

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 T₂ (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

Agenda

Introduction

June Bray, MBA, R.Ph.

Vice President, Regulatory Affairs
Organon, a part of Schering-Plough Corporation

Unmet Medical Need

Ronald D. Miller, M.D.

Professor and Chairman, Department of Anesthesia
and Perioperative Care – University of California,
San Francisco, School of Medicine, San Francisco, CA

Mechanism of Action and Pharmacology and Pharmacokinetics

Anton Bom, M.D., Ph.D.

Senior Research Fellow, Pharmacology,
Organon, a part of Schering-Plough Corporation

Non-clinical Safety Overview

Diels van den Dobbelsteen, Ph.D.

Principal Toxicologist
Organon, a part of Schering-Plough Corporation

Efficacy & Safety Clinical Overview

Patrick Boen, M.D.

Senior Director Medical Services, Anesthesia
Organon, a part of Schering-Plough Corporation

Summary

Ronald D. Miller, M.D.

List of Respondents

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

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,
School of Medicine, 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
- Eliminate 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%

* Murphy et al: Anesth Analgesia 2008 (In press)

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 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?

* Van Vlymen et al: The effects of reversal of neuromuscular blockade on autonomic control in the perioperative period: *Anesth Analgesia* 1997;84:148-154

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

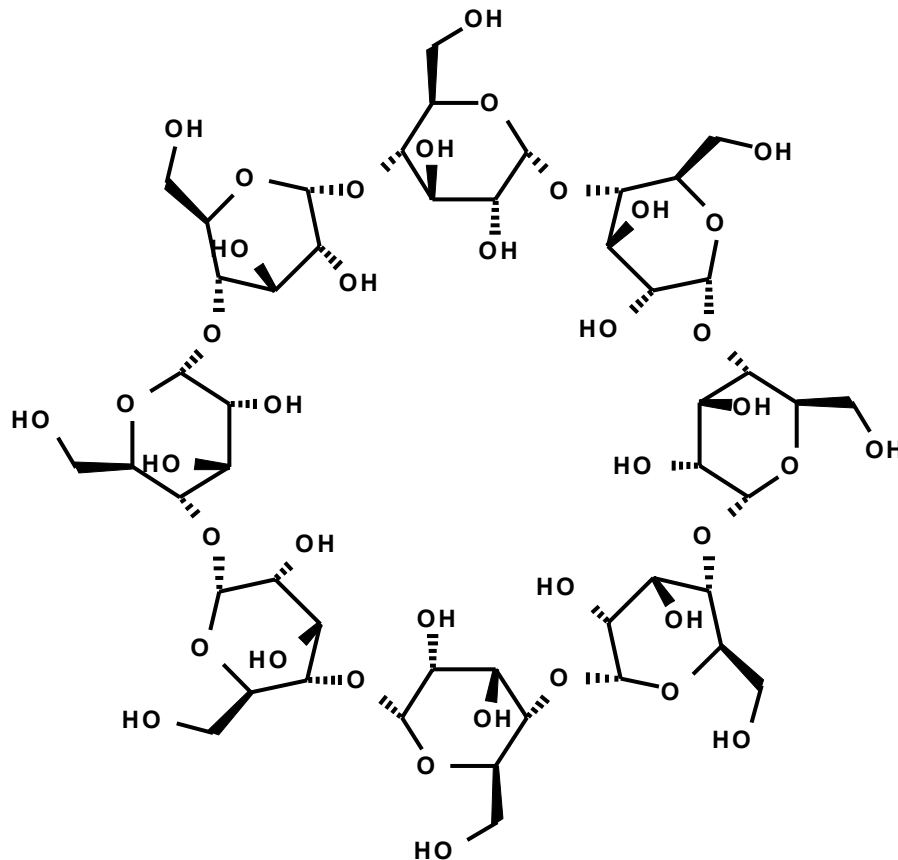
- **Inactivation of the NMBA**
- **Rapid chemical interaction between NMBA and encapsulating agent**

Cyclodextrins

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

Cyclodextrins

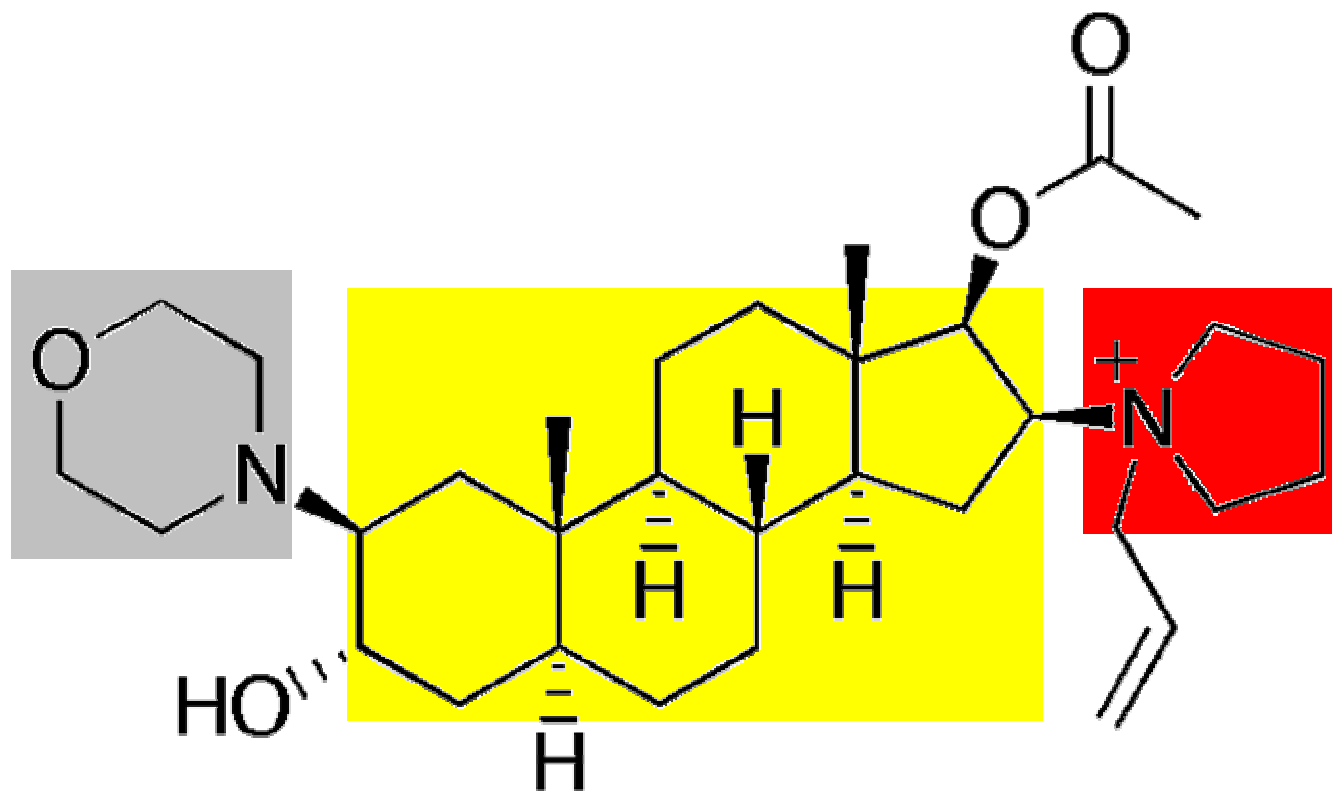
γ -cyclodextrin: 8 sugar molecules forming a rigid ring with a central lipophilic cavity



Properties of Cyclodextrins

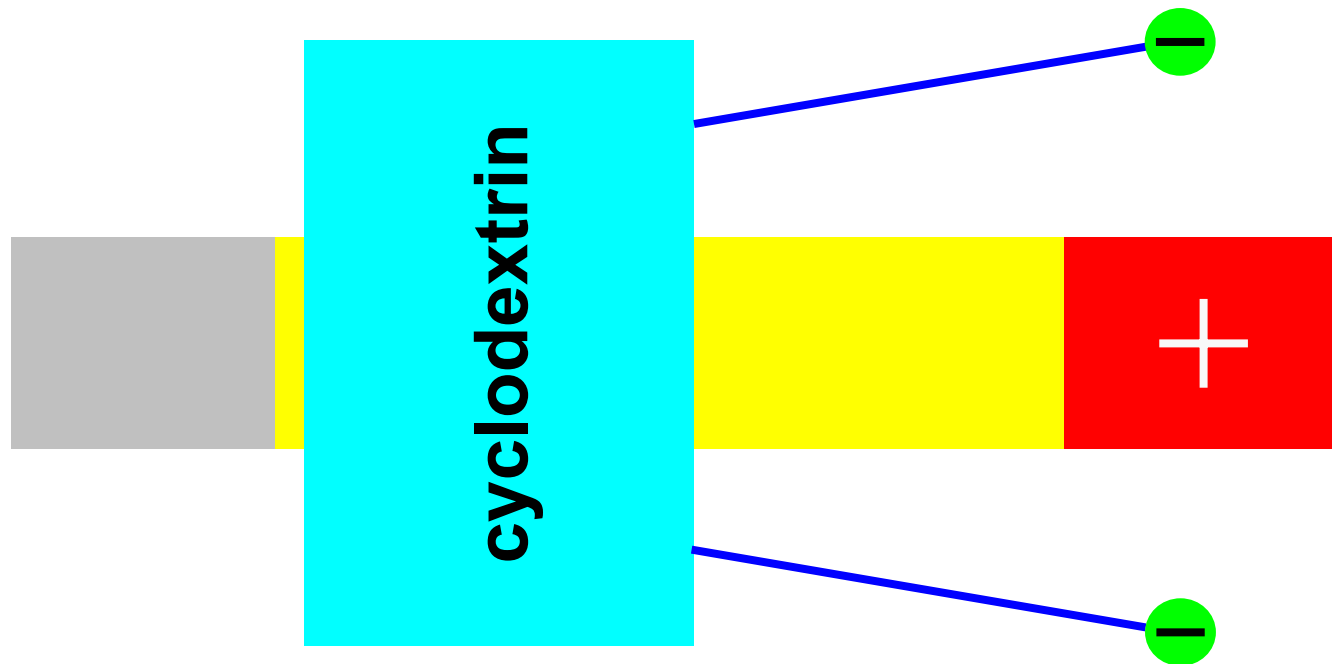
- **Very water-soluble**
- **Not metabolized**
- **Renally excreted**

Properties of Rocuronium

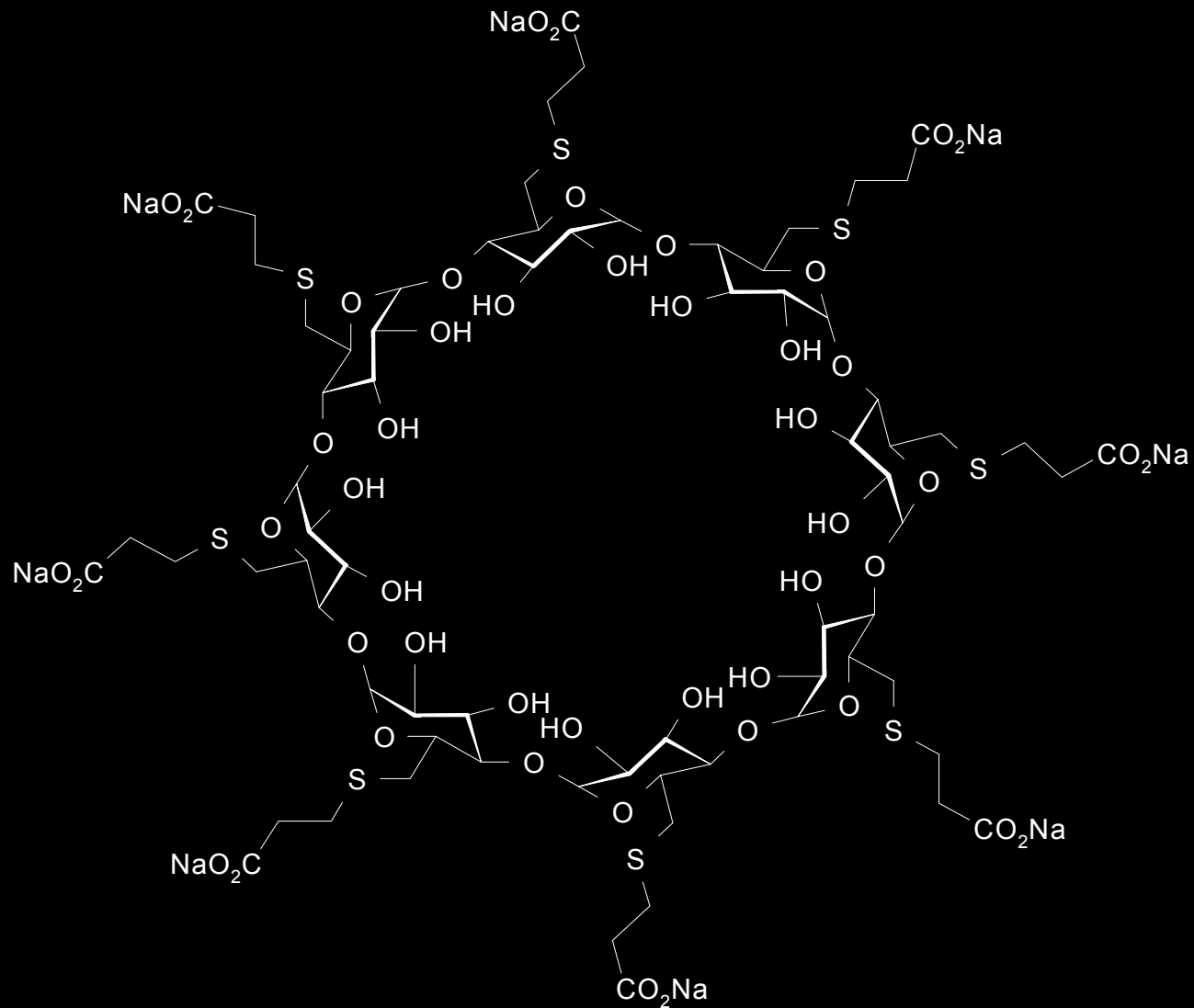


Design of Reversal Agent

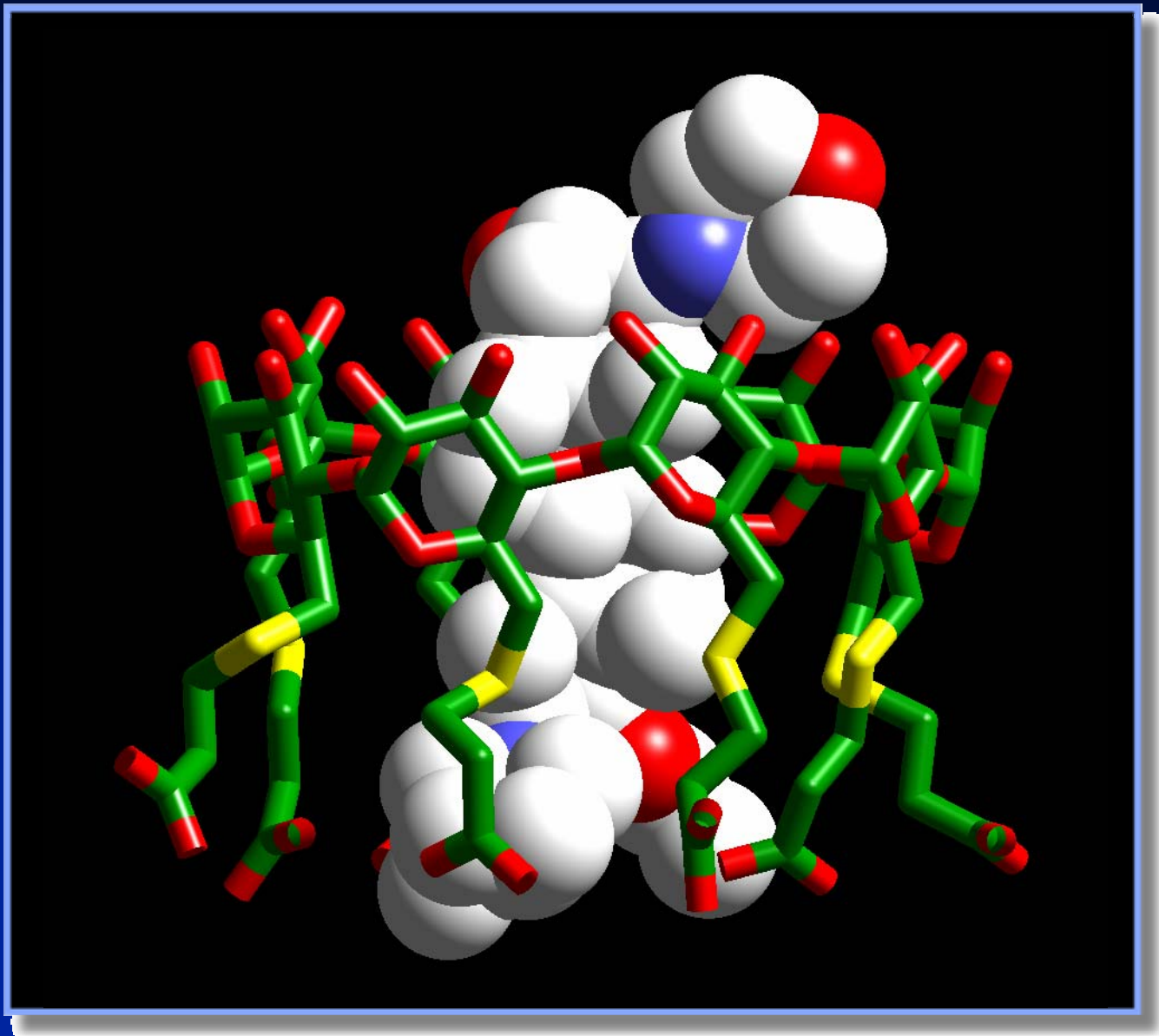
γ -cyclodextrins can be modified to increase affinity for rocuronium



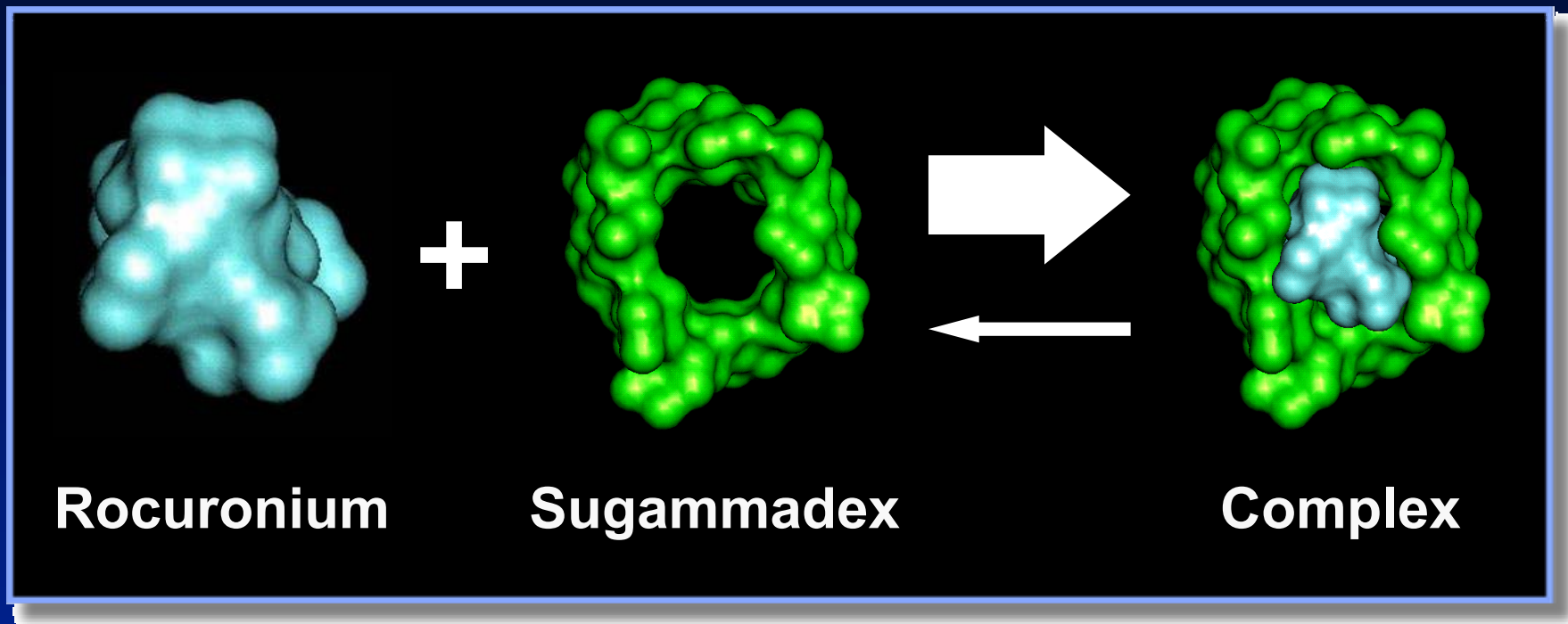
Sugammadex



Rocuronium – Sugammadex Complex



Mechanism of Action

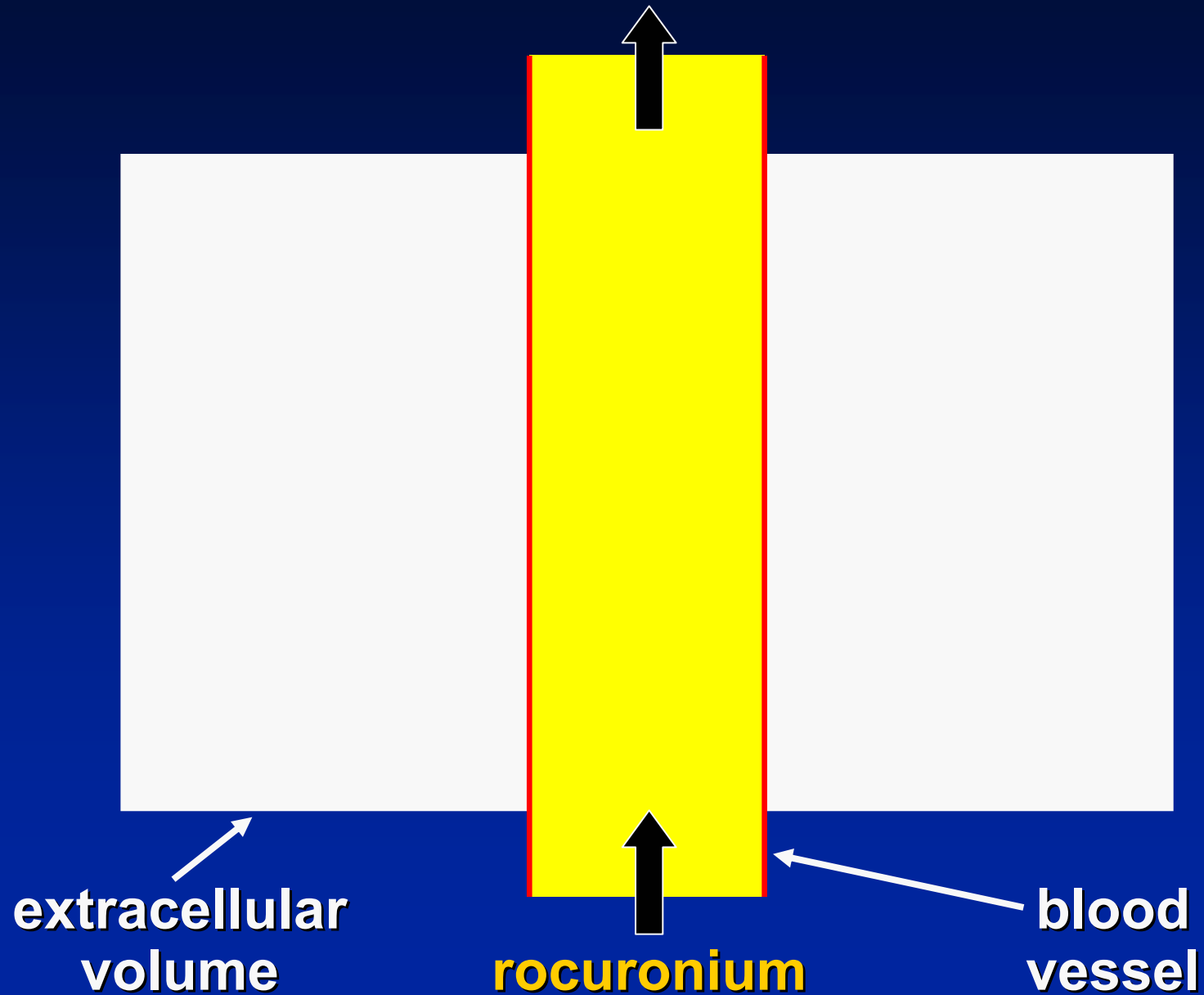


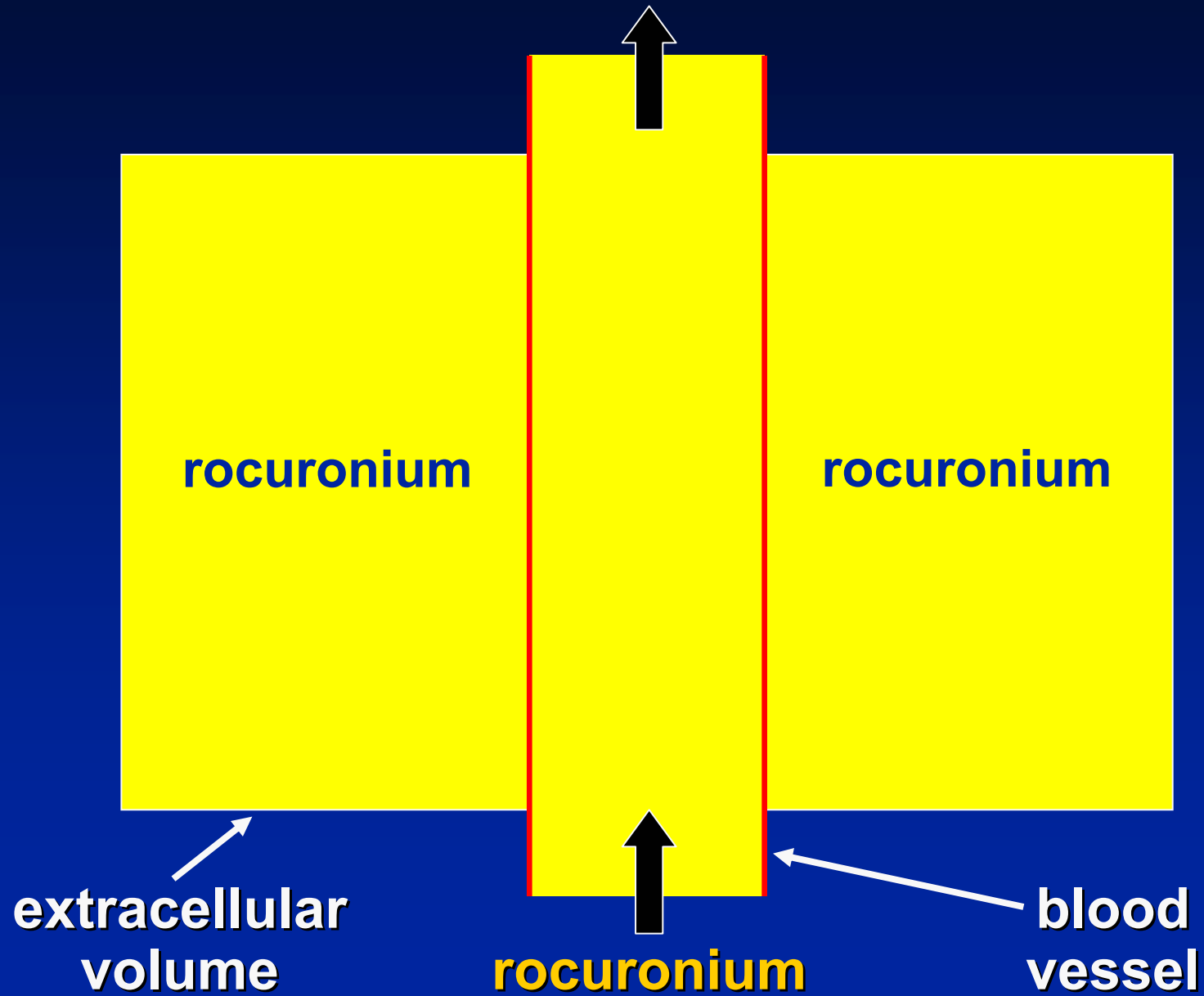
affinity ($K_A \text{ M}^{-1}$)	rocuronium	vecuronium
γ -cyclodextrin	13,200	1,176
sugammadex	25,000,000	10,000,000

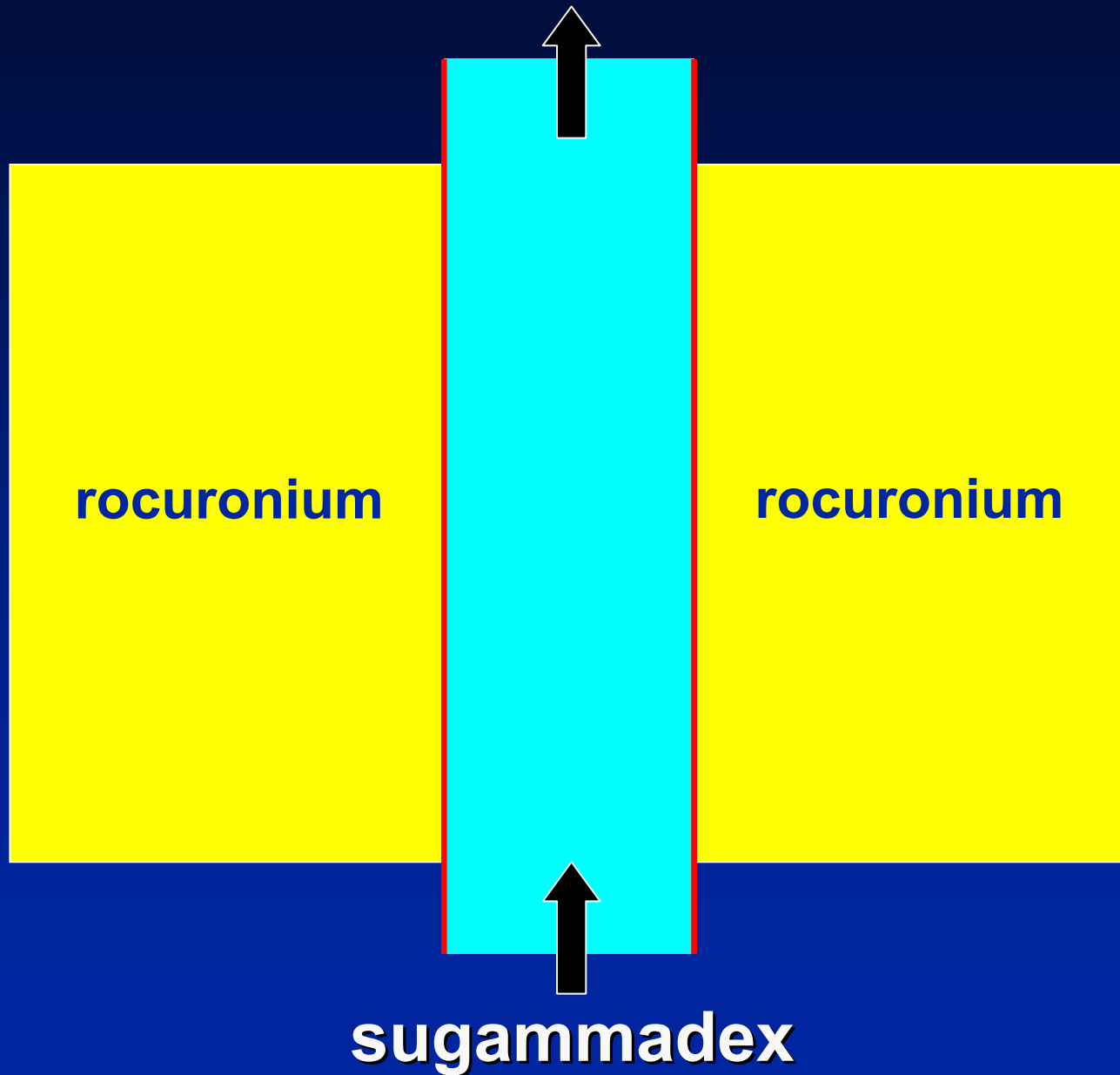
Selectivity

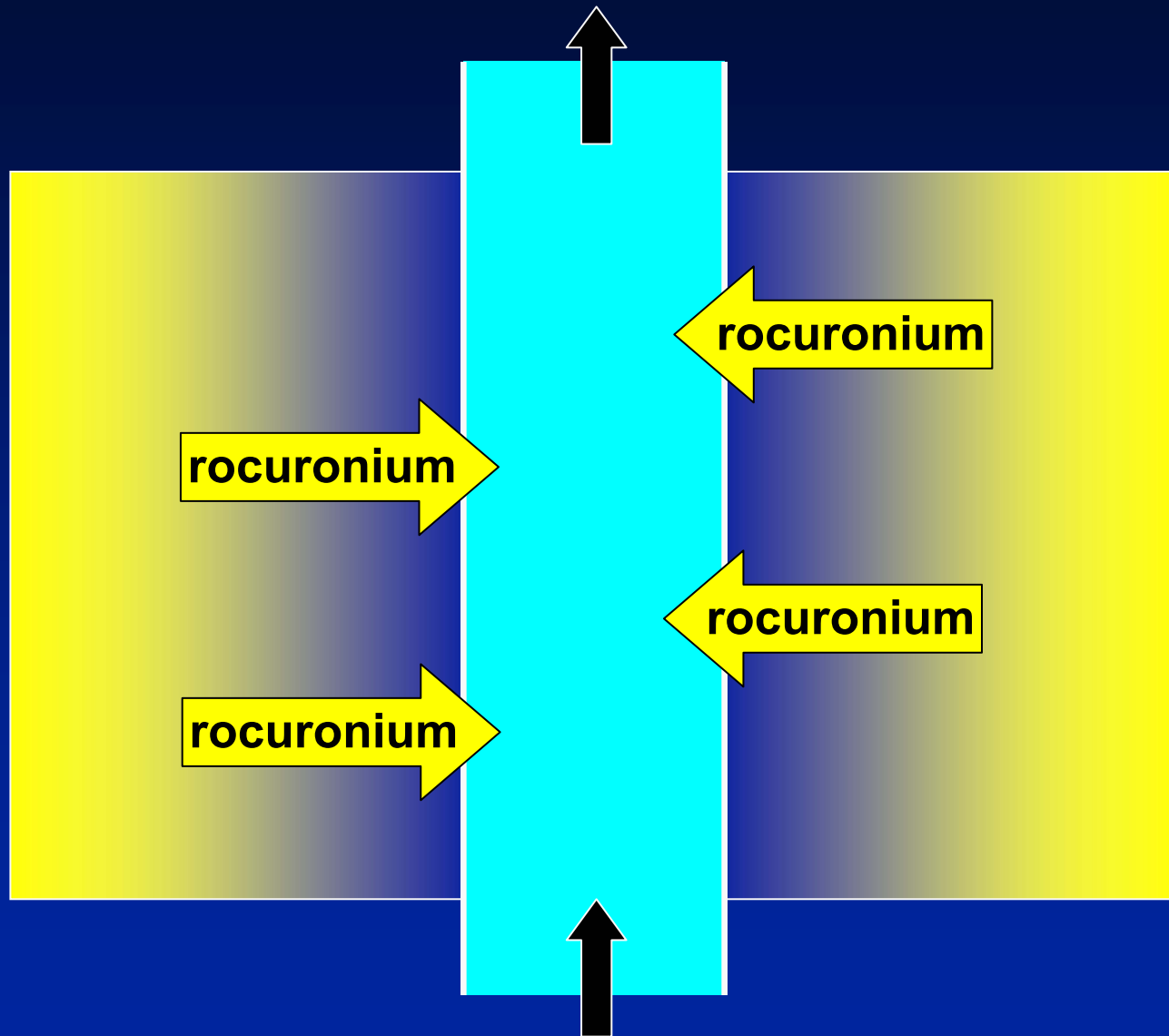
NMBA	K_A value (megaM⁻¹)
Rocuronium	25.0
Vecuronium	10.0
Pancuronium	2.6
Cisatracurium	0.005
Succinylcholine	0.000

Speed of Reversal

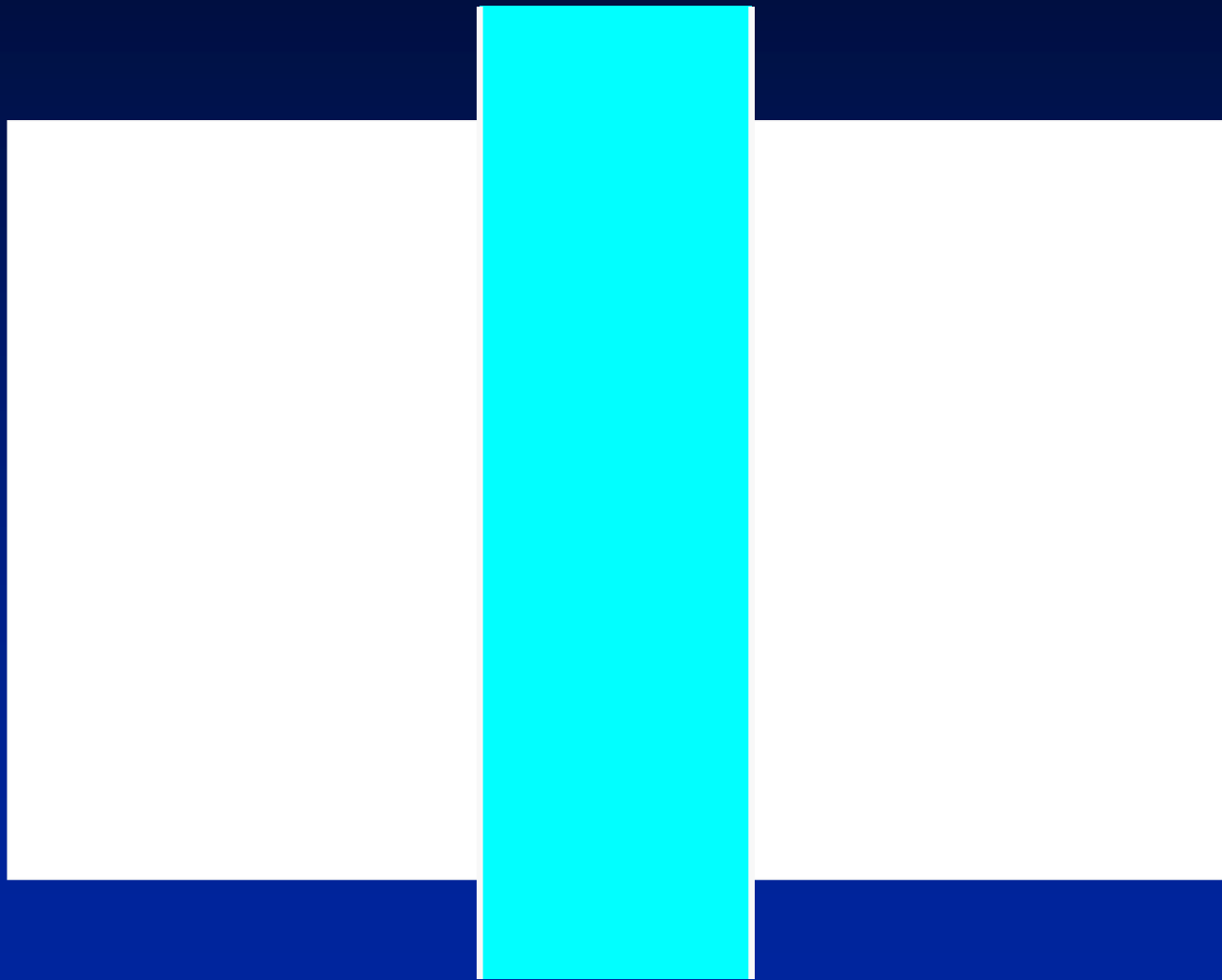




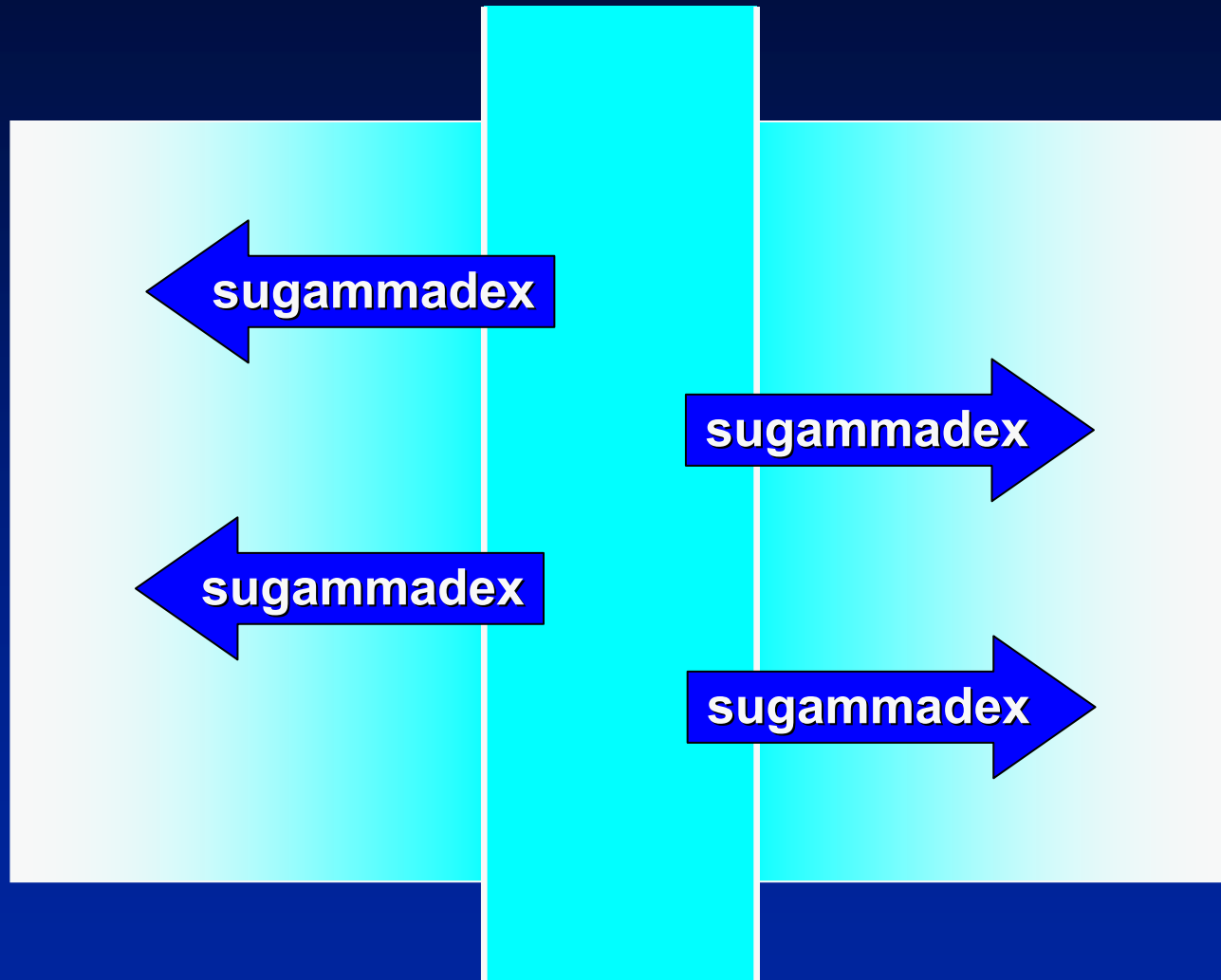




sugammadex

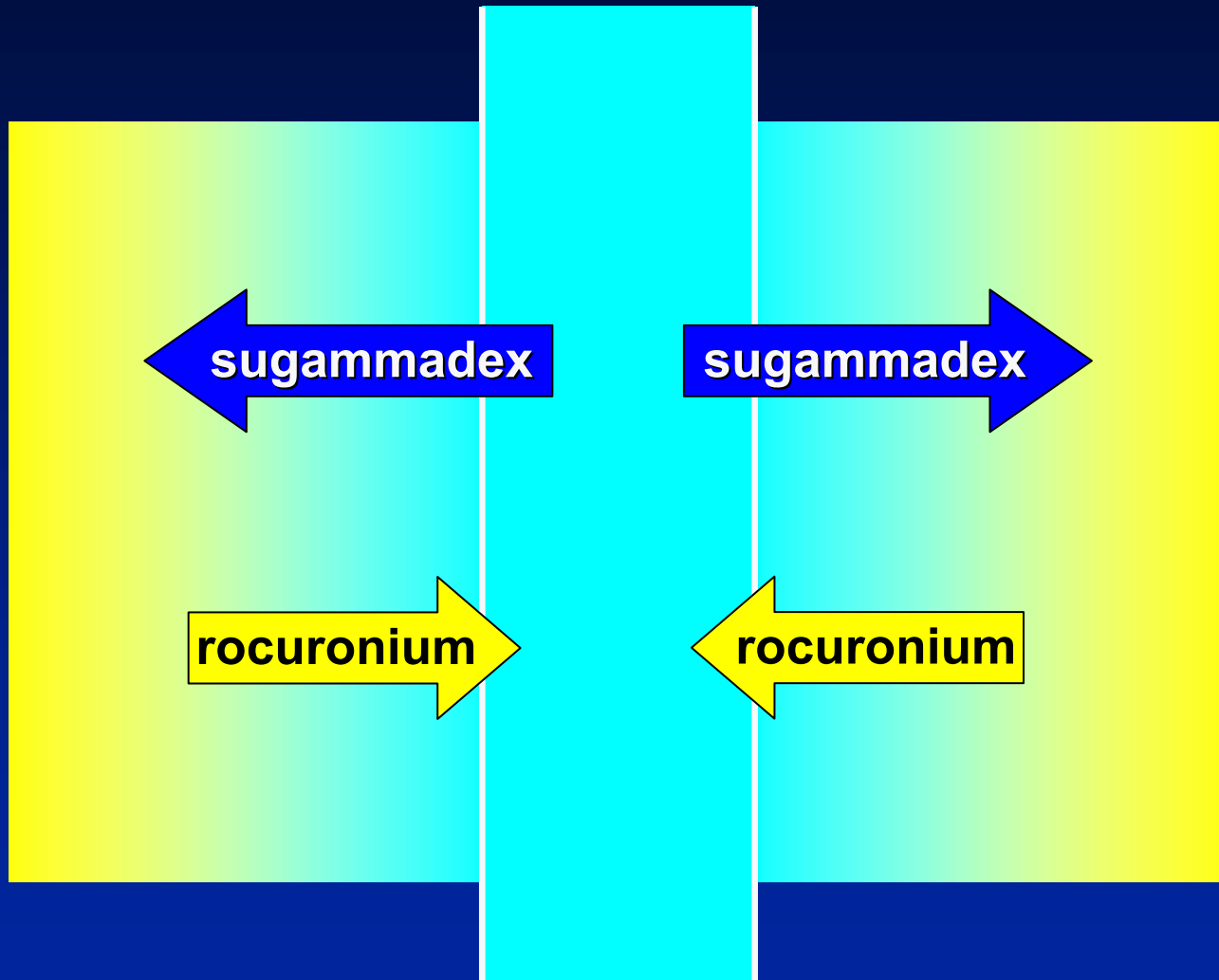


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sugammadex

Opposite Direction of Flow of Molecules



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

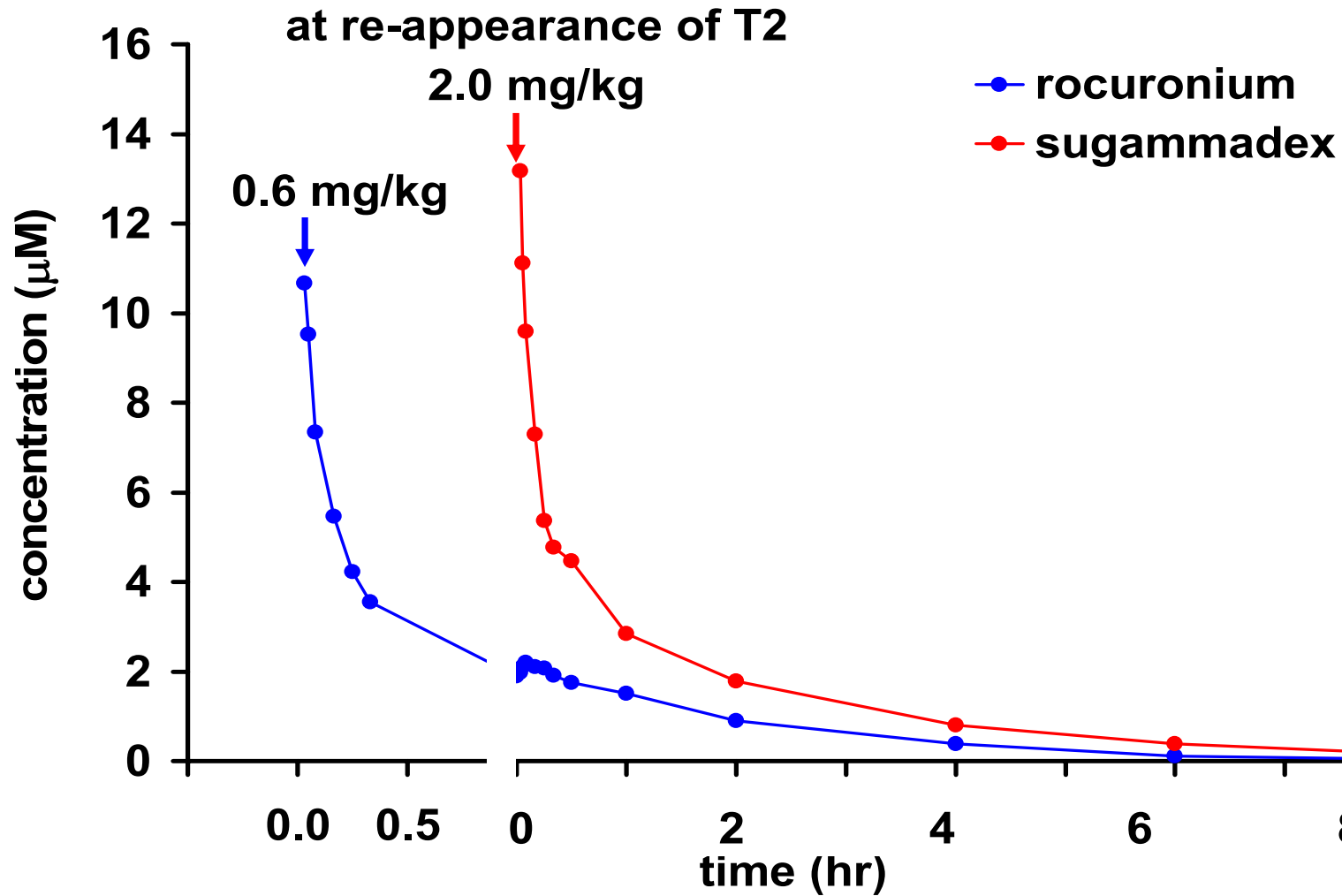
Basic PK of Sugammadex

- Volume of distribution: $\approx 12\text{-}15\text{ L}$
- Plasma half-life: $\approx 2.2\text{ h}$
- Clearance: $\approx 91\text{ mL/min}$ ($\approx \text{GFR}$)
- 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



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_A)
- *In vitro* tissue studies
- *In vivo* animal studies
- Pharmacokinetic-Pharmacodynamic interaction model
- Clinical considerations

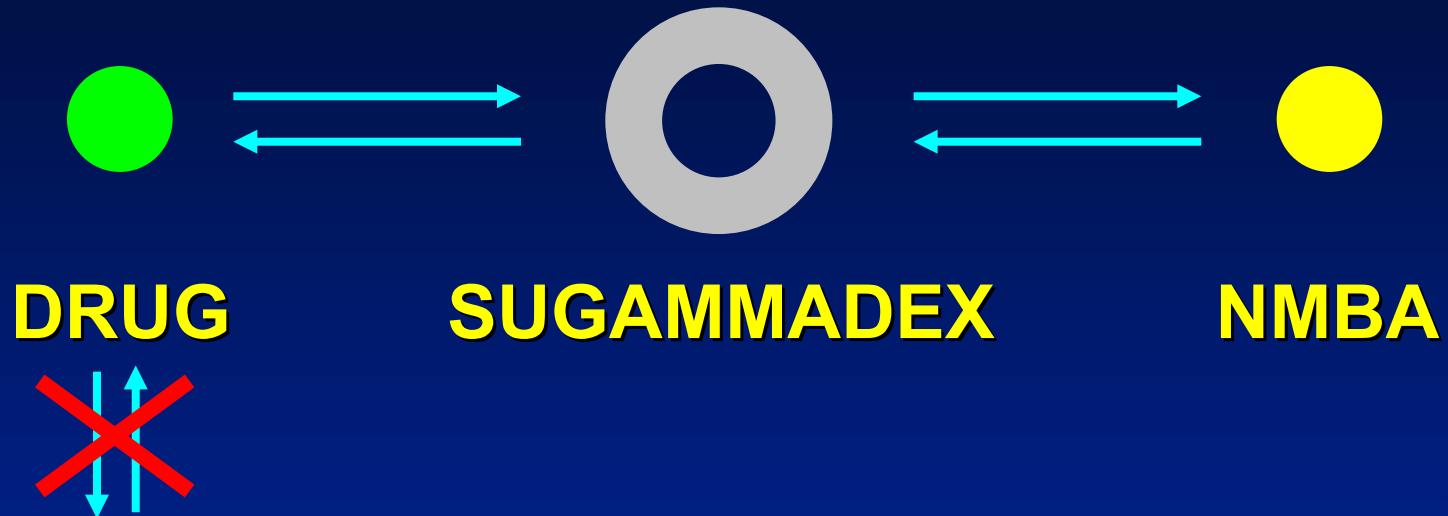
Drugs Selected for Determination of Binding Affinity for Sugammadex

- **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 remifentanyl, 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

<i>Sugammadex</i>	<i>Sulfobutylether-β-CD in Vfend[®]</i>	<i>Hydroxypropyl- β-CD in Sporanox[®]</i>
Single dose	\pm 7-10 daily doses	\pm 7 daily doses
0.12, 0.24, 0.96 g/day*	9-13.5 g/day*	16-32 g/day*

* 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 (μ 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:

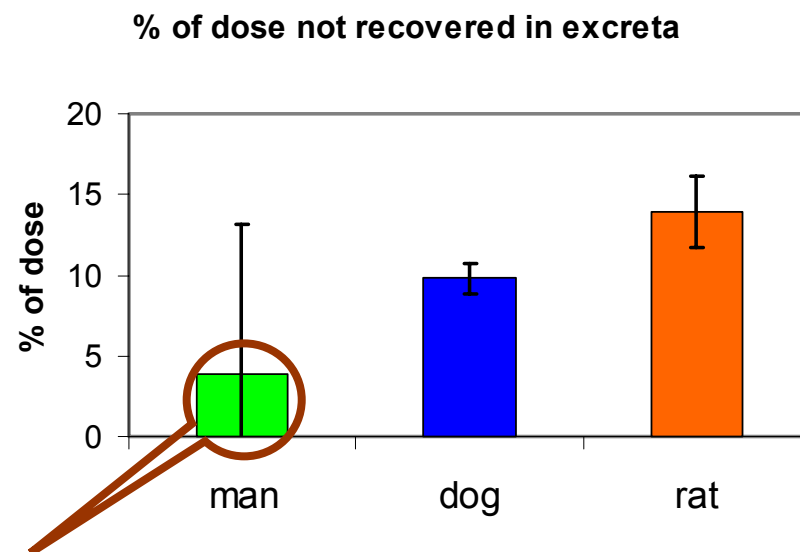
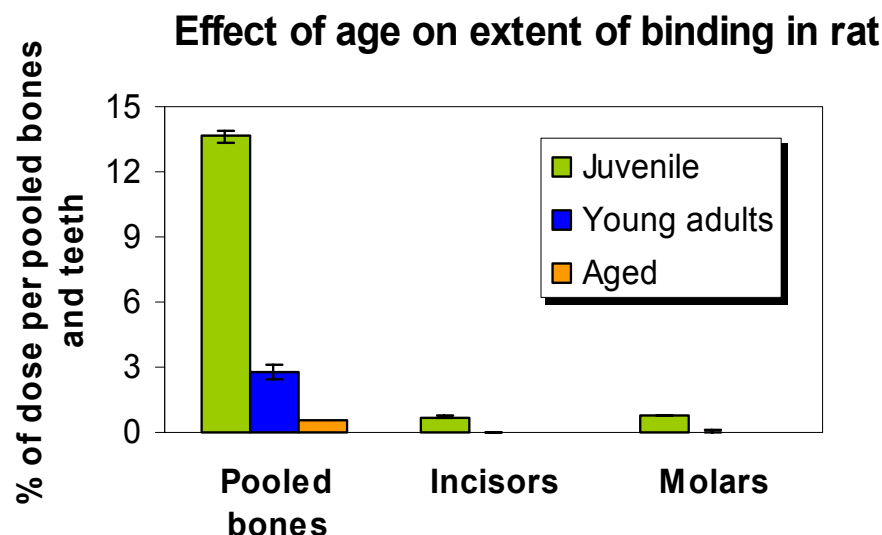
- Reversible (terminal $t_{1/2}$ rat bone: 70-250 days)
- To rat teeth is 3-5 fold less compared to bone
- Extracellular at site of mineralization: hydroxy apatite
- Significantly reduced by presence of NMBA
- Not to epiphyseal disc & (joint) cartilage

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

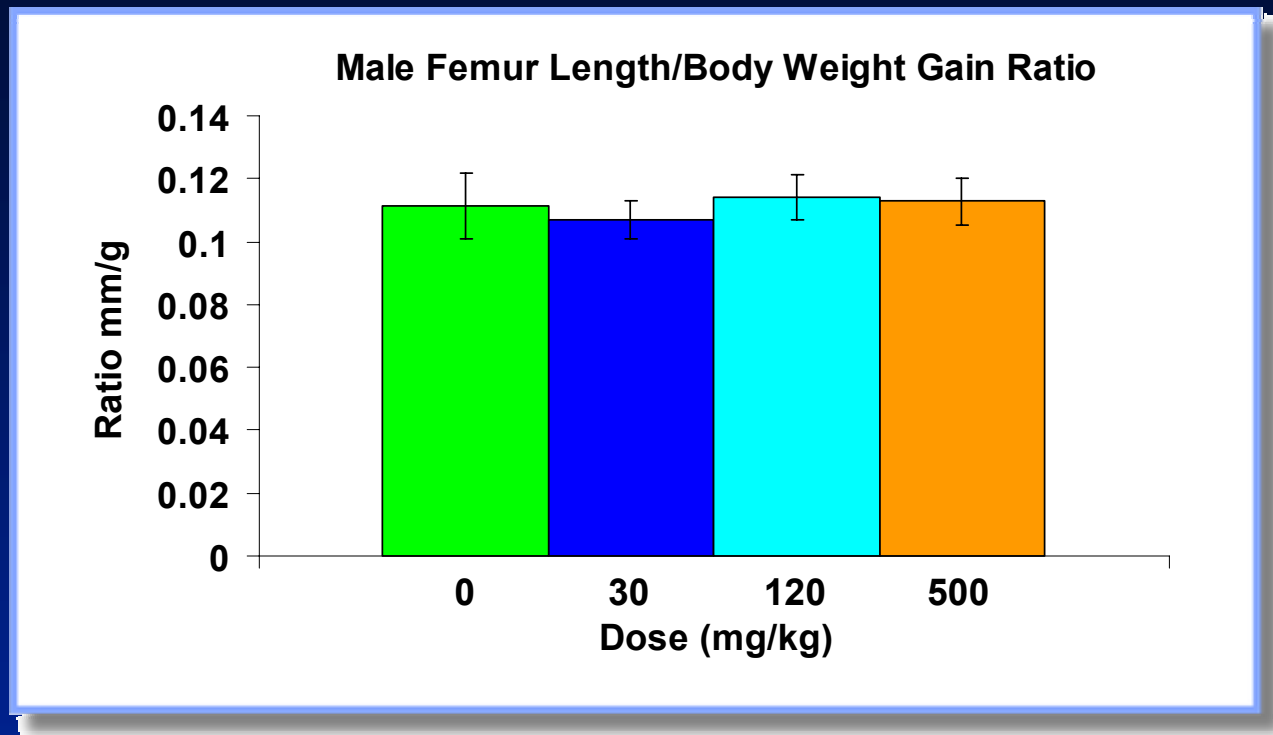
- No effect on bone at single dose ≤ 500 mg/kg
- Bone concentration rat : human = 313 : 4.5 $\mu\text{g/g}$

➡ ***Safety Margin: 70***

- 4-week rat toxicity study: no effect on bone histopathology and bone mineral density with sugammadex at > 5000 $\mu\text{g/g}$

➡ ***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 \approx
 $> 5000 : 4.5$ $\mu\text{g/g}$

➡ **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*

* Kuijpers MHM et al. Tox. Path. 24(3): 346-360 (1996)

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 → no binding to early callus

➔ ***Fracture healing should not be impaired***

* Ferrara and Davis-Smyth, Endocr. Rev. 18: 4-25 (1997); Ferguson et al. Mech. Dev. 87: 57-66 (1999); Tsiridis et al. Injury 38S1: S11-S25 (2007); Little et al. J Bone Joint Surg. 89(4):425-433 (2007)

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

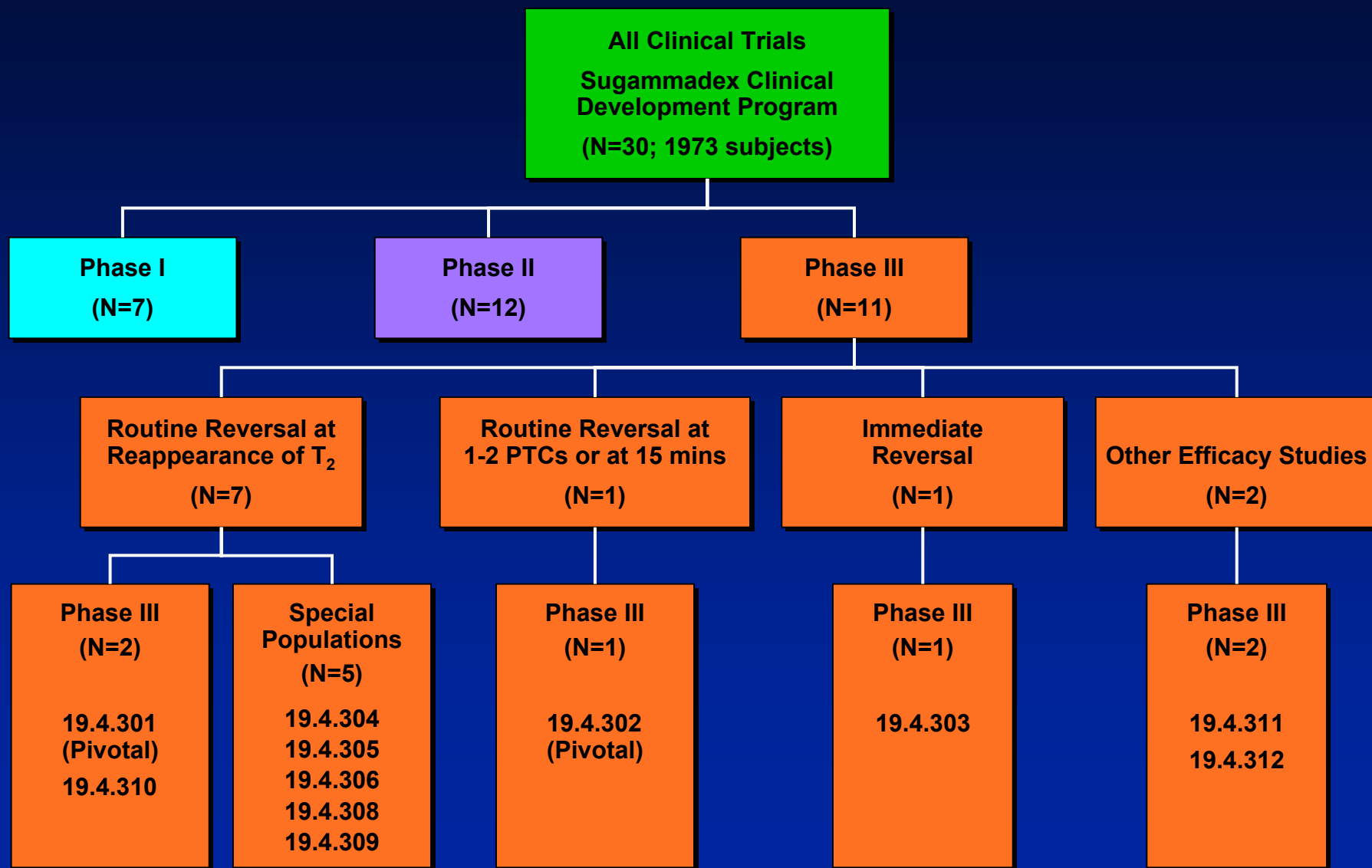
Routine Reversal

- 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



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

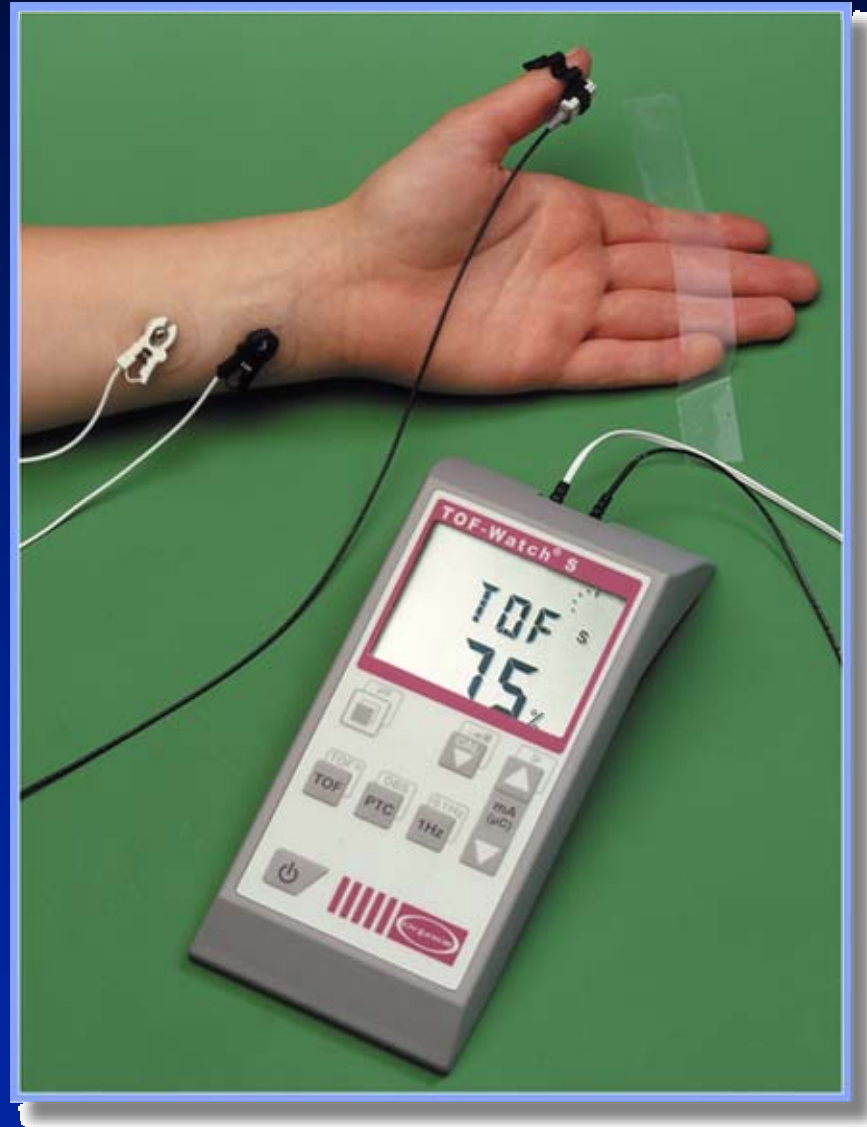
- **Neuromuscular disorders, significant renal dysfunction (except for Trial 19.4.304), history of malignant hyperthermia**
- **Allergy to narcotics, muscle relaxants or other medication used during general anesthesia**
- **Medications known to interfere with the NMBA**
- **Contraindications for the comparator**

Exclusion Criteria

Phase II and III Trials

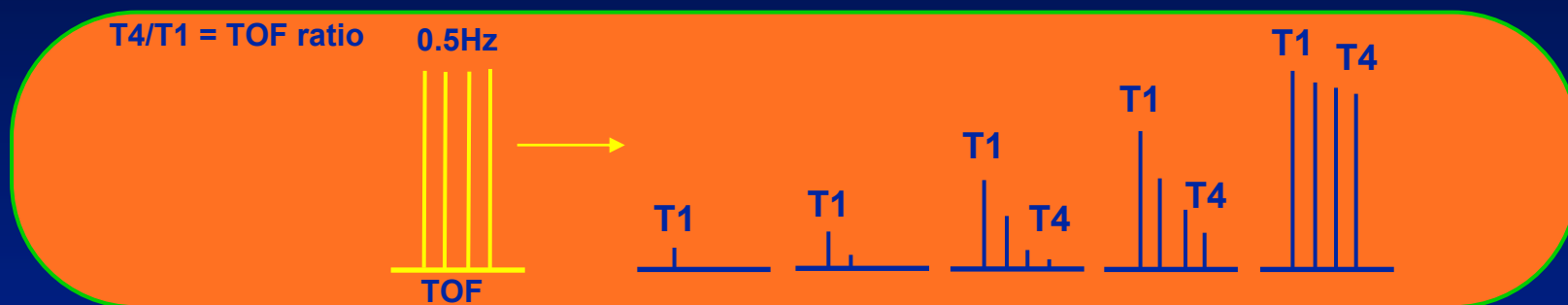
- **Pregnancy**
 - Childbearing potential not using appropriate methods of birth control
 - Breast-feeding
- **Prior participation in the trial**
- **Participation in another clinical trial, not pre-approved by Organon, part of Schering-Plough Corp**

Neuromuscular Monitoring

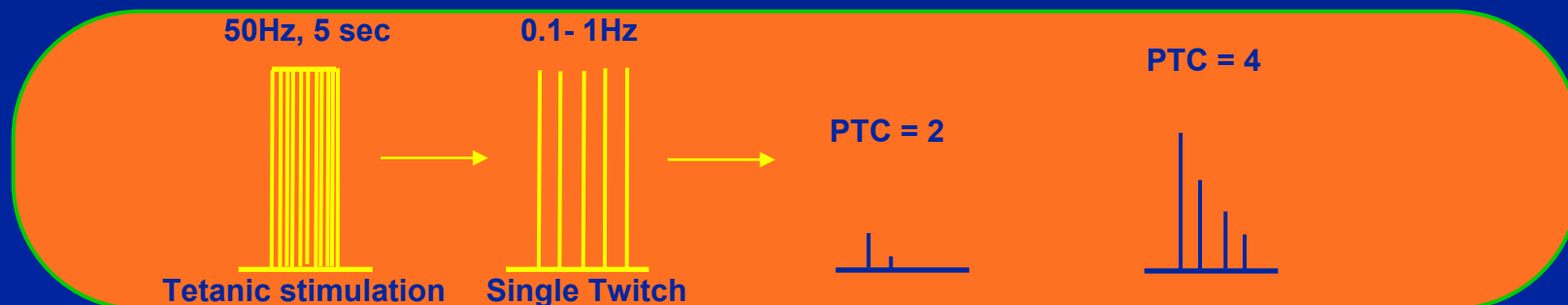


Methods of Stimulation

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



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



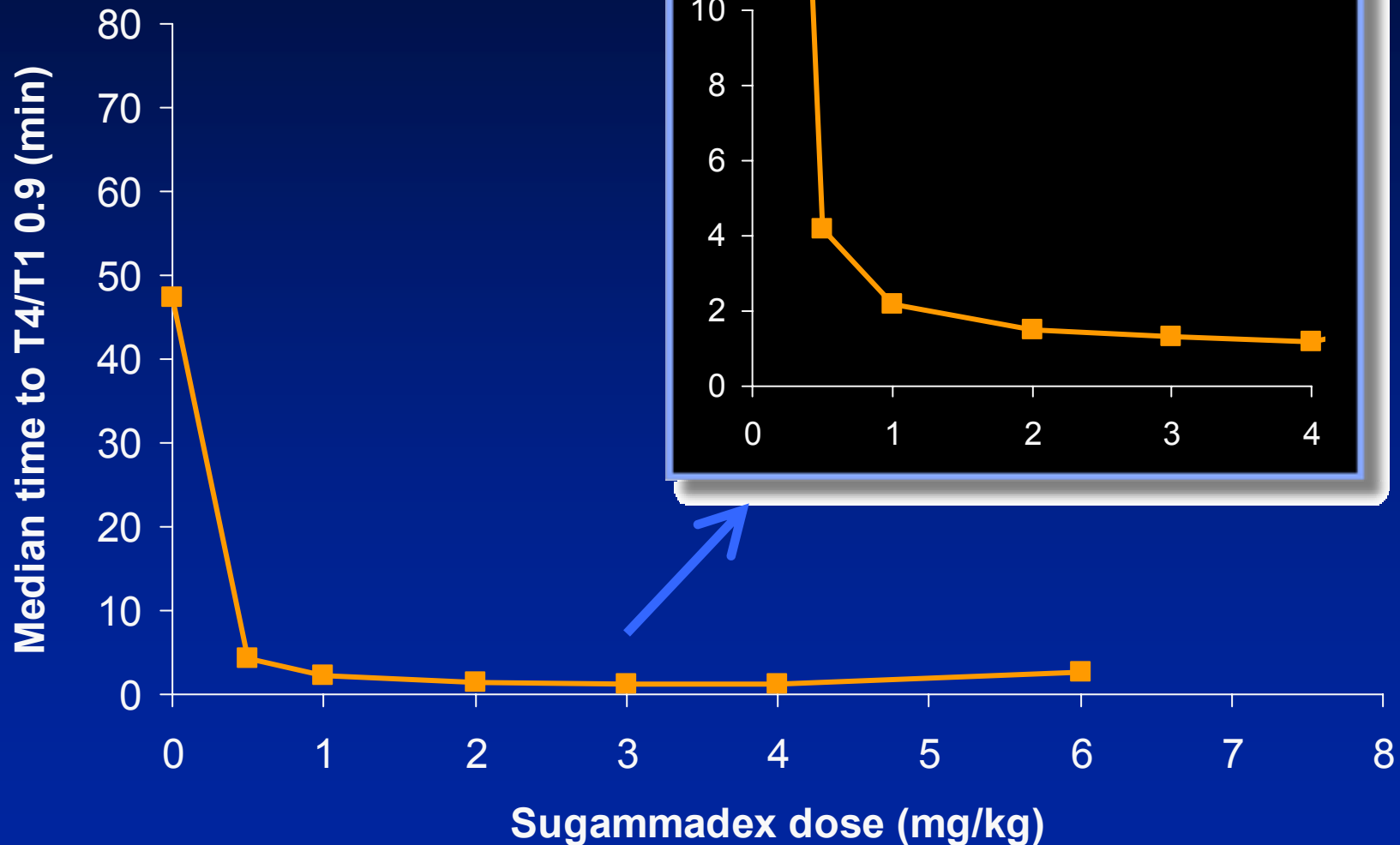
Dose Finding Trials – Phase II

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

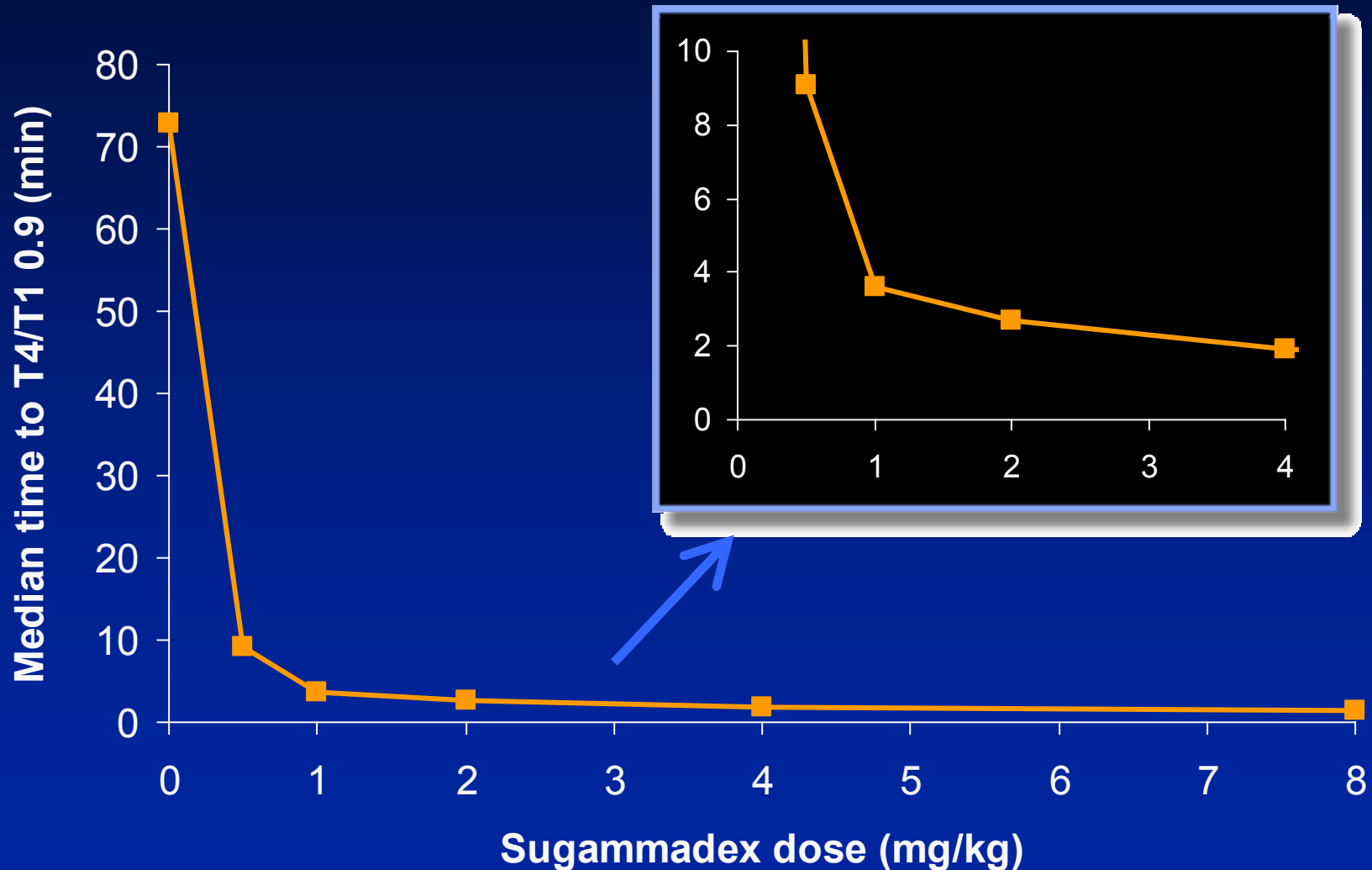
Time to Recovery T_4/T_1 to 0.9

Sugammadex at T_2 after Rocuronium – Phase II



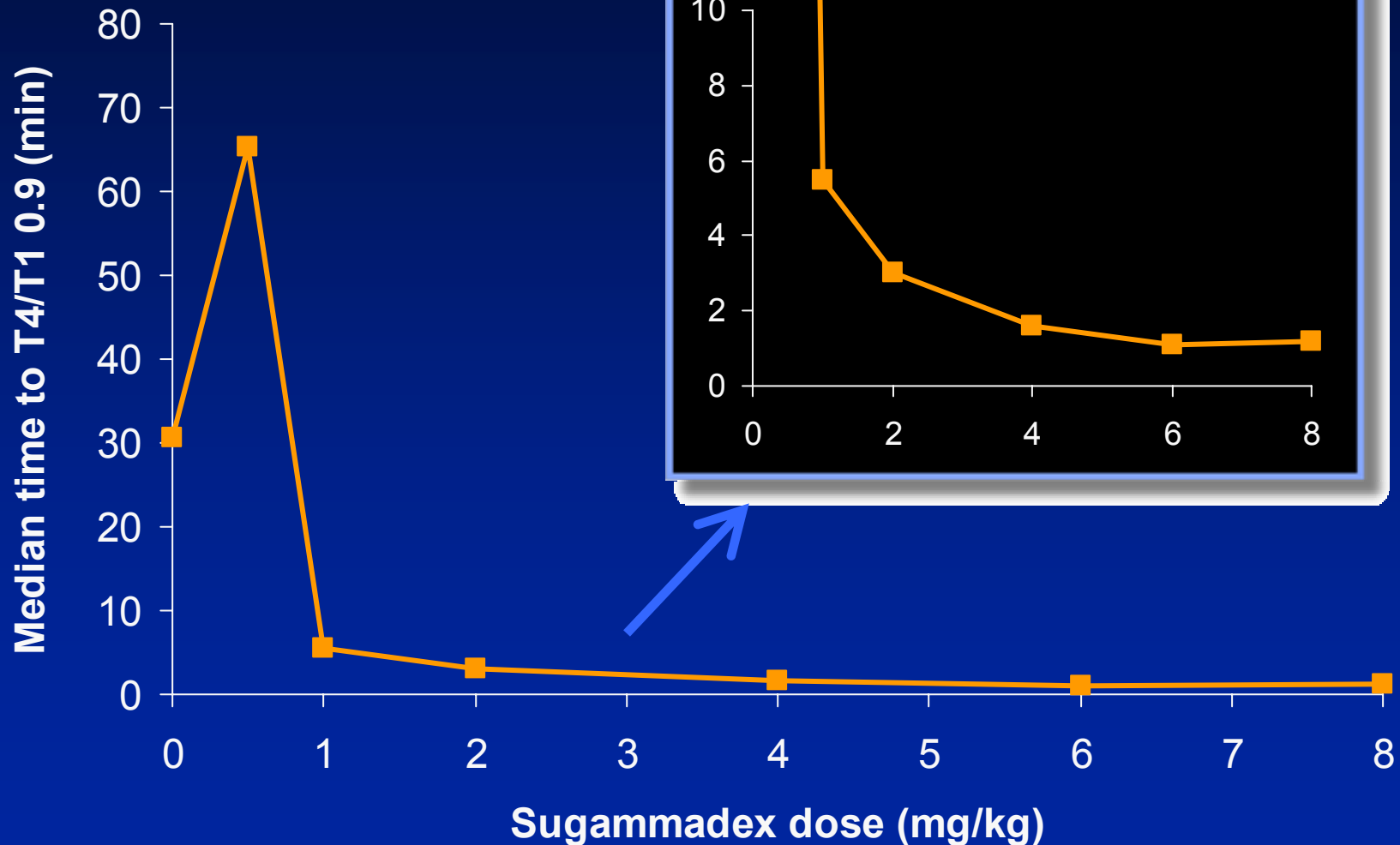
Time to Recovery T_4/T_1 to 0.9

Sugammadex at T_2 after Vecuronium – Phase II



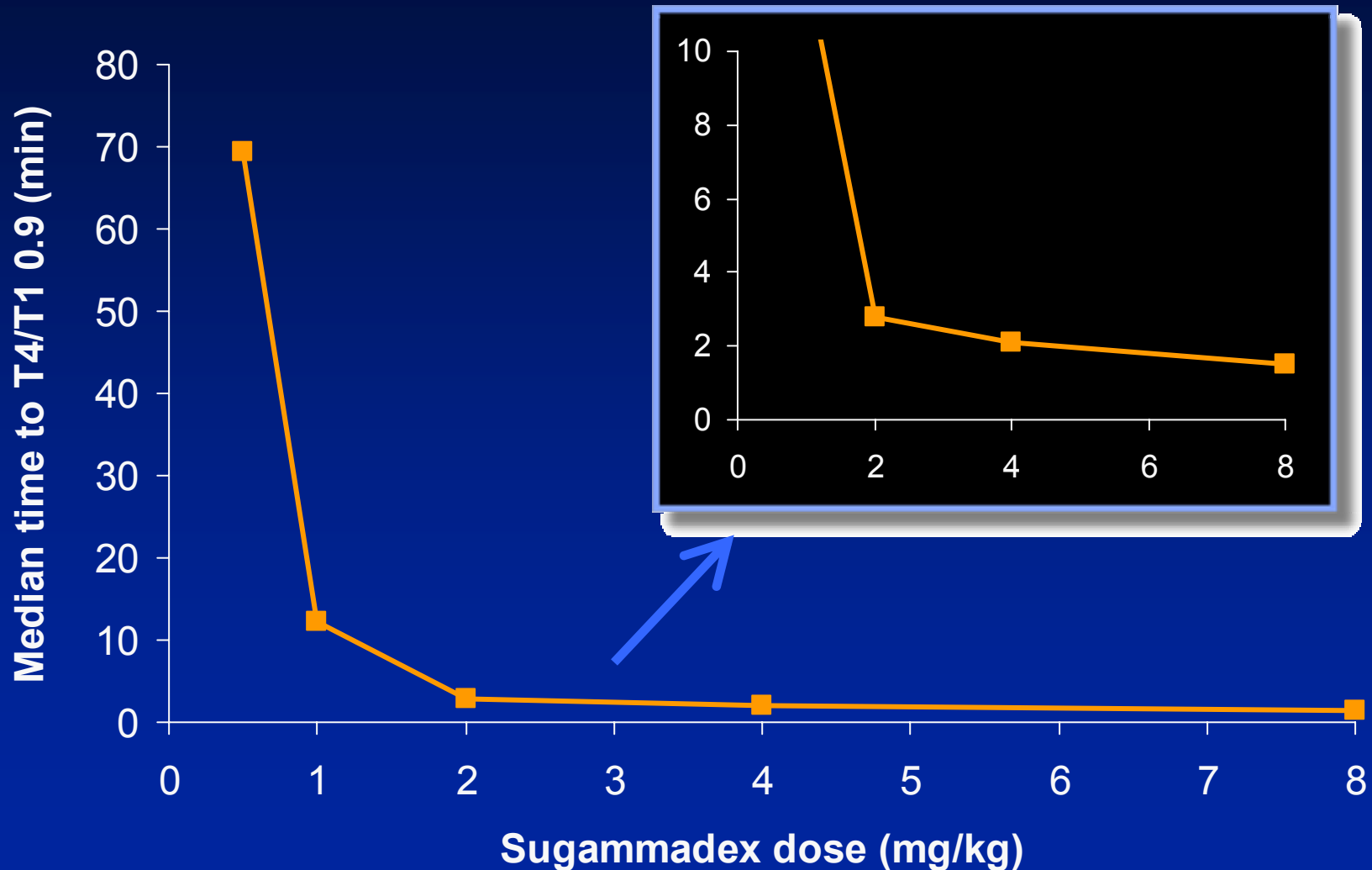
Time to Recovery T_4/T_1 to 0.9

Sugammadex at 1-2 PTC after Rocuronium – Phase II



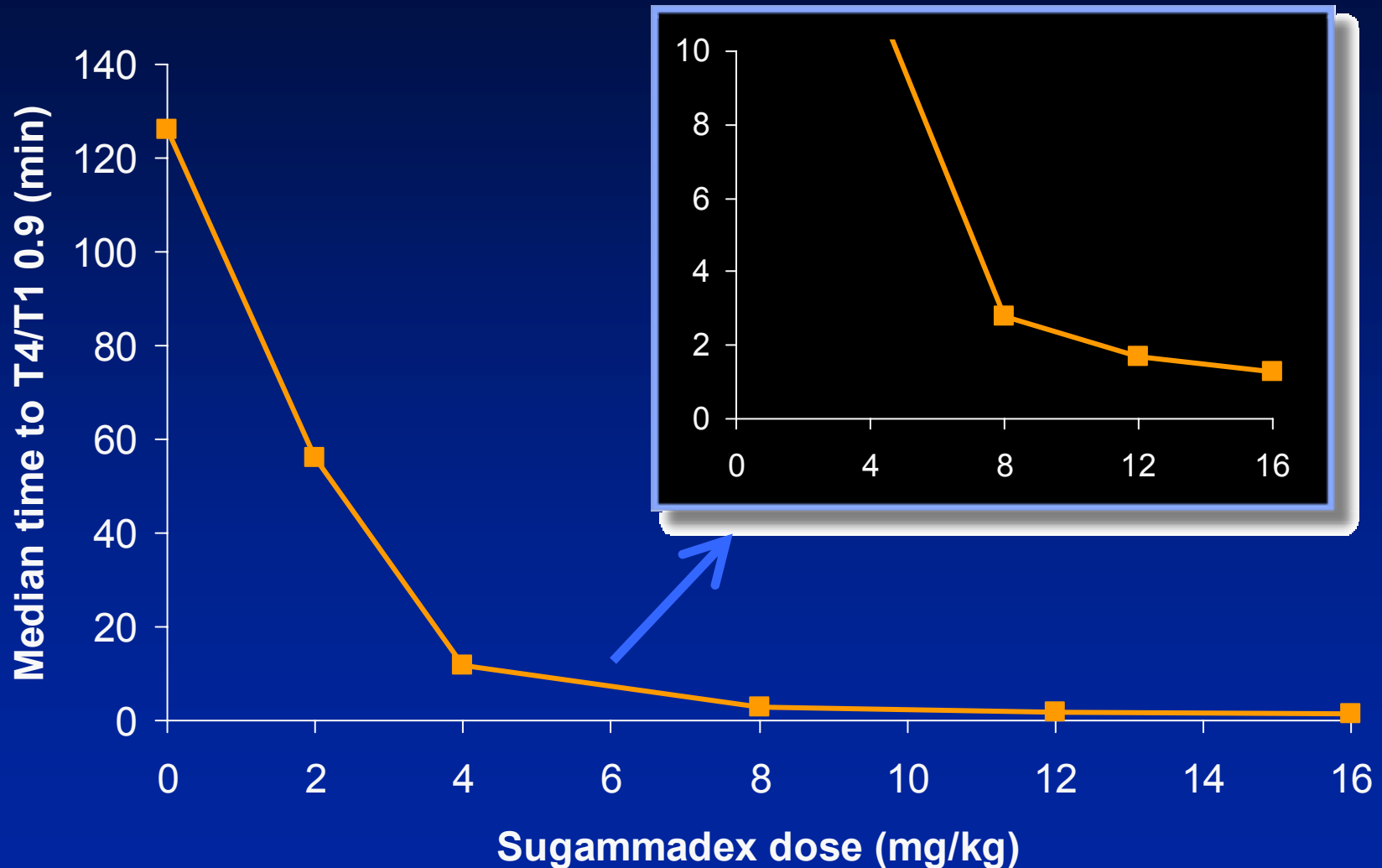
Time to Recovery T_4/T_1 to 0.9

Sugammadex at 1-2 PTC after Vecuronium – Phase II



Time to Recovery T_4/T_1 to 0.9

Sugammadex at 3-5 min after Rocuronium – Phase II



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 Trial 19.4.301
 - Profound Block Trial 19.4.302
- vs. succinylcholine Trial 19.4.303
- vs. cisatracurium Trial 19.4.310

Routine Use

- 15 min after last dose of rocuronium Trial 19.4.311

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

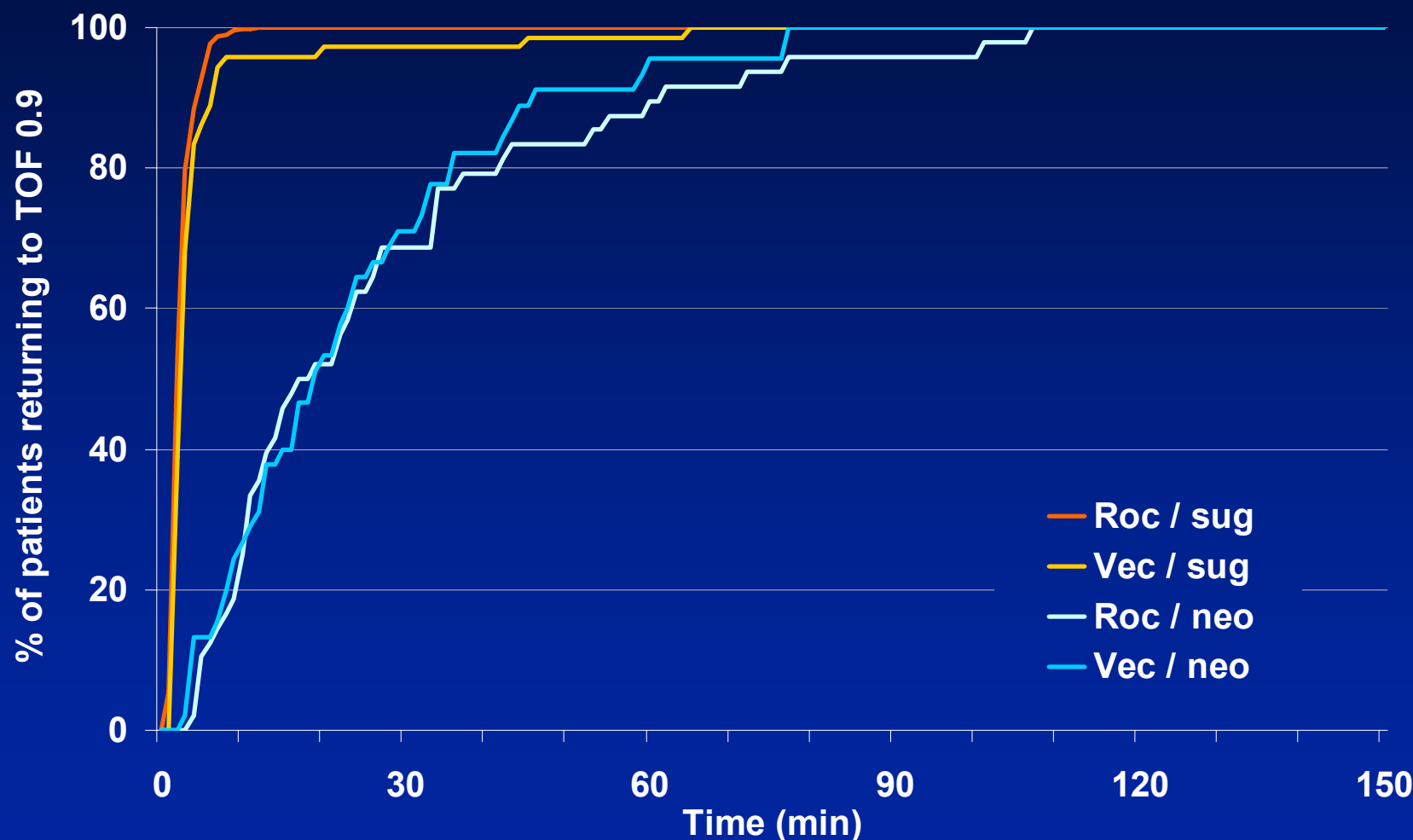
Recovery of TOF Ratio to 0.9*

Trial 19.4.301

Neuromuscular Blocking Agent	Sugammadex 2.0 mg/kg	Neostigmine 50 mcg/kg
<u>Rocuronium</u>		
n	48	48
Median (minutes)	1.4*	17.6
Range	0.9-5.4	3.7-106.9
<u>Vecuronium</u>		
n	48	45
Median (minutes)	2.1*	18.9
Range	1.2-64.2	2.9-76.2

* P<0.0001 versus neostigmine

Recovery after Sugammadex 2.0 mg/kg or Neostigmine 50 mcg/kg at Reappearance of T₂



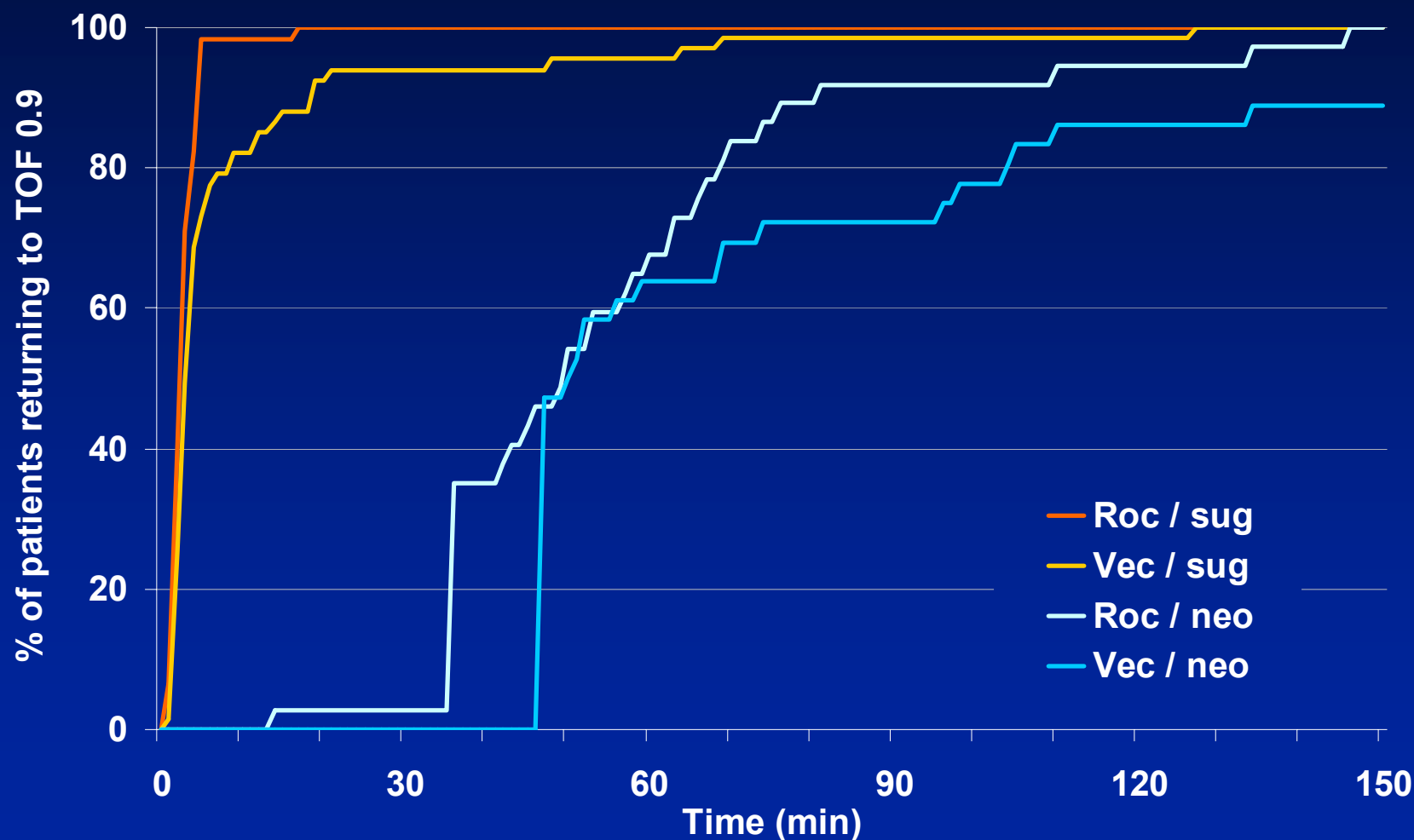
Recovery of TOF Ratio to 0.9*

Trial 19.4.302

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

* P<0.0001 versus neostigmine

Recovery after Sugammadex 4.0 mg/kg or Neostigmine 70 mcg/kg at 1-2 PTC



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

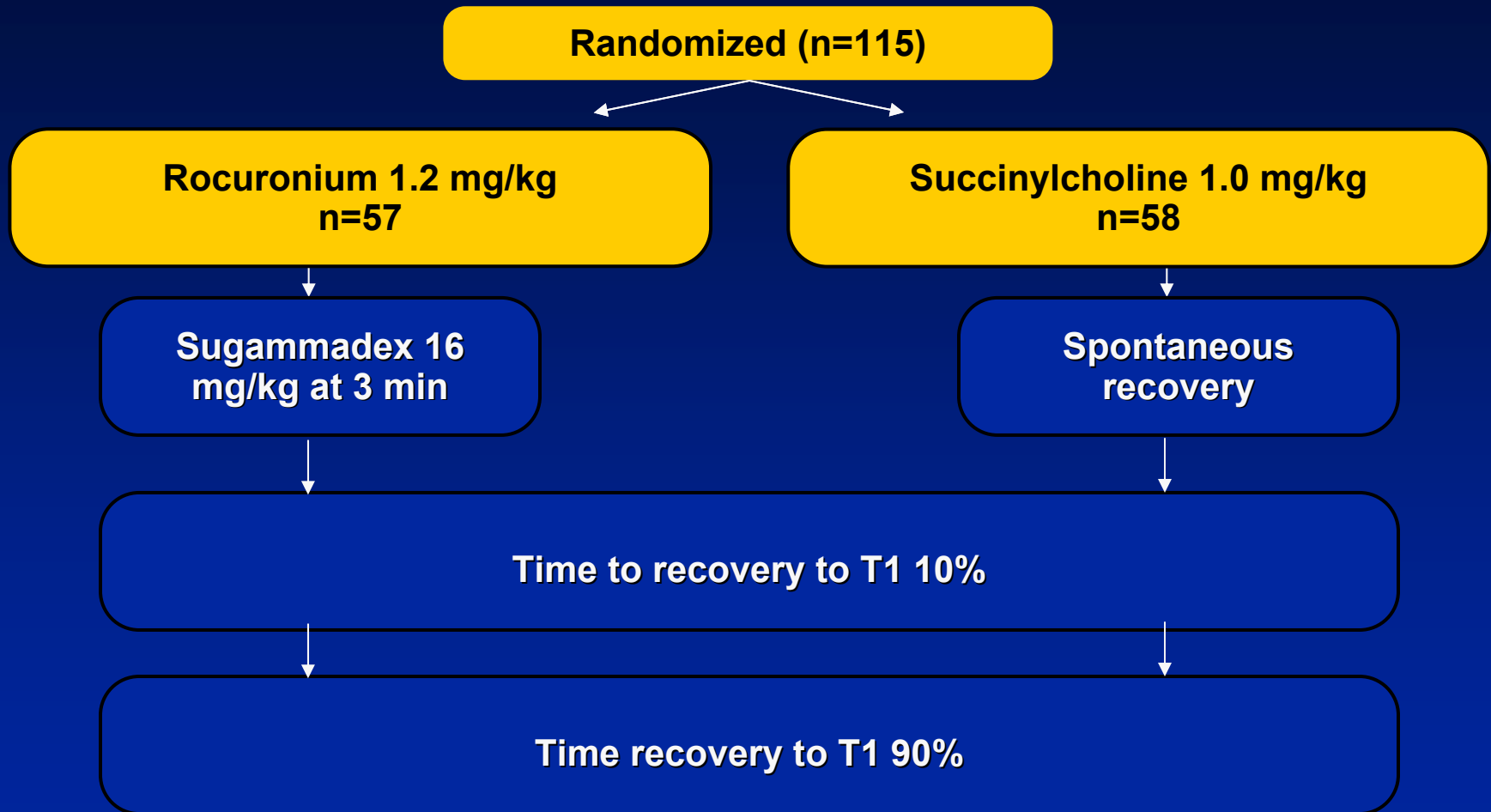
Efficacy Variables

- **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

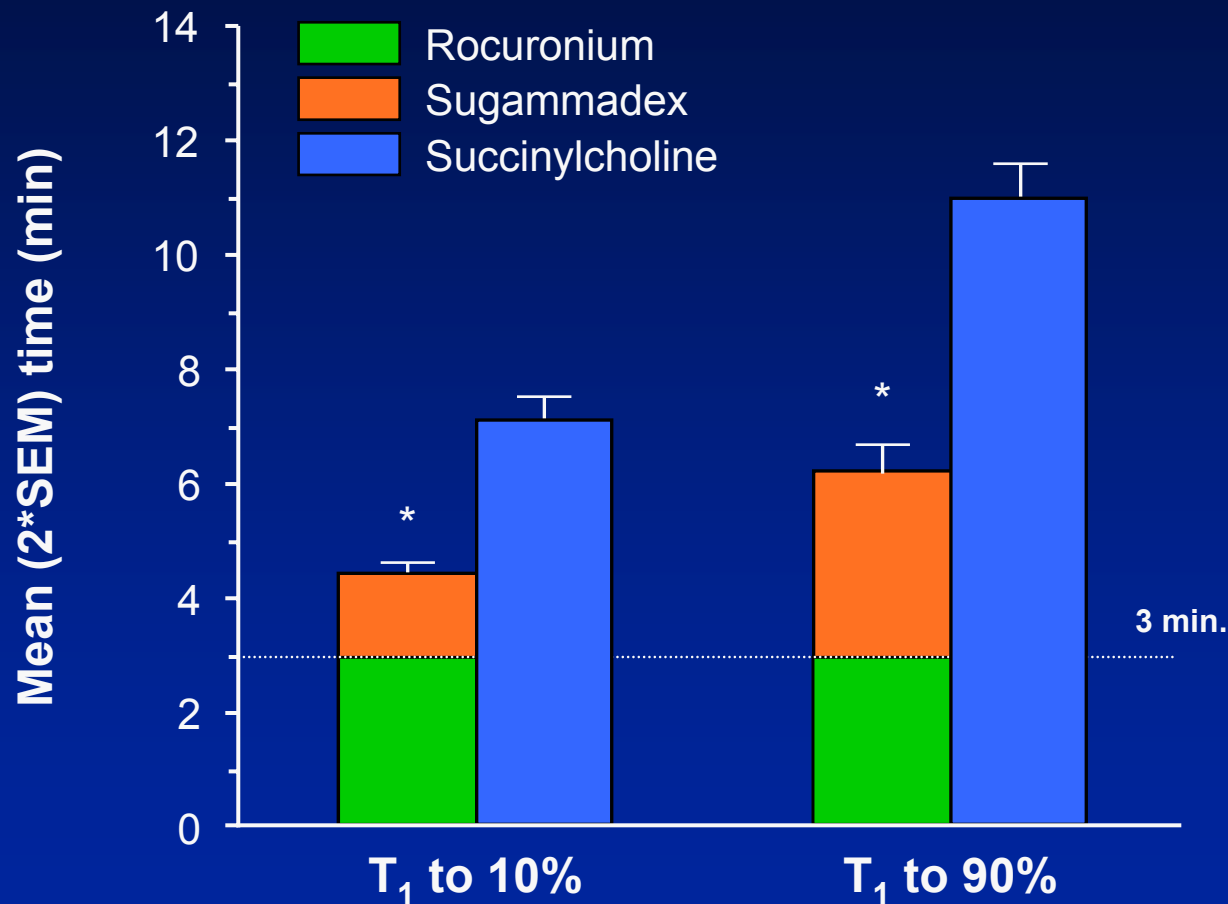
Design Elements

- 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

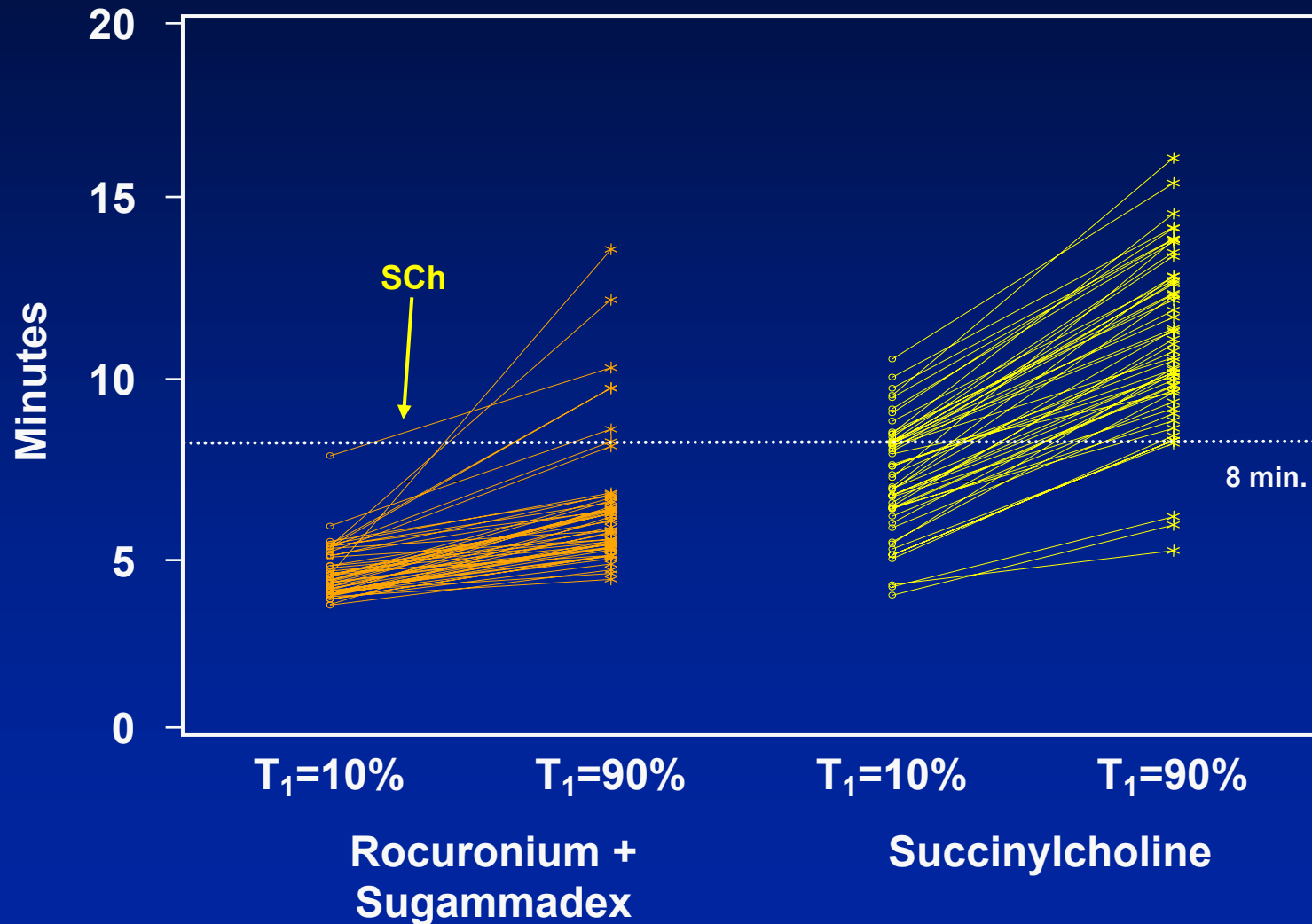


Trial 19.4.303, Mean (2xSEM) Times to T₁ 10% and 90%



* 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)

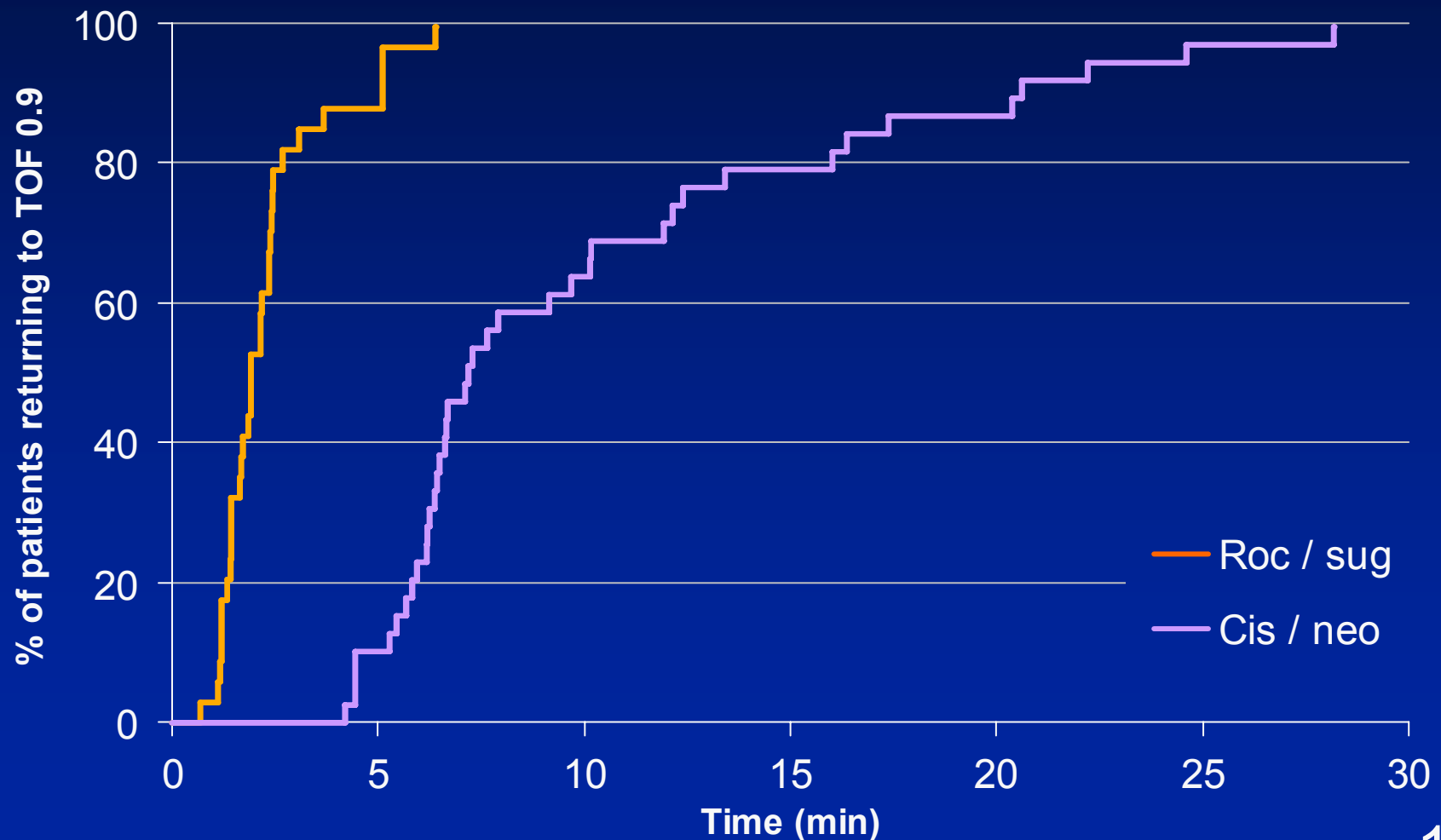
Objective:

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

Neuromuscular Blocking Agent	Rocuronium and Sugammadex 2.0 mg/kg	Cisatracurium and Neostigmine 50 mcg/kg
n	34	39
Median (minutes)	1.9*	7.2
Range	0.7-6.4	4.2-28.2

* 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

Treatment Group 4.0 mg/kg Sugammadex

n	177
Median (minutes)	1.8
Range	0.7 - 22.3

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

	Impaired Renal Function	Normal Renal Function
Group	$CR_{CL} < 30$ ml/min	$CR_{CL} \geq 80$ ml/min
n	15	14
Median (minutes)	1.6	1.4
Range	1.2-3.7	0.9-3.1

Recovery of TOF Ratio to 0.9

Geriatrics (Trial 19.4.305)

	Age Group			
	Adult	Geriatrics		
	18-64 yrs (n=48)	65-74 yrs (n=62)	≥ 75 yrs (n=40)	Subtotal ≥ 65 yrs (n=102)
Median (min)	2.2	2.6	3.6	2.9
Range (min)	1.2 - 7.4	0.9 - 8.8	1.0 - 9.9	0.9 - 9.9

Recovery of TOF Ratio to 0.9

Pulmonary and Cardiac Risk Factors

(Trials 19.4.308 and 19.4.309)

Trial 19.4.308 – Pulmonary	Sugammadex 2.0 mg/kg	Sugammadex 4.0 mg/kg
n	33	33
Median (min)	2.1	1.9
Range	0.8 - 12.0	0.7 - 11.5

Trial 19.4.309 – Cardiac	Placebo	Sugammadex 2.0 mg/kg	Sugammadex 4.0 mg/kg
n	36	37	36
Median (min)	34.7	1.7	1.3
Range	16.9 - 66.5	0.9 - 6.9	0.7 - 3.2

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

Parameter	Statistic/ Category	Placebo	Total Sugammadex
Age (yrs)	n	140	1845
	Mean (SD)	51 (16)	50 (16)
	Median	52	50
	Min. - max.	19 - 86	18 - 92
Age (n [%])	n	140	1845
	18 - 64 yr	113 (81)	1491 (81)
	65 - 74 yr	15 (11)	232 (13)
	≥ 75 yr	12 (9)	122 (7)
Gender (n[%])	n	140	1845
	Male	85 (61)	966 (52)
	Female	55 (39)	879 (48)

Exposure to Sugammadex

Phase I-III

In Association with Rocuronium or Vecuronium

	Subjects	
	Rocuronium	Vecuronium
Total	1509	398

Sugammadex Only (Volunteer Studies)

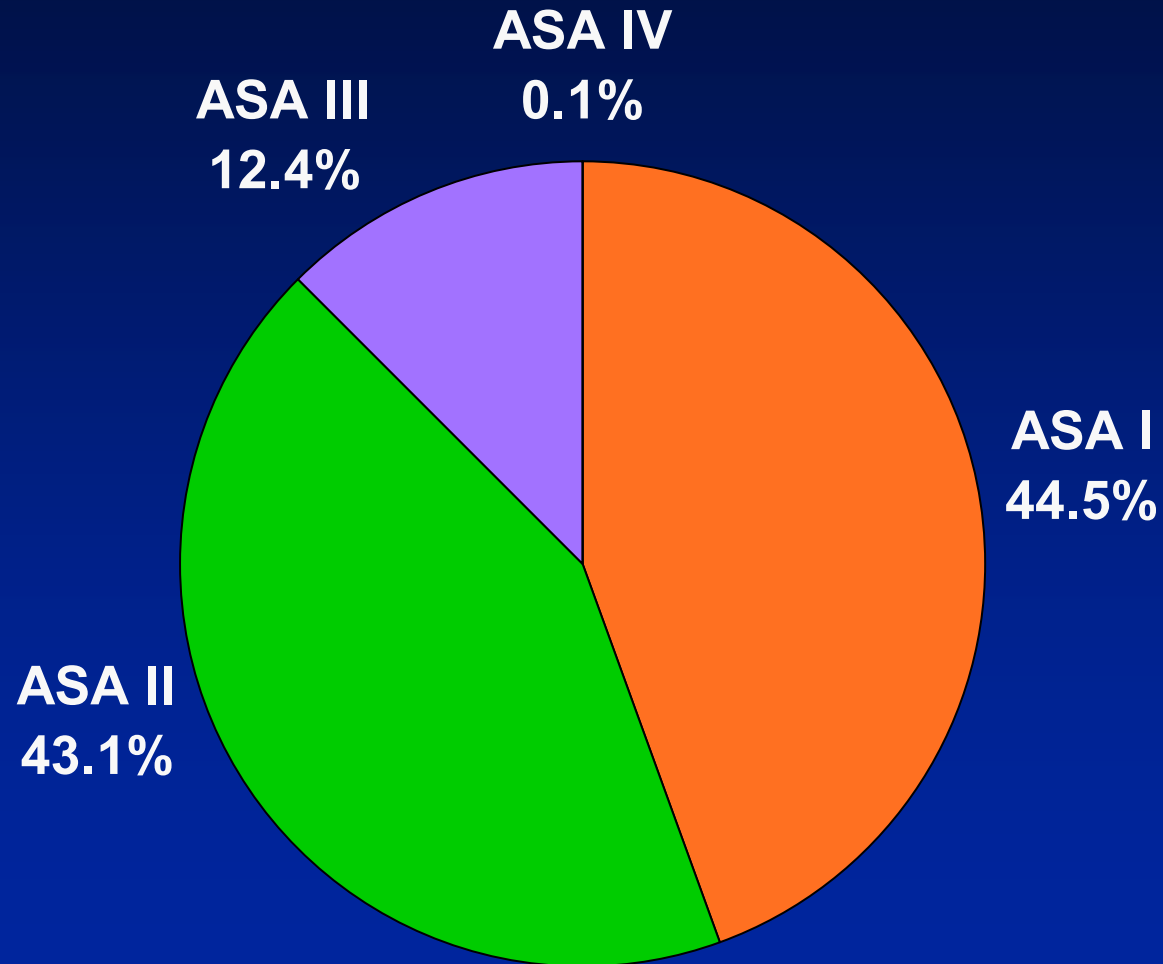
Exposures (subjects)	
Total	443 (196)

Exposure to Sugammadex

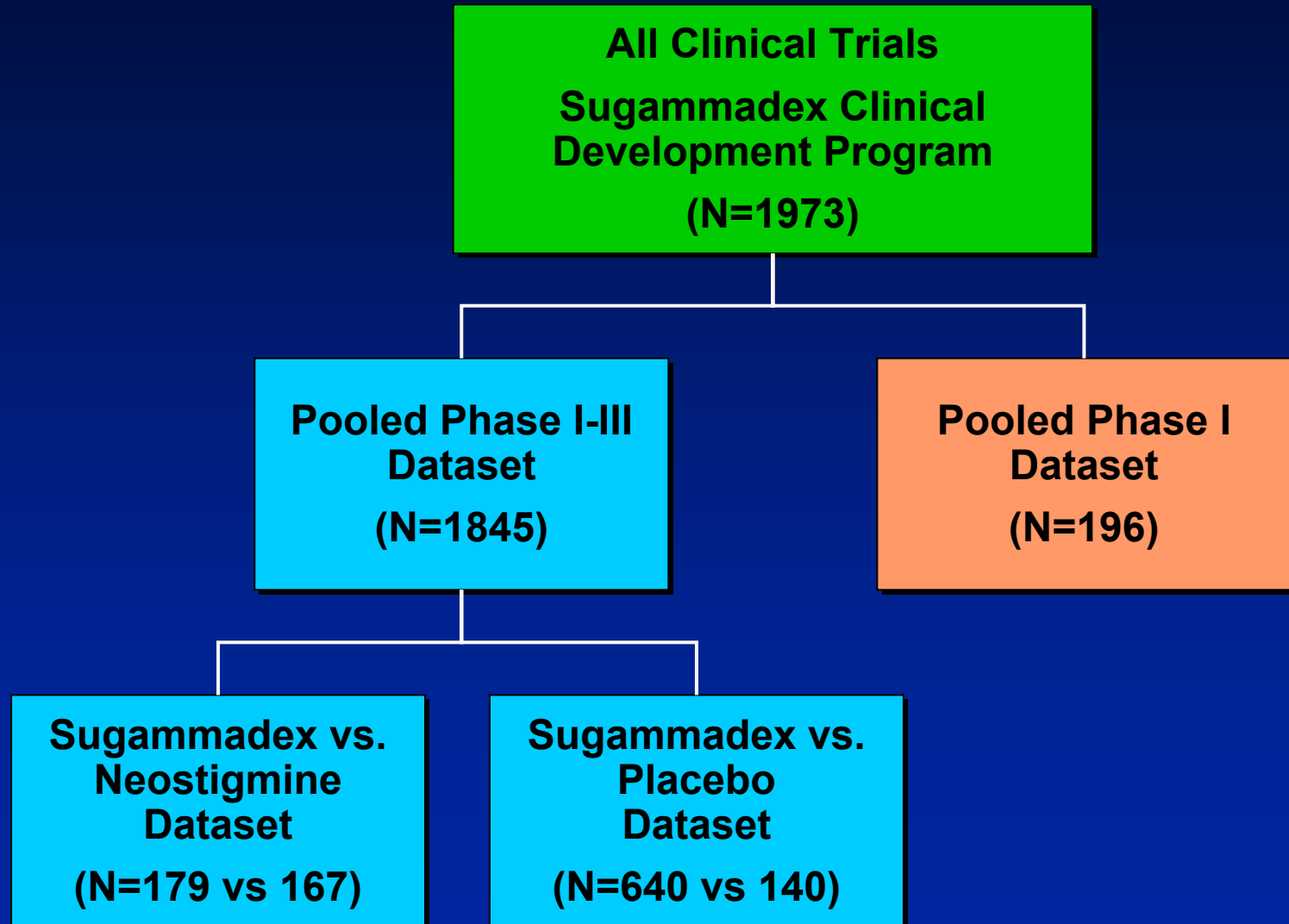
Special Populations

Special Population		Subjects
Cardiac Impaired	Medical History	188
	Dedicated Study (19.4.309)	76
Renal Impaired (GFR < 80 ml/min)	Baseline Blood Sample GFR acc. Cockcroft	226
	Dedicated Study (19.4.304)	15
Pulmonary Impaired	Medical History	136
	Dedicated Study (19.4.308)	68
Hepatic Impaired	Medical History	77

ASA Class Allocation



Exposure to Sugammadex Datasets



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

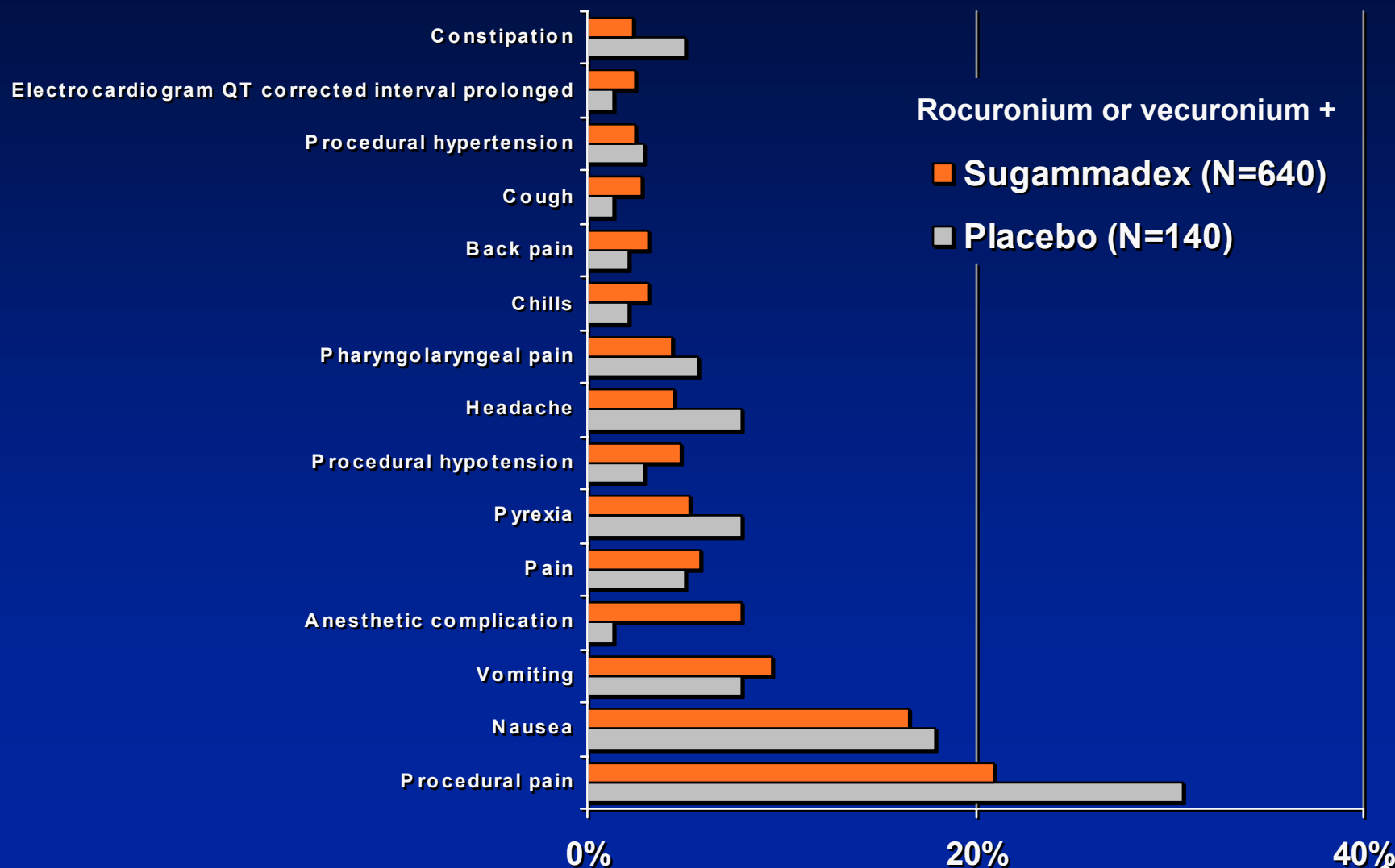
AEs and SAEs

Sugammadex vs. Placebo: Incidence of Subjects with at Least one AE

	Sugammadex* (N=640)	Placebo (N=140)
Total	68.3%	72.1%
Rocuronium	66.7%	69.8%
Vecuronium	75.4%	83.3%

* Followed by administration of rocuronium or vecuronium

Sugammadex vs. Placebo: Most Frequently Reported AEs (at Least 2.0%)



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

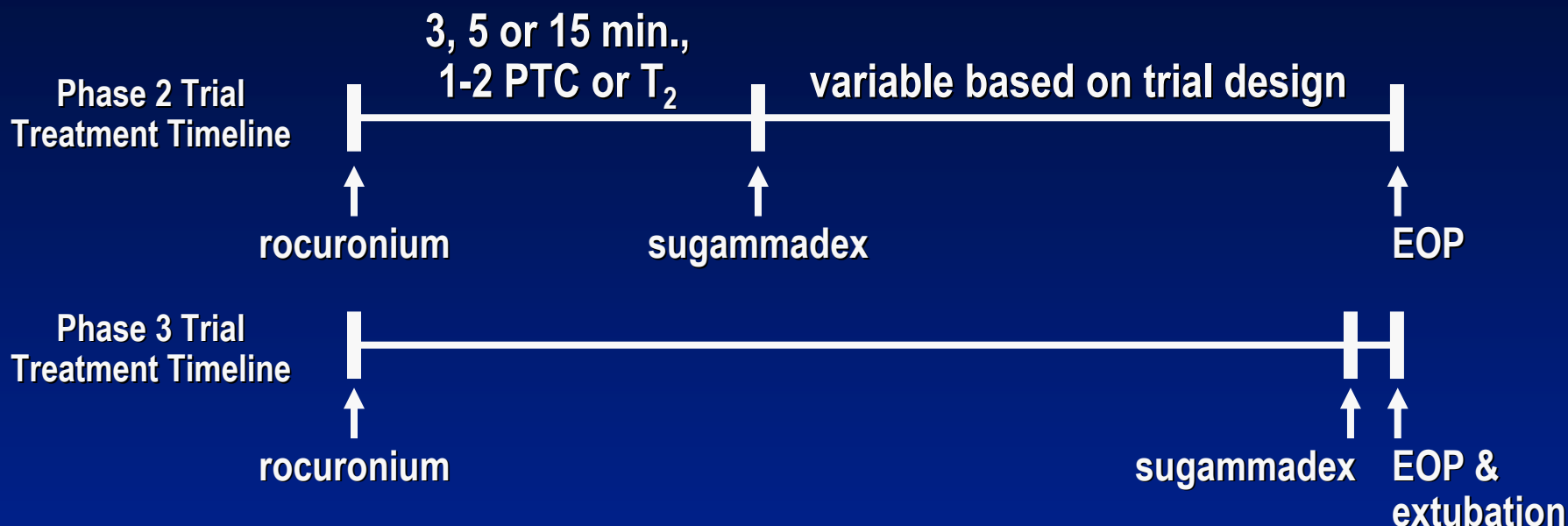
- **Anesthetic complication**
- **Dysgeusia**
- **Hypersensitivity**

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

	Sugammadex	Neostigmine	Placebo
All Trials	3.0%	0.5%	1.4%
Phase 2	5.9%	—	2.4%
Phase 3	0.7%	0.5%	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

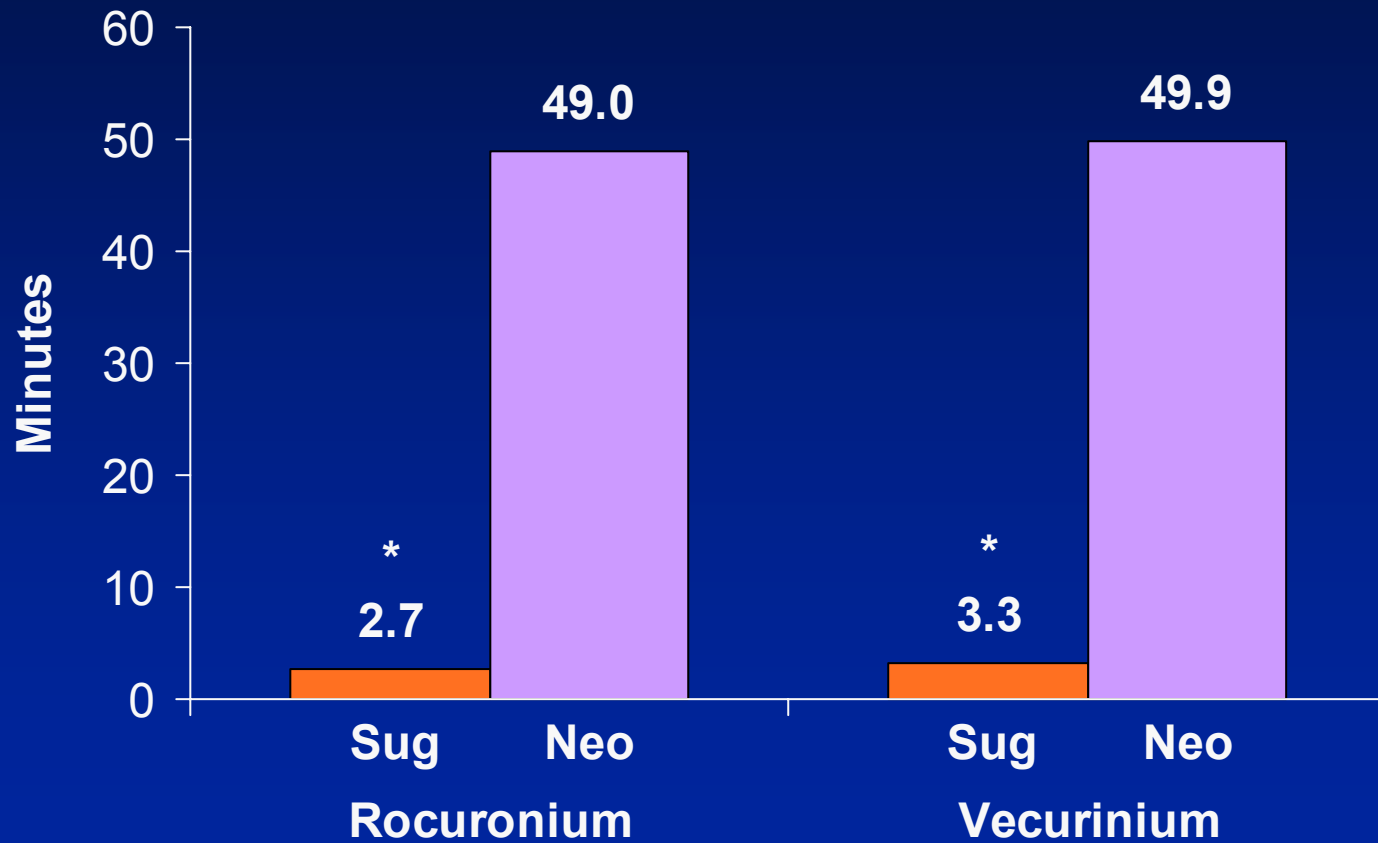
Summary

Ronald D. Miller, M.D.

Are We Meeting an Unmet Need?

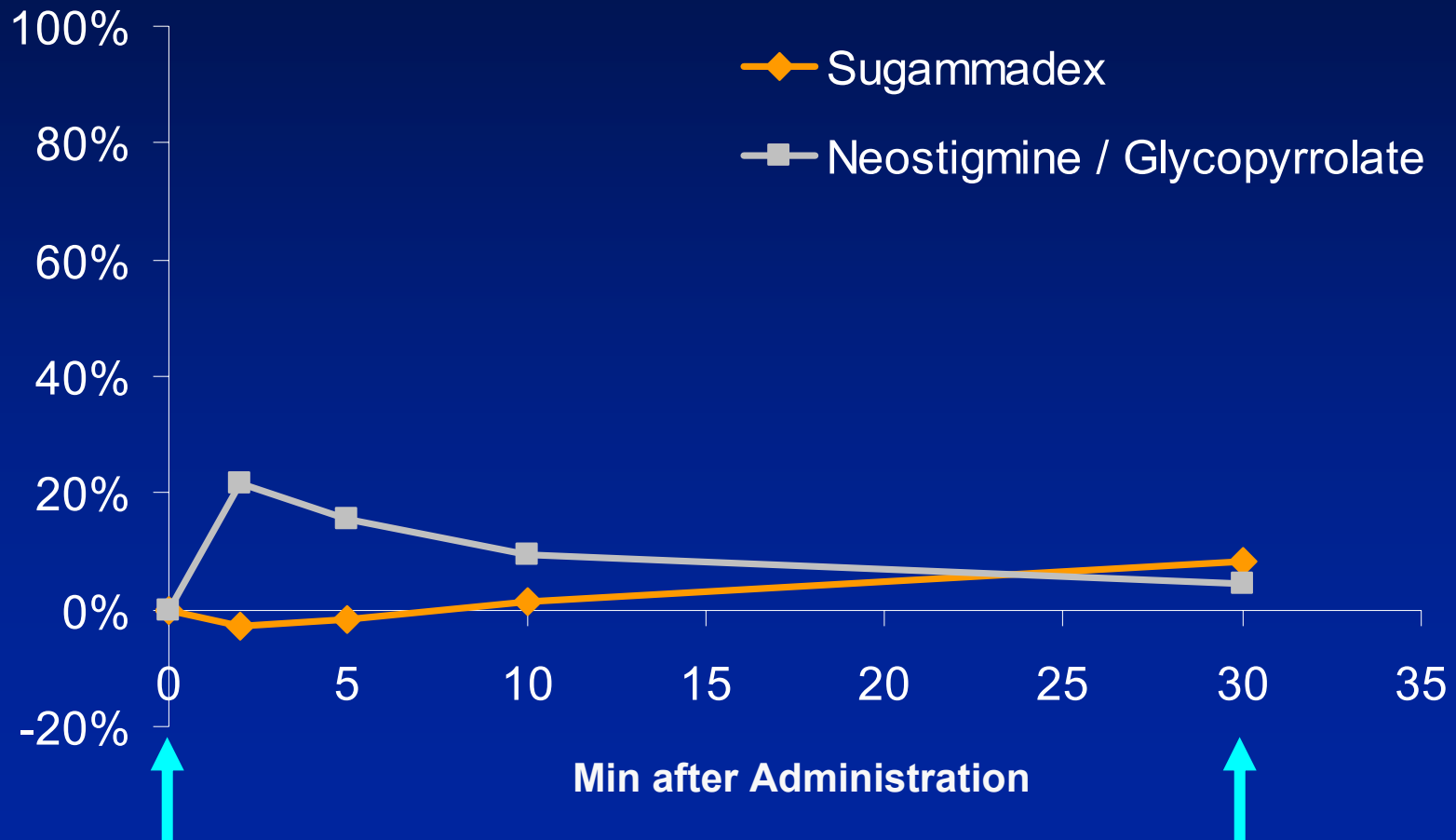
- **Minimize or eliminate neostigmine**
- **Minimize or eliminate succinylcholine**
- **Residual Postoperative Paralysis**
- **Increase Intraoperative Flexibility**
- **Increase Perioperative Safety**

Recovery after Sugammadex 4.0 mg/kg or Neostigmine 70 mcg/kg at 1-2 PTC, Median Time to Recovery TOF 0.9

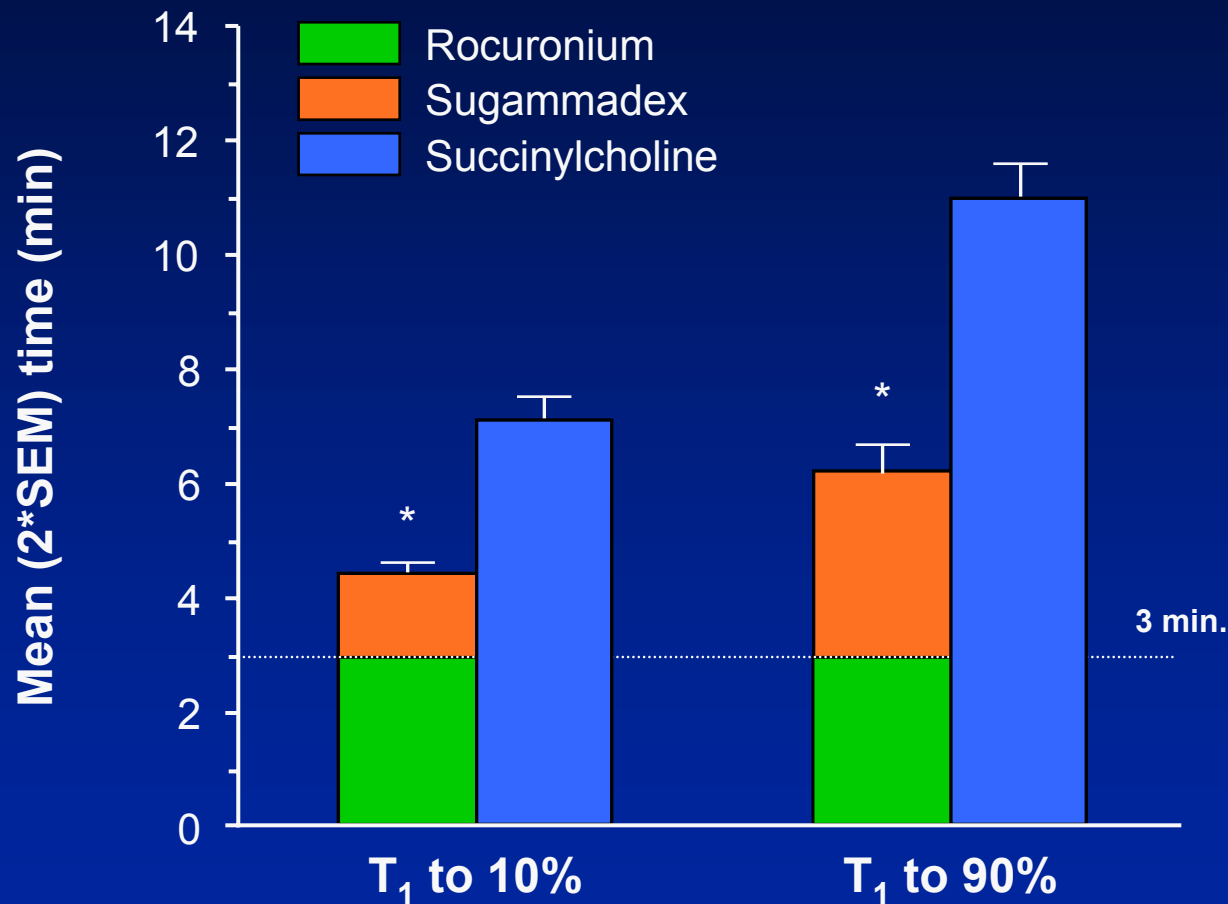


* $P < 0.0001$ versus neostigmine treatment group

Percentage Change in Heart Rate after Administration of Sugammadex or Neostigmine/Glycopyrrolate



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