Sugammadex

NDA 22-225
Anesthetic and Life Support Drugs Advisory Committee
March 11, 2008

Organon, a part of Schering-Plough Corporation
Sugammadex

- First in class – a selective relaxant binding agent that encapsulates rocuronium or vecuronium, preventing its action.

- Sugammadex is an innovative drug that will enable anesthesiologists to rapidly reverse shallow and profound neuromuscular block (NMB) induced by rocuronium or vecuronium.
Regulatory History

• Key FDA Interactions and Submissions
  – Pre-IND meeting (July 2003)
  – IND submission (August 2003)
  – End of Phase 2 meeting (May 2005)
  – Pre-NDA meeting (October 2006)
  – NDA submission (October 2007)
  – Acceptance of NDA and Priority Review classification (December 2007)

• Other FDA Interactions
  – Special Protocol Assessment – Pivotal trials (19.4.301 and 19.4.302)
  – Agreement of QTc protocol design
Sugammadex

This NDA was classified as a priority review, indicating that sugammadex has the potential to address an unmet medical need.
Sugammadex Is Unique:

- **First product than can reverse a profound neuromuscular block**
- **Can provide immediate reversal when required**
- **Avoids the need to use acetylcholinesterase inhibitors (AChEIs) and muscarinic antagonists**
Proposed Indication

- Sugammadex is indicated in adults for:
  - Routine reversal of shallow and profound neuromuscular blockade induced by rocuronium or vecuronium
  - Immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium
Dosing Recommendations

The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed

- **Routine Reversal:**
  - A dose of 2.0 mg/kg is only recommended if spontaneous recovery has occurred up to the reappearance of $T_2$ (shallow blockade) following rocuronium or vecuronium induced blockade.
  - A dose of 4.0 mg/kg is recommended if recovery has reached 1-2 post-tetanic counts (PTC) (profound blockade) following rocuronium or vecuronium induced blockade.
Dosing Recommendations (cont.)

• Immediate Reversal
  – A dose of 16.0 mg/kg is recommended 3 minutes following the administration of rocuronium*

* There are no data to support the use of sugammadex for immediate reversal following vecuronium induced blockade
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# List of Respondents

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<td><strong>Ronald D. Miller, M.D.</strong></td>
<td>Professor and Chairman, Department of Anesthesia and Perioperative Care</td>
<td>University of California, San Francisco, School of Medicine, San Francisco, CA</td>
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<tr>
<td><strong>Terri G. Monk, M.D.</strong></td>
<td>Professor, Department of Anesthesiology</td>
<td>Duke University Medical Center, Durham, NC</td>
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<td><strong>Scott Groudine, M.D.</strong></td>
<td>Professor of Anesthesiology</td>
<td>Albany Medical Center, Albany, NY</td>
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<td><strong>Harry K. Genant, M.D.</strong></td>
<td>Professor Emeritus</td>
<td>Departments of Radiology, Medicine and Orthopedic Surgery, University of California, San Francisco, CA</td>
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Unmet Medical Need

Ronald D. Miller, M.D.

Professor and Chairman,
Department of Anesthesia and Perioperative Care,
Professor of Cellular and Molecular Pharmacology

University of California, San Francisco, San Francisco, CA
Presentation Outline

• Role of neuromuscular blocking drugs (NMBDs) in general anesthesia
• Current pharmacologic (neostigmine) reversal of non-depolarizing neuromuscular blockade
• The need for an improved reversal drug
Role of Neuromuscular Blocking Drugs in General Anesthesia

- **Use of neuromuscular blocking drugs**
  - Facilitate endotracheal intubation (mechanical ventilatory support)
  - To provide skeletal muscle relaxation (optimal surgical conditions)

- **NMBDs carry the risk of postoperative residual neuromuscular blockade**
  - Important to reverse NM Block
The Ideal Reversal Drug

- Minimizes risk of residual paralysis
- Eliminates side effects associated with neostigmine and muscarinic antagonists
- Provides rapid reversal in minutes
- Enables the reversal of profound NMB
  - Which will provide the possibility of flexible dosing of the NMBDs
- Alternative to succinylcholine in combination with a fast onset NMBD
The Postoperative Period

Postoperative Neuromuscular Block

Is It a Real Problem?
Critical Respiratory Events in the PACU*

- Upper airway obstruction
- Inadequate ventilation
- Hypoxemia
- Incidence varies from 0.8 to 6.9%

Causes (Anesthetic Variables) of Critical Respiratory Events in PACU*

- Residual neuromuscular blockade
- Opioids
- Emergency surgery
- Long duration of surgery
- Abdominal surgery

* Arbous et al: Anesthesiology 2005; 102:257-68
  Murphy et al: Anesth Analgesia 2008 (In press)
Residual Paralysis

- Incidence of residual paralysis remains a serious clinical concern despite the use of intermediate-acting NMBDs and administration of neostigmine.
Current Pharmacologic Reversal of NMB

• Only available products are AChEIs (e.g., neostigmine)
  – Indirect mechanism of action
  – Potential for postoperative reappearance of NMB
  – Wide variability in time required for complete reversal of NMB

• To manage the side effects of neostigmine
  – Co-administration of muscarinic antagonists (e.g., glycopyrrolate)
    • Side effects of muscarinic antagonists
      – Cardiovascular
      – Matching two drugs
Problems with Neostigmine/Glycopyrrolate Combinations

- Ineffective in reversing profound NMB
- Cardiac arrhythmias: tachycardia or bradycardia
- Combination of two powerful cardiovascular drugs
  - Is the combination correct for each patient?
  - Errors – how many are reported?

Flexible Dosing of the NMBA

• As current reversal drugs are unable to reverse profound NMB
  – May prevent flexible NMBD dosing

• A future drug should allow reversal (in minutes) at any depth of block

• Provides the possibility to continue the NMBD until the end of the procedure and reverse as needed
An Alternative to Succinylcholine?
Problems with Succinylcholine

- Hyperkalemia
- Malignant hyperthermia (trigger)
- Occasional irreversible prolonged neuromuscular block
- Cardiac arrhythmias
- Muscle pain
- Biochemical changes
Alternative to Succinylcholine

• Despite its side effect profile, succinylcholine is still widely used because of its fast onset and short duration.

• Rocuronium, followed by an improved reversal drug, can produce a NMB with rapid onset and short duration.
The Medical Need for an Improved Reversal Drug

• An improved reversal drug should quickly and completely reverse NMB, irrespective of the depth of blockade and without the need to manage the side effects of currently available reversal drugs

• In combination with a fast onset NMBD, an improved reversal drug may provide an alternative to succinylcholine

• The properties of an improved reversal drug will offer real and important patient benefits
Mechanism of Action of Sugammadex

Anton Bom, M.D., Ph.D.
Senior Research Fellow, Pharmacology
Overview

• Design of sugammadex
• Mechanism of action of sugammadex
• Selectivity
• Speed of reversal
• Pharmacokinetics
• Assessment of drug-drug interactions
Recovery from Neuromuscular Blockade:

- Decrease in NMBA concentration
  - Metabolism
  - Excretion
- Increase in acetylcholine concentration
New Concept

- Inactivation of the NMBA
- Rapid chemical interaction between NMBA and encapsulating agent
Cyclodextrins

- Starting point for encapsulating agents
- Used since 1953 as solubilising agents
- Low affinity complexes with lipophilic drugs
Cyclodextrins

\(\gamma\)-cyclodextrin: 8 sugar molecules forming a rigid ring with a central lipophilic cavity
Properties of Cyclodextrins

• Very water-soluble
• Not metabolized
• Renally excreted
Properties of Rocuronium
Design of Reversal Agent

$\gamma$-cyclodextrins can be modified to increase affinity for rocuronium
Rocuronium – Sugammadex Complex
Mechanism of Action

<table>
<thead>
<tr>
<th>affinity (K&lt;sub&gt;A&lt;/sub&gt; M&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>rocuronium</th>
<th>vecuronium</th>
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<tbody>
<tr>
<td>γ-cyclodextrin</td>
<td>13,200</td>
<td>1,176</td>
</tr>
<tr>
<td>sugammadex</td>
<td>25,000,000</td>
<td>10,000,000</td>
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## Selectivity

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<th>NMBA</th>
<th>$K_A$ value (megaM$^{-1}$)</th>
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<tr>
<td>Rocuronium</td>
<td>25.0</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>10.0</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>2.6</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.005</td>
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<tr>
<td>Succinylcholine</td>
<td>0.000</td>
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Speed of Reversal

- Extracellular volume
- Rocuronium
- Blood vessel
sugammadex

rocuronium

rocuronium

rocuronium

rocuronium
sugammadex
Opposite Direction of Flow of Molecules

- sugammadex
- sugammadex
- rocuronium
- rocuronium
Conclusion

• Sugammadex rapidly encapsulates rocuronium and vecuronium

• Reversal of any depth of neuromuscular blockade, including profound blockade

• Sugammadex is inactive against non-steroidal neuromuscular blocking agents, like succinylcholine and cisatracurium
Pharmacokinetics & Drug-drug Interactions

Anton Bom, M.D., Ph.D.
Senior Research Fellow, Pharmacology
Basic PK of Sugammadex

- Volume of distribution: ≈ 12-15 L
- Plasma half-life: ≈ 2.2 h
- Clearance: ≈ 91 mL/min (≈ GFR)
- No metabolism
Basic PK of Sugammadex

- Low plasma protein binding
- Blood-brain barrier penetration (< 3% in rat)
- Placental transfer (< 2-6% in rat and rabbit)
Plasma Concentration – Time Plot

- ROCURONIUM
  - 0.6 mg/kg
  - 2.0 mg/kg

- SUGAMMADEX

at re-appearance of T2
Evaluation of Potential Drug-drug Interaction

- Sugammadex has been specifically designed to form high affinity complexes with steroidal NMBAs
- Sugammadex is almost exclusively renally excreted
- Sugammadex has no potential to cause drug-drug interaction (=DDI) due to inhibition or induction of drug metabolizing enzymes
- Mechanism of potential DDI is through binding of sugammadex to other compounds, which cannot be assessed via traditional DDI studies
Two Types of Binding Interactions

• Displacement:
  – Another drug binding to sugammadex, displacing NMBA, causing rise in free NMBA concentration
    → Potential risk of re-occurrence of NMB

• Capturing:
  – Sugammadex binding another drug, decreasing its free concentrations
    → Potential risk of reduction in efficacy
Interaction Strategy Involving:

- Isothermal titration microcalorimetry (determination of binding affinity $K_\text{d}$)
- \textit{In vitro} tissue studies
- \textit{In vivo} animal studies
- Pharmacokinetic-Pharmacodynamic interaction model
- Clinical considerations
Drugs Selected for Determination of Binding Affinity for Sugammadex

- Drugs used in anesthesia
- Drugs / hormones with steroidal nucleus
- Drugs acting on steroidal receptors
- Drugs most commonly prescribed

> 300 compounds tested
For Most Drugs which Are Used during Anesthesia $K_A$ Values Were Determined

- The highest affinity constant was for remifentanil, which was 0.2% of the affinity constant of sugammadex with rocuronium
Conservative Scenario Applied for Drug-drug Interaction Evaluation

- RECEPTOR
- PROTEIN
- ALBUMIN
- TRANSCORTIN
- SEX HORMONE BINDING GLOBULIN
Drugs with Possible Displacement Potential

- **Toremifene**: An orally administered non-steroidal Selective Estrogen Receptor Modulator used for the treatment of metastatic breast cancer

- **Flucloxacillin**: Narrow spectrum beta-lactam penicillin (not available in the US)

- **Fusidic acid**: A steroidal bacteriostatic agent (not available in the US)
Drugs with Possible Capture Potential

- For hormonal contraceptives clinically relevant capturing interaction could not be excluded

- Progestogens and estrogens show some affinity for sugammadex (affinity 2-22% of that of rocuronium)

- In preclinical studies no indications suggesting an interaction with steroid hormones in doses up to 500 mg/kg/day
Hormonal Contraceptives

• A conservative PK simulation predicted a decrease of 34% in unbound progestogen exposure (AUC)

• This decreased exposure is similar to taking an oral contraceptive > 12h too late

• Guidance provided in Package Insert
Conclusion

• The affinity constants for more than 300 compounds tested confirmed the highest affinities for steroid (like) compounds.

• For the compounds discussed, the available data suggest that an interaction cannot be excluded. This will be addressed in the Package Insert.

• No clinical evidence of interactions was found during clinical trials in approximately 2000 patients.
Non-clinical Safety Overview

Diels van den Dobbelsteen, Ph.D.
Principal Toxicologist
Summary of Non-clinical Safety

• Sugammadex’ non-clinical safety profile is comparable to modern cyclodextrins (CDs) used intravenously as excipients in various products.

• Sugammadex’ dose level is considerably lower as compared to CDs used as excipients.

<table>
<thead>
<tr>
<th>Sugammadex</th>
<th>Sulfobutylether-β-CD in Vfend®</th>
<th>Hydroxypropyl- β-CD in Sporanox®</th>
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<tr>
<td>Single dose</td>
<td>± 7-10 daily doses</td>
<td>± 7 daily doses</td>
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<tr>
<td>0.12, 0.24, 0.96 g/day*</td>
<td>9-13.5 g/day*</td>
<td>16-32 g/day*</td>
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* Based on 60 kg body weight
Determination of Safety Margins

Drug concentration at No Observed Effect Level in rat

versus

Drug concentration at the clinical dose in humans

• Bone and teeth: local exposure

• Other: systemic exposure
Summary of Non-clinical Safety

• Sugammadex:
  – No intrinsic pharmacological activity
  – No genotoxicity
  – No relevant reproductive toxicity or teratogenicity
  – At high/repeated doses: kidney, urinary bladder, alveolar macrophages, hemolysis, however findings show a wide safety margin (> 25)

...1 observation for this cyclodextrin: binding to mineralized tissues such as bones and teeth in rat

→ Does not represent a risk for human
No Anticipated Risk for Human for Effects on Bone and Teeth

- Large rat-to-human safety margin:
  - No effect on bone: 70-1000
  - Effect on juvenile rat molar only after 4 wks of daily dosing (accumulation): 48-480

- No effect on bone dev’t/ossification in embryo-fetal development and juvenile animal studies
  - No expected risk from fetal or pediatric exposure
  - No expected risk for impairment of fracture or post operative bone repair
Extensive Investigations on Bone and Teeth

- Studies on young adult and juvenile rats
  - More sensitive model than humans

- Embryofetal development studies (rats and rabbits)
  - Processes important in skeletal tissue formation are very similar to processes important in bone healing

- Localization, reversibility and quantification of binding

- Prevention of binding by rocuronium
Non-clinical Safety Studies on Bone and Teeth

Parameters and Endpoints

- Regular and special histopathology of femur, scapula
- Bone micro architecture ($\mu$CT) of femur
- Bone quality (cortical and trabecular strength)
- Biochemical markers of bone turnover
- Skeletal screening in rat and rabbit teratology

- Tooth color and development
- Bone structure, quality and turnover, growth and development, modeling and remodeling
Results of Distribution Studies

Sugammadex’ binding:

- Reversible (terminal $t_{1/2}$ rat bone: 70-250 days)
- To rat teeth is 3-5 fold less compared to bone
- Extracellular at site of mineralization: hydroxyapatite
  - Significantly reduced by presence of NMBA
  - Not to epiphyseal disc & (joint) cartilage

Bone apposition in femur continues as normal
Results of Distribution Studies (cont.)

Extent of binding depends on age/rate of bone turnover:

- The (juvenile) rat is a most sensitive species
- Species with lower turnover ➔ less sensitive

Dose not recovered in man = 0-15% ➔ estimated concentration human bone at max. 4.5 µg per gram bone/teeth
Young Adult Rat: No Adverse Effects

- No effect on bone at single dose ≤ 500 mg/kg
- Bone concentration rat : human = 313 : 4.5 µg/g

⇒ Safety Margin: 70

- 4-week rat toxicity study: no effect on bone histopathology and bone mineral density with sugammadex at > 5000 µg/g

⇒ Safety Margin: > 1000
Juvenile Rat: No Adverse Effects on Bone

- No adverse effect on bone at ≤ 500 mg/kg/day for 4 weeks
- Bone concentration juvenile rat : human ≈ > 5000 : 4.5 μg/g

⇒ Safety Margin: > 1000
Wide Safety Margins for Effects on Tooth Color and Enamel Formation

- No effect on tooth color young adult rat and dog

**Juvenile rat:**
- No effect in teeth after single dose of 500 mg/kg

  ➤ Safety Margin 48

- No effect in molars at ≤ 120 mg/kg/day for 4 weeks

  ➤ Safety Margin 480

- Effect dose for rat molars: 500 mg/kg/day for 4 weeks
- Effect is reversible (8 weeks)
- Rat molar is most representative for man, rat incisor is overly sensitive*

No Anticipated Risk for the Pediatric Population

- No adverse effect on bone parameters: safety margin: > 1000
- Effect on tooth development: safety margin: 48-480
- Other target organs: comparable sensitivity and no developmental toxicity: safety margin: 32

-No specific risks to pediatric population in clinical use
No Anticipated Risk for the Embryo/Fetus

- Embryofetal development study in rat and rabbit: no specific effect on skeletal development and ossification.
- Estimated skeletal exposure in rat fetus: 450-600 µg/g
- Worst case human fetus bone/teeth concentration: 4.5 µg/g (low placental transfer not accounted)

Safety Margin: > 100-133

No expected risk for the human fetus
No Anticipated Risk for Patients with Fractures or Surgical Injury to Bone

- Processes important in skeletal tissue formation in utero are very similar to processes important in bone healing*:
  - No impact on fetus = no impact on bone healing: safety margin > 100-133

- **No toxicity or functional impairment** to processes important in normal bone physiology:
  - safety margins 70-1000

- Sugammadex is **not** pharmacologically active

- Sugammadex is administered before mineralization occurs in callus \(\rightarrow\) **no binding to early callus**

→ **Fracture healing should not be impaired**

Conclusions

• Sugammadex’ non-clinical safety profile shows wide safety margins relative to human exposure

• Extensive set of 15 non-clinical safety and drug disposition studies characterized risks for mineralized tissues

• The non-clinical models used are relevant and very sensitive
Conclusions (cont.)

- Conservative estimates of safety margins for effects on bone and teeth are very wide (> 48-1000)
- Presence of NMBA further increases the safety margins
- This addresses the use in sensitive patients, e.g. healing fractures, unborn child, pediatric, and potential repeated use

At clinical exposure there are no data to suggest risk for adverse effects on any target organ for all life stages
Efficacy Highlights

Patrick Boen, M.D.
Senior Director Medical Services, Anesthesia
Presentation Outline

• Goals of the Clinical Development Program

• Program standards
  – Inclusion and Exclusion Criteria
  – Neuromuscular Monitoring

• Dose Finding Trials – Phase II

• Phase III Clinical Trial Program

• Efficacy Conclusions
Goals of the Clinical Development Program

Routine Reversal

• Shallow Blockade
  – Reversal at reappearance of $T_2$

• Profound Blockade
  – Reversal at 1-2 Post Tetanic Counts (PTC)

Immediate Reversal

• Reversal at 3 minutes
Sugammadex Clinical Development Program

All Clinical Trials Sugammadex Clinical Development Program (N=30; 1973 subjects)

Phase I (N=7)
- Routine Reversal at Reappearance of T2 (N=7)
  - Phase III (N=2)
    - 19.4.301 (Pivotal)
    - 19.4.310
  - Special Populations (N=5)
    - 19.4.304
    - 19.4.305
    - 19.4.306
    - 19.4.308
    - 19.4.309

Phase II (N=12)
- Routine Reversal at 1-2 PTCs or at 15 mins (N=1)
  - Phase III (N=1)
    - 19.4.302 (Pivotal)
  - Immediate Reversal (N=1)
    - 19.4.303

Phase III (N=11)
- Other Efficacy Studies (N=2)
  - 19.4.309
  - 19.4.311
  - 19.4.312
Inclusion Criteria

Phase II and III Trials

- ASA class 1-xx (2, 3 or 4)
- Adult patients (except for Trial 19.4.306) undergoing general anesthesia, requiring an NMBA
- Surgical procedures in the supine position
- Have given written informed consent
Exclusion Criteria

Phase II and III Trials

- Neuromuscular disorders, significant renal dysfunction (except for Trial 19.4.304), history of malignant hyperthermia

- Allergy to narcotics, muscle relaxants or other medication used during general anesthesia

- Medications known to interfere with the NMBA

- Contraindications for the comparator
Exclusion Criteria
Phase II and III Trials

• Pregnancy
  – Childbearing potential not using appropriate methods of birth control
  – Breast-feeding

• Prior participation in the trial

• Participation in another clinical trial, not pre-approved by Organon, part of Schering-Plough Corp
Neuromuscular Monitoring
Methods of Stimulation

- **Train of Four (TOF)** – measurement of more shallow blockade
  - Ratio of the fourth ($T_4$) to the first ($T_1$) muscle response

  \[ \frac{T_4}{T_1} = \text{TOF ratio} \]

  0.5Hz, 5 sec

- **Post-Tetanic Count (PTC)** – measurement of deeper blockade
  - Tetanic stimulation, followed by single twitch

  50Hz, 5 sec
  0.1-1Hz

  \[ \text{Tetanic stimulation} \rightarrow \text{Single Twitch} \rightarrow \text{PTC} = \begin{cases} 2 \\ 4 \end{cases} \]
Dose Finding Trials – Phase II
Dose Selection Criteria

• Minimize the risk for inadequate recovery

• Clinically significant reduction in recovery time (< 5 min)

• Minimize potential for confusion in dosing; i.e. a limited choice of recommended doses should be preferred
Time to Recovery $T_4/T_1$ to 0.9
Sugammadex at $T_2$ after Rocuronium – Phase II

Median time to $T_4/T_1$ 0.9 (min)

Sugammadex dose (mg/kg)
Time to Recovery $T_4/T_1$ to 0.9
Sugammadex at $T_2$ after Vecuronium – Phase II
Time to Recovery $T_4/T_1$ to 0.9
Sugammadex at 1-2 PTC after Rocuronium – Phase II

Profound Block

Median time to $T_4/T_1$ 0.9 (min)

Sugammadex dose (mg/kg)
Time to Recovery $T_4 / T_1$ to 0.9
Sugammadex at 1-2 PTC after Vecuronium – Phase II

![Graph showing the relationship between Sugammadex dose (mg/kg) and median time to $T_4/T_1$ 0.9 (min)]
Time to Recovery $T_4/T_1$ to 0.9
Sugammadex at 3-5 min after Rocuronium – Phase II

Immediate Reversal

- Median time to $T_4/T_1$ 0.9 (min)
- Sugammadex dose (mg/kg)
Phase II Conclusions

• **Doses:**
  - 2 mg/kg at reappearance of $T_2$
  - 4 mg/kg at 1-2 PTC / 15 min
  - 16 mg/kg for immediate reversal after 1.2 mg/kg rocuronium

• **Dose related speed of recovery**

• **Dose related reversal of depth of NMB**
Types of Phase III Trials

Comparative

• vs. Neostigmine
  – Shallow Block
  – Profound Block

• vs. succinylcholine

• vs. cisatracurium

Routine Use

• 15 min after last dose of rocuronium
Types of Phase III Trials

Special Populations

- 19.4.304 Renal
- 19.4.305 Elderly
- 19.4.308 Pulmonary
- 19.4.309 Cardiac
Pivotal Trials 19.4.301 and 19.4.302

Objectives

- **Trial 19.4.301**
  Reversal of *shallow* rocuronium or vecuronium-induced neuromuscular blockade with sugammadex versus neostigmine

- **Trial 19.4.302**
  Reversal of *profound* rocuronium and vecuronium-induced blockade with sugammadex compared with neostigmine
## Recovery of TOF Ratio to 0.9*

* Trial 19.4.301

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agent</th>
<th>Sugammadex 2.0 mg/kg</th>
<th>Neostigmine 50 mcg/kg</th>
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<tbody>
<tr>
<td><strong>Rocuronium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>1.4*</td>
<td>17.6</td>
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<tr>
<td>Range</td>
<td>0.9-5.4</td>
<td>3.7-106.9</td>
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<tr>
<td><strong>Vecuronium</strong></td>
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<td>Median (minutes)</td>
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<tr>
<td>Range</td>
<td>1.2-64.2</td>
<td>2.9-76.2</td>
</tr>
</tbody>
</table>

* P<0.0001 versus neostigmine

Shallow Block
Recovery after Sugammadex 2.0 mg/kg or Neostigmine 50 mcg/kg at Reappearance of $T_2$
## Recovery of TOF Ratio to 0.9*

*Trial 19.4.302*

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agent</th>
<th>Sugammadex 4.0 mg/kg</th>
<th>Neostigmine 70 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rocuronium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>2.7*</td>
<td>49.0</td>
</tr>
<tr>
<td>Range</td>
<td>1.2-16.1</td>
<td>13.3-145.7</td>
</tr>
<tr>
<td><strong>Vecuronium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>47</td>
<td>36</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>3.3*</td>
<td>49.9</td>
</tr>
<tr>
<td>Range</td>
<td>1.4-68.4</td>
<td>46.0-312.7</td>
</tr>
</tbody>
</table>

* P<0.0001 versus neostigmine
Recovery after Sugammadex 4.0 mg/kg or Neostigmine 70 mcg/kg at 1-2 PTC

% of patients returning to TOF 0.9

Time (min)

Roc / sug
Vec / sug
Roc / neo
Vec / neo

Profound Block
Conclusions – Trials 19.4.301 and 19.4.302

- Faster recovery compared with neostigmine after rocuronium and vecuronium induced block
- No cases of residual paralysis or reoccurrence of blockade during the period of neuromuscular monitoring or at recovery
- Unique ability to rapidly reverse both shallow and profound rocuronium and vecuronium-induced NMB
Trial 19.4.303
Rocuronium/Sugammadex vs. Succinylcholine

- **Objective:**
  Reversal of profound rocuronium-induced neuromuscular block with sugammadex is significantly faster than recovery from succinylcholine.
Efficacy Variables

- **Primary efficacy variable**
  - Time from the start of administration of rocuronium or succinylcholine to recovery of $T_1$ to 10%

- **Secondary efficacy variables**
  - Time from the start of administration of rocuronium or succinylcholine to recovery of $T_1$ to 90%
  - Clinical signs of recovery
Design Elements

- Study in emergency patients impossible
  - Ethical considerations
  - Enrollment (true emergency is very rare)

- High dose of rocuronium (1.2 mg/kg)

- Primary ($T_1$ to 10%) and secondary efficacy variables ($T_1$ to 90%) allow for comparison of full recovery profile

- $T_1$ 10% at the thumb corresponds to ~ 25% at the diaphragm

- Reversal at 3 minutes includes 60-90 seconds onset time, leaving 90-120 seconds for 2 intubation attempts
Patient Allocation and Study Design

Randomized (n=115)

Rocuronium 1.2 mg/kg
n=57

Sugammadex 16 mg/kg at 3 min

Time to recovery to T1 10%

Time recovery to T1 90%

Succinylcholine 1.0 mg/kg
n=58

Spontaneous recovery
Trial 19.4.303, Mean (2xSEM) Times to T₁ 10% and 90%

![Graph showing mean (2xSEM) times for Rocuronium, Sugammadex, and Succinylcholine compared to T₁ 10% and 90%.](image)

- **Rocuronium**
- **Sugammadex**
- **Succinylcholine**

*P<0.0001 versus succinylcholine treatment group*
Trial 19.4.303, Time from T1 10% to 90% within Subject (ITT group)
Conclusions – Trial 19.4.303

- Reversal of profound rocuronium-induced (1.2 mg/kg) neuromuscular block with sugammadex was significantly faster than spontaneous recovery from succinylcholine.

- Sugammadex offers the possibility of immediate reversal of rocuronium-induced block in a possible scenario of failed intubation.
Recovery of TOF Ratio to 0.9
Comparison with Cisatracurium / Neostigmine (Trial 19.4.310)

Objective:
Faster recovery from neuromuscular blockade with sugammadex after rocuronium than with neostigmine after cisatracurium

<table>
<thead>
<tr>
<th>Neuromuscular Blocking Agent</th>
<th>Rocuronium and Sugammadex 2.0 mg/kg</th>
<th>Cisatracurium and Neostigmine 50 mcg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>1.9*</td>
<td>7.2</td>
</tr>
<tr>
<td>Range</td>
<td>0.7-6.4</td>
<td>4.2-28.2</td>
</tr>
</tbody>
</table>

* P<0.0001 versus cisatracurium / neostigmine
Recovery after Rocuronium / Sugammadex 2.0 mg/kg and Cisatracurium / Neostigmine 50 mcg/kg at Reappearance of T₂
Recovery of TOF Ratio to 0.9
*Routine Reversal (Trial 19.4.311)*

**Objective:**
Sugammadex given at least 15 min after last dose of rocuronium is effective in reversing neuromuscular blockade

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>4.0 mg/kg Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>177</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>1.8</td>
</tr>
<tr>
<td>Range</td>
<td>0.7 - 22.3</td>
</tr>
</tbody>
</table>
Conclusions – Trials 19.4.310 and 19.4.311

- Reversal significantly faster than neostigmine reversed cisatracurium-induced NMB (Trial 19.4.310)

- Efficacious also when administered at least 15 min after last dose of rocuronium
Special Population Trials

- Efficacy and safety (and PK in some trials) of rocuronium-induced neuromuscular blockade in:
  - Renally impaired subjects vs. normal renal
  - Adult and Geriatric subjects
  - Subjects with pulmonary and cardiac risk factors
## Similar Recovery Times with Sugammadex in Impaired vs. Normal Renal Function

*Trial 19.4.304*

<table>
<thead>
<tr>
<th>Group</th>
<th>Impaired Renal Function</th>
<th>Normal Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\text{CR}_{\text{CL}} &lt; 30 \text{ ml/min}$</td>
<td>$\text{CR}_{\text{CL}} \geq 80 \text{ ml/min}$</td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Median (minutes)</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Range</td>
<td>1.2-3.7</td>
<td>0.9-3.1</td>
</tr>
</tbody>
</table>
## Recovery of TOF Ratio to 0.9

*Geriatrics (Trial 19.4.305)*

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Adult</th>
<th>Geriatics</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64 yrs</td>
<td>2.2</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>(n=48)</td>
<td></td>
<td>(n=62)</td>
<td>(n=102)</td>
</tr>
<tr>
<td>65-74 yrs</td>
<td>2.6</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>(n=62)</td>
<td></td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>≥ 75 yrs</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=102)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (min)</th>
<th>Adult</th>
<th>Geriatics</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64 yrs</td>
<td>2.2</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>(n=48)</td>
<td></td>
<td>(n=62)</td>
<td>(n=102)</td>
</tr>
<tr>
<td>65-74 yrs</td>
<td>2.6</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>(n=62)</td>
<td></td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>≥ 75 yrs</td>
<td>3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=102)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Range (min)</th>
<th>Adult</th>
<th>Geriatics</th>
<th>Subtotal</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-64 yrs</td>
<td>1.2 - 7.4</td>
<td>0.9 - 8.8</td>
<td>1.0 - 9.9</td>
</tr>
<tr>
<td>(n=48)</td>
<td></td>
<td>(n=62)</td>
<td>(n=102)</td>
</tr>
<tr>
<td>65-74 yrs</td>
<td>0.9 - 8.8</td>
<td>1.0 - 9.9</td>
<td>0.9 - 9.9</td>
</tr>
<tr>
<td>(n=62)</td>
<td></td>
<td>(n=40)</td>
<td></td>
</tr>
<tr>
<td>≥ 75 yrs</td>
<td>1.0 - 9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>0.9 - 9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=102)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Recovery of TOF Ratio to 0.9

*Pulmonary and Cardiac Risk Factors (Trials 19.4.308 and 19.4.309)*

<table>
<thead>
<tr>
<th>Trial 19.4.308 – Pulmonary</th>
<th>Sugammadex 2.0 mg/kg</th>
<th>Sugammadex 4.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Median (min)</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.8 - 12.0</td>
<td>0.7 - 11.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial 19.4.309 – Cardiac</th>
<th>Placebo</th>
<th>Sugammadex 2.0 mg/kg</th>
<th>Sugammadex 4.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Median (min)</td>
<td>34.7</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Range</td>
<td>16.9 - 66.5</td>
<td>0.9 - 6.9</td>
<td>0.7 - 3.2</td>
</tr>
</tbody>
</table>
Conclusions – Special Population Trials

- Rapid and complete recovery from rocuronium-induced NMB in normal and renally impaired patients
- Both doses (2 and 4 mg/kg) were efficacious in pulmonary and cardiac patients
- No clinical evidence of residual NMB or re-occurrence of blockade
Overall Conclusions for Efficacy

• Clear dose response

• Consistent efficacy results over all trials

• Much faster recovery with sugammadex as compared to neostigmine

• No dose adjustments necessary in special patient populations
Safety Summary
Safety Overview

Background Information
• Demographics
• Exposure to sugammadex
• Special population studies

Safety Data
• AEs and SAEs
  – Specific AEs
  – Other safety parameters
• Laboratory changes
## Demographics

*Sugammadex + an Aminosteroidal NMBA*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic/Category</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>n</td>
<td>140</td>
<td>1845</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>51 (16)</td>
<td>50 (16)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Min. - max.</td>
<td>19 - 86</td>
<td>18 - 92</td>
</tr>
<tr>
<td><strong>Age (n [%])</strong></td>
<td>n</td>
<td>140</td>
<td>1845</td>
</tr>
<tr>
<td></td>
<td>18 - 64 yr</td>
<td>113 (81)</td>
<td>1491 (81)</td>
</tr>
<tr>
<td></td>
<td>65 - 74 yr</td>
<td>15 (11)</td>
<td>232 (13)</td>
</tr>
<tr>
<td></td>
<td>≥ 75 yr</td>
<td>12 (9)</td>
<td>122 (7)</td>
</tr>
<tr>
<td><strong>Gender (n [%])</strong></td>
<td>n</td>
<td>140</td>
<td>1845</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>85 (61)</td>
<td>966 (52)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>55 (39)</td>
<td>879 (48)</td>
</tr>
</tbody>
</table>
Exposure to Sugammadex
*Phase I-III*

**In Association with Rocuronium or Vecuronium**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Rocuronium</th>
<th>Vecuronium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1509</td>
<td>398</td>
</tr>
</tbody>
</table>

**Sugammadex Only (Volunteer Studies)**

<table>
<thead>
<tr>
<th>Exposures (subjects)</th>
<th>Total</th>
<th>443 (196)</th>
</tr>
</thead>
</table>

Does not include study 19.4.108
## Exposure to Sugammadex
### Special Populations

<table>
<thead>
<tr>
<th>Special Population</th>
<th>Medical History</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Impaired</td>
<td>Dedicated Study (19.4.309)</td>
<td>76</td>
</tr>
<tr>
<td>Renal Impaired (GFR &lt; 80 ml/min)</td>
<td>Baseline Blood Sample</td>
<td>226</td>
</tr>
<tr>
<td></td>
<td>GFR acc. Cockcroft</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dedicated Study (19.4.304)</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary Impaired</td>
<td>Medical History</td>
<td>136</td>
</tr>
<tr>
<td></td>
<td>Dedicated Study (19.4.308)</td>
<td>68</td>
</tr>
<tr>
<td>Hepatic Impaired</td>
<td>Medical History</td>
<td>77</td>
</tr>
</tbody>
</table>
ASA Class Allocation

ASA I: 44.5%
ASA II: 43.1%
ASA III: 12.4%
ASA IV: 0.1%
Exposure to Sugammadex

Datasets

- All Clinical Trials Sugammadex Clinical Development Program (N=1973)
  - Pooled Phase I-III Dataset (N=1845)
    - Sugammadex vs. Neostigmine Dataset (N=179 vs 167)
    - Sugammadex vs. Placebo Dataset (N=640 vs 140)
  - Pooled Phase I Dataset (N=196)

Sugammadex vs. Neostigmine Dataset (N=179 vs 167)
Sugammadex vs. Placebo Dataset (N=640 vs 140)
Special Populations

- Healthy volunteer cross-over trial (19.4.106)
  - 13 subjects treated, 12 completed
  - Randomized to placebo, sugammadex 32 mg/kg, 64 mg/kg and/or 96 mg/kg
- Sugammadex up to doses of 96 mg/kg was safe and well tolerated
Special Populations (cont.)

- Renal impaired (19.4.304)
  - 15 subjects with creatinine clearance of < 30 ml/min
  - 15 subjects with creatinine clearance of ≥ 80 ml/min
  - Each received dose of 2.0 mg/kg of sugammadex at reappearance of $T_2$
  - The safety profile in renally impaired subjects was not appreciably different from control subjects
  - Clearance 17-fold reduced in severe renal failure
  - Patients were followed up 2-4 weeks

- As measure of caution the use in patients with severe renal impairment is strongly discouraged
Special Populations (cont.)

- Cardiac impaired (19.4.309)
- Pulmonary complications (19.4.308)

The use of sugammadex was safe and effective in these populations.
Special Populations (cont.)

• Bronchospasm (study 19.4.308)
  – Two cases were reported as SAEs in asthmatic patients (considered possibly related by the investigator)
    1. Bronchospasm shortly after reversal, around the time of extubation, successfully treated with terbutaline
    2. Bronchospasm approximately one hour after reversal, close to the time of extubation, successfully treated with albuterol
Safety Data

AEs and SAEs
## Sugammadex vs. Placebo: Incidence of Subjects with at Least one AE

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex* (N=640)</th>
<th>Placebo (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>68.3%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>66.7%</td>
<td>69.8%</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>75.4%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

* Followed by administration of rocuronium or vecuronium
Sugammadex vs. Placebo: Most Frequently Reported AEs (at Least 2.0%)

- Procedural pain
- Nausea
- Vomiting
- Anesthetic complication
- Pain
- Pyrexia
- Procedural hypotension
- Pharyngolaryngeal pain
- Headache
- Chills
- Back pain
- Cough
- Procedural hypertension
- Electrocardiogram QT corrected interval prolonged
- Constipation
- Rocuronium or vecuronium +

- Sugammadex (N=640)
- Placebo (N=140)
Incidence of AEs, Dose Response
*Pooled Phase I-III (N=1891)*

- Overall incidence of AEs
  - 2 mg/kg group: 78.9%
  - 4 mg/kg group: 88.7%
  - 16 mg/kg group: 80.8%

- The overall incidence of AEs does not show a dose-response relationship with the exception of Anesthetic Complication.
Serious Adverse Events (SAEs)

- There were no deaths related to the administration of sugammadex.
- Placebo controlled trials: similar percentage of sugammadex subjects (5.8%) and placebo subjects (4.3%) experienced at least one SAE.
Serious Adverse Events (SAEs) (cont.)

- Pooled Phase I-III:
  - 5.1% of all subjects exposed to any dose of sugammadex plus an NMBA experienced at least one SAE.
  - The overall incidence of SAEs did not show a dose response relationship:
    - 2 mg/kg group: 7.3%
    - 4 mg/kg group: 4.8%
    - 16 mg/kg group: 5.1%
Specific AEs

- Anesthetic complication
- Dysgeusia
- Hypersensitivity
Anesthetic Complication

Including:

- Movement (of a limb or the body)
- Coughing during the anesthetic procedure or during surgery
- Grimacing, sucking on the endotracheal tube
- Light anesthesia
Anesthetic Complication AEs Mostly Related to Trial Design

**Incidence of Anesthetic Complications**

<table>
<thead>
<tr>
<th>Treatment Timeline</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Phase 2 Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Timeline</td>
<td>5.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3 Trial</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Treatment Timeline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EOP = End of procedure</td>
<td></td>
</tr>
</tbody>
</table>

**Incidence by Phase and Treatment**

- **Sugammadex**: 3.0%, 5.9%, 0.7%
- **Neostigmine**: 0.5%, —, 0.5%
- **Placebo**: 1.4%, 2.4%, 0%

**EOP = End of procedure**
Dysgeusia

- Pooled Phase I trials
  - Sugammadex group 12.6% versus 1.5% in the placebo group
  - 100% reported as related
  - 49 of 56 cases occurred at doses of 32 mg/kg sugammadex or higher
  - Short lasting and self limiting

- Pooled Phase II and III trials
  - 6 cases (only 2 were considered related)
Hypersensitivity: Case Description

- Subject had a first exposure to sugammadex in a volunteer study (Study 19.4.106)
- Infusion stopped after 8.4 mg/kg sugammadex due to:
  - Paresthesia
  - Visual disturbance
  - Rash
  - Stomach discomfort
  - Palpitations
  - Nausea
  - Tachycardia
  - Flushing
- Reaction was self limiting, no treatment required
- The subject had no known history of allergy
Hypersensitivity: Case Description

• A slight increase in serum tryptase, suggestive for a possible allergy was found

• Follow-up skin tests:
  – Skin prick tests (SPT): Inconclusive
  – Intradermal skin test (IDT): The subject showed wheals > 50% of the wheal size of histamine (positive control) accompanied by flares at 1:1.000 dilution
  – Conclusion skin tests: Subject probably hypersensitive to sugammadex

• Additional skin testing: No evidence for sensitization to betalactam antibiotics (e.g. penicillin) or breakdown products
Skin Test Study 19.4.110

Study Design

Single center, placebo-controlled study, investigating hypersensitivity with sugammadex, via skin prick and intradermal tests.

• **Primary Objectives:**
  – To evaluate the skin prick test (SPT) and intradermal skin test (IDT) in healthy volunteers not previously exposed to sugammadex.
  – To investigate the sugammadex hypersensitivity status of exposed alleged hypersensitive volunteers of the 19.4.105, 19.4.106 and 19.4.109 trials.
Skin Test Study 19.4.110

Study Design

- **Phase A:** open study, subjects not previously exposed to sugammadex, n=11

- **Phase B:** single blind, previously exposed with alleged hypersensitivity symptoms, n=6
  - Potentially hypersensitive subject from study 19.4.106
  - Clinical trial data from 156 healthy volunteers in cross-over trial were evaluated, retrospectively, possible symptoms of hypersensitivity were identified
    - 6 subjects showed some signs of possible hypersensitivity
    - 5 subjects consented in participation in 19.4.110

- **Phase B:** single blind, previously exposed to sugammadex without hypersensitivity symptoms, n=6
Skin Test Study 19.4.110

Study Results

- Potentially hypersensitive volunteer from 19.4.106 was confirmed positive in skin tests
  - Participated as a volunteer in over 15 trials; unknown drug exposure

- No other allegedly hypersensitive subjects were hypersensitive to sugammadex based on the SPT and IDT results

- One control subject had a positive IDT
  - Previously exposed to sugammadex without previous clinical allergy symptoms
  - Increased and comparable levels of urine methylhistamine both at baseline and post treatment; this may indicate a false positive outcome
Hypersensitivity Conclusion

• 1 hypersensitive reaction in a healthy volunteer

• No hypersensitivity reactions reported in patients

• 182 subjects received more than one dose of sugammadex with no suspected hypersensitivity reported

• No reports of hypersensitivity associated with cyclodextrins in literature
Other Safety Data and Risk Management Plan
No Clinically Important Changes for Other Safety Parameters

- **QTc**
  - Two thorough QTc trials conducted
  - No QTc prolongation of concern

- **No clinically important laboratory changes**
  - Hematology
  - Biochemistry
  - Urinalysis
Risk Management Plan

• Patients with severe renal failure and the feasibility of hemodialysis will be studied separately

• Pharmacovigilance activities are considered to be sufficient for all important risks with the exception of use in severe renal impaired patients. These activities include:
  – Active follow-up on reports to obtain all relevant case information
  – Follow-up on off label use
  – Literature screening (weekly) on case reports
  – Periodic evaluation of reporting rate for selected AEs (e.g. hypersensitivity)
Conclusion on Safety

Available clinical data demonstrate that sugammadex is safe and well tolerated
Summary

Ronald D. Miller, M.D.
Are We Meeting an Unmet Need?

• Minimize or eliminate neostigmine
• Minimize or eliminate succinylcholine
• Residual Postoperative Paralysis
• Increase Intraoperative Flexibility
• Increase Perioperative Safety
Recovery after Sugammadex 4.0 mg/kg or Neostigmine 70 mcg/kg at 1-2 PTC, Median Time to Recovery TOF 0.9

* P<0.0001 versus neostigmine treatment group
Percentage Change in Heart Rate after Administration of Sugammadex or Neostigmine/Glycopyrrolate

-20% 0% 20% 40% 60% 80% 100%
0 5 10 15 20 25 30 35
Min after Administration

Sugammadex
Neostigmine / Glycopyrrolate
Rocuronium/Sugammadex vs. Succinylcholine, Mean (2xSEM) Times to T₁ 10% and 90%

* P<0.0001 versus succinylcholine treatment group

* P<0.0001 versus succinylcholine treatment group

0 2 4 6 8 10 12 14
Mean (2*SEM) time (min)

Rocuronium
Sugammadex
Succinylcholine

3 min.

T₁ to 10%
T₁ to 90%

* P<0.0001 versus succinylcholine treatment group
Summary

• Sugammadex is one of the most innovative drugs in anesthesia in many years

• It is the first drug that encapsulates the NMBD, taking it away from the NMJ and terminating its action

• Allows increased flexibility with NMBDs intraoperatively
Summary

• Provides complete and rapid reversal of profound neuromuscular blockade

• Minimizes risk of residual postoperative paralysis

• Elimination of managing side effects associated with AChEIs (neostigmine) and muscarinic antagonists (atropine/glycopyrrolate) and the mechanical mixing of two drugs

• In combination with rocuronium, may provide an alternative to succinylcholine
Conclusion

- Sugammadex has been shown to be safe and efficacious in more than 2000 administrations in patients and volunteers

- Its properties are expected to lead to safety benefits for patients

- Sugammadex will become a valuable new drug in the management of neuromuscular blockade specifically and general anesthesia, overall