reappearance of T₂ (which can be assessed objectively as well as visually) coincides with the presence of a shallow NMB. Current anesthesia practice utilizes this timepoint to decide to either administer a maintenance dose of the NMBA if the NMB is to be continued, reverse the shallow NMB with a reversal agent, or await spontaneous recovery from the NMB. Eight of the 23 trials (Phase 3 Trials 19.4.301 and 19.4.310 and Phase 2 Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, and 19.4.210) investigated the efficacy of sugammadex in reversing a NMB in normal adult surgical subjects when administered at the reappearance of T₂. In addition, 5 trials were conducted in special populations in which sugammadex was also administered at the reappearance of T₂ (Trials 19.4.304 [renal impairment], 19.4.305 [geriatric subjects], 19.4.306 [pediatric subjects], 19.4.308 [subjects with pulmonary complication(s)], and 19.4.309 [subjects

with cardiac disease]); Trials 19.4.308 and 19.4.309 were conducted since reversal agents like neostigmine must be used cautiously in these subjects.

Routine Reversal at 1-2 PTCs – Profound NMB

During various types of surgical procedures (microsurgery, neurosurgery, vascular surgery, thoracic surgery, open eye surgery, etc.) a profound block is required to ensure elimination of any movement, bucking and coughing in response to surgical stimulation. In the post-tetanic count method, a nerve is stimulated at 50 times per second (50 Hz) followed three seconds later by stimulation once per second (1 Hz) and the number of twitches are counted (the post-tetanic count; PTC). This number can vary between 0 and 12; the occurrence of 1-2 PTCs represents a situation of a profound NMB. Four of the 23 trials (Phase 3 Trial 19.4.302 and Phase 2 Trials 19.4.204, 19.4.209A and 19.4.209B) investigated the efficacy of sugammadex in reversing a profound NMB (i.e., administration of sugammadex at 1-2 PTCs). An additional 2 trials (Trials 19.4.202 and 19.4.206) also evaluated recovery at 15 minutes following the administration of an intubating dose of rocuronium (0.6 mg/kg). It is generally recognized that the depth of blockade 15 minutes after 0.6 mg/kg of rocuronium corresponds well with a blockade at 1-2 PTCs [37]; therefore, the results of Trials 19.4.202 and 19.4.206 were useful in the selection of the sugammadex dose that was investigated in Phase 3 regarding reversal at 1-2 PTCs.

Immediate Reversal

The timepoint of 3 minutes after the administration of rocuronium (1.2 mg/kg) is proposed as the timepoint at which intubation after a NMBA would have failed. It is expected that administration of sugammadex at 3 minutes after a bolus dose of rocuronium will result in recovery before critical desaturation would have occurred in a cannot-intubate-cannot-ventilate situation [38]. Three of the 23 trials (Phase 3 Trial 19.4.303 and Phase 2 Trials 19.4.202 and 19.4.206) investigated the efficacy of sugammadex when administered at 3 minutes following a dose of either 0.6 mg/kg (Trial 19.4.202) or 1.2 mg/kg rocuronium (Trials 19.4.206 and 19.4.303). Additionally, Trial 19.4.205 investigated the efficacy of sugammadex when administered at 5 minutes following rocuronium, also a timepoint representative of an immediate reversal type setting and, in fact, associated with a deeper block compared to 3 minutes. Therefore, the results of Trial 19.4.205 were useful in the selection of the sugammadex dose that was investigated in Phase 3 regarding immediate reversal at 3 minutes.

Other Efficacy Trials

In addition to those efficacy trials described above, two additional efficacy trials were conducted during the sugammadex clinical development program. Trial 19.4.311 was conducted to investigate the use of sugammadex in a wide range of surgical procedures and anesthetic regimens (i.e. assessment of routine use). Specifically, safety and the time-course of recovery to a T_4/T_1 ratio of 0.9 (within 4 minutes) was assessed following the administration of 4.0 mg/kg sugammadex, when given at least 15 minutes after the last dose of rocuronium. Trial 19.4.312 was conducted in order to investigate the efficacy and safety of sugammadex after rocuronium infusion under propofol or sevoflurane anesthesia.

2.4 Regulatory guidance and advice

Guidelines and regulations from regulatory authorities were consulted to assure that the clinical development program complied with all requirements. Advice and/or concurrence with proposals made by the sponsor were provided by the FDA during the clinical development of sugammadex.

The sponsor received feedback and/or concurrence on proposals from the FDA regarding the clinical development of sugammadex during the following meetings or written advice:

- Pre-IND meeting: During this meeting overall agreement was reached on:
 - the timepoints to investigate regarding the reversal of neuromuscular blockade
 - use of the recovery of the T_4/T_1 ratio to 0.9 as the primary efficacy parameter for Phase 2 and Phase 3 trials, provided clinical signs of recovery were added to the clinical trial protocols as a secondary endpoint
 - use of a safety assessor blinded design
 - use of the intent-to-treat analysis set as the primary analysis set rather than the per-protocol analysis set
 - the omission of a trial in hepatically-impaired subjects; however, an exclusion criterion regarding hepatic insufficiency should not be included in the clinical protocols
Comment from the sponsor: a simulation of hepatic impairment with the PK-PD model is described in Section 4.3.5 Population PK-PD model.
 - FDA suggested the trials should include populations where robust reversal is critical and repeated doses of rocuronium have been administered. Trials in pulmonary (Trial 19.4.308) and cardiac

(Trial 19.4.309) subjects have been included in the clinical development program. In addition, some trials included maintenance doses of the NMBA (Section 2.3.2)

- End-of-Phase 2 Meeting: The following is a summary of the agreements from this meeting:
 - overall agreement was reached on the Phase 3 program, including the timepoints (reappearance of T_2 and 1-2 PTCs for routine reversal and 3 minutes for immediate reversal) and the doses selected; however, FDA did caution that doses lower than 16 mg/kg might be warranted for immediate reversal if adverse events related to the dose of sugammadex were observed
 - the acceptance of the use of the PK-PD model and interaction strategy; however, FDA requested further characterization of the model in terms of the proposed cut-off point for remifentanyl.
Comment from the sponsor: The proposed cut-off was lowered from the K_a 0.050 megamol⁻¹ (remifentanyl) to K_a 0.025 megamol⁻¹. For compounds (atropine, naloxone) with a K_a of ~ 0.025 megamol⁻¹ there were no indications for capturing interactions by two independent sources: the PK-PD simulations and preclinical experiments.
 - the use of AMG for measurement of the primary efficacy parameter; however, inclusion of clinical signs of recovery as secondary endpoints protocols was also requested
 - the possibility to extrapolate data from rocuronium-induced blockade for renally impaired and geriatric subjects to vecuronium-induced blockade for these special populations
 - agreement to conduct statistical testing one-sided at a significance level of 0.025
 - deferral of a trial in pediatric subjects below 2 years of age. Subsequently, it was agreed with the FDA that a deferral of all pediatric age groups would be requested.
- Special Protocol Assessments: Phase 3 pivotal Trials 19.4.301 and 19.4.302.
- Design of the thorough QT/QTc trial (Trial 19.4.109). The design for Trial 19.4.105 was not considered to be acceptable because it did not include arms that investigated the combination of sugammadex and the NMBA; therefore, a second QT/QTc trial was required and included in the NDA submission.

3. UNMET MEDICAL NEED: HOW SUGAMMADEX FULFILLS UNMET NEED

3.1 Role of neuromuscular blocking drugs in general anesthesia

General anesthesia is the induction of a state of hypnosis with resultant amnesia, analgesia, reflex suppression, and decreased voluntary muscle activity. Each of these components is achieved selectively through the use of various intravenous, inhaled, and locally applied anesthetic drugs. Light general anesthesia is utilized for hypnosis, intravenous opioids for reflex suppression, and neuromuscular blocking drugs when muscle relaxation is required. Additionally, depending on the depth of anesthesia and the surgical procedure, the patient may not be able to ventilate spontaneously and, therefore, will require mechanical ventilatory support. To facilitate control of the patient's airway during ventilation, an endotracheal tube is usually inserted into the trachea. This process of intubation usually requires profound muscle relaxation (neuromuscular blockade) or profound levels of general anesthesia. The clinician administering the anesthetic, either an anesthesiologist, nurse anesthetist, or other deliverer of anesthesia, is responsible for the administration of all drugs that produce general anesthesia and the conditions necessary for safe endotracheal intubation.

Other types of anesthesia include regional (transmission along a specific nerve is blocked) and local (transmission along nerves only in the area of the drug application is blocked) anesthesia. In these 2 types of anesthesia, drugs that produce muscle relaxation are not required since the methods do not involve the total loss of consciousness of the patient, but rather the loss of sensation to a specific part of the body.

Muscle relaxants, or neuromuscular blocking drugs, including rocuronium and vecuronium, are often needed as an essential adjunct to general anesthesia, providing muscle relaxation or paralysis. These drugs facilitate endotracheal intubation, allow for optimal surgical conditions, and prevent both voluntary and involuntary movements. Specifically, neuromuscular blocking drugs help achieve a rapid, safe endotracheal intubation, which secures the airway for the administration of mechanical ventilation. When used at appropriate doses, they also help create optimal surgical conditions by allowing adequate exposure of the surgical field at lighter and safer depths of anesthesia. Unintended patient movement, whether voluntary or involuntary, can lead to patient injury during surgery, but these movements can be prevented with the adequate use of neuromuscular blocking drugs.

When a surgical procedure is completed, some degree of neuromuscular blockade is usually still present. In order for the patient to regain muscle strength and protective reflexes before removal of the endotracheal tube, the residual blockade (paralysis) must be reversed. This can occur by spontaneous dissipation of the drug effect or by pharmacologic antagonism of the residual paralysis. Cessation of neuromuscular blockade facilitates the recovery of skeletal muscle function and carotid body oxygen chemoreceptor function, allowing for safe removal of the endotracheal tube and maintenance of a patent airway, so that the patient can breathe adequately and have full protective reflexes in the postanesthesia care unit.

Approximately 27.8 million surgical procedures utilizing general anesthesia are performed annually in the United States. It is estimated that 18.7 million of these surgical procedures involve the administration of neuromuscular blocking drugs, with rocuronium or vecuronium being used in as many as 67% of these cases.

3.2 Current pharmacologic reversal of a nondepolarizing neuromuscular blockade

Drugs used to reverse or antagonize a neuromuscular blockade induced by nondepolarizing neuromuscular blocking drugs are usually administered at the end of surgery. All of the currently available reversal drugs, such as neostigmine and edrophonium, are acetylcholinesterase inhibitors. These drugs indirectly increase the concentration of acetylcholine available to compete with the neuromuscular blocking drug for the nicotinic receptor at the neuromuscular junction by inhibiting the action of acetylcholinesterase. There is no effect on the metabolism or elimination of the neuromuscular blocking drug molecules themselves. As more acetylcholine molecules interact with nicotinic receptors, normal muscle function follows. However, there is an upper limit to the effect of the current reversal drugs: once all acetylcholinesterase enzyme is inhibited, neural release of additional acetylcholine becomes the rate-limiting step in restoration of normal muscle function. Indeed, these drugs are ineffective for reversing profound neuromuscular blockade.[1,2,3] Additionally, the duration of action of some of these reversal drugs may be shorter than the activity of the neuromuscular blocking drugs, leading to reappearance of the neuromuscular blockade.[4]

The current reversal drugs also have potentially significant side effects due to increased acetylcholine concentrations. Neostigmine (and other acetylcholinesterase inhibitors) can cause hypotension, bradycardia, cardiac arrhythmias, abdominal cramps, bronchoconstriction, increased salivation, vomiting, and diarrhea due to nonselective stimulation at all muscarinic receptors, especially those in the heart and

smooth muscle.[4,16,17,18,19] In practice, a muscarinic antagonist such as atropine or glycopyrrolate is administered with the acetylcholinesterase inhibitor to antagonize these muscarinic side effects. The muscarinic antagonists themselves may cause a number of side effects such as tachycardia, dry mouth, cardiac arrhythmias, urinary retention, and blurred vision.[20,21,22,23]

Overall, acetylcholinesterase inhibitors are used for reversal of neuromuscular blockade in approximately 54% of surgical procedures requiring general anesthesia and mechanical ventilation, or in approximately 10 million procedures annually in the United States. Despite the side effects of currently available reversal drugs, these drugs are administered to avoid residual paralysis and its associated complications.

An ideal reversal drug should have a rapid onset of action, be capable of reversing a profound neuromuscular blockade, have an adequate duration of action to prevent neuromuscular blockade from reappearing, and have a favorable side-effect profile. Sugammadex appears to be such a drug.

3.3 Sugammadex

Cyclodextrins are a group of oligosaccharides with internal hydrophobic cavities that can attract a lipophilic molecule, forming an inclusion complex by encapsulation. The cyclodextrins are well-known for their ability to form complexes with various drugs. The advantage of using cyclodextrins for reversal of neuromuscular blockade is that they are generally very water-soluble, do not possess intrinsic biologic activity, and, therefore, are unlikely to cause side effects. Sugammadex is a modified γ -cyclodextrin that was designed to form a complex with the steroidal neuromuscular blocking drug rocuronium, and was found to form a complex with vecuronium as well. When administered to a patient who has received rocuronium or vecuronium, sugammadex encapsulates the neuromuscular blocking drug, and a shift in the concentration gradient of the neuromuscular blocking drug between the neuromuscular junction and plasma enhances the redistribution or diffusion of the neuromuscular blocking drug from the nicotinic acetylcholine receptor. Furthermore, sugammadex diffuses from plasma into the extra-cellular volume. These opposing movements of sugammadex and NMBA explain the rapid reversal.

The mechanism of action of sugammadex does not result in stimulation of the cholinergic nervous system, thereby avoiding the undesirable autonomic system side effects associated with neostigmine and similar drugs [4,16,17,22]. Additionally, because of its mechanism of action, there is no need for concomitant administration of antimuscarinic drugs, which have their own side effects.[18,20,21,23] Furthermore, due to the removal of the muscle relaxant from its site of action,

sugammadex is able to reverse even a very profound rocuronium-induced neuromuscular blockade, unlike the currently available reversal drug neostigmine.[1,2,3] Sugammadex, as well as the sugammadex-rocuronium complex, is almost entirely eliminated via the kidneys.

3.4 Differences between sugammadex and acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors such as neostigmine need to be used with caution in many patients due to their cardiac effects. Neostigmine produces a nonspecific enhancement of neurotransmission at all synapses where acetylcholine is the transmitter. [4,16,22] The principal cardiovascular effect is bradycardia, which may, in rare circumstances, result in cardiac arrest.[16] To counteract this effect, an antimuscarinic drug such as glycopyrrolate or atropine is given simultaneously with neostigmine. Unfortunately, these drugs themselves cause a number of side effects such as tachycardia, dry mouth, blurred vision, and possibly cardiac conduction effects leading to cardiac arrhythmias.[18,20,21,23] Atropine can cause central nervous system effects as well, including sedation and confusion, which may be more pronounced in geriatrics.[20]

Acetylcholinesterase inhibitors should be used with caution in patients with epilepsy, asthma, bradycardia, recent coronary artery occlusion, vagotonia, hyperthyroidism, cardiac arrhythmias, or peptic ulcer.[16] Since the mechanism of action of sugammadex is not based on acetylcholinesterase inhibition, but rather on its ability to form an inclusion complex with the steroidal neuromuscular blocking drug, autonomic system side effects are not expected.

Sugammadex also distinguishes itself from neostigmine by its superior efficacy in the reversal of both shallow (reappearance of second twitch in response to train-of-four (TOF) stimulation, or T₂) and profound (1-2 post tetanic counts, or PTCs) rocuronium- and vecuronium-induced neuromuscular blockade as demonstrated in pivotal trials 19.4.301 and 19.4.302. (Section 5.5.1 and 5.5.2)

3.5 Potential role of sugammadex in neuromuscular blockade

3.5.1 Reversal of profound neuromuscular blockade

Administration of a neuromuscular blocking drug near the end of a procedure can result in a significantly delayed patient recovery and/or the potential consequences of residual paralysis, given the inability of current reversal drugs to completely antagonize such a blockade. A profound blockade may be required in some cases of

microsurgery, neurosurgery, ophthalmic surgery, vascular surgery, and also in some open abdominal surgeries and laparoscopic procedures. With the availability of sugammadex, the clinician can safely maintain the appropriate depth of neuromuscular blockade for the duration required, while being able to reverse the blockade rapidly and completely at the end of surgery, enhancing patient safety.

General anesthesia patients who received 4.0 mg/kg of sugammadex at 1 to 2 PTCs after rocuronium-induced neuromuscular blockade (Trial 19.4.302) experienced a median time to recovery of 2.7 min (to a TOF of 0.9), 17 times faster than that experienced by patients receiving neostigmine (combined with glycopyrrolate), who demonstrated a mean recovery time of 49.0 min (Table 21). Trial 19.4.302 also included a patient cohort who received a vecuronium-induced profound blockade. Median recovery time with sugammadex in this cohort was 3.3 min, nearly 15 times faster than the comparative cohort who received neostigmine (49.9 min) (Table 24).

3.5.2 Residual Paralysis

In the immediate postoperative period, patients need to be able to breathe spontaneously and adequately, and to maintain a patent airway. One of the complications of neuromuscular blockade is residual paralysis, which could interfere with a patient's spontaneous ventilation. This could potentially lead to hypoxia, ventilatory arrest, and, subsequently, cardiac arrest.

The dangers of residual paralysis have been documented in a number of trials. Hypoxemia and hypercapnia have been demonstrated in 60% and 30% of surgical patients, respectively, who suffered from residual paralysis postoperatively.[39] Additionally, hypoxic ventilatory responses can be depressed by as much as 30% at a TOF of 0.7, which may reflect the finding that residual paralysis interferes with the function of the carotid chemoreceptor for oxygen.[6,40] Upper airway impairment has also been documented. Coordination of pharyngeal muscles was markedly impaired with an associated reduction in upper esophageal sphincter tone in healthy volunteers at a TOF as high as 0.7.[41] In another trial in healthy volunteers, a TOF ratio of 0.8 led to frequent upper airway obstruction, and FIV₁ remained impaired until a TOF of 0.9 was attained.[42] Physical discomfort also occurs with residual paralysis. Persistent visual disturbances can occur at a TOF as high as 0.9, and a general feeling of "uncomfortableness" was present in healthy volunteers at a TOF of <0.75.[5]

Despite these findings, the incidence of residual paralysis postoperatively remains high. Research demonstrates that not only longer-acting neuromuscular blocking drugs but even intermediate-acting neuromuscular blocking drugs can be associated with residual paralysis, despite the administration of a reversal drug. In several trials

with surgical patients, 25% of whom received reversal drugs, the incidence of residual paralysis, depending on the TOF end point used, ranged from 13% to 47%.^[43,44,45] Two series of surgical patients, 68% to 100% of whom received reversal drugs, still experienced residual paralysis at a rate of 41% to 88%.^[46,47]

Outcome data reveal the respiratory consequences of residual paralysis. From an analysis of recovery room incidents obtained from an Australian database, AIMS, inadequate reversal of neuromuscular blockade was cited as the most common reason for postoperative respiratory failure, at 39% of incidents.^[48] Other pulmonary complications such as pneumonia and/or atelectasis were as high as 17% in patients who suffered residual paralysis postoperatively after pancuronium administration.^[15] Recently, researchers at the University of Washington estimated at their institution an incidence of clinically severe residual paralysis, severe enough to have caused the need for continued mechanical ventilation in the operating room or postanesthesia care unit, as high as 1% in patients who receive neuromuscular blocking drugs, based on preliminary analysis.^[49]

In Phase 3 trials, sugammadex has been shown to effectively reverse rocuronium-induced neuromuscular blockade to a TOF ratio of 0.9, the accepted standard for safe extubation, at doses of 2.0 mg/kg for reversal of shallow blockade (reappearance of T₂) and 4.0 mg/kg for reversal of profound blockade (1-2 PTCs) in less than 3 minutes in the majority of patients. Vecuronium-induced neuromuscular blockade, likewise, can be reversed from any depth in less than 5 minutes in the majority of patients at recommended dosages. As Figures 2 and 3 from pooled clinical data demonstrate, reversal with sugammadex significantly lowers the incidence of inadequate reversal in comparison to reversal with neostigmine.

Figure 2 Recovery after sugammadex 2.0 mg/kg or neostigmine 50 mcg/kg at reappearance of T₂

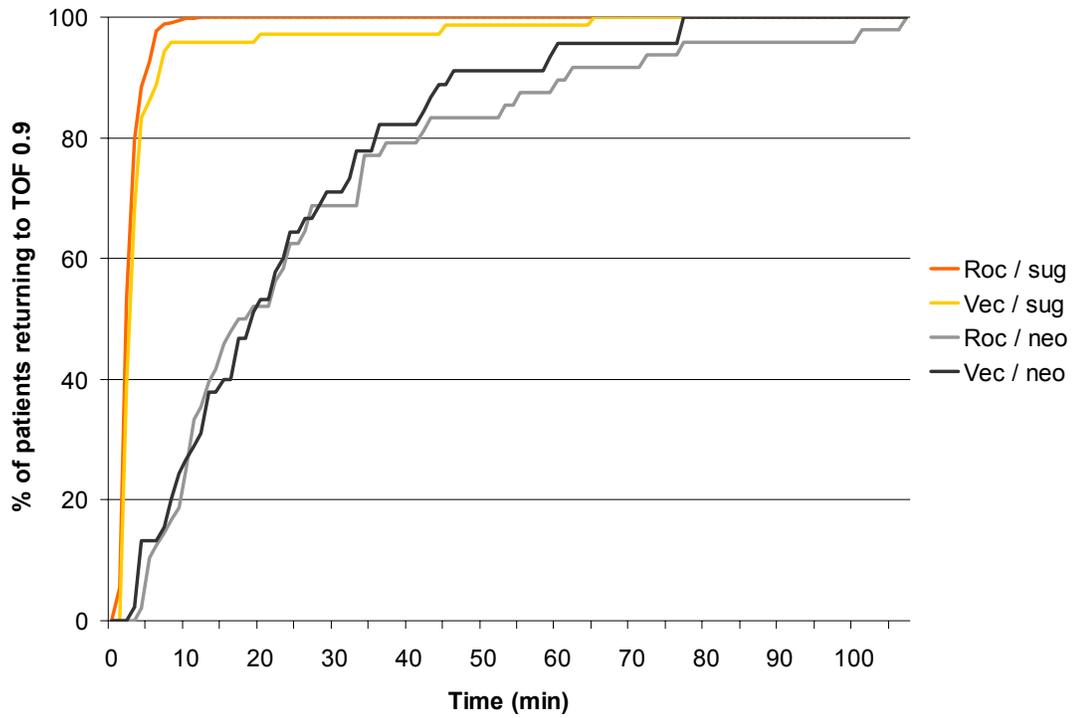
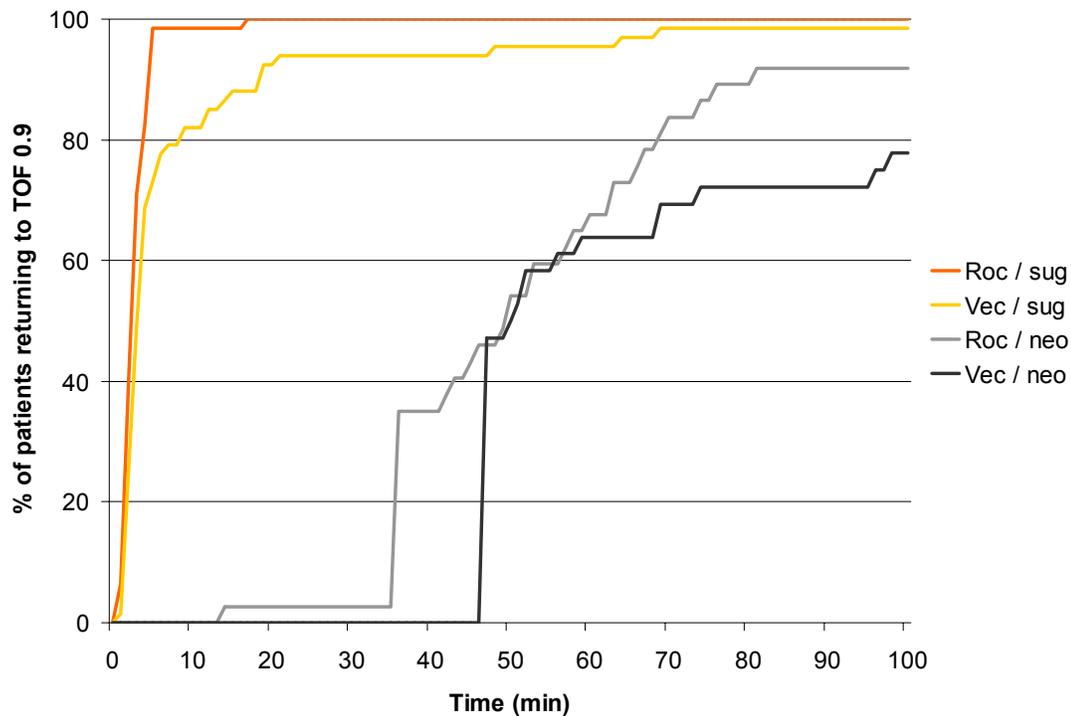


Figure 3 Recovery after sugammadex 4.0 mg/kg or neostigmine 70 mcg/kg at 1-2 PTCs



One would expect that administration of sugammadex in the recommended doses would, at a minimum, attenuate and hopefully eliminate residual paralysis in the recovery room. If so, this would dramatically improve the safety of clinical anesthesia.

3.5.3 Special patient populations

The capability of sugammadex to be used in special patient populations is of clinical importance as the use of acetylcholinesterase inhibitor drugs in these patients may result in unwanted side effects. Neostigmine should be used with caution in patients with cardiac arrhythmias due to its side effects (see Section 3.4). With sugammadex, however, no cardiac effects were apparent in Phase 2 trials. In Phase 3 sugammadex was studied in cardiac patients (NYHA Class II to III) with ischemic heart disease, chronic heart failure, or arrhythmias (Trial 19.4.309). (Section 5.2, 5.6.3) The geometric mean times from the start of the administration of sugammadex at the reappearance of T_2 to recovery of the TOF ratio to 0.9 were 34.3 min in the placebo group versus 1.7 min and 1.4 min, respectively, in the 2.0 mg/kg and 4.0

mg/kg sugammadex dose groups. The data indicated that sugammadex can be used safely in cardiac patients at doses up to 4.0 mg/kg. There was no evidence of residual paralysis or re-occurrence of blockade in any of the subjects receiving sugammadex.

Sugammadex has also been shown to be safe and effective in reversing rocuronium-induced neuromuscular blockade in geriatric patients (aged 65 years and older) in trial 19.4.305. (Section 5.2, 5.6.1) The geometric mean time from administration of 2.0 mg/kg of sugammadex at reappearance of T_2 to recovery of the TOF ratio to 0.9 was 2.3 min in the adult group and 2.9 min in the 65 years or older group. None of the serious adverse events reported in this trial were determined to be related to sugammadex by the investigator or the sponsor. Procedural pain was the most common adverse event reported. There was no clinical evidence of residual paralysis or re-occurrence of blockade in any subjects in this trial.

In clinical practice, hepatically impaired patients may receive lower and, therefore, suboptimal doses of rocuronium (0.3 mg/kg, instead of 0.6 mg/kg or higher), because of concern for prolonged neuromuscular blockade in these patients. Since sugammadex is cleared mainly via the kidney, it may be used safely in this patient population, and may allow the clinician to administer optimal doses of rocuronium.

For patients with certain muscle diseases, the dose-response curves of neuromuscular blocking drugs are not well-defined. Sugammadex will likely be a more effective reversal drug than neostigmine in these patients due to its lack of direct neuromuscular effects. Additionally, for patients with previously undiagnosed muscle disease who experience adverse events due to the administration of rocuronium or vecuronium during a surgical procedure, sugammadex may provide a means of immediate reversal of the neuromuscular blockade.

3.5.4 Cannot intubate/cannot ventilate (CICV) scenarios

While CICV was not studied in our clinical trials, this commonly used terminology refers to the clinical situation when, following the administration of an intubating dose of a neuromuscular blocking drug, the clinician is unable to perform endotracheal intubation in an attempt to establish a patent airway, and is also unable to subsequently ventilate the patient via either a face mask or a laryngeal mask airway. Although the CICV scenario is rare with an incidence between 0.01% and 0.05% of attempted intubations, it presents a potential serious outcome.[50,51,52] The “Difficult Airway” has been associated with morbidities such as brain injury, cardiopulmonary arrest, unnecessary tracheostomy, and airway and dental trauma, and also has been associated with mortality.[53]

In a CICV scenario, it is life-saving to immediately re-establish the patient's spontaneous ventilation by attempting to reverse neuromuscular blockade, even to a partial degree. Acetylcholinesterase inhibitors such as neostigmine are unable to antagonize a profound neuromuscular blockade such as that required for endotracheal intubation, and therefore, are not effective as rescue drugs.[1,2,3] Reversal of a very profound rocuronium-induced blockade (rocuronium dose of up to 1.2 mg/kg) has been shown to be possible with sugammadex at a dose of 16 mg/kg at 3 minutes after NMBA administration. The median time to recovery to a TOF ratio of 0.9 from start of sugammadex administration was 1.7 min (Trial 19.4.303). While recovery to a TOF ratio of 0.9 is important to avoid residual paralysis and for regaining full pharyngeal function, recovery to a considerably lesser degree in a CICV scenario would be enough to allow the patient to breathe sufficiently to prevent hypoxia, and therefore, may be life-saving.[54,55,56] The median time to a TOF ratio of 0.7 (a few years ago the accepted standard for extubation) after sugammadex administration was 1.1 min in this Phase 3 trial.

The use of sugammadex in a CICV situation following rocuronium administration may prevent the need for emergency noninvasive airway ventilation including rigid bronchoscopy, Combitube ventilation, or transtracheal jet ventilation, and may prevent the need for emergency invasive airway access such as surgical or percutaneous tracheostomy or cricothyrotomy. Sugammadex in a CICV situation following rocuronium could very well be life-saving. This potential use of sugammadex may have a direct impact on the Difficult Airway Algorithm as developed by the American Society of Anesthesiologists Task Force on Difficult Airway Management (see B2 of the flow chart of the Difficult Airway Algorithm [53]), enabling fast return of spontaneous ventilation.[41]

Succinylcholine, the only depolarizing neuromuscular blocking drug available today, is widely used despite an unfavorable safety profile, and is the first-line drug for rapid sequence intubation due to its rapid onset and offset. It is estimated that in the United States, succinylcholine is used in approximately 7.5 million surgical procedures annually. In situations where succinylcholine is used for intubation and a CICV scenario develops, there is no antagonist available. There is also evidence to suggest that even at the usual dose of 1.0 mg/kg, some patients receiving succinylcholine may experience severe arterial oxygen desaturation before spontaneous recovery from neuromuscular blockade occurs.[38] In a Phase 3 trial (19.4.303), recovery from a rocuronium-induced blockade with sugammadex was directly compared with the spontaneous recovery pattern of succinylcholine. In this trial, elective surgery patients received either sugammadex (16 mg/kg) 3 minutes after an intubating dose of rocuronium, or an intubating dose of succinylcholine (1

mg/kg) followed by spontaneous recovery. The median time from start of neuromuscular blocking drug administration to recovery of T_1 to 10% was 4.2 min in the rocuronium/sugammadex group versus 7.1 min in the succinylcholine group (Table 27). The replacement of succinylcholine with a combination of rocuronium followed by sugammadex to reverse the neuromuscular blockade would potentially markedly reduce morbidity and mortality caused by the scenario described.

3.5.5 Alternative to succinylcholine

One of the most important indications for the administration of a neuromuscular blocking drug is to facilitate endotracheal intubation, thereby allowing control of the airway. As described above, succinylcholine, which was introduced more than 50 years ago, continues to be used today for intubation despite serious disadvantages. First, if a succinylcholine-induced neuromuscular blockade is prolonged for any reason (including congenital pseudocholinesterase deficiency), there is no reversal drug. Second, succinylcholine is associated with a host of complications, including cardiac dysrhythmias (sinus bradycardia, nodal rhythms, ventricular dysrhythmias, and cardiac arrest), hyperkalemia, increased ocular pressure, increased intragastric pressure, increased intracranial pressure, myalgias, and masseter spasm.[57,58,59] While an appropriate dose of rocuronium (1.0-1.2 mg/kg) has a rapid onset of action, which is comparable with that of succinylcholine, it has a much longer duration of action. This means that with the currently available reversal drugs, one cannot terminate the neuromuscular blockade quickly. As neostigmine cannot reverse profound neuromuscular blockade, the availability of sugammadex will allow clinicians to benefit from the rapid onset of rocuronium, particularly in rapid sequence intubation, and to benefit from the rapid and complete termination of neuromuscular blockade with sugammadex. At appropriate doses, the rocuronium/sugammadex combination can produce a neuromuscular blockade of a total duration even less than that of succinylcholine. As described above in trial 19.4.303, sugammadex administered after rocuronium yielded a median recovery time of 4.2 min versus 7.1 min for spontaneous recovery after succinylcholine, as measured from start of neuromuscular blocking drug administration to recovery of T_1 to 10%. Consequently, with the availability of sugammadex, in combination with rocuronium, succinylcholine can be avoided and its multiple associated complications eliminated.

4. CLINICAL PHARMACOLOGY OF SUGAMMADEX

4.1 Introduction and trial design

The sugammadex development program included 5 in vitro trials using human biomaterials and 22 clinical trials (7 Phase 1 trials and 12 Phase 2 clinical pharmacology trials and 3 Phase 3 special population trials) that assessed the PK, PD and/or PK-PD relationships of sugammadex and, in part, served as the basis for selecting the doses investigated in the Phase 3 trials (Figure 1).

With regard to the five in vitro trials, NL0046285 and NL0047787 were performed to determine the extent of binding of sugammadex and rocuronium to human plasma protein and human erythrocytes, respectively. Trials 19.4.004 and 19.4.007 were conducted to assess possible interferences of sugammadex and Org 48302 on the results of a number of relevant clinical chemistry parameters. Org 48302 is a related cyclodextrin that contributes to the pharmacological activity of sugammadex. Trial 19.4.006 was performed to determine the dialysability of sugammadex alone, rocuronium alone, and the combination of sugammadex/rocuronium using either a low flux or high flux filter. Although the efficacy of sugammadex is not believed to be impacted by renal function (due to its organ independent efficacy), Trial 19.4.006 was important in helping to determine the feasibility of using sugammadex in subjects with impaired renal function.

With regard to the Phase 1 clinical trials, Trial 19.4.101 (first Phase 1 trial) was a 2-part trial that first investigated the safety, tolerability and PK of single, escalating doses of sugammadex; the second part (Part II) was a pilot efficacy trial in subjects under general anesthesia, including rocuronium-induced NMB. Trial 19.4.102 compared the safety, tolerability and PK in healthy Japanese volunteers vs. Caucasian volunteers; male and females were enrolled into each ethnic group to also compare the male vs. female PK profile of sugammadex. In Trial 19.4.106, high doses (up to 96 mg/kg) of sugammadex were administered to healthy male and female volunteers, which permitted an investigation of the plasma concentrations and urinary excretion of both sugammadex. The excretion balance, metabolic profile and PK of sugammadex were investigated in Trial 19.4.107 following the administration of [¹⁴C]-labeled sugammadex to healthy volunteers. Trial 19.4.105 was a trial in healthy volunteers that investigated the effects of sugammadex on the QT/QTc interval as well as the relation between sugammadex plasma concentrations and any changes, if any, to the QT/QTc interval. In anticipation of having to conduct the thorough QTc trial with the combination of sugammadex and rocuronium/vecuronium (Trial 19.4.109), Trial 19.4.108 was conducted to assess the safety of the

simultaneous administration of sugammadex with either rocuronium or vecuronium (dosed at a ratio not expected to cause NMB) in healthy volunteers with or without anesthesia. Trial 19.4.109 was a single center, randomized, placebo-controlled six period thorough QTc cross-over trial. The trial was open-label for moxifloxacin and double-blind for placebo, sugammadex/rocuronium, sugammadex/vecuronium and sugammadex alone.

In addition to the 7 Phase 1 trials (in all of which plasma and urine samples or plasma samples only were collected for the assessment of sugammadex or the concomitantly administered NMBA), 12 Phase 2 trials were conducted. Of these 12 trials, plasma and urine or plasma samples only were collected in 6 of the trials (Trials 19.4.201, 19.4.202, 19.4.205, 19.4.207, 19.4.208A and 19.4.208B).

Seven of the 12 Phase 2 trials investigated the dose-response relationship of sugammadex in reversing a rocuronium-induced NMB (all 7 trials), a vecuronium-induced NMB (Trial 19.4.207), or pancuronium-induced NMB (Trial 19.4.207) when administered at various times following the NMBA. Specifically, Trials 19.4.201, 19.4.203 and 19.4.207 investigated various doses of sugammadex (ranging from 0.5 mg/kg to 8.0 mg/kg) when administered at the reappearance of T_2 , a timepoint representative of a shallow NMB. Trials 19.4.202, 19.4.204 and 19.4.206 investigated various doses of sugammadex (ranging from 0.5 mg/kg to 16.0 mg/kg) when administered either at 1-2 PTCs (Trial 19.4.204) or at 15 minutes (Trials 19.4.202 and 19.4.206) following rocuronium, timepoints representative of a profound block. Trials 19.4.202, 19.4.205, and 19.4.206 investigated various doses of sugammadex (ranging from 1.0 mg/kg to 16.0 mg/kg) when administered either at 3 minutes or at 5 minutes following rocuronium, timepoints representative of an immediate reversal setting.

Trials 19.4.208 (A and B) and 19.4.209 (A and B) were prospective bridging trials in Caucasian and Japanese subjects. Sugammadex (doses ranging from 0.5 to 8.0 mg/kg) was administered at the reappearance of T_2 following a rocuronium- or vecuronium-induced NMB in Trials 19.4.208A and B and at 1-2 PTCs following a rocuronium- or vecuronium-induced NMB in Trials 19.4.209A and B.

Since the type of anesthetic agent used can affect the depth and duration of a NMB, Trial 19.4.210 was conducted to investigate the effect of sevoflurane (a volatile agent with the strongest enhancing effect on rocuronium-induced NMB as compared to other volatile agents) on the efficacy of 2.0 mg/kg sugammadex when administered at the reappearance of T_2 . Phase 3 Trial 19.4.312 was conducted in order to investigate the efficacy and safety of sugammadex after rocuronium infusion under propofol or sevoflurane anesthesia. In addition, the plasma levels of rocuronium

under both anesthetic regimens (before administration of sugammadex) were studied in this trial.

Three special population trials were conducted in Phase 3 that contributed data to the clinical pharmacology profile for sugammadex. Trial 19.4.305 and 19.4.306 assessed the safety, efficacy and PK of sugammadex when administered at the reappearance of T₂ following a rocuronium-induced NMB in geriatric vs. adult subjects and in pediatric vs. adult subjects, respectively. Since sugammadex is almost exclusively eliminated via the kidneys, renal impairment is expected to have a significant effect on the PK of sugammadex (free or bound to the NMBA), although the efficacy of sugammadex is not believed to be impacted by renal function due to its CD-based mechanism of action. As a result, Trial 19.4.304 was conducted to compare the efficacy of sugammadex and the PK profile of 2.0 mg/kg sugammadex (and rocuronium) when administered at the reappearance of T₂ following rocuronium-induced NMB in subjects with renal disease.

4.2 PK-PD modelling

Plasma concentration-time and efficacy data collected in several clinical trials contributed to the development and validation of a population PK-PD model that has been used to describe the mechanism of complex formation between sugammadex and the NMBA leading to reversal of NMB. The population PK-PD database included densely as well as sparsely sampled PK data from healthy volunteers (Trial 19.4.101), geriatric subjects (Trial 19.4.305), pediatric subjects (Trial 19.4.306), subjects with impaired renal function (Trial 19.4.304), and normal adult subjects studied in several of the Phase 2 trials (Trials 19.4.201, 19.4.202, 19.4.205, 19.4.206, 19.4.207 and 19.4.210). Extensive PD data were available since neuromuscular function was monitored continuously during these trials. The PK-PD model was used as a reference to evaluate the PK-PD relationship of geriatric and pediatric subjects compared to adult subjects (Trials 19.4.305 and 19.4.306, respectively) and it was applied to simulate the use of sugammadex to reverse rocuronium-induced NMB in subjects with hepatic impairment. The clinical situation during which rocuronium would be required for reintubation following the administration of sugammadex was also simulated with the PK-PD model. The PK-PD model has been used to help predict the potential of compounds other than rocuronium and vecuronium to interact with sugammadex.

4.3 Interpretation of results from clinical pharmacology trials

4.3.1 In vitro human biomaterials

Results from Trials NL0046285 and NL0047787 have demonstrated that sugammadex does not bind to human plasma proteins or human erythrocytes. In addition, these trials have demonstrated that rocuronium does not bind to erythrocytes in either the presence or absence of sugammadex. With regard to human plasma proteins, approximately 37% of rocuronium is bound to plasma proteins; however, the extent of plasma protein binding decreases with increasing concentrations of sugammadex as a result of the complexation of sugammadex with rocuronium.

Sugammadex has been shown to be eliminated exclusively by the kidneys. Trial 19.4.006, which investigated the dialysability of sugammadex, was performed prior to the conduct of a trial in renally-impaired subjects (19.4.304). Results from this in vitro trial indicated that sugammadex and rocuronium are efficiently removed from plasma via dialysis using a high flux membrane (mean clearances, respectively, of 86.3 and 89.0 mL/min).

In Trials 19.4.004 and 19.4.007, differences in some clinical lab parameters between un-spiked samples and samples spiked with 100 µg/mL sugammadex were shown. (100 µg/mL sugammadex is approximately maximum plasma concentration at human dose of 16 mg/kg) For clinical chemistry tests of activated partial thromboplastin time (aPTT), prothrombin time (PT) and the PT international normalized ratio (PT [inr]), mean increases of 12-17% were observed mean values were statistically significantly higher for samples spiked with sugammadex compared with un-spiked samples. However, the mean values of the spiked samples were within the normal ranges as defined by the Clinical Chemistry lab 'Lab Noord' (Groningen, The Netherlands) and would not result in notification of a physician according to the criteria of Lab Noord. Based on the results from Trial 19.4.004, a clinically relevant effect of sugammadex was found in samples from female subjects for the progesterone assay. As a result, conclusions from the progesterone assay may be compromised when used in the presence of sugammadex for the purpose of identifying reproductive phases in female subjects. Based on the results from Trial 19.4.007, for Org 48302 spiked at the approximate C_{max} of 10 mcg/mL in plasma, no clinically relevant differences were observed between spiked and un-spiked samples.

4.3.2 Human pharmacokinetics

Five clinical trials (Trials 19.4.101 [Part I only], 19.4.102, 19.4.105, 19.4.106 and 19.4.107) investigated the PK of sugammadex (doses ranging from 1 to 96 mg/kg) in healthy, non-anesthetized volunteers. For sugammadex no patient PK was studied without investigating the pharmacodynamic effect. The reason for this is that sugammadex is not intended to treat a specific disease but, depending on the situation, anybody could be elective to surgery and consequently sugammadex might be administered. As a result, in contrast with a lot of other drugs, the population of volunteers is the same as the population of subjects undergoing surgery.

Distribution

Across the five trials, the V_{ss} of sugammadex ranged from 12 to 15 L, indicating that sugammadex distributes into the extracellular water of the body, which is in line with the physicochemical properties of the molecule and the fact that it does not bind to human plasma proteins and erythrocytes to a significant extent.

Elimination

Results from the five volunteer trials demonstrated that the rate of clearance of sugammadex is similar to the glomerular filtration rate in healthy humans (97 to 138 mL/min), not unexpected since the drug is cleared nearly exclusively by the kidneys. Excretion of sugammadex (in urine) is rapid (> 70% of the dose within 6 hours and > 90% within 24 hours). In accordance with other cyclodextrins, metabolism plays a very minor role in the clearance of sugammadex, if at all.

Excretion of sugammadex into human breast milk has not been studied, but can be expected based on preclinical data. Specifically, in rats, sugammadex was excreted into milk up to a maximum level of 0.22% of the dose per gram of milk; the level decreased as plasma levels declined.

Determination of terminal half-life ($t_{1/2,\beta}$) from the five volunteer trials resulted in a wide range of mean values (66 to 260 minutes) since $t_{1/2,\beta}$ is largely dependent upon the part of the concentration-versus-time curve used for its estimation. As a result, lower doses of sugammadex are associated with shorter $t_{1/2,\beta}$ and higher doses are associated with longer $t_{1/2,\beta}$ values.

Dose Linearity

Overall, across the five volunteer trials and across all dose groups (ranging from 0.1 to 96.0 mg/kg), similar values of CL of sugammadex were observed. Therefore, overall the data indicate dose linearity with respect to exposure to sugammadex.

Gender

No gender effects, following normalization of data for body weight, on the sugammadex PK profile were noted in the 2 volunteer trials (Trials 19.4.102 and 19.4.106) that investigated gender. In the pooled population analysis of the PK of sugammadex as part of the PK-PD interaction model, gender was not identified as a significant covariate, confirming the absence of a gender effect on the PK of sugammadex.

Race

Following administration of 1.0, 8.0 and 16.0 mg/kg sugammadex, no major differences in the PK of sugammadex were observed between Japanese and Caucasian subjects (Trial 19.4.102). Small differences in CL and V_{ss} disappeared after normalization for body weight.

The pooled dataset used in the population PK-PD evaluation containing data from a total of 709 subjects included 13 black subjects and 6 subjects of other races. These relatively low numbers did not allow for separate evaluation of these race effects on the PK of sugammadex.

Extrinsic factors

Sugammadex is metabolized to a minimal extent and almost exclusively excreted via the kidneys. In addition it is administered IV during surgery as a single bolus dose. As a result of the route of administration, interactions with food or other drugs in the gastrointestinal tract which might have an impact on bioavailability can be excluded. Furthermore no effects of smoking or alcohol use prior to surgery are expected since sugammadex is not metabolized nor excreted to a significant extent by the liver. Consequently, no trials have been conducted to study the effect of these extrinsic factors.

Other PK Results

Results from crossover trials (Trials 19.4.102 and 19.4.106) demonstrated minimal within-subject and between-subject variation in AUC, indicating that sugammadex is a drug of low variability. Trials in anesthetized subjects with normal renal function indicate that the PK profile of sugammadex is generally the same in non-anesthetized versus anesthetized subjects.

Renal Impairment

Trial 19.4.304 compared the efficacy of sugammadex and the PK profile of 2.0 mg/kg sugammadex (and rocuronium) when administered at the reappearance of T_2 following rocuronium-induced NMB. This trial demonstrated clearance was reduced 16-fold, and $t_{1/2,\beta}$ was increased 15-fold in severe renally-impaired subjects relative to healthy subjects; this resulted in a prolonged and 17-fold higher exposure to sugammadex in severe renally-impaired subjects. With regard to rocuronium, clearance was reduced 3.7-fold, $t_{1/2,\beta}$ was increased 2.5-fold, and V_{ss} was increased 25% in severe renally-impaired subjects relative to healthy subjects; this resulted in a prolonged and 4-fold higher exposure to rocuronium (bound and unbound) in renally-impaired subjects. The relatively smaller impact of renal impairment on the PK of rocuronium is due to the fact that rocuronium is eliminated, in part, via the liver.

Although the results of Trial 19.4.006 indicated that sugammadex and rocuronium are efficiently removed from plasma via dialysis using a high flux membrane, effective dialysis was not consistently demonstrated in Trial 19.4.304. As a result of these limited findings, the use of sugammadex in severe renally-impaired subjects (creatinine clearance < 30 mL/min) is strongly discouraged.

Effect of Propofol versus Sevoflurane Anesthesia on Rocuronium Plasma Levels

Trial 19.4.312 was conducted in order to trial the efficacy and safety of reversal at reappearance of T_2 with sugammadex after rocuronium infusion under propofol or sevoflurane anesthesia. In addition, the plasma levels of rocuronium under both anesthetic regimens (before administration of sugammadex) were studied in this trial.

Plasma concentrations of rocuronium just before administration of sugammadex, at $T_1=3-10\%$, were 33% lower during maintenance anesthesia with sevoflurane than during maintenance anesthesia with propofol. The variability (as expressed by geometric CV) in rocuronium concentrations was similar in both groups 30% for

sevoflurane and 31% for propofol. No statistically significant gender effect and treatment-by-gender interaction were found. An analysis was then performed without the gender factor which showed a statistically significant treatment effect was found between the two maintenance anesthesia treatments.

4.3.3 Human pharmacodynamics

The reversal of a rocuronium- or vecuronium-induced NMB by sugammadex is based on its ability to form an inclusion complex with the NMBA; this mechanism of action was supported by PK data across a number of the clinical pharmacology trials. In Trials 19.4.101, 19.4.201, 19.4.202, 19.4.205, 19.4.207, 19.4.208A, 19.4.208B, 19.4.304, and 19.4.306, a slight increase in rocuronium and vecuronium plasma concentrations was observed following the administration of sugammadex as a result of the NMBA being redistributed due to complex formation with sugammadex. Secondly, free rocuronium is eliminated, in part, via the liver. However, once complexed with sugammadex, the biliary route is no longer available and renal excretion of the complex becomes important for clearance. Results from various trials demonstrated that the total clearance of rocuronium decreases following administration of sugammadex, with clearance rates approaching the glomerular filtration rate. This is not unexpected since sugammadex (free and following complexation with an NMBA) is exclusively eliminated by the kidneys. In addition to diminished rocuronium clearance rates following administration of sugammadex, the presence of rocuronium in urine increases, again the result of a transition from biliary/renal excretion to exclusively renal clearance following complexation.

4.3.4 Dose-response and dose selection

As part of the sugammadex clinical pharmacology program, 12 trials were conducted to investigate the dose-response relationship of sugammadex and to determine doses for use in the Phase 3 program in reversing a rocuronium- or vecuronium-induced NMB at various timepoints following the administration of the NMBA. To support the dose selection, the time to recovery of the T_4/T_1 ratio to 0.9 was used as the primary efficacy variable.

Reversal at Reappearance of T_2 – Shallow NMB

Rocuronium-induced NMB

Data from Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, and 19.4.306 allowed for the evaluation of the efficacy of sugammadex in reversing a rocuronium-induced NMB at the reappearance of T_2 , shallow NMB. Pooled results from these trials showed a clear relationship between the dose of sugammadex and

recovery of the T_4/T_1 ratio to 0.9, with a dose of 2.0 mg/kg being effective for reversal of rocuronium-induced NMB at the reappearance of T_2 (Table 1). At this dose level, sugammadex reversed the NMB, on average within 1.6 minutes, an appreciable reduction in recovery time as compared to spontaneous recovery (average of 60 minutes) and to recovery times associated with currently available reversal agents. Based on the calculation of tolerance intervals, it can be expected with 97.5% confidence that 90% of subjects will recover to a T_4/T_1 ratio of 0.9 within 3 minutes following a 2.0 mg/kg dose of sugammadex when administered at the reappearance of T_2 following a rocuronium-induced NMB (Table 2). Therefore, the decision to investigate the safety and efficacy of 2.0 mg/kg sugammadex in reversing a rocuronium-induced NMB when administered at the reappearance of T_2 in the Phase 3 program would be appropriate. The choice of this dose in reversing a shallow rocuronium-induced block also appears to be appropriate regardless of the anesthetic used (i.e., propofol or sevoflurane; Trials 19.4.208A, 208B, and 210); sevoflurane appears to prolong spontaneous recovery or recovery following sub-optimal doses of sugammadex, but does not have a clinically relevant effect on the efficacy of 2.0 mg/kg sugammadex.

Table 1 Sugammadex administered at reappearance of T₂ following rocuronium administration: summary of the time to recovery of T₄/T₁ to 0.9 (min) by dose, within and across trials (PP group)

| Trial | | Dose of sugammadex (mg/kg) | | | | | | |
|-----------|-------------|----------------------------|-------------|------------|-----------|-----------|-----------|-----------|
| | | Placebo | 0.5 | 1.0 | 2.0 | 3.0 | 4.0 | 6.0 |
| 19.4.201 | n | 4 | 5 | 4 | 3 | 5 | 3 | 0 |
| | Mean (SD) | 23.1 (8.8) | 5.0 (2.8) | 3.2 (1.7) | 1.3 (0.4) | 1.5 (1.0) | 1.2 (0.2) | |
| | Median | 21.0 | 4.3 | 3.3 | 1.3 | 1.2 | 1.1 | |
| | Min. – max. | 15.0 – 35.4 | 1.3 – 8.5 | 1.4 – 4.9 | 0.9 – 1.7 | 0.7 – 3.2 | 1.0 – 1.4 | |
| 19.4.203 | n | 0 | 4 | 4 | 6 | 0 | 6 | 4 |
| | Mean (SD) | | 6.8 (3.1) | 2.7 (1.0) | 1.8 (0.6) | | 1.4 (0.6) | 2.6 (1.3) |
| | Median | | 5.5 | 2.7 | 1.8 | | 1.1 | 2.7 |
| | Min. – max. | | 4.8 – 11.4 | 1.8 – 3.7 | 1.0 – 2.5 | | 1.0 – 2.3 | 1.1 – 3.9 |
| 19.4.207 | n | 2 | 8 | 7 | 8 | 3 | 8 | 0 |
| | Mean (SD) | 31.8 (21.0) | 3.7 (1.0) | 2.3 (0.6) | 1.7 (0.6) | 1.9 (1.2) | 1.1 (0.3) | |
| | Median | 31.8 | 3.7 | 2.2 | 1.7 | 1.5 | 1.1 | |
| | Min. – max. | 17.0 – 46.7 | 2.1 – 4.9 | 1.5 – 3.4 | 0.9 – 2.8 | 1.0 – 3.2 | 0.7 – 1.6 | |
| 19.4.208A | n | 6 | 5 | 10 | 7 | 0 | 9 | 0 |
| | Mean (SD) | 82.1 (27.6) | 3.9 (2.5) | 2.5 (1.3) | 2.2 (1.2) | | 1.8 (1.2) | |
| | Median | 86.0 | 3.2 | 2.3 | 1.6 | | 1.6 | |
| | Min. – max. | 47.3 – 108.5 | 1.9 – 8.3 | 1.3 – 5.6 | 1.4 – 4.8 | | 0.8 – 4.8 | |
| 19.4.208B | n | 7 | 8 | 8 | 9 | 0 | 8 | 0 |
| | Mean (SD) | 96.3 (33.1) | 16.3 (20.6) | 4.6 (6.0) | 1.4 (0.5) | | 1.5 (0.4) | |
| | Median | 86.2 | 5.2 | 2.6 | 1.5 | | 1.3 | |
| | Min. – max. | 55.7 – 153.0 | 1.3 – 55.5 | 1.5 – 19.3 | 0.7 – 2.4 | | 1.2 – 2.2 | |
| Total | n | 25 | 35 | 38 | 38 | 8 | 39 | 4 |
| | Mean (SD) | 60.0 (38.8) | 7.2 (10.8) | 2.9 (2.9) | 1.6 (0.7) | 1.6 (1.0) | 1.4 (0.7) | 2.6 (1.3) |
| | Median | 47.3 | 4.2 | 2.2 | 1.5 | 1.3 | 1.2 | 2.7 |
| | Min. – max. | 15.0 – 153.0 | 1.3 – 55.5 | 1.2 – 19.3 | 0.7 – 4.8 | 0.7 – 3.2 | 0.7 – 4.8 | 1.1 – 3.9 |

Table 2 Tolerance intervals for 2.0 mg/kg sugammadex administered at reappearance of T₂ after rocuronium, 97.5% confidence (PP group)

| Proportion of subjects who will recover to TOF \geq 0.9 within the upper limit | Upper limit of tolerance interval (min) |
|--|---|
| 80% | 2.5 |
| 85% | 2.7 |
| 90% | 3.0 |
| 95% | 3.6 |

Vecuronium-induced NMB

Data from three trials (Trials 19.4.207, 19.4.208A and 19.4.208B) allowed for an investigation of the efficacy of sugammadex in reversing a vecuronium-induced NMB at the reappearance of T₂. Pooled results from these trials showed a clear relationship between the dose of sugammadex and recovery of the T₄/T₁ ratio to 0.9, with a dose of 2.0 mg/kg being effective for reversal of vecuronium-induced NMB at the reappearance of T₂ (Table 3). At this dose level, sugammadex reversed, on average, the NMB within 2.8 minutes, an appreciable reduction in recovery time as compared to spontaneous recovery (average of 74 minutes) and to recovery times associated with currently available reversal agents. Doubling the dose of sugammadex to 4.0 mg/kg resulted in only approximately a 30-second reduction in the mean recovery time across the three trials. Based on the calculation of tolerance intervals, it can be expected with 97.5% confidence that 90% of subjects will recover to a T₄/T₁ ratio of 0.9 within 5.9 minutes following a 2.0 mg/kg dose of sugammadex when administered at the reappearance of T₂ following a vecuronium-induced NMB (Table 4).

Table 3 Sugammadex administered at reappearance of T₂ following vecuronium administration: summary of the time to recovery of T₄/T₁ to 0.9 (min) by dose group, within and across trials (PP group)

| Trial | | Dose of sugammadex (mg/kg) | | | | | |
|-----------|-------------|----------------------------|-------------|-------------|-----------|-----------|-----------|
| | | Placebo | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| 19.4.207 | n | 4 | 6 | 8 | 8 | 7 | 4 |
| | Mean (SD) | 48.7 (27.9) | 7.7 (2.6) | 2.5 (0.8) | 2.3 (0.8) | 1.5 (0.5) | 1.4 (0.5) |
| | Median | 39.8 | 7.1 | 2.3 | 2.3 | 1.4 | 1.4 |
| | Min. – max. | 27.1 – 88.4 | 5.5 – 11.5 | 1.4 – 3.9 | 1.3 – 3.5 | 1.1 – 2.5 | 0.8 – 2.0 |
| 19.4.208A | n | 7 | 3 | 8 | 6 | 10 | 0 |
| | Mean (SD) | 83.2 (20.6) | 52.0 (64.9) | 10.6 (19.2) | 2.8 (0.8) | 2.1 (0.9) | |
| | Median | 82.7 | 26.1 | 4.1 | 2.9 | 1.9 | |
| | Min. – max. | 55.4 – 118.3 | 4.1 – 125.9 | 2.7 – 58.2 | 1.7 – 3.9 | 1.0 – 3.9 | |
| 19.4.208B | n | 8 | 9 | 10 | 7 | 9 | 0 |
| | Mean (SD) | 79.0 (26.0) | 35.5 (42.1) | 5.1 (2.4) | 3.4 (1.9) | 3.0 (2.2) | |
| | Median | 70.6 | 13.3 | 4.5 | 2.5 | 2.5 | |
| | Min. – max. | 59.8 – 141.1 | 3.5 – 113.5 | 1.6 – 8.8 | 2.1 – 7.1 | 1.3 – 8.5 | |
| Total | n | 19 | 18 | 26 | 21 | 26 | 4 |
| | Mean (SD) | 74.2 (26.8) | 29.0 (40.1) | 6.0 (10.8) | 2.8 (1.3) | 2.3 (1.5) | 1.4 (0.5) |
| | Median | 72.8 | 9.1 | 3.6 | 2.7 | 1.9 | 1.4 |
| | Min. – max. | 27.1 – 141.1 | 3.5 – 125.9 | 1.4 – 58.2 | 1.3 – 7.1 | 1.0 – 8.5 | 0.8 – 2.0 |

Table 4 Tolerance intervals for 2.0 mg/kg sugammadex administered at reappearance of T₂ after vecuronium, 97.5% confidence (PP group)

| Proportion of subjects who will recover to TOF _{0.9} within the upper limit | Upper limit of tolerance interval (min) |
|--|---|
| 80% | 4.7 |
| 85% | 5.2 |
| 90% | 5.9 |
| 95% | 7.2 |

Given the small difference in recovery times between the 2.0 and 4.0 mg/kg dose and the desire to ultimately propose only one dose for use in reversing a NMB at the reappearance of T₂, 2.0 mg/kg was chosen for investigation in the Phase 3 program.

Reversal at 1-2 PTCs and at 15 Minutes After Rocuronium – Profound NMB

Rocuronium-induced NMB

Data from three trials (Trials 19.4.204, 19.4.209A and 19.4.209B) allowed for an investigation of the efficacy of sugammadex in reversing a rocuronium-induced NMB at 1-2 PTCs (profound block). An additional 2 trials (Trials 19.4.202 and 19.4.206) also evaluated recovery at 15 minutes following the administration of an intubating dose of rocuronium (0.6 mg/kg; Figure 1). It has been generally recognized that the depth of blockade 15 minutes after 0.6 mg/kg rocuronium corresponds well with a blockade at 1-2 PTCs (the time to a first response to PTC was found to be

12 minutes).[37] Therefore, pooling 1-2 PTC data with 15 minute data was considered to be justified for the selection of the sugammadex dose for Phase 3 investigation of reversal of a profound blockade. It should be noted, however, that only data collected at 1-2 PTCs have been used to make dosing recommendations on sugammadex for routine reversal of a profound blockade.

Pooled results from these trials showed a clear relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9 (Table 5). The mean recovery time decreased from 35.6 minutes following placebo and 66.3 minutes following 0.5 mg/kg sugammadex to 1.8 minutes following a dose of 4.0 mg/kg. Doubling the dose of sugammadex to 8.0 mg/kg resulted in only approximately a 30-second faster reduction in the mean recovery time across the trials. Based on the calculation of tolerance intervals, it can be expected with 97.5% confidence that 90% of subjects will recover to a T_4/T_1 ratio of 0.9 within 3.9 minutes following a 4.0 mg/kg dose of sugammadex when administered at 1-2 PTCs or 15 minutes following a rocuronium-induced NMB (Table 6).

Table 5 Sugammadex administered at 1–2 PTC after rocuronium administration or 15 min after 0.6 mg/kg rocuronium: summary of the time to recovery of T_4/T_1 to 0.9 (min) by dose, within and across trials (PP group)

| Trial | | Dose of sugammadex (mg/kg) | | | | | | |
|-----------|-----------|----------------------------|-------------|-------------|------------|-----------|-----------|-----------|
| | | Placebo | 0.5 | 1.0 | 2.0 | 4.0 | 6.0 | 8.0 |
| 19.4.202 | n | 3 | 0 | 6 | 6 | 6 | 6 | 6 |
| | Mean (SD) | 35.6 (9.0) | | 6.5 (1.7) | 2.7 (0.7) | 2.0 (1.2) | 2.1 (2.0) | 1.3 (0.2) |
| | Median | 30.6 | | 6.2 | 2.5 | 1.5 | 1.1 | 1.3 |
| | Min.–max. | 30.1 – 46.0 | | 4.8 – 9.0 | 2.1 – 4.0 | 1.1 – 4.2 | 1.0 – 5.9 | 1.1 – 1.7 |
| 19.4.204 | n | 0 | 4 | 5 | 8 | 4 | 0 | 8 |
| | Mean (SD) | | 38.3 (30.6) | 14.5 (13.6) | 5.0 (4.3) | 2.6 (1.3) | | 1.3 (0.5) |
| | Median | | 24.2 | 5.1 | 4.1 | 2.3 | | 1.0 |
| | Min.–max. | | 20.6 – 84.1 | 4.5 – 33.2 | 1.8 – 15.2 | 1.5 – 4.5 | | 0.8 – 2.1 |
| 19.4.209A | n | 0 | 6 | 7 | 10 | 11 | 0 | 10 |
| | Mean (SD) | | 66.9 (34.6) | 4.7 (1.7) | 3.4 (2.5) | 1.6 (0.9) | | 1.3 (0.6) |
| | Median | | 62.7 | 4.7 | 2.9 | 1.2 | | 1.2 |
| | Min.–max. | | 15.5–114.2 | 1.6 – 7.5 | 1.4 – 9.3 | 0.8 – 4.0 | | 0.6 – 2.4 |
| 19.4.209B | n | 0 | 8 | 9 | 10 | 10 | 0 | 10 |
| | Mean (SD) | | 79.8 (33.0) | 28.0 (43.7) | 3.2 (1.5) | 1.6 (0.7) | | 1.1 (0.3) |
| | Median | | 87.5 | 7.4 | 3.2 | 1.5 | | 1.1 |
| | Min.–max. | | 24.4–131.7 | 3.6 – 117.1 | 1.1 – 6.6 | 0.8 – 2.9 | | 0.8 – 2.0 |
| Total | n | 3 | 18 | 27 | 34 | 31 | 6 | 34 |
| | Mean (SD) | 35.6 (9.0) | 66.3 (35.2) | 14.7 (26.9) | 3.6 (2.6) | 1.8 (1.0) | 2.1 (2.0) | 1.3 (0.4) |
| | Median | 30.6 | 65.4 | 5.5 | 3.0 | 1.6 | 1.1 | 1.2 |
| | Min.–max. | 30.1 – 46.0 | 15.5–131.7 | 1.6 – 117.1 | 1.1 – 15.2 | 0.8 – 4.5 | 1.0 – 5.9 | 0.6 – 2.4 |

Table 6 Tolerance intervals for 4.0 mg/kg sugammadex administered at 1–2 PTC after rocuronium administration or 15 min after 0.6 mg/kg rocuronium, 97.5% confidence (PP group)

| Proportion of subjects who will recover to TOF \geq 0.9 within the upper limit | Upper limit of tolerance interval (min) |
|--|---|
| 80% | 3.0 |
| 85% | 3.4 |
| 90% | 3.9 |
| 95% | 4.8 |

Given that this represents a clinically significant decrease in recovery time relative to spontaneous recovery and the fact that currently available reversal agents (e.g., neostigmine) are not indicated for and are not efficacious in reversing a profound NMB, the decision to investigate, in the Phase 3 program, the safety and efficacy of 4.0 mg/kg sugammadex in reversing a rocuronium-induced NMB when administered at 1-2 PTCs is appropriate.

Vecuronium-induced NMB

Data from 2 trials (Trials 19.4.209A and 19.4.209B) allowed for an investigation of the efficacy of sugammadex in reversing a vecuronium-induced NMB at 1-2 PTCs (Figure 1). Pooled results from these trials showed a clear relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9 (Table 7). The mean recovery time decreased from 73.0 minutes following 0.5 mg/kg sugammadex to 3.2 minutes following a dose of 4.0 mg/kg. Doubling the dose of sugammadex to 8.0 mg/kg resulted in an approximate one-minute reduction in the mean recovery time (down to 2.3 minutes) across the three trials.

Table 7 Sugammadex administered at 1–2 PTC following vecuronium administration: summary of the time to recovery of T_4/T_1 to 0.9 (min) by dose, within and across trials (PP group)

| Trial | | Dose of sugammadex (mg/kg) | | | | |
|-----------|-------------|----------------------------|-------------|-------------|------------|------------|
| | | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 |
| 19.4.209A | n | 5 | 7 | 10 | 10 | 10 |
| | Mean (SD) | 79.5 (46.2) | 39.8 (45.8) | 16.0 (42.2) | 3.0 (2.4) | 2.9 (3.8) |
| | Median | 76.5 | 8.9 | 2.8 | 1.9 | 1.4 |
| | Min. – max. | 17.7 – 143.9 | 3.9 – 116.2 | 1.5 – 136.1 | 0.9 – 8.4 | 1.2 – 13.5 |
| 19.4.209B | n | 7 | 9 | 11 | 8 | 10 |
| | Mean (SD) | 68.4 (31.9) | 25.1 (24.9) | 9.1 (20.6) | 3.3 (3.5) | 1.7 (0.7) |
| | Median | 59.1 | 15.7 | 2.8 | 2.3 | 1.6 |
| | Min. – max. | 29.4 – 124.9 | 2.7 – 66.9 | 1.6 – 71.0 | 1.0 – 11.7 | 0.7 – 2.9 |
| Total | n | 12 | 16 | 21 | 18 | 20 |
| | Mean (SD) | 73.0 (37.0) | 31.6 (35.0) | 12.4 (32.0) | 3.2 (2.8) | 2.3 (2.7) |
| | Median | 69.3 | 12.3 | 2.8 | 2.1 | 1.5 |
| | Min. – max. | 17.7 – 143.9 | 2.7 – 116.2 | 1.5 – 136.1 | 0.9 – 11.7 | 0.7 – 13.5 |

Taking into account that currently available reversal agents are not efficacious in this anesthesia setting and the fact that only one dosing recommendation is ideal for the use of a reversal agent in a given anesthesia setting (in this case, reversing a profound block), 4.0 mg/kg sugammadex was chosen for investigation in the Phase 3 program.

Immediate Reversal of a Rocuronium-Induced NMB

Data from 2 trials (Trials 19.4.205 and 19.4.206) allowed for an investigation of the efficacy of sugammadex in immediate reversal situations following a rocuronium-induced NMB (Figure 1). Pooled results from these trials showed a clear relationship between the dose of sugammadex and recovery of the T_4/T_1 ratio to 0.9 (Table 8). The mean recovery time decreased from 122.5 minutes following placebo (i.e., spontaneous recovery) to 1.8 minutes following a dose of 12.0 mg/kg and 1.6 minutes following a dose of 16.0 mg/kg. When a single outlier in the 16.0 mg/kg group (recovery time of 6.9 minutes, likely due to technical issues with neuromuscular monitoring) was excluded from the analysis, the pooled mean recovery time decreased to 1.2 minutes.

Table 8 Sugammadex administered at 3 or 5 minutes after 1.2 mg/kg rocuronium: summary of the time to recovery of T₄/T₁ to 0.9 (min) by dose, within and across trials (PP group)

| Trial | | Dose of sugammadex (mg/kg) | | | | | |
|----------|-----------|----------------------------|--------------|-------------|-----------|-----------|-----------|
| | | Placebo | 2.0 | 4.0 | 8.0 | 12.0 | 16.0 |
| 19.4.205 | n | 4 | 5 | 5 | 12 | 7 | 7 |
| | Mean (SD) | 122.1 (18.1) | 56.5 (5.4) | 15.8 (17.7) | 2.8 (0.5) | 1.4 (0.3) | 1.9 (2.2) |
| | Median | 126.1 | 55.3 | 12.3 | 2.5 | 1.3 | 1.3 |
| | Min.–max. | 96.8 - 139.4 | 50.5 - 65.1 | 3.3 - 46.6 | 2.2 - 3.7 | 1.0 - 1.9 | 0.7 - 6.9 |
| 19.4.206 | n | 4 | 9 | 8 | 11 | 10 | 11 |
| | Mean (SD) | 123.0 (28.5) | 65.7 (24.6) | 13.8 (7.6) | 3.2 (1.0) | 2.1 (0.9) | 1.3 (0.4) |
| | Median | 124.3 | 63.3 | 11.3 | 3.6 | 1.9 | 1.3 |
| | Min.–max. | 87.3 - 156.1 | 36.3 - 117.2 | 5.3 - 28.5 | 1.5 - 4.7 | 1.2 - 4.1 | 0.8 - 2.3 |
| Total | n | 8 | 14 | 13 | 23 | 17 | 18 |
| | Mean (SD) | 122.5 (22.1) | 62.4 (20.0) | 14.6 (11.8) | 3.0 (0.8) | 1.8 (0.8) | 1.6 (1.4) |
| | Median | 126.1 | 56.1 | 11.8 | 2.8 | 1.7 | 1.3 |
| | Min.–max. | 87.3 - 156.1 | 36.3 - 117.2 | 3.3 - 46.6 | 1.5 - 4.7 | 1.0 - 4.1 | 0.7 - 6.9 |

Given the urgency of needing to immediately reverse a NMB (e.g., in a CICV setting where critical desaturation must be prevented), the higher dose of 16.0 mg/kg was chosen for investigation in the Phase 3 program. It should be noted that no trials were conducted to investigate the efficacy of sugammadex in immediate reversal situations following a vecuronium-induced NMB because the relatively slower onset of vecuronium precludes its potential usefulness when immediate reversal is needed.

4.3.5 Population PK-PD model

Plasma concentration-time data and data on the efficacy of sugammadex in reversing rocuronium- and vecuronium-induced NMB were collected during the clinical development program in order to develop and validate a population PK-PD model describing the mechanism of complex formation between sugammadex and the NMBA. The first version of the model was developed using data from healthy volunteers (Trial 19.4.101) and from ASA Class 1 and 2 subjects undergoing surgery (Trials 19.4.201, 19.4.202, and 19.4.207). The model was updated to include data from ASA Class 1-3 subjects undergoing surgery (Trials 19.4.205, 19.4.206, and 19.4.210). In addition, data from subjects with severe renal failure, elderly subjects, and pediatric subjects (Trials 19.4.304, 19.4.305 and 19.4.306, respectively) were subsequently included in the model, allowing for identification and quantification of possible covariate effects of age, body weight and creatinine clearance rates on the PK of sugammadex. The model describes the depth of a NMB in response to the PK interaction between rocuronium and sugammadex. Factors which influence the PD response of rocuronium through a different mechanism, such as co-administration of antibiotics, magnesium or inhalation anesthetics, are not incorporated in the PK-PD

interaction model. The fact that the PK-PD interaction model can appropriately describe data from trials investigating a wide range of scenarios and populations indicates the general consistency of the results of the clinical program.

The purpose of the model was to simulate situations that were not studied in clinical trials. Specifically, the model has been used to: (1) simulate the reversal of rocuronium-induced NMB by sugammadex in subjects with hepatic impairment; (2) verify the guidance with respect to re-administration of rocuronium shortly after the reversal of a previous NMB by sugammadex by simulating onset times according to various scenarios; and (3) estimate the effect of sugammadex on the free concentration of other drugs that bind to sugammadex. In addition, the PK of sugammadex has also been simulated in geriatric and pediatric subjects as well as in subjects with renal impairment.

Hepatic Impairment

With regard to hepatic impairment, different sugammadex dosing scenarios (representing its use in routine reversal of a NMB either at the reappearance of T_2 or at 15 minutes or in immediate reversal settings) were simulated. According to the simulations, the recovery time of 2.55 minutes is predicted when a dose of 2.0 mg/kg is used to reverse rocuronium-induced NMB at the reappearance of T_2 . A prolongation of the recovery time in severe hepatically-impaired subjects may be at most 4.12 minutes longer than in normal subjects, when a dose of 4.0 mg/kg is used to reverse a NMB at 15 minutes after administration of 1.2 mg/kg rocuronium. The predicted effect on the recovery time for reversal of a NMB 3 minutes after rocuronium using 16 mg/kg sugammadex was limited. Based on these simulations, a possible prolongation of recovery time in hepatically-impaired subjects will be noted in the labeling of sugammadex.

Re-use of Rocuronium or Vecuronium

A situation may occur where a subject, who has received rocuronium or vecuronium for NMB and sugammadex to reverse that NMB, needs to be treated again with rocuronium or vecuronium after reversal by sugammadex. When sugammadex is still present in the circulation, the effectiveness of the re-treatment with the NMBA may be affected, to a degree, depending on the dose of sugammadex administered and on the time elapsed between reversal and re-treatment with NMBA. For practical reasons such a situation is difficult to evaluate in a clinical trial. As a result, utilization of the PK-PD model contributed to predicting waiting times for readministration relative to administration of sugammadex (Table 9). Specifically, readministration of 0.6 mg/kg rocuronium would not be fully efficacious until 6, 8 and

12 hours following single doses of 2.0, 4.0, and 16.0 mg/kg, respectively, of sugammadex. A dose of 1.2 mg/kg rocuronium would not be fully efficacious until 2 and 4 hours following single doses of 4.0 and 16.0 mg/kg, respectively, of sugammadex; no wait time would be required following a 2.0 mg/kg dose of sugammadex. For vecuronium, re-administration of 0.1 mg/kg vecuronium would not be fully efficacious until 10, 12 and 16 hours following single doses of 2.0, 4.0, and 16.0 mg/kg, respectively, of sugammadex. Predicted times for rocuronium and vecuronium would be doubled in subjects with mild renal impairment and tripled in subjects with moderate renal impairment.

Table 9 Recommended waiting times for re-administration with rocuronium or vecuronium after reversal with sugammadex

| Administered dose of sugammadex | In subjects with normal renal function ($CL_{CR} \geq 80$ mL/min) | | |
|---------------------------------|--|--|--|
| | Time before re-administration (in hours) | | |
| | Re-administration dose of 0.6 mg/kg rocuronium | Re-administration dose of 1.2 mg/kg rocuronium | Re-administration dose of 0.1 mg/kg vecuronium |
| 2.0 mg/kg | 6 | 0 | 10 |
| 4.0 mg/kg | 8 | 2 | 12 |
| 16.0 mg/kg | 12 | 6 | 16 |

In subjects with mild renal impairment (CL_{CR} between 50 and 80 mL/min) these times should be doubled.

In subjects with moderate renal impairment (CL_{CR} between 30 and 50 mL/min) these times should be tripled.

Drug Interaction Potential

With respect to drug interaction potential, 2 possible types of interactions were investigated: (1) capturing interaction potential and (2) displacement interaction potential. With regard to capturing interaction potential, due to the administration of sugammadex, certain drugs could become less effective due to a lowering of the (free) plasma concentrations. Theoretically, for certain drugs (acute) withdrawal effects could also be expected after administration of sugammadex. Displacement interaction potential would involve another drug or molecule binding to sugammadex, decreasing the amount of free sugammadex available to reverse a NMB and/or displacing sugammadex that is complexed with a NMBA. This could result in an increase in the amount of NMBA available, resulting in either re-occurrence of NMB if given after sugammadex or in slower recovery if the NMBA is given before sugammadex.

With respect to capturing interaction potential, it has been concluded that, based on a worst-case scenario model (assuming no binding to sex hormone-binding globulin), a clinically relevant interaction cannot be ruled out for hormonal contraceptives.

However, it is important to stress that there are no indications, from preclinical trials or clinical trials, that this interaction occurs in vivo. Nonetheless, because of the nature of this potential interaction, the current proposal is to list hormonal contraceptives as a potential interaction in the labeling for sugammadex. Specifically, the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids. Physicians will be instructed to refer to the missed dose advice in the package insert of the oral contraceptive for any actions required if an oral contraceptive is taken on the same day that sugammadex is administered. In the case of non-oral hormonal contraceptives, it will be recommended that the subject must use an additional non-hormonal contraceptive method for the next 7 days.

With respect to displacement interaction potential, toremifene, flucloxacillin and fusidic acid were identified as three compounds that carry a risk of causing a clinically relevant displacement interaction with sugammadex. Any risk of clinically relevant displacement by another drug is likely to exist only during a period of approximately three half-lives after administration of sugammadex. After that time less than 13% of sugammadex and bound rocuronium or vecuronium present at the time of reversal remains. As there is no further information available to assess these potential interactions, the current proposal is to list these three drugs in the labeling. Specifically, for toremifene, which has a relatively high affinity constant and relatively high plasma concentrations, some displacement of rocuronium or vecuronium from the complex with sugammadex could occur. The recovery of the T_4/T_1 ratio to 0.9 could therefore be delayed in subjects who have received toremifene on the same day of the operation. It should be noted that flucloxacillin and fusidic acid are not available in the US.

In addition to interactions with sugammadex, when drugs which potentiate neuromuscular blockade are used in the postoperative period, special attention should be paid to the possibility of re-occurrence of blockade. Physicians should refer to the package insert of rocuronium or vecuronium for a list of the specific drugs which potentiate NMB.

Age and Renal Impairment

With respect to age (geriatric subjects and pediatric subjects) and renal function, the PK-PD model predicts that after 4.0 mg/kg of sugammadex administered 15 minutes after 0.6 mg/kg of rocuronium, the typical adult with normal renal function and a body weight of 75 kg will have a recovery time of 1.5 minutes. The pediatric population is predicted to have shorter recovery times (0.2 to 0.7 minutes), and the geriatric population is predicted to have slightly longer recovery times (1.7 to 2.1 minutes) as expected with age-related decrease in circulation times. After 2.0 mg/kg of sugammadex administered at the reappearance of T_2 , the typical adult with normal renal function and a body weight of 75 kg is predicted to have a recovery time of 1.5 minutes. The pediatric population is predicted to have shorter recovery times (0.4 to 0.8 minutes), and the geriatric population is predicted to have a similar recovery time as the typical normal adult population.

In both simulated scenarios, all recovery times were predicted to be well under 3 minutes except for the situation of reversal at 15 minutes after rocuronium in the adult with severe renal impairment, who has a predicted recovery time of 3.6 minutes. Thus, even in a severe renally-impaired subject, recovery times are predicted to be typically less than 4 minutes.

The PK-PD interaction model confirmed the observation from the separate clinical trials that population differences in PK and PD typically do not result in prolongation of recovery times to over 4 minutes, whereas without sugammadex spontaneous recovery can be expected only after 60 minutes. Therefore, the PK-PD model supports the recommendation that no dose adjustment is required in these special populations (geriatric, pediatric, and severe renally-impaired).

5. SUMMARY OF EFFICACY

5.1 Description of trials supporting clinical efficacy

The efficacy of sugammadex as a NMB reversal agent was evaluated in 23 trials (Figure 1): 12 Phase 2 trials (Trials 19.4.201-19.4.210); and 11 Phase 3 trials (19.4.301-19.4.306 and 19.4.308-19.4.312).

As noted in Section 2.1, 8 of the 23 trials (Phase 3 Trials 19.4.301 and 19.4.310 and Phase 2 Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, and 19.4.210)

investigated the efficacy of sugammadex in reversing a NMB when administered at the reappearance of T₂, 4 of the 23 trials (Phase 3 Trial 19.4.302 and Phase 2 Trials 19.4.204, 19.4.209A, and 19.4.209B) investigated the efficacy of sugammadex in reversing a NMB when administered at 1-2 PTCs, and 3 of the 23 trials (Phase 3 Trial 19.4.303 and Phase 2 Trials 19.4.202 and 19.4.206) investigated the efficacy of sugammadex in an immediate reversal setting (i.e., administration of sugammadex 3 minutes following a dose of rocuronium). In addition, five trials were conducted in special populations in which sugammadex was administered at the reappearance of T₂ (Trials 19.4.304 [renal impairment], 19.4.305 [geriatric subjects], 19.4.306 [pediatric subjects], 19.4.308 [subjects with pulmonary complication(s)], and 19.4.309 [subjects with cardiac disease]).

Trial 19.4.311 was also conducted to determine the safety and time-course of recovery to a T₄/T₁ ratio of 0.9 within 4 minutes after 4.0 mg/kg sugammadex is given at least 15 minutes after the last administration of rocuronium in a wide range of surgical procedures and anesthetic regimens (i.e., assessment of routine use). Trial 19.4.312 was conducted in order to investigate the efficacy and safety of sugammadex after rocuronium infusion under propofol or sevoflurane anesthesia. In addition, the plasma levels of rocuronium under both anesthetic regimens (before administration of sugammadex) were studied in this trial.

The efficacy of sugammadex was assessed following rocuronium-induced NMB (at intubating doses ranging from 0.6 - 1.2 mg/kg) in all efficacy trials conducted. In addition to the intubating dose of rocuronium, standardized maintenance doses (0.1 - 0.2 mg/kg) were administered at fixed points during recovery at the discretion of the Investigator in 11 of the 23 trials (Trials 19.4.204, 19.4.208A, 19.4.208B, 19.4.209A, 19.4.209B, 19.4.301, 19.4.302, 19.4.305, 19.4.308, 19.4.309 and 19.4.311), and maintenance doses, administered at the discretion of the Investigator in accordance with doses given in routine clinical practice, were permitted in one other trial (Trial 19.4.203). In Trial 19.4.310 the combination of rocuronium with sugammadex was compared with cisatracurium (intubating dose of 0.15 mg/kg) and neostigmine. In Trial 19.4.312, the bolus administration of rocuronium was followed by continuous infusion of rocuronium for maintenance, starting with an infusion rate of 7 µg/kg/min, with subsequent adjustment by titration to maintain a depth of NMB of zero responses to TOF and PTC of ≤10 responses.

The efficacy of sugammadex was also assessed following vecuronium-induced NMB (at an intubating dose of 0.1 mg/kg) in 7 of the 23 efficacy trials conducted (Trials 19.4.207, 19.4.208A, 19.4.208B, 19.4.209A, 19.4.209B, 19.4.301 and 19.4.302). In addition to the intubating dose of vecuronium, standardized maintenance doses (0.015-0.04 mg/kg) were administered at the discretion of the

Investigator in 6 of the 7 trials (Trials 19.4.208A, 19.4.208B, 19.4.209A, 19.4.209B, 19.4.301 and 19.4.302).

In all active-controlled trials (other than Trial 19.4.303), neostigmine was used as the active comparator. For reversal of a block at the reappearance of T_2 , 50 µg/kg neostigmine was administered since this is the most commonly reported dose in the literature [60,61,62]. For reversal of a block at 1-2 PTCs, 70 µg/kg neostigmine was administered in accordance with the literature and the package insert [63,16]. Because of its side effects, neostigmine is administered in combination with an antimuscarinic agent. Current anesthesia practice typically uses a 5:1 combination of neostigmine and glycopyrrolate (rather than neostigmine and atropine) because of the similarities in their onset and duration of action [64,65].

In order to investigate the efficacy of sugammadex (16.0 mg/kg) with regard to immediate reversal of rocuronium (1.2 mg/kg), the spontaneous recovery from NMB-induced by succinylcholine (1.0 mg/kg) served as the “active comparator” in Trial 19.4.303.

Impact of Outliers on the Interpretation of Efficacy Results

Review of efficacy data collected during the sugammadex clinical development program revealed that in certain subjects recovery of the T_4/T_1 ratio to 0.9 is prolonged compared to other subjects under comparable circumstances. These outlier results can potentially impact the analysis of efficacy data and, as a result, have been noted in Section 4 and will be noted throughout this section, as appropriate. Subjects with prolonged recovery times are considered “outliers”. Outliers were only defined for cases where a dose of sugammadex equal to or higher than the recommended dose was administered for the three proposed uses (i.e., subjects with prolonged recovery times following the administration of sub-optimal doses of sugammadex were not considered in the outlier report). As noted in the Outlier Report, two methods were employed to define subjects as outliers: a clinical approach and a statistical approach. With regard to the clinical approach, outliers were defined as subjects with recovery times ≥ 3 times the geometric mean recovery time of the T_4/T_1 ratio to 0.9. With regard to the statistical approach, 2 analyses were applied; one analysis identified outliers from the entire efficacy database based on a 2-way ANOVA model, the other analysis, also based on a 2-way ANOVA, identified outliers for each proposed use of sugammadex (i.e., administration at the reappearance of T_2 , administration at 1-2 PTCs or at 15 minutes following the NMBA, or in immediate reversal settings [three and five minutes]) following either rocuronium or vecuronium.

Overall, 31 subjects (out of the 1470 subjects included in the ITT population) with prolonged recovery times were defined as outliers; none of these subjects were excluded from the efficacy analysis. The possible causes of the prolonged recovery times were divided into 4 groups. First, technical issues with neuromuscular monitoring can result in outlier results. An abnormal first twitch (T_1) can have a significant influence on the T_4/T_1 ratio. Close scrutiny allowed for the identification of 10 cases where the duration to recovery of the T_4/T_1 ratio to 0.9 was prolonged because the amplitude of T_1 was abnormally high. Second, protocol non-compliance (i.e., incorrect dose of sugammadex or NMBA administered, sugammadex not administered at the correct level of NMB, etc.) was the primary cause of outlier results in 6 subjects. Third, prolonged recovery was attributed to old age in one subject, and possible prolongation due to the use of inhalation anesthetic agents (sevoflurane causes a concentration-dependent inhibition of neuromuscular transmission) was determined to be the primary cause in the remaining 14 subjects. Of these 31 subjects, 19 received rocuronium as the NMBA, with sugammadex being administered at: the reappearance of T_2 , (n=8); 1-2 PTCs (n=2); at 15 minutes (n=4); at 3 minutes (n=4); or at 5 minutes (n=1). The remaining 12 subjects received vecuronium as the NMBA, with sugammadex administered at either the reappearance of T_2 (n=4) or at 1-2 PTCs (n=8).

5.2 Summary of trial designs

Four Phase 3 trials provide substantial evidence of the efficacy of sugammadex for routine reversal at the reappearance of T_2 [shallow blockade] or at 1-2 PTCs [profound block] or immediate reversal 3 minutes following an intubating dose of 1.2 mg/kg rocuronium. The designs of these 4 Phase 3 trials are described below.

Trial 19.4.301 was a multi-center, randomized, parallel group, active-controlled, safety-assessor blinded pivotal Phase 3 trial in adult subjects comparing sugammadex with neostigmine as a reversal agent of a NMB induced by rocuronium or vecuronium at the reappearance of T_2 . The primary objectives were to demonstrate: (1) faster recovery from a NMB induced by rocuronium after reversal at the reappearance of T_2 by 2.0 mg/kg sugammadex compared to 50 μ g/kg neostigmine; and (2) faster recovery from a NMB induced by vecuronium after reversal at the reappearance of T_2 by 2.0 mg/kg sugammadex compared to 50 μ g/kg neostigmine.

Trial 19.4.310 was a multi-center, randomized, parallel group, active-controlled, safety assessor blinded Phase 3 trial in adult subjects comparing rocuronium and sugammadex with cisatracurium and neostigmine when the NMB is reversed at the reappearance of T_2 . The primary objective was to demonstrate faster recovery from

a NMB with sugammadex (after a rocuronium-induced NMB) compared to neostigmine (after a cisatracurium-induced NMB) when administered at the reappearance of T_2 .

Trial 19.4.302 was a multi-center, randomized, parallel group, active-controlled, safety assessor blinded pivotal Phase 3 trial in adult subjects comparing sugammadex with neostigmine as a reversal agent of a NMB induced by maintenance dosing of rocuronium or vecuronium at 1-2 PTCs. The primary objectives were to demonstrate: (1) faster recovery from a NMB induced by rocuronium after reversal at 1-2 PTCs by 4.0 mg/kg sugammadex compared to 70 µg/kg neostigmine, and (2) faster recovery from a NMB induced by vecuronium at 1-2 PTCs by 4.0 mg/kg sugammadex compared to 70 µg/kg neostigmine.

Trial 19.4.303 was a multi-center, randomized, parallel group, active-controlled, safety assessor blinded Phase 3 trial in adult subjects comparing reversal of a NMB induced by 1.2 mg/kg rocuronium with 16 mg/kg sugammadex (administered at 3 minutes following rocuronium) versus spontaneous recovery from 1.0 mg/kg succinylcholine. The primary objective was to demonstrate faster recovery to a T_1 of 10% after a NMB induced by 1.2 mg/kg rocuronium was reversed by 16.0 mg/kg sugammadex at 3 minutes (i.e., immediate reversal) compared to spontaneous recovery after a NMB induced by 1.0 mg/kg succinylcholine. Times to recovery of T_1 to 10% (primary endpoint) and 90% (secondary endpoint) were used in this trial since, following administration of a depolarizing muscle relaxant like succinylcholine, fading is not observed and, therefore, the T_4/T_1 ratio cannot be used in the evaluation of efficacy.

In addition to the four aforementioned trials, seven supportive Phase 3 trials were conducted during the clinical development program to assess the efficacy (and safety) of sugammadex in special subject populations or specific surgical situations. (Appendix 1) Due to its cholinergic activity, neostigmine should be used cautiously in subjects with cardiac and pulmonary disease. Therefore, a trial in subjects with pulmonary complication(s) (Trial 19.4.308) and a trial in subjects with cardiac complication(s) (Trial 19.4.309) have been conducted to assess the efficacy (and safety) of sugammadex in these subject populations. Although the PD of sugammadex are not dependent on its clearance (renal function) and, therefore, no dose adjustment is required in subjects with renal impairment, the PK profile of sugammadex was nonetheless investigated in subjects with renal failure (Trial 19.4.304). The efficacy (and safety) of sugammadex were assessed in geriatric subjects (Trial 19.4.305) and pediatric subjects (Trial 19.4.306). Trial 19.4.311 was conducted to evaluate the efficacy and safety of sugammadex when used at the end of the surgical procedure to reverse a NMB induced by

rocuronium. This trial was designed to mimic as closely as possible the use of sugammadex in normal daily practice by encompassing the various situations studied in the sugammadex Phase 3 program with a more routine anesthetic regimen and a wider range of surgical procedures. Trial 19.4.312 was conducted in order to trial the efficacy and safety of sugammadex after rocuronium infusion under propofol and sevoflurane anesthesia. In Trial 19.4.312 sugammadex was administered at a T_1 of 3-10% to trial the effect after infusion of rocuronium.

5.3 Statistical analyses

The primary population for all efficacy analyses was the full analysis set, consisting of the intent-to-treat (ITT) population following the imputation of missing data. The ITT population consisted of those subjects who were randomized, received investigational product, and had at least one efficacy measurement. When analyzing the ITT group, the analysis was according to the “as randomized” principle; 11 subjects (from Phase 2/Phase 3 trials) who received a treatment that deviated from the randomization schedule were thus analyzed with the treatment group to which they were randomized.

Recovery times were summarized by geometric mean, with corresponding 95% CI, median and range values. The geometric mean was used instead of the arithmetic mean because the assumption that the recovery times follow a Gaussian distribution or a symmetric distribution did not apply. This is due to the fact that, at the recommended sugammadex doses, recovery times faster than 30 seconds are unlikely while slow recovery times are possible and were, in fact, observed.

5.4 Demographics and baseline characteristics

5.4.1 Routine reversal: reversal at reappearance of T₂ (Shallow NMB)

Rocuronium-induced NMB

Two Phase 3 trials conducted during the clinical development program compared sugammadex vs. neostigmine in routine reversal at the reappearance of T₂. Specifically, pivotal Trial 19.4.301 compared sugammadex (2.0 mg/kg) vs. neostigmine (50 µg/kg) in routine reversal of NMB induced by rocuronium, and Trial 19.4.310 compared sugammadex (2.0 mg/kg) vs. neostigmine (50 µg/kg) in routine reversal of a NMB induced by rocuronium and cisatracurium, respectively.

In general, baseline and demographic characteristics (age, body weight, race and subjects classified as ASA Class 2 or 3) were comparable between the rocuronium/sugammadex and rocuronium/neostigmine treatment groups in Trial 19.4.301 and between the rocuronium/sugammadex and cisatracurium/neostigmine treatment groups in Trial 19.4.310. The only notable exceptions were the percentage of female subjects in the rocuronium/sugammadex treatment group in Trial 19.4.301 was lower (35%) compared with the rocuronium/neostigmine treatment group (50%), and the percentage of female subjects in the rocuronium/sugammadex treatment group in Trial 19.4.310 was higher (59%) compared with the cisatracurium/neostigmine treatment group (41%). These differences in gender, however, are not considered to be clinically relevant and are not believed to have impacted the overall efficacy analysis. Across all 13 trials conducted during the sugammadex clinical development program investigating routine reversal at the reappearance of T₂ following rocuronium-induced NMB (Table 10), baseline and demographic characteristics were comparable for body weight and gender. Among subjects who received rocuronium/sugammadex, the mean age and percentage of subjects classified as ASA Class 2 or 3/4 were higher (57 years and 76%, respectively) compared with subjects who received rocuronium/neostigmine (48 years and 50%, respectively); however, these differences are not considered to be clinically relevant and are not believed to have impacted the overall efficacy analysis. It should be noted that the trial in geriatric subjects (Trial 19.4.305) contributed to the higher mean age in the rocuronium/sugammadex grouping of subjects.

Table 10 Demographics and baseline characteristics, IP administered at reappearance of T₂ (ITT group)

| Treatment group ^a | n | Age | Weight | Gender | | ASA class | | |
|------------------------------|-----|-----------|-----------|----------|----------|-----------|----------|--------------------|
| | | (years) | (kg) | Female | Male | 1 | 2 | 3 / 4 ^b |
| | | Mean (SD) | Mean (SD) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Roc+2.0 mg/kg sugammadex | 409 | 57 (17) | 77 (17) | 207 (51) | 202 (49) | 99 (24) | 200 (49) | 110 (27) |
| Roc + neostigmine | 48 | 48 (14) | 76 (15) | 24 (50) | 24 (50) | 24 (50) | 22 (46) | 2 (4) |
| Rocuronium + placebo | 74 | 57 (16) | 77 (17) | 27 (36) | 47 (64) | 16 (22) | 34 (46) | 24 (32) |
| Vec+2.0 mg/kg sugammadex | 75 | 49 (15) | 77 (18) | 40 (53) | 35 (47) | 34 (45) | 38 (51) | 3 (4) |
| Vec + neostigmine | 45 | 50 (15) | 76 (13) | 24 (53) | 21 (47) | 17 (38) | 25 (56) | 3 (7) |
| Vecuronium + placebo | 24 | 49 (12) | 68 (15) | 17 (71) | 7 (29) | 13 (54) | 10 (42) | 1 (4) |
| Cis + neostigmine | 39 | 42 (12) | 78 (13) | 16 (41) | 23 (59) | 21 (54) | 18 (46) | 0 (0) |

^a roc / vec / cis: rocuronium / vecuronium / cisatracurium

^b only one subject was classified as ASA class 4: subject was enrolled in the roc + sugammadex group (in Clinical Trial 19.4.309).

Pooled data from Clinical Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, 19.4.210, 19.4.301, 19.4.304, 19.4.305, 19.4.306, 19.4.308, 19.4.309 and 19.4.310.

Vecuronium-induced NMB

One Phase 3 trial (Trial 19.4.301) conducted during the clinical development program compared sugammadex (2.0 mg/kg) vs. neostigmine (50 µg/kg) in routine reversal at the reappearance of T₂ of a NMB induced by vecuronium.

Baseline and demographic characteristics (age, body weight, gender, race and subjects classified as ASA Class 2 or 3) were comparable between the vecuronium/sugammadex and vecuronium/neostigmine treatment groups in Trial 19.4.301. Across all 4 trials conducted during the sugammadex clinical development program investigating routine reversal at the reappearance of T₂ following vecuronium-induced NMB (Table 10), baseline and demographic characteristics were also generally comparable between the vecuronium/sugammadex and vecuronium/neostigmine treatment groups.

5.4.2 Routine reversal: reversal at 1-2 PTCs (Profound NMB)

Rocuronium-induced NMB

One Phase 3 trial (Trial 19.4.302) conducted during the clinical development program compared sugammadex (4.0 mg/kg) vs. neostigmine (70 µg/kg) in routine reversal at 1-2 PTCs of a NMB induced by rocuronium.

Baseline and demographic characteristics (age, body weight, gender, race and ASA class) were comparable between the rocuronium/sugammadex and rocuronium/neostigmine treatment groups in Trial 19.4.302. Across the 4 trials conducted during the sugammadex clinical development program investigating routine reversal at 1-2 PTCs following rocuronium-induced NMB (Table 11), baseline and demographic characteristics were comparable for age, body weight and gender. Among subjects who received rocuronium/sugammadex, the percentage of subjects classified as ASA Class 2 or 3 was lower (73%) compared with subjects who received rocuronium/neostigmine (92%); however, this difference is not considered to be clinically relevant and is not believed to have impacted the overall efficacy analysis.

Table 11 Demographics and baseline characteristics, IP administered at 1-2 PTC (ITT group)

| Treatment group ^a | n | Age (years) | Weight (kg) | Gender | | ASA class ^b | | |
|------------------------------|----|-------------|-------------|-----------------|---------------|------------------------|------------|------------|
| | | Mean (SD) | Mean (SD) | Female n (%) | Male n (%) | 1 n (%) | 2 n (%) | 3 n (%) |
| Roc+4.0 mg/kg sugammadex | 63 | 51 (14) | 83 (28) | 32 (51) | 31 (49) | 17 (27) | 37 (59) | 9 (14) |
| Roc + neostigmine | 37 | 54 (11) | 86 (22) | 20 (54) | 17 (46) | 3 (8) | 29 (78) | 5 (14) |
| Vec +4.0 mg/kg sugammadex | 67 | 47 (14) | 82 (19) | 37 (55) | 30 (45) | 22 (33) | 39 (58) | 6 (9) |
| Vec + neostigmine | 36 | 57 (12) | 86 (18) | 15 (42) | 21 (58) | 1 (3) | 22 (61) | 13 (36) |

^a roc / vec: rocuronium / vecuronium

^b no subjects were classified as ASA class 4.

Pooled data from Clinical Trials 19.4.204, 19.4.209A, 19.4.209B and 19.4.302.

Vecuronium-induced NMB

Trial 19.4.302 was also conducted to compare sugammadex (4.0 mg/kg) vs. neostigmine (70 µg/kg) in routine reversal at 1-2 PTCs of a NMB induced by vecuronium.

Baseline body weight and race were comparable between the vecuronium/sugammadex and vecuronium/neostigmine treatment groups in Trial 19.4.302. However, mean age and percentage of subjects classified as ASA Class 2 or 3 (50 years and 87%, respectively) were lower among subjects who received vecuronium/sugammadex compared with subjects who received vecuronium/neostigmine (57 years and 97%, respectively); in addition, the percentage of female subjects was higher (63% vs. 42%) in vecuronium/sugammadex-treated vs. vecuronium/neostigmine-treated subjects. These differences among baseline and demographic characteristics are not believed to have impacted the overall efficacy analysis for this trial. Across the three trials conducted during the sugammadex clinical development program investigating routine reversal at 1-2 PTCs following vecuronium-induced NMB (Table 11), baseline and demographic characteristics were comparable for body weight; differences in mean age, gender, and percentage of subjects classified as ASA Class 2 or 3 between the vecuronium/sugammadex and vecuronium/neostigmine treatment groups were similar to those described above for Trial 19.4.302. However, these differences among baseline and demographic characteristics are small given the small pooled sample size and are not believed to have impacted the overall efficacy analysis.

5.4.3 Immediate reversal: reversal at 3 minutes after rocuronium

One Phase 3 trial (Trial 19.4.303) conducted during the clinical development program compared sugammadex (16.0 mg/kg) in reversing rocuronium-induced NMB vs. the spontaneous recovery following succinylcholine (1.0 mg/kg).

Baseline and demographic characteristics (age, body weight, gender, race and ASA class) were comparable between the rocuronium/sugammadex and succinylcholine treatment groups in Trial 19.4.303.

5.5 Efficacy results

5.5.1 Routine reversal: reversal at reappearance of T₂ (Shallow NMB)

Rocuronium-induced NMB

In pivotal Trial 19.4.301, the (geometric) mean time to recovery of the T₄/T₁ ratio to 0.9 after rocuronium-induced NMB was approximately 13 times faster following the administration of sugammadex at the reappearance of T₂ compared with neostigmine (1.5 vs. 18.5 minutes, respectively; Table 12). This large difference in recovery time is both statistically significant (p < 0.0001) and clinically relevant.

It is also noteworthy that, in Trial 19.4.301, the geometric mean time to recovery of the T₄/T₁ ratio to 0.9 in the neostigmine group (18.5 minutes) was longer than what is typically reported (five to 12 minutes) [61]; in addition, there was a wide range in individual recovery times (3.7 to 106.9 minutes). These findings are, in part, likely the result of the ability of sevoflurane to enhance a rocuronium-induced NMB. In addition, “expected” neostigmine recovery times of five to 12 minutes are associated with recovery of the T₄/T₁ ratio to 0.8.[61] However, when the higher standard of a T₄/T₁ ratio to 0.9 is applied, neostigmine recovery times dramatically increase.

Table 12 Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T₂ following rocuronium to recovery of the T₄/T₁ ratio to 0.9 (ITT group)

| | Trial 19.4.301 ^b | |
|----------------------|-------------------------------------|-------------------------------------|
| | Rocuronium + Sugammadex (2.0 mg/kg) | Rocuronium + Neostigmine (50 µg/kg) |
| n | 48 | 48 |
| Geometric Mean | 1.5 | 18.5 |
| 95% CI | 1.3 – 1.7 | 14.3 – 23.9 |
| Median | 1.4 | 17.6 |
| Min. – max. | 0.9 – 5.4 | 3.7 – 106.9 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T₄/T₁ ratio to 0.9.

^b Anesthetic regimen included induction with propofol and maintenance with sevoflurane.

In Trial 19.4.310 (Table 13), the (geometric) mean time to recovery of the T₄/T₁ ratio to 0.9 after rocuronium-induced NMB was approximately 4 times faster following the administration of sugammadex at the reappearance of T₂ compared with neostigmine

(2.0 vs. 8.8 minutes, respectively). This large difference in recovery times is also statistically significant ($p < 0.0001$) and clinically relevant.

Table 13 Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T_2 following rocuronium or cisatracurium, respectively, to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

| | Trial 19.4.310 ^b | |
|----------------------|-------------------------------------|--|
| | Rocuronium + Sugammadex (2.0 mg/kg) | Cisatracurium + Neostigmine (50 µg/kg) |
| n | 34 | 39 |
| Geometric Mean | 2.0 | 8.8 |
| 95% CI | 1.7 – 2.4 | 7.4 – 10.4 |
| Median | 1.9 | 7.2 |
| Min. – max. | 0.7 – 6.4 | 4.2 – 28.2 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

^b Anesthetic regimen included induction and maintenance with propofol.

Across all 13 trials conducted during the sugammadex clinical development program investigating routine reversal at the reappearance of T_2 following rocuronium-induced NMB, (geometric) mean times to recovery of the T_4/T_1 ratio to 0.9 were generally similar (Figure 4). The only noteworthy exception (Trial 19.4.305) is explained by the fact that subjects 75 years of age and older generally demonstrate slightly slower recovery times compared with younger subjects due to slower circulation times. However, these slower recovery times do not warrant a dose adjustment of sugammadex. Pooling of data across these 13 trials (Table 14) provide supportive evidence to the individual results of Trials 19.4.301 and 19.4.310; administration of sugammadex at the reappearance of T_2 results in clinically relevant reductions in recovery times of the T_4/T_1 ratio to 0.9 (and to 0.8 and 0.7) compared with neostigmine following NMB induced by rocuronium or cisatracurium.

Figure 4 Plot of geometric mean with corresponding 95% CI for the time from administration of 2.0 mg/kg sugammadex to recovery of the T_4/T_1 ratio to 0.9 of all individual trials and pooled data, sugammadex administered at reappearance of T_2 after administration of rocuronium (ITT group)

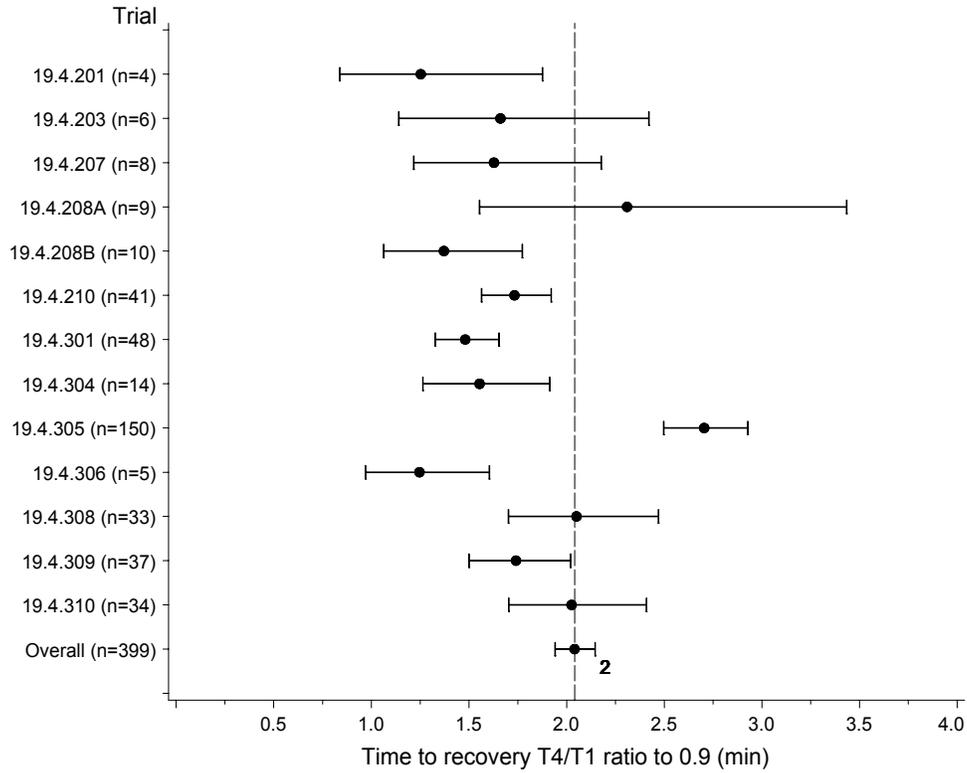


Table 14 Times (min.) from start of administration of IP, administered at reappearance of T₂ after rocuronium/cisatracurium, to recovery of the T₄/T₁ ratio to 0.9, 0.8 and 0.7 (ITT group)

| Time from start adm. of IP ^a to recovery of | | Treatment group | | | |
|--|-------------|-------------------------------------|--------------------------|----------------------|-----------------------------|
| | | Rocuronium + sugammadex (2.0 mg/kg) | Rocuronium + neostigmine | Rocuronium + placebo | Cisatracurium + neostigmine |
| T ₄ /T ₁ ratio to 0.9 | n | 399 | 48 | 68 | 39 |
| | Geom. Mean | 2.0 | 18.5 | 40.1 | 8.8 |
| | 95% CI | 1.9 - 2.1 | 14.3 - 23.9 | 35.0 - 46.0 | 7.4 - 10.4 |
| | Median | 1.9 | 17.6 | 37.8 | 7.2 |
| | Min. – max. | 0.7 - 12.0 | 3.7 - 106.9 | 14.4 - 153.0 | 4.2 - 28.2 |
| T ₄ /T ₁ ratio to 0.8 | n | 403 | 48 | 68 | 39 |
| | Geom. Mean | 1.7 | 10.8 | 33.5 | 6.4 |
| | 95% CI | 1.6 - 1.7 | 8.5 - 13.7 | 29.1 - 38.5 | 5.5 - 7.4 |
| | Median | 1.6 | 9.8 | 33.6 | 5.9 |
| | Min. – max. | 0.7 - 8.8 | 2.7 - 67.9 | 11.4 - 127.6 | 3.2 - 15.6 |
| T ₄ /T ₁ ratio to 0.7 | n | 404 | 48 | 69 | 39 |
| | Geom. Mean | 1.5 | 7.2 | 28.4 | 4.9 |
| | 95% CI | 1.4 - 1.5 | 5.8 - 8.9 | 24.8 - 32.6 | 4.2 - 5.6 |
| | Median | 1.4 | 6.2 | 27.6 | 4.5 |
| | Min. – max. | 0.7 - 8.3 | 2.4 - 41.1 | 9.7 - 120.8 | 2.4 - 10.9 |

^a IP is either sugammadex, neostigmine or placebo

Pooled data from Clinical Trials 19.4.201, 19.4.203, 19.4.207, 19.4.208A, 19.4.208B, 19.4.210, 19.4.301, 19.4.304, 19.4.305, 19.4.306, 19.4.308, 19.4.309 and 19.4.310

Maintenance dosing

Review of pooled data across 7 trials (Trials 19.4.208A, 19.4.208B, 19.4.301, 19.4.305, 19.4.308, 19.4.309 and 19.4.310) that permitted the use of at least one maintenance dose of rocuronium in addition to the intubating dose demonstrated that, although recovery times of the T₄/T₁ ratio to 0.9 (and 0.8 and 0.7) were slightly longer in subjects who were administered at least one maintenance dose of rocuronium (2.3 minutes) compared with subjects who only received an intubating dose (2.0 minutes), the difference is not considered to be clinically relevant (Table 15). Therefore, no sugammadex dose adjustment is required.

Table 15 Time (min.) from start of administration of 2.0 mg/kg sugammadex, administered at reappearance of T₂, to recovery of the T₄/T₁ ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of rocuronium alone and those who received an intubating dose and at least one maintenance dose of rocuronium (ITT group)

| Time from start adm. of sugammadex to recovery of | | Rocuronium | |
|---|-------------|-----------------------|-------------------------------------|
| | | Intubating dose alone | Intubating dose + maintenance doses |
| T ₄ /T ₁ ratio to 0.9 | n | 159 | 162 |
| | Geom. mean | 2.0 | 2.3 |
| | 95% CI | 1.9 - 2.2 | 2.1 - 2.5 |
| | Median | 1.9 | 2.2 |
| | Min. – max. | 0.7 - 9.9 | 0.9 - 12.0 |
| T ₄ /T ₁ ratio to 0.8 | n | 162 | 162 |
| | Geom. mean | 1.6 | 1.9 |
| | 95% CI | 1.5 - 1.8 | 1.7 - 2.0 |
| | Median | 1.5 | 1.7 |
| | Min. – max. | 0.7 - 6.2 | 0.7 - 8.8 |
| T ₄ /T ₁ ratio to 0.7 | n | 163 | 162 |
| | Geom. mean | 1.4 | 1.6 |
| | 95% CI | 1.3 - 1.5 | 1.5 - 1.7 |
| | Median | 1.3 | 1.6 |
| | Min. – max. | 0.7 - 4.9 | 0.7 - 8.3 |

Pooled data from Clinical Trials 19.4.208A, 19.4.208B, 19.4.301, 19.4.305, 19.4.308, 19.4.309 and 19.4.310

Clinical signs of recovery

Pooled data across five trials (Trials 19.4.301, 19.4.305, 19.4.308, 19.4.309 and 19.4.310) that measured clinical signs of recovery (Table 16) from anesthesia demonstrated that nearly all subjects who received sugammadex at the reappearance of T₂ as their reversal agent following rocuronium-induced NMB were awake and oriented, cooperative, able to perform the five-second head lift, and were without muscle weakness prior to discharge from the recovery room. Not surprisingly, these results are similar to those seen following administration of neostigmine or placebo.

Table 16 Clinical signs of recovery, 2.0 mg/kg sugammadex, neostigmine and placebo administered at reappearance of T₂, rocuronium (ITT group)

| | Time point | | | | | |
|--|---|-------------|---------|---|-------------|----------|
| | prior to transfer to the recovery room after extubation | | | prior to discharge from the recovery room | | |
| | Treatment group | | | Treatment group | | |
| | 2.0 mg/kg sugammadex | Neostigmine | Placebo | 2.0 mg/kg sugammadex | Neostigmine | Placebo |
| n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | |
| Subject's level of consciousness | | | | | | |
| Awake and oriented | 173 (57) | 35 (73) | 28 (70) | 288 (97) | 48 (100) | 36 (90) |
| Arousable with minimal stimulation | 112 (37) | 13 (27) | 10 (25) | 10 (3) | 0 (0) | 3 (8) |
| Responsive only to tactile stimulation | 20 (7) | 0 (0) | 2 (5) | 0 (0) | 0 (0) | 1 (3) |
| Subject cooperative ^a | | | | | | |
| No | 40 (13) | 1 (2) | 6 (15) | 0 (0) | 0 (0) | 1 (3) |
| Yes | 266 (87) | 47 (98) | 34 (85) | 298 (100) | 48 (100) | 39 (98) |
| Subject able to perform the 5 s. head lift | | | | | | |
| No | 26 (10) | 10 (21) | 1 (3) | 0 (0) | 0 (0) | 0 (0) |
| Yes | 240 (90) | 37 (79) | 33 (97) | 298 (100) | 48 (100) | 39 (100) |
| General muscle weakness | | | | | | |
| No | 249 (94) | 38 (81) | 33 (97) | 293 (98) | 48 (100) | 38 (97) |
| Yes | 15 (6) | 9 (19) | 1 (3) | 5 (2) | 0 (0) | 1 (3) |

^a in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed
Pooled data from Clinical Trials 19.4.301, 19.4.305, 19.4.308, 19.4.309 and 19.4.310.

Vecuronium-induced NMB

In Trial 19.4.301, the (geometric) mean time to recovery of the T₄/T₁ ratio to 0.9 after vecuronium-induced NMB was 6 times faster following the administration of sugammadex at the reappearance of T₂ compared with neostigmine (2.8 vs. 16.8 minutes, respectively; Table 17). This large difference in recovery time is both statistically significant (p < 0.0001) and clinically relevant.

Table 17 Summary of the time (min) from start of administration of sugammadex or neostigmine administered at reappearance of T₂ following vecuronium to recovery of the T₄/T₁ ratio to 0.9 (ITT group)

| | Trial 19.4.301 ^b | |
|----------------------|-------------------------------------|-------------------------------------|
| | Vecuronium + Sugammadex (2.0 mg/kg) | Vecuronium + Neostigmine (50 µg/kg) |
| n | 48 | 45 |
| Geometric Mean | 2.8 | 16.8 |
| 95% CI | 2.3 – 3.4 | 12.9 – 21.9 |
| Median | 2.1 | 18.9 |
| Min. – max. | 1.2 – 64.2 | 2.9 – 76.2 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T₄/T₁ ratio to 0.9.

^b Anesthetic regimen included induction with propofol and maintenance with sevoflurane.

Across the 4 trials conducted during the sugammadex clinical development program investigating routine reversal at the reappearance of T₂ following vecuronium-induced NMB, (geometric) mean times to recovery of the T₄/T₁ ratio to 0.9 were generally similar for Trials 19.4.207, 19.4.208A, and 19.4.301 (2.1 to 2.8 minutes); the longer (geometric) mean time to recovery in Trial 19.4.208B (4.2 minutes) is likely the result of the large intra-trial variability seen in this bridging trial (n=9; Figure 5). Pooling of data across these 4 trials (Table 18) provide supportive evidence to Trial 19.4.301; administration of sugammadex results in clinically relevant reductions in recovery times of the T₄/T₁ ratio to 0.9 (and to 0.8 and 0.7) compared with neostigmine following NMB induced by vecuronium.

Figure 5 Plot of geometric mean with corresponding 95% CI for the time from administration of 2.0 mg/kg sugammadex to recovery of the T_4/T_1 ratio to 0.9 of all individual trials and pooled data, sugammadex administered at reappearance of T_2 after administration of vecuronium (ITT group)

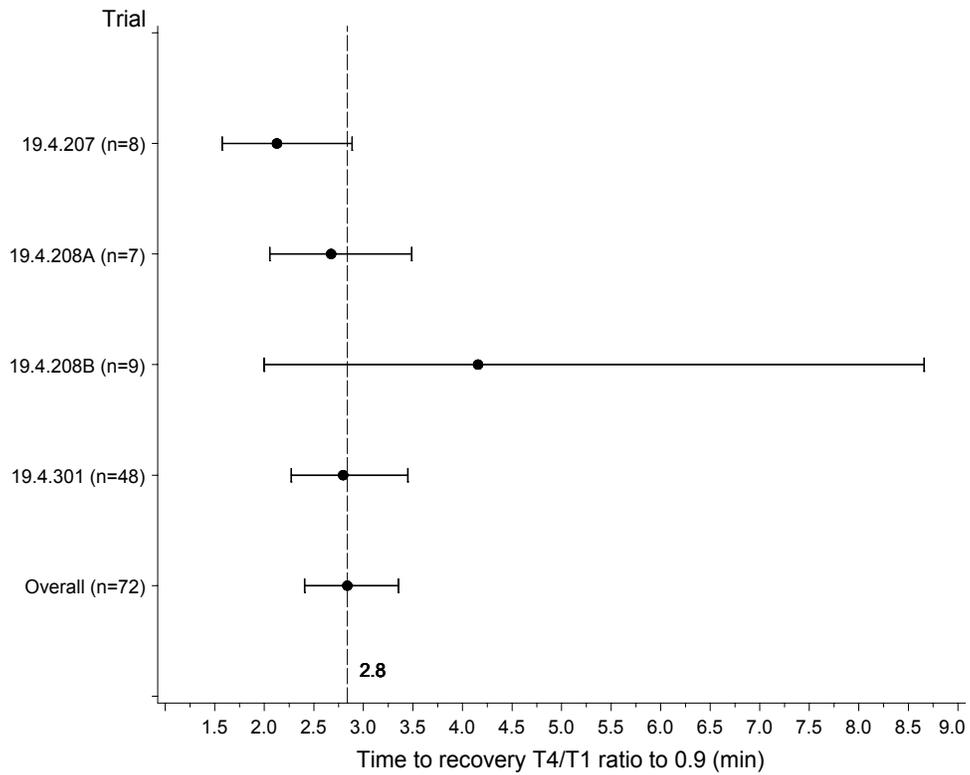


Table 18 Times (min.) from start of administration of IP, administered at reappearance of T₂ after vecuronium, to recovery of the T₄/T₁ ratio to 0.9, to 0.8 and to 0.7 (ITT group)

| Time from start adm. of IP ^a to recovery of | | Treatment group | | |
|--|-------------|-------------------------------------|--------------------------|----------------------|
| | | Vecuronium + sugammadex (2.0 mg/kg) | Vecuronium + neostigmine | Vecuronium + placebo |
| T ₄ /T ₁ ratio to 0.9 | n | 72 | 45 | 23 |
| | Geom. mean | 2.8 | 16.8 | 72.9 |
| | 95% CI | 2.4 - 3.4 | 12.9 - 21.9 | 61.9 - 85.9 |
| | Median | 2.3 | 18.9 | 73.3 |
| | Min. – max. | 1.2 - 64.2 ^b | 2.9 - 76.2 | 27.1 - 141.1 |
| T ₄ /T ₁ ratio to 0.8 | n | 75 | 45 | 23 |
| | Geom. mean | 2.1 | 10.2 | 61.4 |
| | 95% CI | 1.9 - 2.4 | 7.7 - 13.6 | 51.5 - 73.1 |
| | Median | 1.9 | 11.7 | 62.3 |
| | Min. – max. | 1.0 - 36.3 ^b | 2.2 - 59.1 | 24.3 - 109.6 |
| T ₄ /T ₁ ratio to 0.7 | n | 75 | 45 | 24 |
| | Geom. mean | 1.7 | 6.1 | 56.8 |
| | 95% CI | 1.6 - 1.8 | 4.6 - 8.1 | 45.2 - 71.2 |
| | Median | 1.6 | 4.7 | 55.8 |
| | Min. – max. | 0.7 - 5.3 | 1.9 - 54.3 | 21.1 - 281.9 |

^a IP is either sugammadex, neostigmine or placebo

^b Two long recovery times (64.2 minutes at 0.9 and 36.3 minutes at 0.8) are discussed in an outlier report.

Pooled data from Clinical Trials 19.4.207, 19.4.208A, 19.4.208B and 19.4.301.

Maintenance dosing

Review of pooled data across the three trials (Trials 19.4.208A, 19.4.208B, and 19.4.301) that permitted, at the discretion of the Investigator, the use of at least one maintenance dose of vecuronium in addition to the intubating dose demonstrated that, although recovery times of the T₄/T₁ ratio to 0.9 (and 0.8 and 0.7) were longer in subjects who were administered at least one maintenance dose of vecuronium (3.2 minutes) compared with subjects who only received an intubating dose (2.7 minutes), the difference is not considered to be clinically relevant (Table 19). Therefore, no sugammadex dose adjustment is required.

Table 19 Time (min.) from start of administration of 2.0 mg/kg sugammadex, administered at reappearance of T₂, to recovery of the T₄/T₁ ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of vecuronium alone and those who received an intubating dose and at least one maintenance dose of vecuronium (ITT group)

| Time from start adm. of sugammadex to recovery of | | Vecuronium | |
|---|-------------|-----------------------|-------------------------------------|
| | | Intubating dose alone | Intubating dose + maintenance doses |
| T ₄ /T ₁ ratio to 0.9 | n | 31 | 33 |
| | Geom. mean | 2.7 | 3.2 |
| | 95% CI | 1.9 - 3.7 | 2.7 - 3.9 |
| | Median | 2.0 | 3.0 |
| | Min. – max. | 1.2 - 64.2 | 1.7 - 19.8 |
| T ₄ /T ₁ ratio to 0.8 | n | 32 | 35 |
| | Geom. Mean | 2.0 | 2.3 |
| | 95% CI | 1.6 - 2.5 | 2.1 - 2.6 |
| | Median | 1.7 | 2.4 |
| | Min. – max. | 1.0 - 36.3 | 1.2 - 4.3 |
| T ₄ /T ₁ ratio to 0.7 | n | 32 | 35 |
| | Geom. Mean | 1.5 | 1.9 |
| | 95% CI | 1.3 - 1.7 | 1.7 - 2.1 |
| | Median | 1.4 | 1.9 |
| | Min. – max. | 0.7 - 5.3 | 0.9 - 3.4 |

Pooled data from Clinical Trials 19.4.208A, 19.4.208B and 19.4.301. In these trials an intubating dose only or an intubating dose and at least one maintenance dose was administered at the investigator's discretion

Clinical signs of recovery

Data from Trial 19.4.301, which measured clinical signs of recovery (Table 20) from anesthesia, demonstrated that all subjects who received sugammadex as their reversal agent following vecuronium-induced NMB were awake and oriented, cooperative, able to perform the five-second head lift, and were without muscle weakness prior to discharge from the recovery room. Not surprisingly, these results are similar to those seen following administration of neostigmine.

Table 20 Clinical signs of recovery, 2.0 mg/kg sugammadex and neostigmine administered at reappearance of T₂, vecuronium (ITT group)

| | Time point | | | |
|--|---|----------------------|---|----------------------|
| | prior to transfer to the recovery room after extubation | | prior to discharge from the recovery room | |
| | Treatment group | | Treatment group | |
| | 2.0 mg/kg sugammadex n (%) | Neostigmine n (%) | 2.0 mg/kg sugammadex n (%) | Neostigmine n (%) |
| Subject's level of consciousness | | | | |
| Awake and oriented | 29 (60) | 26 (58) | 48 (100) | 43 (98) |
| Arousable with minimal stimulation | 17 (35) | 14 (31) | 0 (0) | 1 (2) |
| Responsive only to tactile stimulation | 2 (4) | 5 (11) | 0 (0) | 0 (0) |
| Subject cooperative ^a | | | | |
| No | 7 (15) | 7 (16) | 0 (0) | 0 (0) |
| Yes | 41 (85) | 38 (84) | 48 (100) | 44 (100) |
| Subject able to perform the 5 s. head lift | | | | |
| No | 1 (2) | 6 (16) | 0 (0) | 0 (0) |
| Yes | 40 (98) | 32 (84) | 48 (100) | 44 (100) |
| General muscle weakness | | | | |
| No | 37 (90) | 32 (84) | 48 (100) | 44 (100) |
| Yes | 4 (10) | 6 (16) | 0 (0) | 0 (0) |

^a in case a subject is not cooperative the head lift test and the general muscle weakness test were not assessed

Data from Clinical Trial 19.4.301.

5.5.2 Routine reversal: reversal at 1-2 PTCs (Profound NMB)

Rocuronium-induced NMB

In pivotal Trial 19.4.302, the (geometric) mean time to recovery of the T₄/T₁ ratio to 0.9 after rocuronium-induced NMB was approximately 17 times faster following the administration of sugammadex at 1-2 PTCs compared with neostigmine (2.9 vs. 50.4 minutes, respectively; Table 21). This large difference in recovery time is both statistically significant (p< 0.0001) and clinically relevant. Of note, the geometric mean recovery time of 50.4 minutes represents neostigmine's lack of efficacy in reversing a profound rocuronium-induced NMB.

Table 21 Summary of the time (min) from start of administration of sugammadex or neostigmine administered at 1-2 PTCs following rocuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

| | Trial 19.4.302 | |
|----------------------|-------------------------------------|-------------------------------------|
| | Rocuronium + Sugammadex (4.0 mg/kg) | Rocuronium + Neostigmine (70 µg/kg) |
| n | 37 | 37 |
| Geometric Mean | 2.9 | 50.4 |
| 95% CI | 2.5 – 3.4 | 43.5 – 58.4 |
| Median | 2.7 | 49.0 |
| Min. – max. | 1.2 – 16.1 | 13.3 – 145.7 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

Across the 4 trials conducted during the sugammadex clinical development program investigating routine reversal at 1-2 PTCs following rocuronium-induced NMB, (geometric) mean times to recovery of the T_4/T_1 ratio to 0.9 varied from 1.4 to 2.9 minutes (Figure 6). This variability is likely the result of the relatively small sample sizes (n=4, 11, and 10, respectively, in Trials 19.4.204, 19.4.209A, and 19.4.209B). Pooling of data across these 4 trials (Table 22) provide supportive evidence to Trial 19.4.302; administration of sugammadex at 1-2 PTCs results in clinically relevant reductions in recovery times of the T_4/T_1 ratio to 0.9 (and to 0.8 and 0.7) compared with neostigmine following NMB induced by rocuronium.

Figure 6 Plot of geometric mean with corresponding 95% CI for the time from administration of 4.0 mg/kg sugammadex to recovery of the T_4/T_1 ratio to 0.9 of all individual trials and pooled data, sugammadex administered at 1-2 PTC after administration of rocuronium (ITT group)

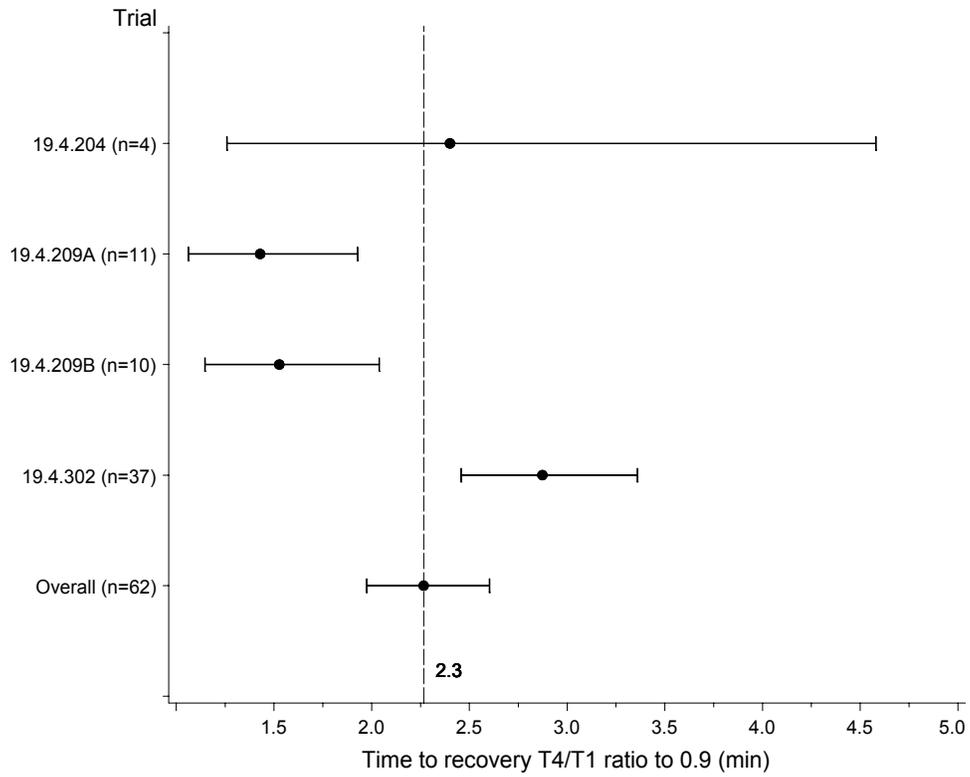


Table 22 Times (min.) from start of administration of IP, administered at 1-2 PTC after rocuronium, to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 (ITT group)

| Time from start adm. of IP to recovery of | | Treatment group | |
|---|-------------|-------------------------------------|--------------------------|
| | | Rocuronium + sugammadex (4.0 mg/kg) | Rocuronium + neostigmine |
| T_4/T_1 ratio to 0.9 | n | 62 | 37 |
| | Geom. mean | 2.3 | 50.4 |
| | 95% CI | 2.0 - 2.6 | 43.5 - 58.4 |
| | Median | 2.2 | 49.0 |
| | Min. – max. | 0.8 - 16.1 | 13.3 - 145.7 |
| T_4/T_1 ratio to 0.8 | n | 62 | 37 |
| | Geom. mean | 1.9 | 40.6 |
| | 95% CI | 1.6 - 2.1 | 34.5 - 47.8 |
| | Median | 1.7 | 40.9 |
| | Min. – max. | 0.8 - 10.1 | 11.3 - 143.7 |
| T_4/T_1 ratio to 0.7 | n | 63 | 37 |
| | Geom. mean | 1.6 | 32.6 |
| | 95% CI | 1.4 - 1.8 | 27.2 - 39.1 |
| | Median | 1.5 | 32.1 |
| | Min. – max. | 0.8 - 7.8 | 9.3 - 123.2 |

Pooled data from Clinical Trials 19.4.204, 19.4.209A, 19.4.209B and 19.4.302

Maintenance dosing

Review of pooled data across the 4 trials that permitted, at the discretion of the Investigator, the use of at least one maintenance dose of rocuronium in addition to the intubating dose demonstrated that, although recovery times of the T_4/T_1 ratio to 0.9 (and 0.8 and 0.7) were longer in subjects who were administered at least one maintenance dose of rocuronium (2.5 minutes) compared with subjects who only received an intubating dose (1.6 minutes), the difference is not considered to be clinically relevant (Table 23). Therefore, no sugammadex dose adjustment is required.

Table 23 Time (min.) from start of administration of 4.0 mg/kg sugammadex at 1-2 PTC to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of rocuronium alone and those who received an intubating dose and at least one maintenance dose of rocuronium (ITT group)

| Time from start adm. of sugammadex to recovery of | | Rocuronium | |
|---|-------------|-----------------------|-------------------------------------|
| | | Intubating dose alone | Intubating dose + maintenance doses |
| T ₄ /T ₁ ratio to 0.9 | n | 13 | 49 |
| | Geom. mean | 1.6 | 2.5 |
| | 95% CI | 1.2 - 2.1 | 2.1 - 2.9 |
| | Median | 1.5 | 2.5 |
| | Min. – max. | 0.8 - 4.0 | 0.8 - 16.1 |
| T ₄ /T ₁ ratio to 0.8 | n | 13 | 49 |
| | Geom. mean | 1.3 | 2.0 |
| | 95% CI | 1.1 - 1.7 | 1.8 - 2.3 |
| | Median | 1.1 | 1.8 |
| | Min. – max. | 0.8 - 3.0 | 0.8 - 10.1 |
| T ₄ /T ₁ ratio to 0.7 | n | 13 | 50 |
| | Geom. mean | 1.2 | 1.8 |
| | 95% CI | 1.0 - 1.3 | 1.5 - 2.0 |
| | Median | 1.1 | 1.6 |
| | Min. – max. | 0.8 - 1.7 | 0.8 - 7.8 |

Pooled data from Clinical Trials 19.4.204, 19.4.209A, 19.4.209B and 19.4.302. In these trials an intubating dose only or an intubating dose and at least one maintenance dose was administered at the investigator's discretion

Vecuronium-induced NMB

In Trial 19.4.302, the (geometric) mean time to recovery of the T_4/T_1 ratio to 0.9 was approximately 15 times faster following the administration of sugammadex compared with neostigmine (4.5 vs. 66.2 minutes, respectively; Table 24). This large difference in recovery time is both statistically significant ($p < 0.0001$) and clinically relevant. Of note, the geometric mean recovery time of 66.2 minutes represents neostigmine's lack of efficacy in reversing a profound vecuronium-induced NMB.

Table 24 Summary of the time (min) from start of administration of sugammadex or neostigmine administered at 1-2 PTCs following vecuronium to recovery of the T_4/T_1 ratio to 0.9 (ITT group)

| | Trial 19.4.302 | |
|----------------------|--|--|
| | Vecuronium + sugammadex (4.0 mg/kg) | Vecuronium + Neostigmine (70 µg/kg) |
| n | 47 | 36 |
| Geometric Mean | 4.5 | 66.2 |
| 95% CI | 3.3 – 6.0 | 55.6 – 78.9 |
| Median | 3.3 | 49.9 |
| Min. – max. | 1.4 – 68.4 | 46.0 – 312.7 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on log transformed times to recovery of the T_4/T_1 ratio to 0.9.

Pooling of data from the three trials (Table 25) conducted during the sugammadex clinical development program that investigated routine reversal at 1-2 PTCs following vecuronium-induced NMB provide supportive evidence to Trial 19.4.302; administration of sugammadex at 1-2 PTCs results in clinically relevant reductions in recovery times of the T_4/T_1 ratio to 0.9 (and to 0.8 and 0.7) compared with neostigmine following NMB induced by vecuronium.

Table 25 Times (min.) from start of administration of IP, at 1-2 PTC after vecuronium, to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 (ITT group)

| Time from start adm. of IP to recovery of | | Treatment group | |
|---|-------------|-------------------------------------|--------------------------|
| | | Vecuronium + sugammadex (4.0 mg/kg) | Vecuronium + neostigmine |
| T_4/T_1 ratio to 0.9 | n | 67 | 36 |
| | Geom. Mean | 3.9 | 66.2 |
| | 95% CI | 3.0 - 5.1 | 55.6 - 78.9 |
| | Median | 3.0 | 49.9 |
| | Min. – max. | 0.9 - 126.7 | 46.0 - 312.7 |
| T_4/T_1 ratio to 0.8 | n | 67 | 36 |
| | Geom. Mean | 2.8 | 58.8 |
| | 95% CI | 2.3 - 3.5 | 50.1 - 69.1 |
| | Median | 2.4 | 43.9 |
| | Min. – max. | 0.8 - 65.2 | 35.3 - 250.9 |
| T_4/T_1 ratio to 0.7 | n | 67 | 36 |
| | Geom. Mean | 2.3 | 48.8 |
| | 95% CI | 1.9 - 2.7 | 41.3 - 57.6 |
| | Median | 2.0 | 36.4 |
| | Min. – max. | 0.8 - 61.9 | 27.5 - 192.2 |

Pooled data from Clinical Trials 19.4.209A, 19.4.209B and 19.4.302.

Maintenance dosing

Review of pooled data across the three trials that permitted, at the discretion of the Investigator, the use of at least one maintenance dose of vecuronium in addition to the intubating dose demonstrated that, although recovery times of the T_4/T_1 ratio to 0.9 (and 0.8 and 0.7) were slightly longer in subjects who were administered at least one maintenance dose of vecuronium (4.2 minutes) compared with subjects who only received an intubating dose (3.2 minutes), the difference is not considered to be clinically relevant (Table 26). Therefore, no sugammadex dose adjustment is required.

Table 26 Time (min.) from start of administration of 4.0 mg/kg sugammadex at 1-2 PTC to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 for subjects who received an intubating dose of vecuronium alone and those who received an intubating dose and at least one maintenance dose of vecuronium (ITT group)

| Time from start adm. of sugammadex to recovery of | | Vecuronium | |
|---|-------------|-----------------------|-------------------------------------|
| | | Intubating dose alone | Intubating dose + maintenance doses |
| T ₄ /T ₁ ratio to 0.9 | n | 15 | 52 |
| | Geom. mean | 3.2 | 4.2 |
| | 95% CI | 1.5 - 6.5 | 3.2 - 5.5 |
| | Median | 2.3 | 3.3 |
| | Min. – max. | 0.9 - 126.7 | 1.2 - 68.4 |
| T ₄ /T ₁ ratio to 0.8 | n | 15 | 52 |
| | Geom. mean | 2.0 | 3.1 |
| | 95% CI | 1.3 - 3.2 | 2.5 - 3.9 |
| | Median | 1.7 | 2.6 |
| | Min. – max. | 0.8 - 13.3 | 1.0 - 65.2 |
| T ₄ /T ₁ ratio to 0.7 | n | 15 | 52 |
| | Geom. mean | 1.6 | 2.5 |
| | 95% CI | 1.2 - 2.2 | 2.1 - 3.0 |
| | Median | 1.5 | 2.3 |
| | Min. – max. | 0.8 - 6.8 | 1.0 - 61.9 |

Pooled data from Clinical Trials 19.4.209A, 19.4.209B and 19.4.302. In these trials an intubating dose only or an intubating dose and at least one maintenance dose was administered at the investigator's discretion

Clinical signs of recovery

Prior to discharge from the recovery room all subjects (except for 1 subject in the neostigmine group) were awake and oriented, cooperative and able to perform the 5-sec head lift test. All, except 5 subjects (2, sugammadex group; 3, neostigmine group) showed no muscle weakness.

5.5.3 Immediate reversal: reversal at 3 minutes after rocuronium

In Trial 19.4.303, the mean time to a T_1 of 10% (relative to the time of administration of rocuronium or succinylcholine) was approximately 2.7 minutes faster in the rocuronium + sugammadex group compared with succinylcholine alone (4.4 vs. 7.1 minutes, respectively; Table 27). Similar differences were seen in the time to a T_1 of 90% (approximately 4.7 minutes faster in the rocuronium + sugammadex group compared with succinylcholine alone). These large differences are both statistically significant ($p < 0.0001$) and particularly clinically relevant (i.e., a faster recovery time is vital in a cannot-intubate-cannot-ventilate setting where critical desaturation must be prevented).

In the 1.2 mg/kg rocuronium + sugammadex group, TOF ratios were also determined. Relative to the time of administration of rocuronium, the recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 4.4, 4.6, and 5.4 minutes, respectively; relative to the time of administration of sugammadex, the recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 1.3, 1.5, and 2.2 minutes, respectively. Similar to the conclusion drawn regarding T_1 recovery times, the TOF ratio recovery times are clinically relevant in a cannot-intubate-cannot-ventilate setting where critical desaturation must be prevented and provide strong evidence that rocuronium (with sugammadex reversal) could be used in situations currently reserved for succinylcholine.

Table 27 Summary of the time (min) from start of administration of rocuronium or succinylcholine to recovery of T₁ to 10% and to 90% (ITT group)

| | Trial 19.4.303 | |
|-------------------------------|--------------------------------------|-----------------------------|
| | Rocuronium + Sugammadex (16.0 mg/kg) | Succinylcholine (1.0 mg/kg) |
| Time to T ₁ of 10% | | |
| n | 55 | 55 |
| Mean (SD) | 4.4 (0.7) | 7.1 (1.6) |
| Median | 4.2 | 7.1 |
| Min. – max. | 3.5 – 7.7 | 3.8 – 10.5 |
| p-value ^a | <0.0001 | |
| Time to T ₁ of 90% | | |
| n | 55 | 55 |
| Mean (SD) | 6.2 (1.8) | 10.9 (2.4) |
| Median | 5.7 | 10.7 |
| Min. – max. | 4.2 – 13.6 | 5.0 – 16.2 |
| p-value ^a | <0.0001 | |

^a P-value obtained from a 2-way ANOVA on the time to T₁ 10% / 90%.

5.5.4 Other trials

Trial 19.4.311

Trial 19.4.311 was conducted to evaluate the efficacy and safety of sugammadex when used at the end of the surgical procedure to reverse a NMB induced by rocuronium. This trial was designed to mimic, as closely as possible, the use of sugammadex in normal daily practice by encompassing the various situations studied in the sugammadex Phase 3 program with a more routine anesthetic regimen and a wider range of anesthetic procedures. Specifically, each subject was to receive an intravenous single bolus dose of 0.6 mg/kg rocuronium. If further NMB was required after endotracheal intubation, maintenance dose(s) of 0.15 mg/kg rocuronium could be administered. The NMB was to be reversed, at least 15 minutes after the intubating dose or the last maintenance dose of rocuronium, with a dose of 4.0 mg/kg sugammadex.

Results from this trial provide strong supportive evidence for the results collected from pivotal Trials 19.4.301 and 19.4.302 regarding the efficacy of sugammadex in reversing a rocuronium-induced NMB. In this trial it was shown that 158 (89%) out of 177 subjects recovered to a T₄/T₁ of 0.9 within 4 minutes of receiving 4.0 mg/kg

sugammadex over a wide range of surgical procedures and anesthetic regimens; 20 subjects (11%) recovered within 1 minute, 87 subjects (49%) recovered between 1 and 2 minutes, 38 subjects (21%) recovered between 2 and 3 minutes, and 13 subjects (7%) recovered between 3 and 4 minutes. The geometric mean time from administration of sugammadex after an intubating dose of rocuronium to recovery of the T_4/T_1 ratio to 0.9 was 2.0 minutes compared to 1.9 minutes in subjects who received an intubating dose and at least one maintenance dose of rocuronium. At discharge from the recovery room, 196 (99.5%) of 197 subjects were cooperative and able to perform the five-second head lift; 184 (93.4%) of 197 subjects were awake and oriented; and 187 (95.4%) of 196 subjects experienced no general muscle weakness.

Trial 19.4.312

Trial 19.4.312 was conducted in order to trial the efficacy and safety of sugammadex after rocuronium infusion under propofol or sevoflurane anesthesia. In Trial 19.4.312, the median recovery time from administration of 4.0 mg/kg sugammadex after continuous infusion of rocuronium to recovery of the T_4/T_1 ratio to 0.9 during sevoflurane anesthesia was 1.3 minutes, and during propofol anesthesia it was 1.2 minutes. The statistical evaluation of the time to recovery of the T_4/T_1 ratio to 0.9 showed that the estimated treatment difference in recovery time was 9 seconds with a corresponding 95% CI ranging from -6 seconds to +20 seconds. Since this 95% CI lies entirely within the pre-defined equivalence interval, which ranged from -60 to +60 seconds, equivalence (recovery from a NMB after a single dose of 4.0 mg/kg sugammadex [administered at T_1 3-10% after continuous infusion of rocuronium] between subjects receiving maintenance anesthesia using propofol versus subjects receiving sevoflurane) can be claimed. Thus, the time from administration of 4.0 mg/kg sugammadex after continuous infusion of rocuronium to recovery of the T_4/T_1 ratio to 0.9 is independent from the anesthetic technique used for maintenance.

5.6 Efficacy in subgroups

5.6.1 Drug-demographic interactions

Trial 19.4.305 was conducted to explore effect of age on the efficacy, PK and safety of sugammadex in 48 adults (18-64 years) and 102 geriatric subjects (≥ 65 years). The geometric mean time from administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9 was 2.3 min (adult group) and 2.9 min sec (geriatric group). In the adult group, 85% of subjects and 75% of geriatric subjects achieved a T_4/T_1 ratio to 0.9 within 4 minutes. Clinical signs of recovery showed that the majority of subjects

were cooperative, able to perform the 5 sec head lift, and showed no general muscle weakness. Additionally, there was no evidence of recurarization in any of the subjects based on the T_4/T_1 ratio decreasing below 0.8 subjects who achieved recovery to 0.9.

Subgroup analyses were conducted to determine the effect of age, body mass index (BMI), gender, race, ethnicity and ASA class on pooled efficacy data following the administration of sugammadex for routine reversal at the reappearance of T_2 or at 1-2 PTCs (following rocuronium- or vecuronium-induced NMB) and for immediate reversal 3 minutes following 1.2 mg/kg rocuronium. In order to investigate the possible effect of trial, age, gender, weight, and ASA class on the recovery time, first a statistical model was used which included these factors and also all first order interactions. Subsequently an evaluation was performed which included only the main factors. Since the vast majority of subjects were Caucasian and not of Hispanic or Latino ethnicity, race and ethnicity were not taken as factors in the statistical evaluation to investigate the effect of race and ethnicity on the time to recovery of the T_4/T_1 ratio to 0.9.

Following the administration of 2.0 mg/kg sugammadex at the reappearance of T_2 after a rocuronium-induced NMB, a statistically significant interaction between gender and age was observed on time to recovery of the T_4/T_1 ratio to 0.9. Based on the size of this interaction this finding is not considered to be relevant. The evaluation that included only the main factors showed an effect of gender (male recovery times were faster than female recovery times), age (recovery times increased with age) and ASA class (recovery times increased with ASA class) on the time to recovery of the T_4/T_1 ratio to 0.9. The differences between males and females and between the age categories are considered to be too small to be of clinical relevance, and thus no dose adjustment is required. The statistical evaluation also revealed a statistically significant trial effect on the observed recovery times. No effect of weight ($p=0.33$) on the recovery time was observed. Similar geometric mean times to recovery were observed between Caucasian, Black and Asian subjects and between Hispanic/Latino and Non-hispanic/Non-latino subjects.

Following the administration of 2.0 mg/kg sugammadex at the reappearance of T_2 after a vecuronium-induced NMB, no statistically significant interaction was observed between any of the subgroups on recovery of the T_4/T_1 ratio to 0.9. In addition, following the evaluation that included only the main factors no effects on recovery time (T_4/T_1 ratio of 0.9) were noted for gender, age, ASA class or weight. Although Non-Hispanic/non-Latino subjects had longer geometric mean recovery times (3.1 minutes) compared with Hispanic/Latino subjects (2.1 minutes), there were too few Hispanic/Latino subjects ($n=7$) to allow definitive conclusions to be drawn.

Following the administration of 4.0 mg/kg sugammadex at 1-2 PTCs after a rocuronium-induced NMB, a statistically significant interaction between age and weight was observed on recovery of the T_4/T_1 ratio to 0.9. Based on the size of this interaction, as well as the fact that an outlier was defined in the geriatric/obese subgroup, this finding is not considered to be relevant. The evaluation that included only the main factors showed no effects based on gender, age, weight and ASA class. Although Caucasian subjects had slightly longer geometric mean recovery times (2.4 minutes) than Asian subjects (1.4 minutes), there were too few Asian subjects (n=11) to allow definitive conclusions to be drawn. Similarly, although Hispanic/Latino subjects had slightly longer geometric mean recovery times (4.0 minutes) compared with Non-hispanic/Non-latino subjects (2.2 minutes), there were too few Hispanic/Latino subjects (n=3) to allow definitive conclusions to be drawn.

Following the administration of 4.0 mg/kg sugammadex at 1-2 PTCs after a vecuronium-induced NMB, no statistically significant interactions were observed between any of the subgroups on recovery of the T_4/T_1 ratio to 0.9. In addition, the evaluation that included only the main factors showed no effects based on gender, age, weight and ASA class. Although Caucasian subjects had slightly longer geometric mean recovery times (3.9 minutes) than Asian subjects (2.9 minutes), there were too few Asian subjects (n=11) to allow definitive conclusions to be drawn. Similarly, although Hispanic/Latino subjects had longer geometric mean recovery times (12.4 minutes) compared with Non-hispanic/Non-latino subjects (3.7 minutes), there were too few Hispanic/Latino subjects (n=3) to allow definitive conclusions to be drawn.

For reversal of a rocuronium-induced NMB at 3 minutes, no statistically significant interactions were observed between any of the subpopulations. Investigation of the time to recovery of the T_4/T_1 ratio to 0.9 revealed no effect of gender or ASA class. Because of the low number of geriatric subjects (n=2) and subjects with a BMI $\geq 30.0 \text{ kg}\cdot\text{m}^{-2}$ (n=1), no investigation was performed to assess their impact on the time to recovery of the T_4/T_1 ratio to 0.9. Similar geometric mean times to recovery were observed between Caucasian, Black and Asian subjects and between Hispanic/Latino and Non-hispanic/Non-latino subjects.

Therefore, with respect to drug-demographic interactions, no dose adjustments are recommended.

5.6.2 Drug-drug interactions

For drug-drug interactions the effect of different anesthetic regimens was studied: propofol versus inhalational anesthesia with sevoflurane in Trials 19.4.210 and 19.4.312. Overall, the recovery time to a T_4/T_1 ratio of 0.9 under maintenance anesthesia with sevoflurane was equivalent to the recovery time under maintenance anesthesia with propofol.

For additional information please see Section 4.3.5 Population PK-PD Model.

5.6.3 Drug-disease interactions

For drug-disease interactions the results obtained from the trials that investigated the effect of sugammadex on renally-impaired subjects, subjects with a cardiac disease or pulmonary complications are summarized below.

Renally-Impaired Subjects

In Trial 19.4.304 the recovery of renally-impaired subjects was studied. The trial was designed to show equivalence with respect to the efficacy of 2.0 mg/kg sugammadex (administered at the reappearance of T_2) in subjects with normal or impaired renal function. Subjects in the renally-impaired group had a creatinine clearance of less than 30 mL/min. Although equivalence was not formally demonstrated in this trial, the results of the trial showed that a dose of 2.0 mg/kg sugammadex is efficacious in subjects with impaired renal function: the median time from the start of administration of sugammadex to recovery of the T_4/T_1 ratio to 0.9 was 1.6 minutes in renally-impaired subjects and 1.4 minutes in control subjects which is not considered clinically significant.

Subjects with pulmonary complications

In Trial 19.4.308 the recovery of subjects diagnosed with or having a history of pulmonary complications was studied (e.g., asthma). The trial showed that for subjects with pulmonary complications treated with rocuronium, the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was 2.1 minutes after a dose of 2.0 mg/kg sugammadex and 1.8 minutes after a dose of 4.0 mg/kg sugammadex. These results indicate sugammadex is efficacious in subjects with pulmonary complications at dose levels of both 2.0 and 4.0 mg/kg. The geometric mean time in the 2.0 mg/kg sugammadex group is similar to the geometric mean values observed in trials in subjects without pulmonary complications (Section 5.5.1).

Subjects with cardiac disease

In Trial 19.4.309 the recovery of cardiac subjects (i.e., subjects with ischemic heart disease, chronic heart failure or arrhythmia) of New York Heart Association (NYHA) class II to III was studied. The trial showed that for subjects with cardiac disease treated with rocuronium, the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was 34.3 minutes in the placebo group and 1.7 and 1.4 minutes, respectively, in the 2.0 and 4.0 mg/kg sugammadex dose groups. These results indicate sugammadex is efficacious in subjects with cardiac disease at dose levels of both 2.0 and 4.0 mg/kg. The geometric mean time in the 2.0 mg/kg sugammadex group is similar to the geometric mean values observed in trials in subjects without cardiac disease (Section 5.5.1).

Therefore, sugammadex has been shown to be efficacious in renally impaired subjects and subjects with pulmonary and cardiac complications.

5.7 Doses recommended for the proposed indication

In selecting the recommended dose of sugammadex in each of the three anesthesia settings (routine reversal at the reappearance of T_2 [shallow blockade] or at 1-2 PTCs [profound block] or immediate reversal 3 minutes following an intubating dose of rocuronium), the following considerations were made: (1) the doses recommended should minimize the possibility of incomplete recovery (and thereby reduce the risks associated with incomplete recovery or residual NMB); (2) the doses recommended should provide clinically significant reductions in recovery time compared to spontaneous recovery and established regimens (e.g., neostigmine); and (3) the doses recommended should minimize the potential for confusion regarding use (i.e., a limited choice of recommended doses is preferred).

The sponsor is seeking approval to market sugammadex as follows; a dose 2.0 mg/kg sugammadex is only recommended if spontaneous recovery has reached the reappearance of T_2 (shallow blockade) following rocuronium- or vecuronium-induced blockade; a dose 4.0 mg/kg sugammadex is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following administration of rocuronium- or vecuronium-induced blockade; and if there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg sugammadex is recommended.

In each case the recommended doses have been shown to be statistically and clinically superior relative to established regimens (e.g., neostigmine in the cases of

routine reversal and the time to spontaneous recovery in situations where the use of 1.0 mg/kg succinylcholine is warranted). The efficacy of each dose of sugammadex has been shown to be independent of the dose of the NMBA and the anesthetic agent(s) used as well as a subject's gender, ASA class and weight. In addition, although the vast majority of subjects enrolled in the clinical development program were Caucasian and not of Hispanic or Latino origin, the limited data available for analysis do not suggest a clinically relevant difference among the race categories and between the two ethnic groups. Therefore, dosing recommendations remain independent of race and ethnicity.

Each dose was associated with very few cases of re-occurrence of blockade or residual blockade during the sugammadex clinical development program (Section 6.10.1). Although the use of higher doses (relative to the currently recommended doses) resulted in faster recovery times in some settings (e.g., following vecuronium-induced NMB at 1-2 PTCs), it is felt that the magnitude of the faster recovery times is not great enough to warrant multiple, complex dosing recommendations based on the NMBA administered.

6. SUMMARY OF SAFETY (INCLUDING TOXICOLOGY)

6.1 Safety monitoring methodology

Safety data were collected in all 30 trials conducted during the sugammadex clinical development program (Figure 7). Two datasets were generated for the integrated analysis of safety:

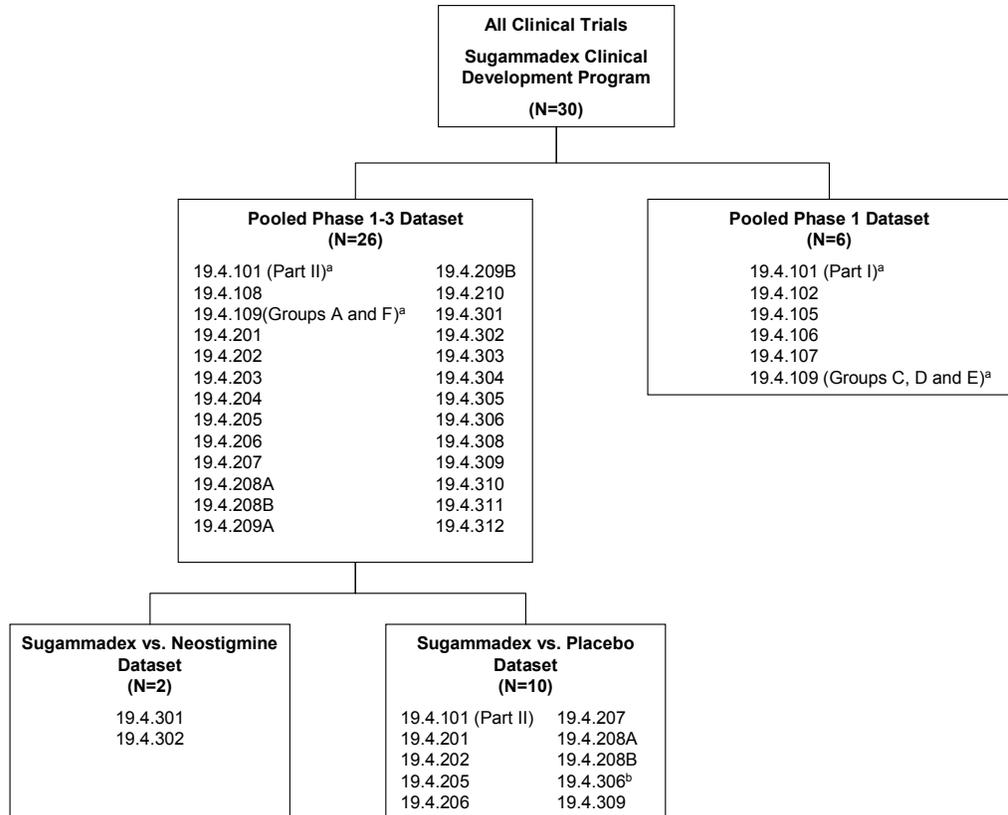
- (1) Pooled Phase 1-3 Dataset: Data were pooled from all 26 trials of the trials in which sugammadex or placebo were administered following an NMBA (e.g., rocuronium). This dataset is hereafter referred to as the total sugammadex group (n=1926) and allows for an analysis of dose response, with a particular interest on the proposed marketing doses of 2.0 mg/kg, 4.0 mg/kg, and 16 mg/kg sugammadex.

Within this dataset, 2 additional subsets were generated and are discussed in this Briefing Document:

- (a) sugammadex vs. neostigmine dataset: Data were pooled from the 2 Phase 3 trials (Trials 19.4.301 and 19.4.302) in which sugammadex (n=179) was directly compared to neostigmine (n=167). This dataset is likely the most clinically relevant, despite the small number of

subjects, because of the direct comparison between sugammadex and neostigmine, the most widely used reversal agent.

- (b) sugammadex vs. placebo dataset: Data were pooled from the 10 trials that included a 0 mg/kg dose group (placebo) in order to compare the safety of sugammadex (n=640) vs. placebo (n=140). This dataset is most important in identifying potential adverse drug reactions.
- (2) Pooled Phase 1 Dataset: The Phase 1 pooled dataset includes data from following six trials with no NMBA: Trials 19.4.101 (Part 1), 19.4.102, 19.4.105, 19.4.106, 19.4.107, and 19.4.109 (Groups C, D and E). Other than Trial 19.4.107, all Phase 1 trials were randomized, double-blind, crossover trials in which adult healthy volunteers received single doses of trial medication but no anesthetic or NMBA. Phase 1 Trial 19.4.107 was an open-label, non-randomized single-center trial to determine the excretion balance, metabolite profile, and pharmacokinetics of sugammadex after an intravenous dose of ¹⁴C-labeled sugammadex. (Since Trial 19.4.107 used a different [i.e., radiolabeled] formulation of sugammadex in a very small number of subjects [N=6], only the demographic and AE data are included in the pooled dataset. Clinical laboratory data, vital signs data, and ECG data are summarized from the clinical trial report [CTR].)

Figure 7 Sugammadex safety datasets

- a. Overall, safety data have been pooled based upon whether or not subjects received an NMBA with sugammadex or placebo. As a result, safety data from Trials 19.4.101 (Part II) and 19.4.109 Groups (A and F) have been pooled with those trials in which subjects received and NMBA, and safety data from Trials 19.4.101 (Part I) and 19.4.109 (Groups C, D and E) have been pooled with those trials in which subjects did not receive an NMBA.
- b. Adults subjects only

In the sections that follow, the primary discussion will involve analysis of data from the sugammadex vs. neostigmine dataset. Secondary discussions will address the sugammadex vs. placebo and pooled 1-3 (total sugammadex) datasets. Data from the Phase 1 trials are not emphasized, unless there were notable differences compared with the pooled Phase 1-3 datasets.

In general, safety was assessed across trials by the reporting of AEs, and assessment of changes from baseline in clinical laboratory values, vital signs, and electrocardiograms (ECGs). All AEs in the integrated database are coded to MedDRA version 10.0.

In addition to the assessment of AEs overall, potential adverse drug reactions (ADRs) were identified during the sugammadex clinical development program, defined as any AE that:

- was considered by the sponsor to be related to sugammadex;
- showed a dose-response;
- occurred in the total sugammadex group with a frequency of 2% or more and at least twice as often as compared to the placebo group (for these events a medical assessment was made taking also into consideration the Investigator's opinion of causality and the intensity of the AE);
- is biologically plausible, irrespective of incidence, including any events that are very likely to be associated with the compound based on its known pharmacological actions, preclinical experiments (animal or lab tests), or previous experience in clinical trials.; and/or
- was considered to be an SAE for which a causal relationship cannot be excluded and which could be clinically relevant in the anticipated setting in which sugammadex will be utilized.

In addition, events particularly relevant to the use of anesthesia (in general) and reversal agents (in particular) have been assessed. These include:

- re-occurrence of blockade/residual blockade based on the TOF Watch SX[®] measurements;
- anesthetic complications; (which include the following preferred terms [with examples of verbatim terms]):
 - (1) anesthetic complication (movement [of a limb or the body], coughing during the anesthetic procedure or during surgery, grimacing, suckling the endotracheal tube, including AEs that in MedDRA versions prior to 10.0 were coded to the preferred term of "light anesthesia"),
 - (2) airway complications of anesthesia (coughing on induction, bucking, and spontaneous breathing),

- (3) delayed recovery from anesthesia (delayed awakening from anesthesia or extended recovery from anesthesia),
 - (4) unwanted awareness during anesthesia (awareness during anesthesia, awake during operation), and
 - (5) anesthetic complication cardiac (changes in cardiac rate and rhythm).
- AEs associated with ventilation (i.e., preferred terms not specifically noted to involve an anesthetic complication); and
 - allergic reactions.

In addition to events particularly relevant to the use of anesthesia (in general) and reversal agents (in particular), special attention was also paid to the effect of sugammadex on renal function since the drug is nearly exclusively removed via the kidneys.

In order to fulfill the requirements for a thorough analysis of drug effects on the QTc interval, two prospective, thorough, QTc trials (Trials 19.4.109 and 19.4.105) were conducted as part of the sugammadex clinical development program. Trial 19.4.109 was conducted in non-anesthetized healthy volunteers who received sugammadex both with and without an NMBA. Trial 19.4.105 was conducted in non-anesthetized healthy volunteers who received sugammadex without an NMBA. In addition to the two QTc interval trials, electrocardiographic data were collected in 10 of the 26 trials in which subjects received an NMBA in addition to the trial medication. Electrocardiographic data from 8 of these trials (Trials 19.4.101 [Part II only], 19.4.202, 19.4.204, 19.4.205, 19.4.206, 19.4.210, 19.4.306, and 19.4.309) were pooled and rigorously analyzed for treatment-related abnormalities.

6.2 Nonclinical data relevant to human safety

The toxicological profile of CDs is well known. Specifically, it has been shown that, following repeated administration of high doses of CDs, effects are seen on the urinary tract and pulmonary tract. These are mild and adaptive effects and reversible in nature. Similar effects have also been seen following administration of sugammadex. However, following single doses of sugammadex (i.e., the most relevant regimen for clinical use), these effects were very mild and only seen after administration of high doses of sugammadex in animals. The No Observed Effect Levels (NOELs) for the effects on rat kidney, urinary bladder and lung after a single dose of sugammadex are 250 mg/kg. Adverse effects are not observed at single doses of 2000 mg/kg. Thus, a significant safety margin has been established.

Sugammadex and all of its related CDs are devoid of genotoxic potential. In addition, sugammadex and its related CDs are devoid of intrinsic primary or secondary pharmacological activity.

Sugammadex is rapidly cleared from most organs; however, retention of the compound has been shown to occur in bone and teeth in the rat, most likely as a result of reversible binding to the hydroxy apatite (the inorganic matrix) present in bone and teeth. Preclinical studies in young adult and mature rats have shown that retention of the compound does not adversely affect tooth color or bone quality, structure, turnover and development. In juvenile rats, whitish discoloration of the incisors and disturbance of enamel formation were observed upon repeated dosing; however, the safety margin (>48-480 for the recommended human dose of 4.0 mg/kg for routine reversal) under the conditions of clinical use is considered to be sufficiently large.

Animal studies do not indicate direct or indirect adverse effects with respect to fertility, pregnancy, embryonic/fetal development, parturition or postnatal development. Sugammadex shows very low transfer over the blood brain barrier and the rat and rabbit placenta.

In vitro and in vivo preclinical studies have demonstrated that administration of a dose of sugammadex (higher than required for reversal) can prevent the re-occurrence of block after administration of magnesium (for the treatment of cardiac arrhythmias) or antibiotics. Other preclinical studies have shown that in the presence of magnesium (for the treatment of pre-eclampsia) or antibiotics, the neuromuscular blocking effect of steroidal NMBA is potentiated, resulting in a higher dose requirement for sugammadex.

6.3 Extent of exposure and characteristics of subject population

6.3.1 Sugammadex vs. neostigmine

In trials comparing sugammadex to neostigmine (Trials 19.4.301 and 19.4.302), similar numbers of subjects received either sugammadex (n=179) or neostigmine (n=167) following a NMB induced by either rocuronium (85 sugammadex-treated subjects, 86 neostigmine-treated subjects) or vecuronium (94 sugammadex-treated subjects, 81 neostigmine-treated subjects). Baseline and demographic characteristics (age, gender, race, ethnicity, body weight and percentage of subjects classified as ASA Class 2 or 3) were comparable between the sugammadex and neostigmine treatment groups (Table 28). In both groups, the mean age was approximately 50 years, the majority of subjects were Caucasian, and there were an equal percentage of males and females. The majority of subjects were ASA Class 2 and the distribution of subjects was similar in each group.

Table 28 Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 controlled trials 19.4.301 and 19.4.302

| Parameter | Statistic/Category | Rocuronium or Vecuronium + | |
|--------------------------------------|---------------------------|----------------------------|-------------|
| | | sugammadex | neostigmine |
| Age (yrs.) | n | 179 | 167 |
| | Mean (SD) | 50 (15) | 52 (14) |
| | Median | 51 | 54 |
| | Min. - max. | 19 - 85 | 18 - 81 |
| Age (no. [%]) | n | 179 | 167 |
| | 18-64 yr. | 145 (81) | 141 (84) |
| | 65-74 yr. | 25 (14) | 24 (14) |
| | ≥ 75 yr. | 9 (5) | 2 (1) |
| Gender (n [%]) | n | 179 | 167 |
| | Male | 90 (50) | 83 (50) |
| | Female | 89 (50) | 84 (50) |
| Race (n [%]) | n | 179 | 167 |
| | Asian | 1 (1) | 6 (4) |
| | Black or African American | 10 (6) | 2 (1) |
| | White/Caucasian | 164 (92) | 159 (95) |
| | Other | 4 (2) | 0 (0) |
| Ethnicity Hispanic or Latino (n [%]) | n | 179 | 167 |
| | Yes | 18 (10) | 22 (13) |
| | No | 161 (90) | 145 (87) |
| | Missing | 0 | 0 |
| Weight (kg) | n | 179 | 167 |
| | Mean (SD) | 82 (22) | 81 (18) |
| | Median | 78 | 79 |
| | Min. - max. | 42 - 182 | 46 - 146 |
| ASA Class (n [%]) | n | 179 | 167 |
| | 1 | 48 (27) | 45 (27) |
| | 2 | 111 (62) | 99 (59) |
| | 3 | 20 (11) | 23 (14) |
| | 4 | 0 (0) | 0 (0) |

Notes: Percentages are based on non-missing data.

6.3.2 Sugammadex vs. placebo

In the pooled Phase 1-3 trials that included a placebo group, approximately five times as many subjects received sugammadex (n=640) compared to placebo (n=140). Overall, more subjects received rocuronium as the NMBA (526 sugammadex-treated subjects, 116 placebo-treated subjects) than vecuronium (114 sugammadex-treated subjects, 24 placebo-treated subjects). Baseline and demographic characteristics (age, gender, race, ethnicity and body weight) were comparable between the sugammadex and placebo treatment groups (Table 29). More sugammadex-treated subjects were ASA Class 1 than ASA Class 2, while the reverse was true for placebo-treated subjects; however, this difference was not considered to be clinically relevant and is not believed to have impacted the overall safety analysis. There was only one ASA Class 4 subject (in the sugammadex group) in this dataset. One hundred forty (140) subjects received placebo. Baseline and demographic characteristics (age, gender, race, ethnicity, body weight and percentage of subjects classified as ASA Class 2 or 3) were comparable among the placebo treatment group and the 2.0 and 4.0 mg/kg treatment groups. The 16 mg/kg group, which included fewer subjects (n=99) compared with the 2.0 (n=606) and 4.0 mg/kg groups (n=582), showed slight differences that were not considered to be clinically relevant.

Table 29 Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials with a placebo group

| Parameter | Statistic/Category | rocuronium or vecuronium + | |
|---|---------------------------|----------------------------|----------|
| | | sugammadex | placebo |
| Age (yrs.) | n | 640 | 140 |
| | Mean (SD) | 49 (16) | 51 (16) |
| | Median | 48 | 52 |
| | Min. - max. | 18 - 90 | 19 - 86 |
| Age (no.[%] Subjects) | n | 640 | 140 |
| | 18-64 yr. | 531 (83) | 113 (81) |
| | 65-74 yr. | 61 (10) | 15 (11) |
| | ≥ 75 yr. | 48 (8) | 12 (9) |
| Gender (n [%]) | n | 640 | 140 |
| | Male | 392 (61) | 85 (61) |
| | Female | 248 (39) | 55 (39) |
| Race (n [%]) | n | 640 | 140 |
| | Asian | 80 (13) | 22 (16) |
| | Black or African American | 2 (< 1) | 0 (0) |
| | White/Caucasian | 556 (87) | 117 (84) |
| | Other | 2 (< 1) | 1 (1) |
| Ethnicity Hispanic or Latino (n [%] subjects) | n | 640 | 140 |
| | Yes | 2 (1) | 3 (3) |
| | No | 252 (99) | 83 (97) |
| | Missing | 386 | 54 |
| Weight (kg) | n | 640 | 140 |
| | Mean (SD) | 75 (15) | 76 (16) |
| | Median | 75 | 76 |
| | Min. - max. | 40 - 145 | 45 - 135 |
| ASA Class (n [%]) | n | 640 | 140 |
| | 1 | 330 (52) | 56 (40) |
| | 2 | 227 (35) | 58 (41) |
| | 3 | 82 (13) | 26 (19) |
| | 4 | 1 ^a (<1) | 0 (0) |
| | Missing | 0 | 0 |

^a This was one subject from trial 19.4.309

Note: Percentages are based on non-missing data

6.3.3 Pooled Phase 1 - 3

In all pooled Phase 1-3 trials where subjects received rocuronium, vecuronium, or pancuronium, a total of 1926 subjects were exposed to sugammadex at doses up to 32 mg/kg (Table 30). A total of 188 subjects were exposed in Phase 1 trials, 866 subjects were exposed in Phase 2 trials, and 872 subjects were exposed in Phase 3 trials. Most subjects received either a 2.0 mg/kg dose (n=606) or a 4.0 mg/kg dose (n=582), the proposed marketed doses for routine reversal when administered at the reappearance of T_2 or at 1-2 PTCs, respectively. A total of 99 subjects received the 16.0 mg/kg dose, which is the proposed marketed dose for immediate reversal at 3 minutes following rocuronium.

Table 30 Number of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group

| Trial Phase | Rocuronium, vecuronium, or pancuronium + sugammadex mg/kg | | | | | | | | | | | |
|-------------|---|-----|-----|---|-----|----|-----|----|----|----|-----|------------------|
| | 0 | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | Total sugammadex |
| Phase 1 | 10 | 4 | 2 | 0 | 2 | 0 | 2 | 0 | 4 | 4 | 170 | 188 |
| Phase 2 | 84 | 250 | 212 | 9 | 167 | 28 | 122 | 39 | 39 | 0 | 0 | 866 |
| Phase 3 | 46 | 11 | 392 | 0 | 413 | 0 | 0 | 0 | 56 | 0 | 0 | 872 |
| Total | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 170 | 1926 |

Notes: Trial 19.4.109 was a crossover trial. In Groups A and F there were 162 total exposures to sugammadex plus rocuronium or vecuronium in 81 unique subjects. Pancuronium was studied in 19.4.207.

In pooled Phase 1-3 trials overall (NMBA was rocuronium, vecuronium, or pancuronium, and excluding the crossover thorough QTc trial 19.4.109), most subjects in the total sugammadex group were between the ages of 18 and 64 years, Caucasian, non-Hispanic/Latino, and ASA class 1 or 2 (Table 31). The percentages of male and female subjects were similar. There was only one ASA class 4 subject. Median body weight for the total sugammadex group was 72 kg.

The demographic profiles of the 2 mg/kg and 4 mg/kg dose groups were similar to each other and also to the total sugammadex group. In comparison, the 16 mg/kg dose group was younger, predominantly female, had a higher percentage of Hispanic/Latino subjects, and had a higher percentage of ASA Class 1 and a lower percentage of ASA Class 3 subjects.

In the crossover thorough QTc trial 19.4.109, there were 40 females and 41 males ranging in age from 19 to 45 years (inclusive) who were exposed to sugammadex

plus rocuronium or vecuronium. Most subjects were Caucasian; two were Asian, and two were Black.

Table 31 Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group

| Parameter | Statistic/ Category | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
|----------------|------------------------|---|----------|----------|---------|----------|---------|----------|---------|---------|---------|----------|---------------------|
| | | 0 (placebo) | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | Total sugammadex |
| Age (yrs) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | Mean (SD) | 51 (16) | 47 (13) | 54 (17) | 46 (14) | 51 (16) | 44 (18) | 47 (13) | 52 (13) | 44 (15) | 25 (7) | 34 (8) | 50 (16) |
| | Median | 52 | 48 | 56 | 43 | 52 | 39 | 48 | 52 | 44 | 24 | 34 | 50 |
| | Min. - max. | 19 - 86 | 19 - 82 | 18 - 91 | 29 - 67 | 18 - 92 | 22 - 81 | 18 - 76 | 19 - 82 | 18 - 80 | 18 - 34 | 19 - 45 | 18 - 92 |
| Age (no.[%]) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | 18-64 yr | 113 (81) | 248 (94) | 410 (68) | 8 (89) | 470 (81) | 23 (82) | 118 (95) | 33 (85) | 88 (89) | 4 (100) | 89 (100) | 1491 (81) |
| | 65-74 yr | 15 (11) | 11 (4) | 124 (20) | 1 (11) | 76 (13) | 3 (11) | 4 (3) | 4 (10) | 9 (9) | 0 (0) | 0 (0) | 232 (13) |
| | ≥ 75 yr | 12 (9) | 6 (2) | 72 (12) | 0 (0) | 36 (6) | 2 (7) | 2 (2) | 2 (5) | 2 (2) | 0 (0) | 0 (0) | 122 (7) |
| Gender (n [%]) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | Male | 85 (61) | 153 (58) | 316 (52) | 8 (89) | 278 (48) | 25 (89) | 74 (60) | 24 (62) | 37 (37) | 4 (100) | 47 (53) | 966 (52) |
| | Female | 55 (39) | 112 (42) | 290 (48) | 1 (11) | 304 (52) | 3 (11) | 50 (40) | 15 (38) | 62 (63) | 0 (0) | 42 (47) | 879 (48) |

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**Table 31 Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group
(continued)**

| Parameter | Statistic/ Category | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
|---|--|---|----------|----------|--------|----------|----------|----------|---------|---------|---------|---------|---------------------|
| | | 0 (placebo) | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | Total sugammadex |
| Race (n [%]) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | Asian | 22 (16) | 78 (29) | 46 (8) | 1 (11) | 46 (8) | 0 (0) | 20 (16) | 0 (0) | 4 (4) | 0 (0) | 2 (2) | 197 (11) |
| | Black or African American | 0 (0) | 0 (0) | 30 (5) | 0 (0) | 34 (6) | 0 (0) | 0 (0) | 0 (0) | 12 (12) | 0 (0) | 2 (2) | 78 (4) |
| | White/ Caucasian | 117 (84) | 186 (70) | 524 (86) | 8 (89) | 496 (85) | 28 (100) | 104 (84) | 37 (95) | 83 (84) | 4 (100) | 85 (96) | 1555 (84) |
| | American Indian or Alaska Native | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (0) |
| | Other | 1 (1) | 1 (0) | 5 (1) | 0 (0) | 6 (1) | 0 (0) | 0 (0) | 2 (5) | 0 (0) | 0 (0) | 0 (0) | 14 (1) |
| Ethnicity Hispanic or Latino (n [%]) | N | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | Yes | 3 (3) | 2 (1) | 23 (5) | 0 (0) | 23 (5) | 0 (0) | 0 (0) | 0 (0) | 15 (25) | 0 (0) | 1 (1) | 64 (5) |
| | No | 83 (97) | 164 (99) | 449 (95) | 0 (0) | 470 (95) | 0 (0) | 41 (100) | 0 (0) | 45 (75) | 4 (100) | 88 (99) | 1261 (95) |
| | Missing | 54 | 99 | 134 | 9 | 89 | 28 | 83 | 39 | 39 | 0 | 0 | 520 |

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Table 31 Demographic and baseline characteristics of adult subjects in pooled Phase 1 - 3 trials by sugammadex mg/kg dose group (continued)

| Parameter | Statistic/ Category | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
|-------------------|------------------------|---|----------|----------|---------|----------|----------|----------|----------|----------|---------|----------|---------------------|
| | | 0 (placebo) | < 2 | 2 | 3 | 4 | 6 | 8 | 12 | 16 | 20 | 32 | Total sugammadex |
| Weight (kg) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | Mean (SD) | 76 (16) | 73 (16) | 76 (17) | 74 (11) | 79 (19) | 85 (14) | 75 (16) | 78 (15) | 72 (15) | 76 (11) | 72 (13) | 77 (17) |
| | Median | 76 | 72 | 75 | 74 | 77 | 84 | 75 | 77 | 69 | 71 | 71 | 75 |
| | Min. - max. | 45 - 135 | 39 - 133 | 42 - 141 | 58 - 87 | 40 - 182 | 54 - 110 | 42 - 145 | 45 - 110 | 44 - 139 | 69 - 92 | 51 - 107 | 39 - 182 |
| ASA Class (n [%]) | n | 140 | 265 | 606 | 9 | 582 | 28 | 124 | 39 | 99 | 4 | 89 | 1845 |
| | 1 | 56 (40) | 150 (57) | 191 (32) | 7 (78) | 158 (27) | 20 (71) | 67 (54) | 19 (49) | 44 (44) | 4 (100) | 89 (100) | 749 (41) |
| | 2 | 58 (41) | 107 (40) | 285 (47) | 2 (22) | 331 (57) | 7 (25) | 53 (43) | 15 (38) | 50 (51) | 0 (0) | 0 (0) | 850 (46) |
| | 3 | 26 (19) | 8 (3) | 129 (21) | 0 (0) | 93 (16) | 1 (4) | 4 (3) | 5 (13) | 5 (5) | 0 (0) | 0 (0) | 245 (13) |
| | 4 | 0 (0) | 0 (0) | 1 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 ^a (0) |

Notes: Pediatric subjects from trial 19.4.306 and subjects from the crossover through QTc trial 19.4.109 are excluded from this table. Percentages are based on non-missing data. Pancuronium was studied in 19.4.207.

^a This was one subject from trial 19.4.309

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6.4 Most common adverse events

6.4.1 Sugammadex vs. neostigmine

The incidence of subjects with at least one AE was similar for sugammadex-treated subjects (87.7%) and neostigmine-treated subjects (89.2%) (Table 32). Of the 37 most common AEs (i.e., those AEs occurring in at least 2% of subjects), approximately one-third (n=13) occurred more often in sugammadex-treated subjects, and 2 (flatulence and GI disorder postoperative) occurred in at least 2% of sugammadex-treated subjects and at a 2-fold higher incidence compared to neostigmine-treated subjects. Both events are typically seen in a surgical/post-surgical population and/or are routinely managed.

Table 32 Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in Phase 3 controlled trials 19.4.301 and 19.4.302

| MedDRA 10.0 | | Rocuronium or vecuronium + | |
|--|---|----------------------------|------------------------|
| | | sugammadex (N=179) | Neostigmine (N=167) |
| SOC | PT | n (%) | n (%) |
| At least one AE | Total | 157 (87.7) | 149 (89.2) |
| Injury, poisoning and procedural complications | Total | 120 (67.0) | 113 (67.7) |
| | Procedural pain | 98 (54.7) | 85 (50.9) |
| | Incision site pain | 19 (10.6) | 14 (8.4) |
| | Procedural nausea | 14 (7.8) | 13 (7.8) |
| | Procedural hypertension | 9 (5.0) | 9 (5.4) |
| | Procedural complication | 6 (3.4) | 14 (8.4) |
| | Gastrointestinal disorder postoperative | 4 (2.2) | 0 (0.0) |
| | Procedural hypotension | 2 (1.1) | 11 (6.6) |
| | Procedural vomiting | 2 (1.1) | 5 (3.0) |
| | Airway complication of anesthesia | 2 (1.1) | 4 (2.4) |
| | Post procedural complication | 2 (1.1) | 4 (2.4) |
| | Neuromuscular block prolonged | 0 (0.0) | 4 (2.4) |
| | Gastrointestinal disorders | Total | 84 (46.9) |
| Nausea | | 63 (35.2) | 61 (36.5) |
| Vomiting | | 28 (15.6) | 22 (13.2) |
| Flatulence | | 10 (5.6) | 4 (2.4) |
| Constipation | | 9 (5.0) | 11 (6.6) |
| Retching | | 6 (3.4) | 8 (4.8) |
| Abdominal pain | | 5 (2.8) | 6 (3.6) |
| Dry mouth | | 4 (2.2) | 14 (8.4) |
| Oral pain | | 3 (1.7) | 6 (3.6) |
| Dyspepsia | | 2 (1.1) | 5 (3.0) |

Table 32 Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in Phase 3 controlled trials 19.4.301 and 19.4.302 (continued)

| MedDRA 10.0 | | Rocuronium or vecuronium + | |
|--|--|----------------------------|------------------------|
| | | sugammadex (N=179) | neostigmine (N=167) |
| SOC | PT | n (%) | n (%) |
| General disorders and administration site conditions | Total | 40 (22.3) | 35 (21.0) |
| | Pain | 18 (10.1) | 14 (8.4) |
| | Chills | 12 (6.7) | 7 (4.2) |
| | Pyrexia | 6 (3.4) | 8 (4.8) |
| Nervous system disorders | Total | 32 (17.9) | 34 (20.4) |
| | Headache | 21 (11.7) | 13 (7.8) |
| | Dizziness | 7 (3.9) | 11 (6.6) |
| Investigations | Total | 20 (11.2) | 18 (10.8) |
| | Blood creatine phosphokinase increased | 6 (3.4) | 3 (1.8) |
| Psychiatric disorders | Total | 22 (12.3) | 27 (16.2) |
| | Insomnia | 10 (5.6) | 9 (5.4) |
| | Anxiety | 3 (1.7) | 8 (4.8) |
| | Sleep disorder | 3 (1.7) | 4 (2.4) |
| Respiratory, thoracic and mediastinal disorders | Total | 19 (10.6) | 23 (13.8) |
| | Pharyngolaryngeal pain | 16 (8.9) | 17 (10.2) |
| Musculoskeletal and connective tissue disorders | Total | 19 (10.6) | 20 (12.0) |
| | Back pain | 7 (3.9) | 7 (4.2) |
| | Muscular weakness | 7 (3.9) | 5 (3.0) |
| | Myalgia | 5 (2.8) | 6 (3.6) |
| Skin and subcutaneous tissue disorders | Total | 14 (7.8) | 13 (7.8) |
| | Pruritus | 8 (4.5) | 6 (3.6) |
| | Erythema | 2 (1.1) | 4 (2.4) |
| Metabolism and nutrition disorders | Total | 11 (6.1) | 7 (4.2) |
| | Hypocalcaemia | 4 (2.2) | 2 (1.2) |
| Infections and infestations | Total | 6 (3.4) | 7 (4.2) |
| Renal and urinary disorders | Total | 5 (2.8) | 9 (5.4) |
| Cardiac disorders | Total | 5 (2.8) | 5 (3.0) |
| Vascular disorders | Total | 5 (2.8) | 2 (1.2) |
| Ear and labyrinth disorders | Total | 4 (2.2) | 3 (1.8) |
| Blood and lymphatic system disorders | Total | 3 (1.7) | 9 (5.4) |
| | Anemia | 1 (0.6) | 6 (3.6) |

Notes: This table includes AEs that occurred in at least 2.0% of a treatment group whether summarized by SOC or by PT. If a SOC is listed with no subordinate PT, there was no subordinate PT in that SOC that occurred in at least 2.0% of a treatment group.

6.4.2 Sugammadex vs. placebo

The incidence of subjects with at least one AE was slightly lower for sugammadex-treated subjects (68.3%) than for placebo-treated subjects (72.1%) (Table 33). Of the 31 most common AEs (i.e., those AEs occurring in at least 2% of subjects), less than one-third (n=9) occurred more often in sugammadex-treated subjects, and 2 (anesthetic complication and cough) occurred in at least 2% of sugammadex-treated subjects and at a 2-fold higher incidence compared to placebo-treated subjects. About 40% of all occurrences of anesthetic complication and about 46% of all occurrences of cough were considered by the Investigators to be related to the administration of sugammadex. Both events are typically seen in a surgical/post-surgical population and/or are routinely managed.

Table 33 Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in pooled Phase 1-3 trials with a placebo group

| MedDRA 10.0 | | Rocuronium or vecuronium + | |
|--|----------------------------------|----------------------------|--------------------|
| | | sugammadex (N=640) | placebo (N=140) |
| SOC | PT | n (%) | n (%) |
| At least one AE | Total | 437 (68.3) | 101 (72.1) |
| Injury, poisoning and procedural complications | Total | 241 (37.7) | 56 (40.0) |
| | Procedural pain | 134 (20.9) | 43 (30.7) |
| | Anesthetic complication | 51 (8.0) | 2 (1.4) |
| | Procedural hypotension | 31 (4.8) | 4 (2.9) |
| | Procedural hypertension | 16 (2.5) | 4 (2.9) |
| | Postoperative wound complication | 13 (2.0) | 3 (2.1) |
| | Procedural nausea | 4 (0.6) | 5 (3.6) |
| | Procedural complication | 6 (0.9) | 3 (2.1) |
| Gastrointestinal disorders | Total | 175 (27.3) | 41 (29.3) |
| | Nausea | 106 (16.6) | 25 (17.9) |
| | Vomiting | 61 (9.5) | 11 (7.9) |
| | Constipation | 15 (2.3) | 7 (5.0) |
| | Abdominal pain | 15 (2.3) | 3 (2.1) |
| | Diarrhea | 14 (2.2) | 4 (2.9) |

Table 33 Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in pooled Phase 1-3 trials with a placebo group (continued)

| MedDRA 9.1 | | Rocuronium or vecuronium + | |
|--|---|--------------------------------|-----------------------------|
| | | sugammadex (N=640) n (%) | Placebo (N=140) n (%) |
| SOC | PT | | |
| General disorders and administration site conditions | Total | 106 (16.6) | 27 (19.3) |
| | Pain | 37 (5.8) | 7 (5.0) |
| | Pyrexia | 34 (5.3) | 11 (7.9) |
| | Chills | 20 (3.1) | 3 (2.1) |
| | Malaise | 5 (0.8) | 3 (2.1) |
| Investigations | Total | 77 (12.0) | 13 (9.3) |
| | Electrocardiogram QT corrected interval prolonged | 16 (2.5) | 2 (1.4) |
| | Beta 2 microglobulin urine increased ^a | 15 (2.3) | 4 (2.9) |
| Respiratory, thoracic and mediastinal disorders | Total | 78 (12.2) | 14 (10.0) |
| | Pharyngolaryngeal pain | 28 (4.4) | 8 (5.7) |
| | Cough | 18 (2.8) | 2 (1.4) |
| Nervous system disorders | Total | 70 (10.9) | 22 (15.7) |
| | Headache | 29 (4.5) | 11 (7.9) |
| | Dizziness | 13 (2.0) | 4 (2.9) |
| | Paraesthesia | 6 (0.9) | 3 (2.1) |
| Musculoskeletal and connective tissue disorders | Total | 49 (7.7) | 9 (6.4) |
| | Back pain | 20 (3.1) | 3 (2.1) |
| Renal and urinary disorders | Total | 44 (6.9) | 10 (7.1) |
| | Dysuria | 9 (1.4) | 5 (3.6) |
| Vascular disorders | Total | 39 (6.1) | 9 (6.4) |
| | Hypertension | 14 (2.2) | 4 (2.9) |
| Psychiatric disorders | Total | 30 (4.7) | 6 (4.3) |
| | Insomnia | 11 (1.7) | 3 (2.1) |
| Skin and subcutaneous tissue disorders | Total | 20 (3.1) | 10 (7.1) |
| | Pruritus | 2 (0.3) | 4 (2.9) |

Table 33 Adverse events by MedDRA SOC and PT in at least 2.0% of any treatment group in pooled Phase 1-3 trials with a placebo group (continued)

| MedDRA 9.1 | | Rocuronium or vecuronium + | |
|--------------------------------------|---------------------------|----------------------------|--------------------|
| | | sugammadex (N=640) | Placebo (N=140) |
| SOC | PT | n (%) | n (%) |
| Metabolism and nutrition disorders | Total | 21 (3.3) | 3 (2.1) |
| Ear and labyrinth disorders | Total | 17 (2.7) | 5 (3.6) |
| | Vertigo | 14 (2.2) | 4 (2.9) |
| Cardiac disorders | Total | 15 (2.3) | 7 (5.0) |
| | Ventricular extrasystoles | 0 (0.0) | 3 (2.1) |
| Infections and infestations | Total | 12 (1.9) | 6 (4.3) |
| Blood and lymphatic system disorders | Total | 6 (0.9) | 3 (2.1) |
| | Anemia | 2 (0.3) | 3 (2.1) |
| Eye disorders | Total | 3 (0.5) | 4 (2.9) |

^a Includes AEs coded to beta 2 microglobulin urine increased (13 sugammadex subjects, 2 placebo subjects) plus AEs coded to beta 2 microglobulin increased (2 sugammadex subjects, 2 placebo subjects).

Notes: This table includes AEs that occurred in at least 2.0% of a treatment group whether summarized by SOC or by PT. If a SOC is listed with no subordinate PT, there was no subordinate PT in that SOC that occurred in at least 2.0% of a treatment group.

6.4.3 Pooled Phase 1 – 3

Overall, 76.3% of all subjects exposed to any dose of sugammadex plus an NMBA (e.g., rocuronium) experienced at least one AE (Table 34). No dose response was apparent for the overall incidence of AEs. The overall incidence of AEs was 78.9% in the 2 mg/kg group, 88.7% in the 4 mg/kg group, and 80.8% in the 16 mg/kg group.

Adverse events that occurred in at least 2.0% of all sugammadex or placebo subjects who received an NMBA in pooled Phase 1-3 trials are summarized by SOC and PT in Table 34. The most frequent (i.e., $\geq 20.0\%$ incidence) SOCs in the total sugammadex group included Injury, Poisoning, and Procedural Complications (51.7% total sugammadex), Gastrointestinal Disorders (35.9% total sugammadex), and General Disorders and Administration Site Conditions (21.2% total sugammadex). No dose response was apparent for AE incidence according to SOC.

No dose trends were apparent for the incidence of individual AEs, with the exception of the PT anaesthetic complication which showed a trend for a dose response. The most frequent (i.e., $\geq 5.0\%$ incidence) AEs (according to PT) in the total sugammadex group included procedural pain, nausea, vomiting, pyrexia, headache, and constipation. Adverse events describing anaesthetic complications each

occurred in 3.0% of less of the total sugammadex group and included the PTs anesthetic complication (3.0%), airway complication of anaesthesia (0.6%), delayed recovery from anesthesia (0.3%), unwanted awareness during anesthesia (0.1%), and anaesthetic complication cardiac (0.1%).

Table 34 Adverse events by MedDRA SOC and PT in at least 2.0% of the total sugammadex group or the placebo group in pooled Phase 1-3 trials

| MedDRA 10.0 | | n (%) of subjects | | | | | | | | | | | Total sugammadex (N=1926) |
|--|----------------------------------|---|------------|------------|----------|------------|-----------|-----------|-----------|-----------|----------|------------|---------------------------|
| | | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
| SOC | PT | 0 (Placebo) (N=140) | <2 (N=265) | 2 (N=606) | 3 (N=9) | 4 (N=582) | 6 (N=28) | 8 (N=124) | 12 (N=39) | 16 (N=99) | 20 (N=4) | 32 (N=170) | |
| At least one AE | Total | 101 (72.1) | 206 (77.7) | 478 (78.9) | 8 (88.9) | 516 (88.7) | 12 (42.9) | 82 (66.1) | 26 (66.7) | 80 (80.8) | 3 (75.0) | 59 (34.5) | 1470 (76.3) |
| Injury, poisoning and procedural complications | Total | 56 (40.0) | 128 (48.3) | 339 (55.9) | 2 (22.2) | 423 (72.7) | 6 (21.4) | 46 (37.1) | 11 (28.2) | 55 (55.6) | 0 (0.0) | 0 (0.0) | 1010 (52.4) |
| | Procedural pain | 43 (30.7) | 94 (35.5) | 290 (47.9) | 0 (0.0) | 346 (59.5) | 0 (0.0) | 25 (20.2) | 0 (0.0) | 32 (32.3) | 0 (0.0) | 0 (0.0) | 787 (40.8) |
| | Procedural hypotension | 4 (2.9) | 5 (1.9) | 19 (3.1) | 1 (11.1) | 32 (5.5) | 1 (3.6) | 5 (4.0) | 3 (7.7) | 10 (10.1) | 0 (0.0) | 0 (0.0) | 76 (3.9) |
| | Incision site pain | 0 (0.0) | 4 (1.5) | 15 (2.5) | 0 (0.0) | 48 (8.2) | 0 (0.0) | 3 (2.4) | 0 (0.0) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 75 (3.9) |
| | Procedural hypertension | 4 (2.9) | 7 (2.6) | 28 (4.6) | 0 (0.0) | 25 (4.3) | 0 (0.0) | 3 (2.4) | 1 (2.6) | 8 (8.1) | 0 (0.0) | 0 (0.0) | 72 (3.7) |
| | Anaesthetic complication | 2 (1.4) | 7 (2.6) | 12 (2.0) | 1 (11.1) | 9 (1.5) | 2 (7.1) | 10 (8.1) | 7 (17.9) | 9 (9.1) | 0 (0.0) | 0 (0.0) | 57 (3.0) |
| | Procedural nausea | 5 (3.6) | 2 (0.8) | 25 (4.1) | 0 (0.0) | 23 (4.0) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 52 (2.7) |
| | Procedural complication | 3 (2.1) | 0 (0.0) | 14 (2.3) | 0 (0.0) | 15 (2.6) | 1 (3.6) | 2 (1.6) | 0 (0.0) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 37 (1.9) |
| | Postoperative wound complication | 3 (2.1) | 11 (4.2) | 6 (1.0) | 0 (0.0) | 11 (1.9) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 30 (1.6) |

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Table 34 Adverse events by MedDRA SOC and PT in at least 2.0% of the total sugammadex group or the placebo group in pooled Phase 1-3 trials (continued)

| MedDRA 10.0 | | n (%) of subjects | | | | | | | | | | | Total sugammadex (N=1926) |
|--|----------------|---|------------|------------|----------|------------|----------|-----------|-----------|-----------|----------|------------|---------------------------|
| | | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
| SOC | PT | 0 (Placebo) (N=140) | <2 (N=265) | 2 (N=606) | 3 (N=9) | 4 (N=582) | 6 (N=28) | 8 (N=124) | 12 (N=39) | 16 (N=99) | 20 (N=4) | 32 (N=170) | |
| Gastrointestinal disorders | Total | 41 (29.3) | 100 (37.7) | 229 (37.8) | 3 (33.3) | 272 (46.7) | 3 (10.7) | 30 (24.2) | 6 (15.4) | 33 (33.3) | 0 (0.0) | 15 (8.8) | 691 (35.9) |
| | Nausea | 25 (17.9) | 66 (24.9) | 142 (23.4) | 1 (11.1) | 188 (32.3) | 1 (3.6) | 18 (14.5) | 5 (12.8) | 22 (22.2) | 0 (0.0) | 4 (2.3) | 447 (23.2) |
| | Vomiting | 11 (7.9) | 36 (13.6) | 64 (10.6) | 2 (22.2) | 70 (12.0) | 1 (3.6) | 11 (8.9) | 3 (7.7) | 15 (15.2) | 0 (0.0) | 0 (0.0) | 202 (10.5) |
| | Constipation | 7 (5.0) | 12 (4.5) | 33 (5.4) | 0 (0.0) | 51 (8.8) | 0 (0.0) | 3 (2.4) | 0 (0.0) | 3 (3.0) | 0 (0.0) | 0 (0.0) | 102 (5.3) |
| | Flatulence | 0 (0.0) | 1 (0.4) | 16 (2.6) | 0 (0.0) | 28 (4.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 46 (2.4) |
| | Abdominal pain | 3 (2.1) | 9 (3.4) | 17 (2.8) | 0 (0.0) | 13 (2.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (2.0) | 0 (0.0) | 0 (0.0) | 41 (2.1) |
| | Diarrhoea | 4 (2.9) | 10 (3.8) | 17 (2.8) | 0 (0.0) | 13 (2.2) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 41 (2.1) |
| General disorders and administration site conditions | Total | 27 (19.3) | 59 (22.3) | 138 (22.8) | 3 (33.3) | 134 (23.0) | 5 (17.9) | 20 (16.1) | 5 (12.8) | 11 (11.1) | 2 (50.0) | 31 (18.1) | 408 (21.2) |
| | Pyrexia | 11 (7.9) | 29 (10.9) | 48 (7.9) | 1 (11.1) | 55 (9.5) | 1 (3.6) | 4 (3.2) | 0 (0.0) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 143 (7.4) |
| | Pain | 7 (5.0) | 10 (3.8) | 36 (5.9) | 2 (22.2) | 17 (2.9) | 2 (7.1) | 8 (6.5) | 5 (12.8) | 3 (3.0) | 0 (0.0) | 0 (0.0) | 83 (4.3) |
| | Chills | 3 (2.1) | 6 (2.3) | 26 (4.3) | 1 (11.1) | 28 (4.8) | 3 (10.7) | 4 (3.2) | 1 (2.6) | 4 (4.0) | 1 (25.0) | 0 (0.0) | 74 (3.8) |
| | Malaise | 3 (2.1) | 4 (1.5) | 1 (0.2) | 0 (0.0) | 3 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 9 (0.5) |
| Nervous system disorders | Total | 22 (15.7) | 41 (15.5) | 94 (15.5) | 3 (33.3) | 117 (20.1) | 1 (3.6) | 11 (8.9) | 0 (0.0) | 17 (17.2) | 1 (25.0) | 38 (22.2) | 323 (16.8) |
| | Headache | 11 (7.9) | 14 (5.3) | 42 (6.9) | 2 (22.2) | 56 (9.6) | 0 (0.0) | 5 (4.0) | 0 (0.0) | 10 (10.1) | 1 (25.0) | 8 (4.7) | 138 (7.2) |

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Table 34 Adverse events by MedDRA SOC and PT in at least 2.0% of the total sugammadex group or the placebo group in pooled Phase 1-3 trials (continued)

| MedDRA 10.0 | | n (%) of subjects | | | | | | | | | | | Total sugammadex (N=1926) |
|---|------------------------|---|------------|-----------|----------|-----------|----------|-----------|-----------|-----------|----------|------------|---------------------------|
| | | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
| SOC | PT | 0 (Placebo) (N=140) | <2 (N=265) | 2 (N=606) | 3 (N=9) | 4 (N=582) | 6 (N=28) | 8 (N=124) | 12 (N=39) | 16 (N=99) | 20 (N=4) | 32 (N=170) | |
| | Dizziness | 4 (2.9) | 11 (4.2) | 28 (4.6) | 0 (0.0) | 35 (6.0) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 6 (6.1) | 0 (0.0) | 6 (3.5) | 88 (4.6) |
| | Hypoaesthesia | 1 (0.7) | 7 (2.6) | 10 (1.7) | 1 (11.1) | 18 (3.1) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 3 (3.0) | 0 (0.0) | 1 (0.6) | 42 (2.2) |
| | Paraesthesia | 3 (2.1) | 3 (1.1) | 6 (1.0) | 0 (0.0) | 6 (1.0) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 1 (1.0) | 0 (0.0) | 1 (0.6) | 18 (0.9) |
| Investigations | Total | 13 (9.3) | 39 (14.7) | 87 (14.4) | 1 (11.1) | 81 (13.9) | 3 (10.7) | 8 (6.5) | 4 (10.3) | 7 (7.1) | 1 (25.0) | 0 (0.0) | 231 (12.0) |
| Respiratory, thoracic and mediastinal disorders | Total | 14 (10.0) | 40 (15.1) | 68 (11.2) | 3 (33.3) | 81 (13.9) | 4 (14.3) | 17 (13.7) | 3 (7.7) | 8 (8.1) | 0 (0.0) | 4 (2.3) | 228 (11.8) |
| | Pharyngolaryngeal pain | 8 (5.7) | 13 (4.9) | 28 (4.6) | 0 (0.0) | 43 (7.4) | 0 (0.0) | 2 (1.6) | 2 (5.1) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 93 (4.8) |
| Musculoskeletal and connective tissue disorders | Total | 9 (6.4) | 28 (10.6) | 61 (10.1) | 1 (11.1) | 82 (14.1) | 0 (0.0) | 4 (3.2) | 1 (2.6) | 15 (15.2) | 0 (0.0) | 2 (1.2) | 194 (10.1) |
| | Back pain | 3 (2.1) | 14 (5.3) | 26 (4.3) | 0 (0.0) | 31 (5.3) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 3 (3.0) | 0 (0.0) | 0 (0.0) | 76 (3.9) |
| Psychiatric disorders | Total | 6 (4.3) | 22 (8.3) | 52 (8.6) | 0 (0.0) | 83 (14.3) | 0 (0.0) | 3 (2.4) | 0 (0.0) | 10 (10.1) | 0 (0.0) | 0 (0.0) | 170 (8.8) |
| | Insomnia | 3 (2.1) | 11 (4.2) | 15 (2.5) | 0 (0.0) | 42 (7.2) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 75 (3.9) |
| Renal and urinary disorders | Total | 10 (7.1) | 16 (6.0) | 41 (6.8) | 1 (11.1) | 57 (9.8) | 2 (7.1) | 6 (4.8) | 1 (2.6) | 4 (4.0) | 0 (0.0) | 1 (0.6) | 129 (6.7) |
| | Dysuria | 5 (3.6) | 3 (1.1) | 8 (1.3) | 0 (0.0) | 4 (0.7) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 17 (0.9) |
| Skin and subcutaneous tissue disorders | Total | 10 (7.1) | 17 (6.4) | 44 (7.3) | 0 (0.0) | 45 (7.7) | 0 (0.0) | 7 (5.6) | 0 (0.0) | 6 (6.1) | 0 (0.0) | 2 (1.2) | 121 (6.3) |
| | Pruritus | 4 (2.9) | 4 (1.5) | 16 (2.6) | 0 (0.0) | 30 (5.2) | 0 (0.0) | 3 (2.4) | 0 (0.0) | 2 (2.0) | 0 (0.0) | 0 (0.0) | 55 (2.9) |
| Metabolism and nutrition disorders | Total | 3 (2.1) | 10 (3.8) | 48 (7.9) | 0 (0.0) | 37 (6.4) | 0 (0.0) | 3 (2.4) | 1 (2.6) | 2 (2.0) | 0 (0.0) | 0 (0.0) | 101 (5.2) |

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Table 34 Adverse events by MedDRA SOC and PT in at least 2.0% of the total sugammadex group or the placebo group in pooled Phase 1-3 trials (continued)

| MedDRA 10.0 | | n (%) of subjects | | | | | | | | | | | Total sugammadex (N=1926) |
|--|---------------------------|---|------------|-----------|----------|-----------|----------|-----------|-----------|-----------|----------|------------|---------------------------|
| | | Rocuronium, vecuronium, or pancuronium + sugammadex (mg/kg) | | | | | | | | | | | |
| SOC | PT | 0 (Placebo) (N=140) | <2 (N=265) | 2 (N=606) | 3 (N=9) | 4 (N=582) | 6 (N=28) | 8 (N=124) | 12 (N=39) | 16 (N=99) | 20 (N=4) | 32 (N=170) | |
| Vascular disorders | Total | 9 (6.4) | 16 (6.0) | 31 (5.1) | 2 (22.2) | 24 (4.1) | 1 (3.6) | 8 (6.5) | 5 (12.8) | 5 (5.1) | 0 (0.0) | 0 (0.0) | 92 (4.8) |
| | Hypertension | 4 (2.9) | 6 (2.3) | 13 (2.1) | 0 (0.0) | 9 (1.5) | 1 (3.6) | 3 (2.4) | 3 (7.7) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 36 (1.9) |
| Infections and infestations | Total | 6 (4.3) | 7 (2.6) | 26 (4.3) | 1 (11.1) | 22 (3.8) | 0 (0.0) | 3 (2.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (1.8) | 62 (3.2) |
| Blood and lymphatic system disorders | Total | 7 (5.0) | 7 (2.6) | 21 (3.5) | 0 (0.0) | 15 (2.6) | 2 (7.1) | 4 (3.2) | 0 (0.0) | 2 (2.0) | 0 (0.0) | 0 (0.0) | 51 (2.6) |
| | Ventricular extrasystoles | 3 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.1) |
| Cardiac disorders | Total | 3 (2.1) | 9 (3.4) | 23 (3.8) | 0 (0.0) | 15 (2.6) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 4 (4.0) | 0 (0.0) | 0 (0.0) | 52 (2.7) |
| | Anaemia | 3 (2.1) | 4 (1.5) | 19 (3.1) | 0 (0.0) | 12 (2.1) | 0 (0.0) | 1 (0.8) | 0 (0.0) | 3 (3.0) | 0 (0.0) | 0 (0.0) | 39 (2.0) |
| Reproductive system and breast disorders | Total | 1 (0.7) | 3 (1.1) | 9 (1.5) | 0 (0.0) | 12 (2.1) | 0 (0.0) | 4 (3.2) | 0 (0.0) | 2 (2.0) | 0 (0.0) | 1 (0.6) | 31 (1.6) |
| Ear and labyrinth disorders | Total | 5 (3.6) | 8 (3.0) | 7 (1.2) | 1 (11.1) | 7 (1.2) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 25 (1.3) |
| | Vertigo | 4 (2.9) | 6 (2.3) | 3 (0.5) | 1 (11.1) | 5 (0.9) | 0 (0.0) | 0 (0.0) | 1 (2.6) | 1 (1.0) | 0 (0.0) | 0 (0.0) | 17 (0.9) |
| Eye disorders | Total | 4 (2.9) | 2 (0.8) | 5 (0.8) | 0 (0.0) | 3 (0.5) | 1 (3.6) | 1 (0.8) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (3.5) | 18 (0.9) |

Notes: This table includes AEs that occurred in at least 2.0% of the total sugammadex group or the placebo group whether summarized by SOC or by PT. If a SOC is listed with no subordinate PT, there was no subordinate PT in that SOC that occurred in at least 2.0% of the total sugammadex group or the placebo group. Pancuronium was studied in 19.4.207

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6.5 Adverse events at least possibly trial-drug related

6.5.1 Sugammadex vs. neostigmine

The incidence of AEs judged by the Investigator to be related to trial medication was lower in sugammadex-treated subjects (18.4%) compared to neostigmine-treated subjects (25.1%). Of the 58 related AEs only 1 (vomiting) occurred at a 2-fold higher incidence in sugammadex-treated subjects compared to neostigmine-treated subjects. This sugammadex-related AE occurred at a low incidence (< 4%) and is typically seen in a post-surgical population.

6.5.2 Sugammadex vs. placebo

The incidence of AEs judged by the Investigator to be related to trial medication was slightly higher in sugammadex-treated subjects (13.3%) compared to placebo-treated subjects (7.9%). Of the 60 related AEs, only 1 (anesthetic complication) occurred at a 2-fold higher incidence in sugammadex-treated subjects compared to placebo-treated subjects. This sugammadex-related AE occurred at a low incidence (< 4%). The AE of anesthetic complication is discussed in greater detail in Section 6.10.2.

6.6 Deaths

There were no deaths related to the administration of sugammadex in the clinical trials.

Three subjects died after completing a sugammadex clinical trial: 2 sugammadex-treated subjects and one placebo-treated subject. All deaths were judged to be unrelated to trial medication by both the Investigator and the Sponsor; all three deaths are detailed below:

- A 65-year-old Caucasian female died 42 days after surgery and administration of 0.5 mg/kg sugammadex (Trial 19.4.203) from a combination of factors, including post-trial SAEs (myocardial infarction, cardiogenic shock, and pulmonary edema) that were judged by the Investigator to be unlikely related to trial medication.
- A 61-year-old Caucasian male died 18 days after surgery and administration of 2.0 mg/kg sugammadex (Trial 19.4.208B) due to a pulmonary embolus. According to the Investigator, thrombosis and embolus were complications of the subject's radical prostatectomy, and pelvic thrombosis was a known complication of surgery of the lower abdomen.
- A 73-year-old Caucasian male died 12 days after surgery and administration of placebo (Trial 19.4.309) due to cerebral edema and ventricular bleeding

with hydrocephalus. Autopsy results showed a lesion in the left middle cerebral artery that had been caused by the surgery during removal of a meningioma.

6.7 Serious adverse events

Overall, 5.1% of all subjects exposed to any dose of sugammadex plus an NMBA (e.g., rocuronium) experienced at least one SAE. Related SAEs (in the investigator's opinion) were reported in 8 total sugammadex subjects (i.e., in 0.4% of the total sugammadex group). Each was considered to be unrelated to the administration of sugammadex by the sponsor. The related SAEs included the following:

- Electrocardiogram QT corrected interval prolonged (one 2 mg/kg subject and two 4 mg/kg subjects),
- Bronchospasm (two 4 mg/kg subjects),
- Respiratory failure (one < 2 mg/kg subject),
- Hypotension (one 3 mg/kg subject), and
- Atrial fibrillation (one < 2 mg/kg subject).

A similar percentage of sugammadex subjects (5.8%) and placebo subjects (4.3%) experienced at least one SAE. Individual SAEs (by PT) most often occurred in only one subject in a treatment group. Those that occurred in more than one subject per group included electrocardiogram QT corrected (2.5% [16 subjects] sugammadex, 1.4% [2 subjects] placebo) and small intestinal perforation (0.3% [2 subjects] sugammadex, and no placebo subject).

Related (per the investigator) SAEs were reported in a similar percentage of sugammadex subjects (0.6%) and placebo subjects (0.7% placebo). These included electrocardiogram QT corrected interval prolonged in 2 sugammadex subjects and one placebo subject, hypotension in one sugammadex subject, and electrocardiogram QT prolonged in one sugammadex subject. The sponsor considered these SAEs to be unrelated to the administration of sugammadex.

In the controlled Phase 3 trials 19.4.301 and 19.4.302, the incidence of SAEs was similar for sugammadex (3.4%) and neostigmine (3.6%), and none were considered to be related to the trial medication by the investigator. Only two SAEs occurred in more than one subject per group: post procedural haemorrhage (2 sugammadex subjects, no neostigmine subject), and procedural complication (no sugammadex subject, 2 neostigmine subjects).

6.8 Discontinuations due to an adverse event

Overall, in the total sugammadex group (n=1926), very few sugammadex-treated subjects (< 1%, 4 subjects) discontinued from a trial due an AE; the AEs leading to trial discontinuation were NMB prolonged (2 subjects who received < 2.0 mg/kg), unwanted awareness during anesthesia (1 subject who received 16.0 mg/kg), and large intestine perforation, sepsis and electromechanical dissociation (in 1 subject who received who received 4.0 mg/kg). Two of these AEs, unwanted awareness during anesthesia (in the subject who received 16.0 mg/kg sugammadex) and NMB prolonged (in 1 of the 2 subjects who received < 2.0 mg/kg sugammadex), were judged by the Investigator to be related to trial medication. In the trials comparing sugammadex to neostigmine or placebo, one neostigmine-treated subject discontinued from a trial due to multiple AEs (Trial 19.4.302).

6.9 Adverse events by subgroups

Exploratory analyses of the incidence of AEs by the demographic subgroups of age (< 65 years vs. \geq 65 years), gender (male vs. female), race (Caucasian vs. non-Caucasian), and ethnicity (Hispanic or Latino vs. non-Hispanic or non-Latino) were performed. Subgroups were analyzed in the total sugammadex group and the pooled Phase 1 dataset. Data for the placebo and neostigmine groups did not contribute to these analyses due to the small sample size. The integrated safety database was also used to assess for possible interactions between sugammadex and concomitant medications which may displace the NMBA or potentiate neuromuscular blockade (i.e., by comparing subjects taking vs. not taking intravenous magnesium or peri-operative antibiotics).

In addition to conducting subgroup analyses using the integrated dataset, 2 prospective trials were conducted to specifically explore safety in different age groups (Trial 19.4.305 compared adult vs. geriatric subjects and Trial 19.4.306 compared adult vs. pediatric subjects), one explored safety in subjects with normal or impaired renal function (Trial 19.4.304), one explored safety in subjects with an increased risk for pulmonary complications during anesthesia (Trial 19.4.308), and one explored safety in subjects with cardiac disease (Trial 19.4.309).

6.9.1 Demographic characteristics using the integrated dataset

The main events of interest for exploration included anesthetic complications, dysgeusia, allergic reactions, hypersensitivity reactions, and re-occurrence of blockade or residual blockade recorded during neuromuscular monitoring or observed during recovery. Comparisons within subgroups were difficult due to the large imbalances in the number of subjects in each age, race, and ethnicity category,

as well as the fact that these events occurred at a very low incidence. Given these limitations, the incidence of these AEs in the total sugammadex group was similar with respect to age groups, gender, race, and ethnicity.

6.9.2 Concomitant medication usage using the integrated dataset

From extensive nonclinical trials, it was concluded that no clinically relevant interactions (either complexation and subsequent altered PK or PD, or displacement of the NMBA) would be expected with several drugs which are used during anesthesia or during emergency treatment. In addition, from the toxicology trials there were no indications suggesting that the potential complexation of endogenous molecules resulted in adverse effects. Nonetheless, the integrated safety database was also used to assess for possible interactions between sugammadex and the following concomitant medications, which may displace the NMBA or potentiate neuromuscular blockade: (1) intravenous magnesium (which can potentiate neuromuscular blockade); and (2) peri-operative antibiotics (which can potentiate neuromuscular blockade). The main comparisons of interest were re-occurrence of blockade, residual blockade (i.e., the AE of NMB prolonged), or other anesthetic complications in subjects from the total sugammadex group who were administered these concomitant medications.

Overall, AEs describing anesthetic complications or re-occurrence of NMB occurred at a low and similar incidence between subjects taking these concomitant medications vs. subjects not taking these medications. Of the 24 subjects who experienced re-occurrence of blockade or residual blockade based on TOF Watch SX[®] measurements (Section 6.10.1), one received intravenous magnesium and 7 received concomitant antibiotics. Potential drug interactions, as identified by the Investigator, were seen in three subjects, each of whom received 2.0 mg/kg sugammadex. The suspect medications were propofol and remifentanyl in 2 subjects and atracurium in the third subject.

6.9.3 Geriatric and pediatric subjects

Based on the results from Trials 19.4.305 and 19.4.306 the AE profile of sugammadex appears to be similar in adult subjects (< 65 years) vs. either pediatric subjects (≥ 28 days - ≤ 17 years) or geriatric subjects (≥ 65 years).

6.9.4 Renal function

Subjects with normal ($CR_{CL} \geq 80$ mL/min) or impaired ($CR_{CL} < 30$ mL/min) renal function were studied because sugammadex is predominantly cleared via the kidneys; therefore, renal impairment would be expected to increase subjects' exposure to sugammadex and the NMBA. In Trial 19.4.304, renally-impaired

subjects had a prolonged and 17-fold higher exposure to sugammadex and a prolonged and 4-fold higher exposure to rocuronium compared to subjects with normal renal function. Nonetheless, the safety profiles between subjects with normal renal function vs. subjects with impaired renal function were not appreciably different. This is an important finding also considering the fact that effective dialysis (using a high flux filter) of sugammadex and rocuronium was not consistently demonstrated in Trial 19.4.304.

6.9.5 Pulmonary and cardiac function

Overall, sugammadex (at doses of 2.0 mg/kg or 4.0 mg/kg) was shown to be both safe (and effective) in reversing a rocuronium-induced NMB when administered at the reappearance of T_2 in subjects diagnosed with or without a history of cardiac complication(s) (Trial 19.4.309). The results of this trial are of particular interest since cholinesterase inhibitor-based reversal agents like neostigmine must be used cautiously in subjects with cardiac disease. In Trial 19.4.308 which was conducted in subjects with pulmonary complications, sugammadex was also well tolerated in the majority of subjects. However, it should be noted that bronchospasm in subjects with bronchial hyperreactivity has been identified as an ADR (Section 6.12) as a result of 2 SAEs reported by 2 asthmatic patients who participated in this trial.

6.10 Additional safety findings

Events particularly relevant to the use of anesthesia (in general) and reversal agents (in particular) have been assessed during the sugammadex clinical development program. The safety issues of specific interest include:

- re-occurrence of blockade/residual blockade based on the TOF Watch SX[®] measurements;
- anesthetic complications; (which include the following preferred terms [with examples of verbatim terms]):
 - (1) anesthetic complication (movement [of a limb or the body], coughing during the anesthetic procedure or during surgery, grimacing, suckling the endotracheal tube, including AEs that in MedDRA versions prior to 10.0 were coded to the preferred term of “light anesthesia”),
 - (2) airway complications of anesthesia (coughing on induction, bucking, and spontaneous breathing),
 - (3) delayed recovery from anesthesia (delayed awakening from anesthesia or extended recovery from anesthesia),
 - (4) unwanted awareness during anesthesia (awareness during anesthesia, awake during operation), and
 - (5) anesthetic complication cardiac (changes in cardiac rate and rhythm).

- AEs associated with ventilation (i.e., preferred terms not specifically noted to involve an anesthetic complication); and
- allergic reactions.

6.10.1 Reoccurrence of blockade/residual blockade

During the clinical development program, 24 of 1926 subjects in the total sugammadex group had evidence of re-occurrence of blockade or residual blockade based on TOF Watch SX[®] measurements during the period of neuromuscular monitoring. Four of the 24 sugammadex subjects also reported clinical evidence of reoccurrence of blockade or residual blockade at recovery. In addition, two subjects reported clinical evidence of reoccurrence of blockade or residual blockade at recovery. This resulted in a total of 6 subjects (0.3%) with clinical evidence of reoccurrence of blockade or residual blockade. The majority (20) of the 24 cases of re-occurrence of blockade or residual blockade (based on neuromuscular monitoring) were reported after the administration of < 2 mg/kg sugammadex. At higher doses of sugammadex only 2 subjects had evidence of re-occurrence of blockade or residual blockade during neuromuscular monitoring (one subject received 2.0 mg/kg sugammadex, and the other received 16.0 mg/kg sugammadex), and only one had evidence of re-occurrence of blockade or residual blockade at recovery (subject received 2.0 mg/kg sugammadex).

In the pooled Phase 1-3 trials with a placebo group, where the NMBA was rocuronium or vecuronium and where doses of sugammadex ranged from < 2 mg/kg to 16 mg/kg, 11 (1.7%) sugammadex subjects and no placebo subject had evidence of re-occurrence of blockade or residual blockade during the period of neuromuscular monitoring. In these trials, a slightly higher percentage of sugammadex subjects had evidence of re-occurrence of blockade or residual blockade during neuromuscular monitoring after receiving vecuronium (3.5%) than after receiving rocuronium (1.3%). One of the 11 sugammadex subjects (a subject who received 0.5 mg/kg sugammadex) also had clinical evidence of re-occurrence of blockade or residual blockade at recovery, described as being unable to lift her head for more than 3 seconds upon arrival into the recovery room. In the pooled Phase 3 controlled Trials 19.4.301 and 19.4.302, where the NMBA was rocuronium or vecuronium and where doses of sugammadex were 2.0 mg/kg or 4.0 mg/kg, there were no cases of re-occurrence of blockade or residual blockade during the period of neuromuscular monitoring or at recovery.

Adverse events representative of re-occurrence of blockade or residual blockade include neuromuscular block prolonged, neuromuscular blockade, and re-occurrence of blockade. These AEs were reported in 7 of 1926 (0.4%) sugammadex-treated subjects (at doses ranging from 0.5 mg/kg to 16 mg/kg), 4 of 167 (2.4%) neostigmine-treated subjects, and in 0 of 140 (0%) placebo-treated subjects. The AEs were considered to be treatment-related by the Investigator in 3 of the 7 sugammadex-treated subjects and in 2 of the 4 neostigmine-treated subjects.

6.10.2 Anesthetic complications

Events of interest due to the administration of anesthesia included the overall category of anesthetic complications. Adverse events representative of anesthetic complications included the preferred terms anesthetic complication (used for verbatim terms such as movement of a limb or the body, coughing during the anesthetic procedure or during surgery, grimacing, suckling on the endotracheal tube, or light anesthesia), airway complication of anesthesia, delayed recovery from anesthesia, unwanted awareness during anesthesia, and anesthetic complication cardiac.

The individual AE of anesthetic complication included verbatim descriptions such as movement (of a limb or the body) or coughing during the anesthetic procedure or, during surgery, grimacing or suckling on the endotracheal tube. Anesthetic complication occurred at a low incidence (3.0%, 57 of 1926 subjects) in the total sugammadex group, and was judged to be related to trial medication in less than half (40%) of subjects who experienced the AE; 2 cases (< 1% overall) were severe. Anesthetic complication occurred most frequently during trials in which sugammadex was administered early during the surgical procedure (e.g., Trials 19.4.202, 19.4.205 and 19.4.206) thereby removing one of the components of balanced anesthesia. As a result, the level of anesthesia may not have been deep enough for the ongoing surgical procedure, resulting in the reported cases of anesthetic complications. In fact, in pivotal Trials 19.4.301 and 19.4.302, in which the timing of sugammadex administration was standardized for use in routine clinical settings (i.e., at the reappearance of T₂ and at 1-2 PTCs, respectively), no anesthetic complications were reported.

The individual AE of airway complication of anesthesia included verbatim descriptions such as coughing on induction, bucking, and spontaneous breathing. Airway complication of anesthesia occurred at a very low incidence (< 1%, 12 of 1926 subjects) in the total sugammadex group, and was judged to be related to trial medication in about 25% of subjects who experienced the AE; one case (< 1%

overall) was severe. In pivotal Trials 19.4.301 and 19.4.302, more neostigmine-treated subjects (2.4%) experienced airway complication of anesthesia compared to sugammadex-treated subjects (1.1%), indicating that sugammadex has a favorable safety profile relative to neostigmine with respect to airway complications due to anesthesia.

The remaining anesthetic complications, including delayed recovery from anesthesia (verbatim terms such as delayed awakening from anesthesia or extended recovery from anesthesia), unwanted awareness during anesthesia (verbatim terms such as awareness during anesthesia and awake during anesthesia), and cardiac anesthetic complications (verbatim term was “bradycardia, associated with recovery from anesthesia”), occurred at very low incidences (< 1%) in the total sugammadex group. Fewer than half of these AEs were judged by the Investigator to be related to sugammadex.

Based on these data, administration of sugammadex does not appear to result in significant complications during anesthesia. Although 3.0% of subjects in the total sugammadex group experienced a verbatim term coded to “anesthetic complication”, these typically occurred during trials in which sugammadex was administered early during the surgical procedure, thereby removing one of the components of balanced anesthesia. As a result, the level of anesthesia may not have been deep enough for the ongoing surgical procedure. Airway complications, delayed recovery from anesthesia, unwanted awareness during anesthesia, and cardiac-related anesthetic complications in sugammadex-treated subjects occurred at very low incidences and/or occurred at incidences that were comparable to or lower than incidences observed in neostigmine-treated subjects.

6.10.3 Adverse events related to ventilation

Adverse events related to ventilation encompass the following preferred terms that are not specifically noted to involve an anesthetic complication: dyspnea, oxygen saturation decreased, respiratory depression, wheezing, respiratory rate decreased, hypoxia, bradypnea, bronchospasm, hyperventilation, hypoventilation, apnea, respiratory disorder, respiratory failure, breath sounds abnormal, painful respiration, respiratory distress, respiratory rate increased, and tachypnea. Most of these AEs occurred at a very low incidence ($\leq 0.4\%$) in the total sugammadex group. Two occurred at an incidence of 1.0% or greater but were similar in incidence to placebo; these AEs were dyspnea (1.5% total sugammadex, 1.4% placebo) and oxygen saturation decreased (1.0% total sugammadex, 0% placebo).

Few occurrences overall were considered by the Investigator to be related to treatment with sugammadex: respiratory failure (related in 1 of 2 subjects); oxygen saturation decreased (related in 1 of 20 subjects); dyspnea (related in 2 of 29 subjects); wheezing (related in 1 of 6 subjects); and bronchospasm (related in 2 of 3 subjects).

Bronchospasm was reported as a (related) SAE in two subjects. Both subjects were asthmatic patients participating in Trial 19.4.308. One other subject, with a history without any known respiratory complications, experienced a bronchospasm reported as an AE of moderate severity and considered to be unlikely related by the investigator. There was one report of an AE with the PT obstructive airways disorder of which the relation to trial drug was indicated by the Investigator as "none". When all (S)AEs with the PTs bronchospasm, wheezing and obstructive airways disorder are pooled, the incidence was 0.5% (n=10) in all sugammadex subjects vs. 0% in placebo. Four of these patients were from Trial 19.4.308. The incidence of related (S)AEs according the Investigator in all sugammadex subjects was 0.2% (n=3).

6.10.4 Allergic reactions

Allergic or hypersensitivity reactions occurred at a very low frequency (< 1%) in the total sugammadex group. Of the AEs suggestive of allergic reactions or hypersensitivity (i.e., contact dermatitis, allergic pruritus, drug hypersensitivity or transfusion reaction), none were judged by the Investigator to be related to trial medication. There were no SAEs or discontinuations from the trial due to allergic reactions.

One healthy volunteer had a probable hypersensitivity reaction following his first exposure to sugammadex in Trial 19.4.106; the event resulted in discontinuation of the infusion of sugammadex. The reaction was self limiting and did not require treatment. Skin prick and intradermal tests were conducted and it was concluded that the subject was probably hypersensitive to sugammadex.

Six subjects in the thorough QTc Trials 19.4.105 (n=5) and 19.4.109 (n=1), showed signs of possible hypersensitivity to sugammadex (following the administration of 32 mg/kg sugammadex). In one case in Trial 19.4.109, the infusion of sugammadex was discontinued. The reaction was self limiting and did not require treatment.

6.11 Relationship of adverse events to treatment duration or dose

In order to assess for a possible dose response regarding AEs, the pooled Phase 1-3 dataset (26 trials) was utilized (total sugammadex group, n=1926). This dataset

provided sufficient sample size for each of the proposed marketing doses of 2.0 mg/kg (n=606), 4.0 mg/kg (n=582) and 16 mg/kg (n=99).

No dose response was apparent for the overall incidence of AEs in pooled Phase 1-3 trials; AE incidences in subjects who received 2, 4 or 16 mg/kg sugammadex was 78.9%, 88.7%, and 80.8%, respectively, compared to 72.1% in subjects who received placebo. A dose trend was observed for only one individual AE, anesthetic complication (2.0% [2 mg/kg], 1.5% [4 mg/kg], 9.1% [16 mg/kg]). Although these data indicate a dose relationship, the 16 mg/kg sugammadex dose group was the only one with a noticeable difference from placebo or the two lower sugammadex dose groups. This finding may be the result of the efficacy associated with this high dose at relatively light anesthesia (i.e., potent reversal of the NMB and the consequent loss of one of the components of balanced anesthesia).

In pooled Phase 1-3 trials, no dose trend was apparent for the overall incidence of related AEs (based on the Investigator's opinion); related AE incidences in subjects who received 2, 4 or 16 mg/kg sugammadex were 9.5%, 12.5%, and 15.2%, respectively, compared to 7.9% in subjects who received placebo. In addition, no dose trends were apparent for any of the individual related AEs. In the pooled Phase 1 dataset, however, a dose trend was observed for the overall incidence of related AEs (incidence in dose groups up to 16 mg/kg ranged from 0.0% to 19.9%, and in the higher dose groups ranged from 33.3% to 75.0%) and also for related occurrences of dysgeusia (incidences of 0.0% to 7.1% at doses up to 16 mg/kg, 25.6% at 32 mg/kg, and 66.7% at 96 mg/kg).

In pooled Phase 1-3 trials, there was no dose trend for the overall incidence of SAEs; SAE incidences in subjects who received 2, 4 or 16 mg/kg sugammadex were 7.3%, 4.8%, and 5.1%, respectively, compared to 4.3% in subjects who received placebo. No dose response was apparent for the incidence of any individual SAE. There were too few discontinuations due to AEs to judge dose response.

The highest sugammadex dose studied in the clinical development program was 96 mg/kg (n=12 in Trial 19.4.106; included in the pooled Phase 1 dataset). The most frequent AE in subjects who received this dose of sugammadex was dysgeusia (8 subjects, 66.7%). Other AEs in this dose group included headache (2 subjects, 16.7%), nausea (2 subjects, 16.7%), fatigue (2 subjects, 16.7%), pharyngolaryngeal pain (2 subjects, 16.7%), dizziness postural (1 subject, 8.3%), abdominal pain (1 subject, 8.3%), and micturition urgency (1 subject, 8.3%). No clinically relevant effects on vital signs, clinical laboratory tests, or ECGs were observed at this dose in Trial 19.4.106.

6.12 Adverse drug reactions

Based on the criteria defined in Section 6.1, the following ADRs have been identified:

- **Anesthetic complication:** In pooled Phase 1-3 trials, this AE occurred at nearly 6 times the incidence in the sugammadex group (8.0%) compared with the placebo group (1.4%), and it showed a trend towards a dose response. Also, Investigators frequently (in 21 of 52 cases [about 40%]) judged this AE to be related to treatment with sugammadex.
- **Dysgeusia:** In pooled Phase 1 trials, this AE occurred in the sugammadex treatment group at nearly 8 times the incidence in the sugammadex group (12.6%) compared with the placebo group (1.5%), and it showed a dose response. Most cases of dysgeusia (49 of 56) occurred at doses of sugammadex 32 mg/kg or higher. Also, Investigators judged each AE of dysgeusia to be related to treatment with sugammadex (or placebo).
- **Allergic reaction:** This AE is chosen as an ADR based on the documented allergic reaction of one subject from Trial 19.4.106, as well as the suspected hypersensitivity reactions of 6 Phase 1 subjects. Although the etiologies of these suspected hypersensitivity reactions have not yet been specifically identified, a causal relationship to sugammadex could not be excluded.
- **Re-occurrence of neuromuscular blockade or residual neuromuscular Blockade:** This event (reported in the sugammadex trials as the preferred terms “neuromuscular block prolonged”, “neuromuscular blockade”, or “re-occurrence of blockade”) is chosen as an ADR because it is a biologically plausible effect of lower doses of sugammadex (especially at doses less than 2 mg/kg).
- **Other: Bronchospasm:** In addition to the ADRs identified above, it has been decided to add the event bronchospasm in patients with bronchial hyperreactivity (such as asthmatics) to the labeling as an ADR. The incidence of bronchospasm in all sugammadex subjects (who also received an NMBA) was 0.2%. Bronchospasm was reported for two asthmatic patients as an SAE that the investigator considered to be possibly related to the use of sugammadex. According to the sponsor’s assessment these two SAEs were considered to be unlikely related to the administration of sugammadex. The reason for this is that in both cases there were circumstances that are more likely to have contributed to the observed event and which had a strong temporal relation with the events. Nevertheless, because of the severity of

this SAE in clinical practice and because a causal relationship can not be fully excluded, bronchospasm in patients with bronchial hyperreactivity (PT bronchospasm) is considered to be an ADR for sugammadex.

6.13 Clinical laboratory evaluations

Based on a review of clinical laboratory data for each Phase 1 trial, no clinically important effects of sugammadex were observed for hematology, biochemistry, or urinalysis analytes in Phase 1 subjects who were not anesthetized and who received no NMBA, or in Phase 1 subjects who received an NMBA in Trials 19.4.101 (Part II only), 19.4.108 and 19.4.109 (Groups A and F).

In subjects who received an NMBA in the pooled Phase 2 and 3 trials, observed changes in hematological parameters consistent with a population of surgical subjects. In general, subjects from all treatment groups showed decreases in hemoglobin, hematocrit, and red blood cell count, increases in total white blood cell count, increases in absolute neutrophil count, and decreases in absolute lymphocyte count, and little change in platelet count. No dose trends were observed for any of the hematology analytes, and the incidence of hematology-related AEs was very low overall.

In subjects who received an NMBA in the pooled Phase 2 and Phase 3 trials, the biochemistry results showed no clinically relevant effects of sugammadex on the liver or kidneys. The percentage of sugammadex- and placebo-treated subjects with markedly high values for aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, gamma glutamyltransferase (GGT), blood urea nitrogen (BUN), and creatinine was low and similar between the 2 treatment groups. Sugammadex- and placebo-treated subjects had similar post-baseline decreases in total protein and albumin, which was an appropriate finding in this surgical population. Creatine phosphokinase (CK) tended to increase similarly in all treatment groups, likely the result of muscular tissue trauma from the surgical procedures. Other biochemistry analytes, such as alkaline phosphatase, lactate dehydrogenase (LDH), haptoglobin, minerals and electrolytes, glucose, total cholesterol, and triglycerides, were also unaffected by the administration of sugammadex compared to placebo or neostigmine. No dose trends were observed for any of the biochemistry analytes, and the incidence of biochemistry-related AEs was very low overall.

Since sugammadex is excreted primarily through the kidneys, additional sensitive biomarkers of renal damage, including urinary beta-2-microglobulin, microalbumin, and N-acetyl glucosaminidase (NAG), were measured. There was no evidence of

acute or delayed renal toxicity after the administration of sugammadex. In the pooled Phase 1-3 trials, there was little post-baseline change overall within 24 hours after dosing for beta-2-microglobulin, urine creatinine, urine pH, or microalbumin (noncreatinine-dependent). Creatinine-dependent microalbumin increased similarly in sugammadex- and placebo-treated subjects, and no dose trend was apparent. N-acetyl glucosaminidase tended to decrease to a greater degree in sugammadex-treated subjects compared to placebo-treated subjects. Similar percentages of sugammadex- and placebo-treated subjects had markedly high values for beta-2-microglobulin, microalbumin, and NAG, and more sugammadex-treated subjects compared to placebo-treated subjects had markedly low values for NAG. At 2-4 weeks post-dose in Trial 19.4.304, there was no evidence of delayed renal toxicity in normal and renally-impaired subjects. There was little change from screening to follow-up in beta-2-microglobulin and urine creatinine, and in the renally-impaired subjects, median observed microalbumin and NAG values were lower at follow-up than at screening.

6.14 Vital signs, ECGs and other physical findings

6.14.1 Vital signs

No clinically important effects of sugammadex were observed on blood pressure, pulse rate, respiratory rate, body temperature, or body weight in Phase 1 subjects who were not anesthetized and who received no NMBA. There was an overall tendency for these subjects to have increased pulse rate starting at 3 hours post-baseline. However, the changes were generally similar in the total sugammadex group and the placebo group and no dose trend was observed.

In sugammadex subjects who received an NMBA, and at the 2 mg/kg and 4 mg/kg doses of sugammadex, there was a tendency for increased systolic blood pressure at 30 minutes post-dose. However, at the higher dose of 16 mg/kg, there was a tendency for decreased systolic blood pressure, diastolic blood pressure, and pulse rate through 30 minutes post-dose. While the reasons for these findings are not certain, they are thought to be artifactual and related to the timing of administration of the trial medications rather than an effect of sugammadex. No clinically relevant effects of sugammadex were observed on respiratory rate or body temperature.

Mean and median baseline pulse rate values were similar in the sugammadex group and the neostigmine group (mean: 65.4 bpm sugammadex vs. 65.6 bpm neostigmine; median 63 bpm sugammadex vs. 63 bpm neostigmine). In the sugammadex group, pulse rate decreased at 2 min and 5 min post-baseline; in the neostigmine group, pulse rate increased at each timepoint. At 2 min, 5 min, and 10

min post-baseline, mean and median changes from baseline were about 5 to 16 bpm higher in the neostigmine group than in the sugammadex group; at 30 min post-baseline, they were about 2 bpm (median absolute) to 3 bpm (mean absolute) higher in the sugammadex group than the neostigmine group. The mean percent (mean absolute) changes from baseline at each timepoint were as follows:

- 2 min: -2.7% (-1.9 bpm) sugammadex, 21.8% (13.7 bpm) neostigmine,
- 5 min: -1.7% (-1.3 bpm) sugammadex, 15.6% (9.8 bpm) neostigmine,
- 10 min: 1.5% (0.8 bpm) sugammadex, 9.5% (5.8 bpm) neostigmine, and
- 30 min: 8.3% (4.7 bpm) sugammadex, 4.5% (2.1 bpm) neostigmine.

Results were similar for the two subsets of subjects whose NMBA was rocuronium or vecuronium.

6.14.2 Electrocardiograms

Two prospective, thorough, QTc trials (Trials 19.4.109 and 19.4.105) demonstrated that therapeutic (4 mg/kg sugammadex) and supra-therapeutic doses (32 mg/kg of sugammadex alone and in combination with rocuronium or vecuronium) did not lead to QTc interval prolongations of regulatory concern (i.e., the one-sided upper 95% confidence limit of the largest time-matched mean difference in QTc change compared to placebo did not exceed 10 ms). Therefore, in the presence of assay sensitivity, the two thorough QTc trials were both negative according to the criteria of the ICH E14 guideline.

Pooled electrocardiographic data were also rigorously analyzed for treatment-related abnormalities, and the results were consistent with conclusions of the two thorough QTc trials. The analyses of pooled ECG data show that sugammadex has limited effects on the electrocardiogram of subjects with or without administration of an NMBA (e.g., rocuronium).

7. BENEFIT RISK ASSESSMENT

The data collected during the sugammadex clinical development program support the conclusion that sugammadex, a novel Selective Relaxant Binding Agent (SRBA), is safe and effective for routine reversal of a rocuronium- or vecuronium-induced NMB following the administration of: (1) 2.0 mg/kg at the reappearance of T_2 , a timepoint that correlates with a shallow NMB; (2) 4.0 mg/kg at 1-2 PTCs, a timepoint that correlates with profound NMB; and (3) 16.0 mg/kg at 3 minutes following a bolus dose of rocuronium when there is a clinical need for immediate reversal (e.g., management of a difficult airway).

Overall, the proposed indication for sugammadex is strongly supported by the safety and efficacy data presented. Clinical pharmacology trials thoroughly characterized the PK profile of sugammadex in anesthetized and non-anesthetized individuals, including subjects with impaired renal function. A sufficient number of dose-response trials were conducted in Phase 2 to allow for a careful determination of which sugammadex doses to investigate in Phase 3. A population PK-PD model was developed and validated to allow for the simulation of scenarios that were not studied during the clinical development program. This model allowed predictions to be made regarding whether drugs (other than the target NMBA) or endogenous molecules might interact with sugammadex; in addition, situations requiring the need to re-block with rocuronium following the use of sugammadex were simulated. The model also allowed for simulations in subjects with impaired hepatic function.

In terms of efficacy, nearly all 23 efficacy trials conducted during the program utilized the time to recovery of the T_4/T_1 ratio to 0.9 (which has been shown to correlate well with a safe recovery from a NMB) as the primary endpoint. Overall, efficacy was investigated in three anesthesia settings (i.e., reversal at the reappearance of T_2 [shallow NMB], reversal at 1-2 PTCs [profound NMB], and immediate reversal) following the administration of intubating or intubating plus maintenances doses of rocuronium and, to a lesser extent, vecuronium. In addition, the influence of the use of sevoflurane vs. propofol on the efficacy of sugammadex was also assessed. The safety of sugammadex was adequately characterized across all 30 trials through the reporting of AEs, and assessment of changes from baseline in clinical laboratory values, vital signs, and ECGs. In addition, events particularly relevant to the use of anesthesia (in general) and reversal agents (in particular) have been assessed (e.g., re-occurrence of blockade/residual blockade, anesthetic complications, ventilation AEs, and allergic reactions).

Overall, 4 of the 23 efficacy trials (Trials 19.4.301, 19.4.302, 19.4.303 and 19.4.310) provide substantial evidence of the efficacy and clinical benefits of sugammadex in the three aforementioned anesthesia settings.

Pivotal Trial 19.4.301 directly evaluated the efficacy of 2.0 mg/kg sugammadex vs. neostigmine in reversal (at the reappearance of T_2) of a NMB induced by rocuronium or vecuronium; Trial 19.4.310 evaluated the efficacy of sugammadex in reversal (at the reappearance of T_2) of a rocuronium-induced NMB vs. neostigmine in reversal (at the reappearance of T_2) of a cisatracurium-induced NMB. In both trials sugammadex resulted in statistically significant ($p < 0.0001$) and clinically relevant reductions in the (geometric) mean times to recovery of the T_4/T_1 ratio to 0.9 compared to neostigmine. Pooling results of all trials that assessed reversal (at the reappearance of T_2) of a rocuronium- or vecuronium-induced NMB provide supportive evidence to the individual results of Trials 19.4.301 and 19.4.310. In addition, no clinically relevant increases in recovery times that would require a sugammadex dose adjustment were seen in subjects who received a maintenance dose of the NMBA (compared with subjects who only received an intubating dose) or in subjects who received sevoflurane vs. subjects who received propofol.

Pivotal Trial 19.4.302 directly evaluated the efficacy of 4.0 mg/kg sugammadex vs. neostigmine in routine reversal of a profound block (i.e., at 1-2 PTCs) induced by either rocuronium or vecuronium. In this trial, sugammadex resulted in a statistically significant ($p < 0.0001$) and clinically relevant reduction in the (geometric) mean time to recovery of the T_4/T_1 ratio to 0.9 compared to neostigmine. Pooling results of all trials that assessed reversal of a profound rocuronium- or vecuronium-induced NMB provide supportive evidence to the individual results of Trial 19.4.302.

Trial 19.4.303 directly evaluated the efficacy of 16.0 mg/kg sugammadex in an immediate reversal setting (3 minutes following a NMB induced by 1.2 mg/kg rocuronium) compared to spontaneous recovery from a NMB induced by 1.0 mg/kg succinylcholine. In this trial, sugammadex resulted in a statistically significant ($p < 0.0001$) and clinically relevant reduction in the (geometric) mean time to recovery of T_1 to 10% compared to spontaneous recovery from succinylcholine (2.7 minutes faster). In the 1.2 mg/kg rocuronium + sugammadex group, T_4/T_1 ratios were also determined. Relative to the time of administration of rocuronium, the mean recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 4.4, 4.6 and 5.4 minutes, respectively; relative to the time of administration of sugammadex, the mean recovery times of T_4/T_1 ratios to 0.7, 0.8 and 0.9 were 1.3, 1.5, and 2.2 minutes.

Safety data collected across all 30 trials conducted during the clinical development program support the conclusion that sugammadex is generally safe and well

tolerated. The most commonly reported AEs (all AEs and related AEs) in sugammadex-treated subjects are routinely managed events that are typically seen in a surgical/post-surgical population. Two deaths occurred in sugammadex-treated subjects following their trial participation; neither death was considered to be related to sugammadex. The pattern and incidence of SAEs did not appear to be notably different in sugammadex-treated subjects compared with placebo- and neostigmine-treated subjects. Only 4 out of 1926 subjects treated with sugammadex experienced re-occurrence of blockade (based on TOF Watch SX[®] measurements) at the proposed marketed doses (2 subjects treated with 2.0 mg/kg and 2 subjects treated with 16.0 mg/kg); all other cases occurred at sub-optimal doses (< 2.0 mg/kg) of sugammadex.

The overall incidence of AEs and SAEs did not appear to be related to the dose of sugammadex administered. The only individual AE (irrespective of relationship) that appeared to be dose-related was anesthetic complication, and dysgeusia was the only related AE that appeared to be dose-related (among healthy non-anesthetized volunteers enrolled in the Phase 1 trials). With regard to anesthetic complication, the fact that the 16 mg/kg sugammadex treatment group was the only dose group whose incidence was notably higher relative to placebo suggests that this AE may be related to the efficacy associated with this high dose.

Although 3.0% of all subjects in the total sugammadex group experienced a verbatim term coded to “anesthetic complication”, these typically occurred during trials in which sugammadex was administered early during the surgical procedure, thereby removing one of the components of balanced anesthesia. As a result, the level of anesthesia may not have been deep enough for the ongoing surgical procedure. Airway complications, delayed recovery from anesthesia, unwanted awareness during anesthesia, and cardiac-related anesthetic complications in sugammadex-treated subjects occurred at very low incidences and/or occurred at incidences that were comparable to or lower than incidences observed in neostigmine-treated subjects. Few AEs (and SAEs) related to ventilation were reported. One subject (a healthy volunteer) had a possible allergic reaction following his first exposure to sugammadex, and 6 Phase 1 subjects showed signs of possible hypersensitivity to sugammadex, one of whom had a known allergy to penicillin.

As expected, although there were large imbalances in the numbers of subjects across demographic subgroups, the incidences of AEs of special interest (anesthetic complications, dysgeusia, allergic reactions, hypersensitivity reactions, and re-occurrence of blockade/residual blockade [i.e., the AEs that met the criteria established for an ADR; (see Section 6.12)] among subgroups who received sugammadex were similar with respect to age, gender, ethnicity, and race. Subjects

with impaired renal function (vs. subjects with normal renal function) were also studied because sugammadex is predominantly cleared via the kidneys; therefore, renal impairment would be expected to increase subjects' exposure to sugammadex and the NMBA. In Trial 19.4.304, renally-impaired subjects had a prolonged and 17-fold higher exposure to sugammadex and a prolonged and 4-fold higher exposure to rocuronium compared to subjects with normal renal function. Nonetheless, the safety profiles between subjects with normal renal function vs. subjects with impaired renal function were not appreciably different. This is an important finding given that effective dialysis was not consistently demonstrated in Trial 19.4.304. Nonetheless, the use of sugammadex in severe renally-impaired subjects (creatinine clearance < 30 mL/min) will be strongly discouraged.

Extensive data collected from nonclinical trials and the population PK-PD simulations identified 3 specific drugs (toremifene, flucloxacillin and fusidic acid) and a class of compounds (hormonal contraceptives) that may potentially interact with sugammadex. However, because no formal clinical interaction trials have been conducted in adults with sugammadex and other drugs, anesthesiologists should monitor subjects for any potential drug interactions once sugammadex is used in clinical practice.

In subjects who received a NMBA in the pooled Phase 2 and Phase 3 trials, observed changes in hematological parameters occurred as expected for a population of surgical subjects; no dose trends were observed for any of the hematology analytes, and the incidence of hematology-related AEs was very low overall. In addition, no dose trends were observed for any of the biochemistry analytes, and the incidence of biochemistry-related AEs was very low overall. Laboratory data indicative of kidney function showed no evidence of renal damage in subjects after the administration of sugammadex. In addition, biochemistry results showed no clinically important effects of sugammadex on the liver.

No clinically important findings related to the administration of sugammadex were observed on vital signs that would limit its use. Based on the two thorough QTc trials as well as the pooled Phase 1-3 data, it is unlikely that sugammadex will have a clinically important effect on the ECG.

The availability of sugammadex may allow clinicians to improve subject safety with the use of neuromuscular blocking drugs in five key areas, resulting in a favorable benefit/risk profile. First, in the immediate postoperative period, subjects need to breathe spontaneously and adequately, and a patent airway needs to be maintained. One of the complications of neuromuscular blockade is residual paralysis, which can interfere with a subject's spontaneous ventilation, possibly leading to hypoxia,

ventilatory and, subsequently, cardiac arrest. Despite this, the incidence of residual paralysis postoperatively remains unacceptably high, even in subjects who receive reversal agents. Research demonstrates that not only longer-acting neuromuscular blocking drugs but, even intermediate-acting neuromuscular blocking drugs, can be associated with residual paralysis, despite the administration of a reversal drug. In several trials with surgical patients, 25% of whom received reversal drugs, the incidence of residual paralysis, depending upon the TOF endpoint used, ranged from 13 to 47%. [43,44,45] Two series of surgical patients, 68 to 100% of whom received reversal drugs, still experienced residual paralysis at a rate of 41% to 88%. [46,47] The findings obtained during this development program demonstrate sugammadex effectively reverses rocuronium-induced NMB to a TOF ratio of 0.9, the accepted standard for safe extubation. As a result, sugammadex has the ability to attenuate and possibly eliminate residual NMB in the recovery room, thereby dramatically improving the safety of clinical anesthesia. During the Phase 3 trials, sugammadex has been shown to effectively and consistently reverse rocuronium- or vecuronium-induced NMB to a T_4/T_1 ratio of 0.9 within 3 minutes in the vast majority of subjects when administered either at the reappearance of T_2 (2.0 mg/kg) or at 1-2 PTCs (4.0 mg/kg). In these trials, mean reversal times with neostigmine were between 16 and 18 minutes when administered at the reappearance of T_2 and between 50 and 60 minutes when administered at 1-2 PTCs following rocuronium- or vecuronium-induced NMB.

Second, administration of a NMBA near the end of a surgical procedure can result in a significantly delayed subject recovery and the potential consequences of residual paralysis, given the inability of current reversal agents to completely antagonize such a blockade. However, a profound blockade is required for delicate surgeries such as microsurgery, neurosurgery, ophthalmic surgery, vascular surgery, and in some open abdominal surgeries and laparoscopic procedures. The availability of sugammadex provides clinicians with the ability and flexibility to maintain optimal surgical conditions until the very end of surgery for various surgical procedures because of the predictability of a rapid reversal of neuromuscular blockade, including a profound NMB. As demonstrated by pivotal Trial 19.4.302, administration of 4.0 mg/kg sugammadex at 1-2 PTCs (i.e., a profound NMB) resulted in mean recovery times of the T_4/T_1 ratio to 0.9 of 2.9 minutes and 4.5 minutes, respectively, following a rocuronium- or vecuronium-induced NMB compared with recovery times of 50.4 minutes and 66.2 minutes, respectively, following reversal with 70 μ g/kg neostigmine.

Third, the availability of sugammadex will also allow optimal and safe use of neuromuscular blockade in vulnerable patient populations. As previously discussed, the use of neostigmine in subjects with cardiac disease should be used with caution

as a result of its side effects. During Phase 3, a trial conducted in subjects with cardiac disease (Trial 19.4.309) demonstrated that sugammadex can be safely used in this special subject population group. It is also known that in clinical practice, hepatically-impaired subjects may receive lower and, therefore, suboptimal doses of rocuronium (0.3 mg/kg instead of 0.6 mg/kg or higher) because of concern for prolonged NMB in these subjects. Since sugammadex is cleared mainly via the kidney, it may be used safely in this subject population, and may allow the clinician to administer optimal doses of rocuronium. The dose-response curves of NMBA are not well-defined for subjects with muscle diseases. Sugammadex will likely be a more effective reversal agent than neostigmine in these patients due to its lack of direct neuromuscular effects. Additionally, for subjects with previously undiagnosed muscle disease who experience adverse events due to the administration of rocuronium or vecuronium during a surgical procedure, sugammadex provides a means of immediate reversal of the NMB.

Fourth, sugammadex will allow for easier management of the CICV scenario. In a CICV scenario, it is life-saving to immediately re-establish the subject's spontaneous ventilation by attempting to reverse neuromuscular blockade, even to a partial degree. As previously stated, acetylcholinesterase inhibitors such as neostigmine are unable to antagonize a profound NMB such as that required for endotracheal intubation and, therefore, are not effective as rescue agents in a CICV scenario.[1,2,3] Based on the results from Trial 19.4.303, reversal of a very profound rocuronium-induced NMB by 16 mg/kg sugammadex has been demonstrated. As a result, use of sugammadex in a CICV situation following rocuronium administration may prevent the need for emergency non-invasive airway ventilation including rigid bronchoscopy, combitube ventilation, or transtracheal jet ventilation, and may prevent the need for emergency invasive airway access such as surgical or percutaneous tracheostomy or cricothyrotomy. In situations where succinylcholine is used for intubation and a CICV scenario develops, there is no antagonist available. Furthermore, there is also evidence to suggest that even at the usual dose of 1.0 mg/kg, some subjects receiving succinylcholine may experience severe arterial oxygen desaturation before spontaneous recovery from the NMB occurs [38]. As described above, the results from Trial 19.4.303 support the conclusion that replacement of succinylcholine with a combination of rocuronium followed by sugammadex to reverse the neuromuscular blockade would potentially markedly reduce the morbidity and mortality caused by a CICV scenario.

The ability of sugammadex to quickly and consistently reverse a rocuronium-induced NMB gives the field of anesthesia the opportunity to replace succinylcholine, the current drug of choice for rapid sequence intubation despite serious disadvantages. For example, if a succinylcholine-induced NMB is prolonged for any reason (including

congenital pseudocholinesterase deficiency), there is no reversal agent available. There is both theoretical and clinical evidence that suggests that even at the usual dose of 1.0 mg/kg, succinylcholine may cause severe arterial oxygen desaturation before the subject is able to breathe spontaneously.[27,32,38] Succinylcholine is associated with a host of other complications, including cardiac dysrhythmias (sinus bradycardia, nodal rhythms, ventricular dysrhythmias and cardiac arrest), hyperkalemia, increased intraocular pressure, increased intragastric pressure, increased intracranial pressure, myalgias, and masseter spasm.[57,58,59] While an appropriate dose of rocuronium (1.0 – 1.2 mg/kg) has a very rapid onset of action that is comparable to that of succinylcholine, it has a much longer duration of action. Given the reversal agents currently available, one cannot quickly reverse a rocuronium-induced NMB. Since neostigmine cannot reverse a profound NMB, the availability of sugammadex will allow clinicians to benefit from the rapid onset of rocuronium, particularly in rapid sequence intubation, as well as the rapid and complete termination of the NMB with sugammadex. At appropriate doses, the rocuronium/sugammadex combination can produce a NMB whose total duration is even less than that produced by succinylcholine. As described above for Trial 19.4.303, sugammadex administered after rocuronium resulted in a mean recovery time of 4.4 minutes versus 7.1 minutes for spontaneous recovery after succinylcholine. Consequently, with the availability of sugammadex, in combination with rocuronium, succinylcholine can be avoided and its multiple associated complications eliminated.

In conclusion, sugammadex is one of the most innovative drugs to have entered the field of anesthesia in many years. Its novel mechanism of action does not result in stimulation of the cholinergic nervous system, thereby avoiding the undesired autonomic nervous system side effects associated with neostigmine and other similar drugs. Additionally, because of its mechanism of action, there is no need for concomitant administration of antimuscarinic drugs, drugs that carry their own unfavorable side effect profile. Due to the removal of the muscle relaxant from its site of action, sugammadex is able to reverse even very profound NMB, unlike currently available reversal agents. As a result of these findings, sugammadex has the potential to dramatically change the paradigm of anesthesia practice.

Appendix 1: Tabular Listing of Clinical Trials

| Trial identifier | Objective(s) of the trial | Trial design and type of control | Test product(s); Dosage regimen; Route of administration | Number of treated subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|------------------|--|--|---|-------------------------------|---|---|
| 19.4.004 | Possible effects of sugammadex on clinical chemistry analysis | In vitro clinical chemistry analysis | sugammadex | Samples from 6 subjects (M/F) | Healthy subjects | NA |
| 19.4.006 | Dialysability of sugammadex in presence and absence of rocuronium | In vitro dialysability trial | 100 µg / mL sugammadex; 30 µg / mL rocuronium | NA | NA | NA |
| 19.4.007 | Possible effects of Org 48302 on clinical chemistry analysis | In vitro clinical chemistry analysis | Org 48302 / sugammadex | Samples from 6 subjects (M/F) | Healthy subjects | NA |
| 19.4.101 | Safety, PK, renal excretion, dose-response and tolerability of sugammadex given alone (Part 1) and given 3 minutes after rocuronium (Part 2) | Randomized double-blind placebo-controlled single rising dose followed by a double-blind placebo-controlled crossover part | 0.1, 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv | 29 male subjects | Healthy subjects | Part 1: Single dose sugammadex / placebo Part 2: General anesthesia using 0.6 mg/kg rocuronium bromide, followed by single dose sugammadex / placebo |
| 19.4.102 | Safety, PK and dose-proportionality of sugammadex in Japanese and Caucasian subjects | Double blind, placebo-controlled single ascending iv dose trial | 1, 8 and 16 mg/kg sugammadex iv; Placebo | 28 subjects (M/F) | Healthy subjects | Three single doses of sugammadex in ascending order plus one interspersed placebo treatment |
| 19.4.105 | Effect of IV single doses of sugammadex on the QT/QTc interval and open label active control with moxifloxacin | Randomized double-blind placebo-controlled five-period cross-over trial | 4.0 and 32.0 mg/kg sugammadex iv; 400 mg moxifloxacin iv; neostigmine + glycopyrrolate: discount | 62subjects (M/F) | Healthy subjects | Single intravenous infusion |
| 19.4.106 | Safety and tolerability of high doses of sugammadex | Randomized double-blind placebo-controlled 4 periods ascending single dose trial | 32.0, 64.0 and 96.0 mg/kg sugammadex iv; Placebo | 12 subjects (M/F) | Healthy subjects | Single intravenous infusion |
| 19.4.107 | Excretion balance, metabolite profile and pharmacokinetics of sugammadex | Open non-randomized trial | 4.0 mg/kg sugammadex, 0.025 MBq/kg of ¹⁴ C | 6 male subjects | Healthy subjects | Single dose [¹⁴ C]-labeled sugammadex |

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| Trial identifier | Objective(s) of the trial | Trial design and type of control | Test product(s); Dosage regimen; Route of administration | Number of treated subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|-------------------------|--|--|--|-----------------------------------|--|------------------------------|
| 19.4.108 | Safety, tolerability and pharmacokinetics of sugammadex in combination with rocuronium or vecuronium | Open-label trial | 16, 20 and 32 mg/kg sugammadex iv; 1.2 mg/kg rocuronium iv; 0.1 mg/kg vecuronium iv | 16 subjects (M/F) | Healthy subjects | Single intravenous infusion |
| 19.4.109 | Effect of IV single doses of sugammadex/rocuronium, sugammadex/vecuronium and sugammadex alone on the QTc interval and open label active control with moxifloxacin | Randomized double-blind placebo-controlled six-period cross-over trial | 4.0 and 32 mg/kg sugammadex iv, 1.2 mg/kg rocuronium iv, 0.1 mg/kg vecuronium iv 400 mg moxifloxacin iv | 83 subjects (M/F) | Healthy subjects | Single intravenous infusion |
| 19.4.201 | Dose-response, PK/PD and safety of sugammadex after rocuronium | Randomized, placebo-controlled, parallel dose-finding trial | 0.5, 1.0, 2.0, 3.0 or 4.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium; Placebo | 27 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.202 | Dose-response, PK/PD and safety of sugammadex after rocuronium | Randomized, placebo-controlled, parallel dose-finding trial | 1.0, 2.0, 4.0, 6.0 or 8.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv; Placebo | 98 male subjects | Surgical subjects | Single bolus dose |
| 19.4.203 | Dose-response of sugammadex following deep block induced by rocuronium and safety | Randomized parallel dose-finding trial | 0.6 mg/kg rocuronium iv + maintenance dosing; 0.5, 1.0, 2.0, 4.0 or 6.0 mg/kg sugammadex iv | 30 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.204 | Dose-finding, efficacy and safety of 5 doses of sugammadex after rocuronium | Randomized assessor-blinded parallel dose-finding trial | 0.6 and 1.2 mg/kg rocuronium iv; 0.5, 1.0, 2.0, 4.0 or 8.0 mg/kg sugammadex iv | 43 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.205 | Dose-finding, safety and PK | Randomized, placebo-controlled dose-finding trial | 1.2 mg/kg rocuronium iv; 2.0, 4.0, 8.0, 12.0 or 16.0 mg/kg sugammadex iv; Placebo | 43 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.206 | Dose-response relation of sugammadex after rocuronium and safety | Randomized, placebo-controlled, parallel dose-finding trial | 2.0, 4.0, 8.0, 12.0 or 16.0 mg/kg sugammadex iv; 1.0 or 1.2 mg/kg rocuronium iv; Placebo | 173 subjects (M/F) | Surgical subjects | Single bolus dose |

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| Trial identifier | Objective(s) of the trial | Trial design and type of control | Test product(s); Dosage regimen; Route of administration | Number of treated subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|-------------------------|--|---|---|-----------------------------------|--|------------------------------|
| 19.4.207 | Dose-response of sugammadex after vecuronium, pancuronium or rocuronium, and safety, PK, and PK/PD after vecuronium or pancuronium | Partially randomized dose-finding trial | 0.6 mg/kg rocuronium iv, 0.1 mg/kg vecuronium iv, 0.1 mg/kg pancuronium iv; 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 mg/kg of sugammadex iv; Placebo | 98 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.208A | Safety of sugammadex after rocuronium or vecuronium in Japanese subjects | Randomized open-label prospective bridging, parallel dose-finding trial | 0.5, 1.0, 2.0, and 4.0 mg/kg sugammadex iv; 0.9 mg/kg rocuronium iv (optional maintenance doses 0.1-0.2 mg/kg); 0.1 mg/kg vecuronium iv (optional maintenance doses 0.02-0.04 mg/kg) | 98 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.208B | Efficacy, safety and PK of sugammadex after rocuronium or vecuronium in Caucasian subjects | Randomized open-label prospective bridging, parallel dose-finding trial | 0.5, 1.0, 2.0 or 4.0 mg/kg sugammadex iv; 0.9 mg/kg rocuronium iv (optional maintenance doses 0.1-0.2 mg/kg); 0.1 mg/kg vecuronium iv (optional maintenance doses 0.02-0.03 mg/kg); Placebo | 98 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.209A | Safety of sugammadex after rocuronium or vecuronium in Japanese subjects | Randomized open-label prospective bridging, parallel dose-finding trial | 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg sugammadex iv; 0.9 mg/kg rocuronium iv (optional maintenance doses 0.1-0.2 mg/kg); 0.1 mg/kg vecuronium iv (optional maintenance doses 0.02-0.04 mg/kg) | 99 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.209B | Efficacy and safety of sugammadex after rocuronium or vecuronium in Caucasian subjects | Randomized open-label prospective bridging, parallel dose-finding trial | 0.5, 1.0, 2.0, 4.0 and 8.0 mg/kg sugammadex iv; 0.9 mg/kg rocuronium iv (optional maintenance doses 0.1-0.2 mg/kg); or 0.1 mg/kg vecuronium iv (optional maintenance doses 0.02-0.03 mg/kg) | 101 subjects (M/F) | Surgical subjects | Single bolus dose |

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| Trial identifier | Objective(s) of the trial | Trial design and type of control | Test product(s); Dosage regimen; Route of administration | Number of treated subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|-------------------------|---|--|---|--|--|------------------------------|
| 19.4.210 | Efficacy of sugammadex after rocuronium in subjects on propofol or sevoflurane anesthesia, and evaluation of safety | Randomized, parallel group, comparative trial | 0.6 mg/kg rocuronium iv; 2.0 mg/kg sugammadex iv | 42 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.301 | Demonstrate faster recovery with sugammadex compared to neostigmine as reversal agents after rocuronium or vecuronium | Randomized, parallel group, comparative, active-controlled trial | 2.0 mg/kg sugammadex iv; 50 µg/kg neostigmine iv (premix with 10 µg/kg glycopyrrolate); single and maintenance dosing of rocuronium and vecuronium according to local treatment practice | 189 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.302 | Demonstrate faster recovery with sugammadex compared to neostigmine as reversal agents after maintenance dosing of rocuronium or vecuronium | Randomized, parallel group, comparative, active-controlled trial | 4.0 mg/kg sugammadex iv; 70 µg/kg neostigmine iv +14 µg/kg glycopyrrolate; 0.6 mg/kg rocuronium (optional maintenance doses 0.15 mg/kg); 0.1 mg/kg vecuronium (optional maintenance doses 0.015 mg/kg) | 157 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.303 | Demonstrate faster recovery with sugammadex compared to succinylcholine from rocuronium-induced NMB | Randomized, parallel group, comparative, active-controlled trial | 16.0 mg/kg sugammadex iv; 1.2 mg/kg rocuronium iv; 1.0 mg/kg succinylcholine | 110 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.304 | Efficacy, PK and safety of sugammadex after rocuronium in subjects with normal or impaired renal function | Parallel group comparative trial | 2.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv | 30 subjects (M/F) (15 patients / 15 control subjects) | Renal patients and surgical subjects | Single bolus dose |
| 19.4.305 | Efficacy, safety, and PK of sugammadex after rocuronium in geriatric subjects with adult subjects | Parallel group, comparative trial | 2.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv (optional maintenance doses 0.15 mg/kg) | 150 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.306 | Efficacy, safety and PK of sugammadex after rocuronium in pediatric and adult subjects | Randomized, placebo-controlled, parallel dose-finding trial | 0.5, 1.0, 2.0 and 4.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv; Placebo | 91 subjects (M/F) | Surgical subjects | Single bolus dose |

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Appendix 1: Tabular Listing of Clinical Trials

| Trial identifier | Objective(s) of the trial | Trial design and type of control | Test product(s); Dosage regimen; Route of administration | Number of treated subjects | Healthy subjects or diagnosis of patients | Duration of treatment |
|-------------------------|---|---|---|-----------------------------------|--|------------------------------|
| 19.4.308 | Safety and efficacy of sugammadex after rocuronium in pulmonary patients | Randomized, parallel group, comparative trial | 2.0 and 4.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv (optional maintenance doses 0.15 mg/kg) | 77 subjects (M/F) | Surgical subjects with pulmonary complications | Single bolus dose |
| 19.4.309 | Safety and efficacy of sugammadex after rocuronium in cardiac patients | Randomized, parallel group, placebo-controlled trial | 2.0 and 4.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv (optional maintenance doses 0.1-0.2 mg/kg); Placebo | 116 patients (M/F) | Surgical subjects with a cardiac disease | Single bolus dose |
| 19.4.310 | Demonstrate faster recovery from NMB with sugammadex after rocuronium as compared to neostigmine after cis-atracurium | Randomized, parallel group, active controlled comparative trial | 2.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv (with optional maintenance dosing); 0.15 mg/kg cis-atracurium iv (with optional maintenance dosing); 50 µg/kg neostigmine iv | 73 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.311 | Efficacy and safety of sugammadex after rocuronium when used at the end of surgical procedure following routine anesthesia | Open label trial | 4.0 mg/kg sugammadex iv; 0.6 mg/kg rocuronium iv (optional maintenance doses 0.15 mg/kg) | 197 subjects (M/F) | Surgical subjects | Single bolus dose |
| 19.4.312 | Efficacy of sugammadex after rocuronium continuous infusion in subjects on propofol or sevoflurane anesthesia, and evaluation of safety | Randomized, parallel group comparative, safety assessor-blinded trial | 0.6 mg/kg rocuronium bolus followed by continuous infusion 7 µg/kg/min iv; 4.0 mg/kg sugammadex iv | 51 subjects (M/F) | Surgical subjects | Single bolus dose |

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