

# 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<sub>2</sub> (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

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## 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

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## Mechanism of Action and Pharmacology and Pharmacokinetics

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

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

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## Non-clinical Safety Overview

***Diels van den Dobbelsteen, Ph.D.***

Principal Toxicologist  
Organon, a part of Schering-Plough Corporation

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## Efficacy & Safety Clinical Overview

***Patrick Boen, M.D.***

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

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## Summary

***Ronald D. Miller, M.D.***

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# List of Respondents

**Name, Title**

**Affiliation**

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**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

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**Terri G. Monk, M.D.**

Professor, Department of Anesthesiology

Duke University Medical Center,  
Durham, NC

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**Scott Groudine, M.D.**

Professor of Anesthesiology

Albany Medical Center  
Albany, NY

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**Harry K. Genant, M.D.**

Professor Emeritus

Departments of Radiology,  
Medicine and Orthopedic Surgery  
University of California  
San Francisco, CA

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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,  
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**

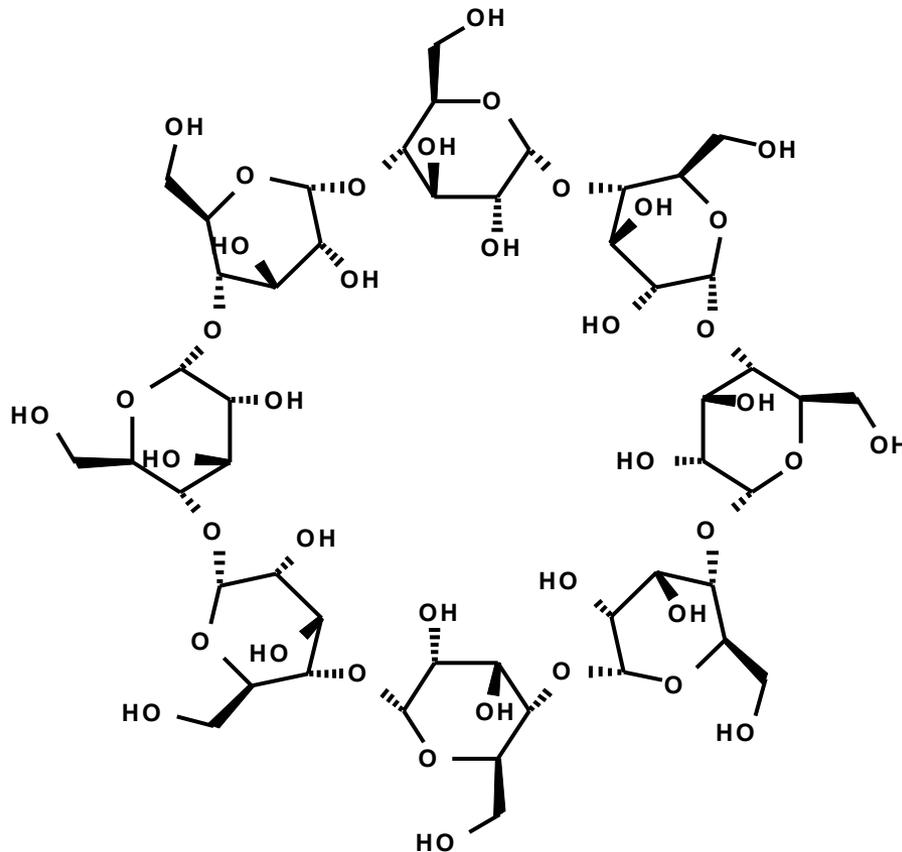
- **Inactivation of the NMBA**
- **Rapid chemical interaction between NMBA and encapsulating agent**

# Cyclodextrins

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

# Cyclodextrins

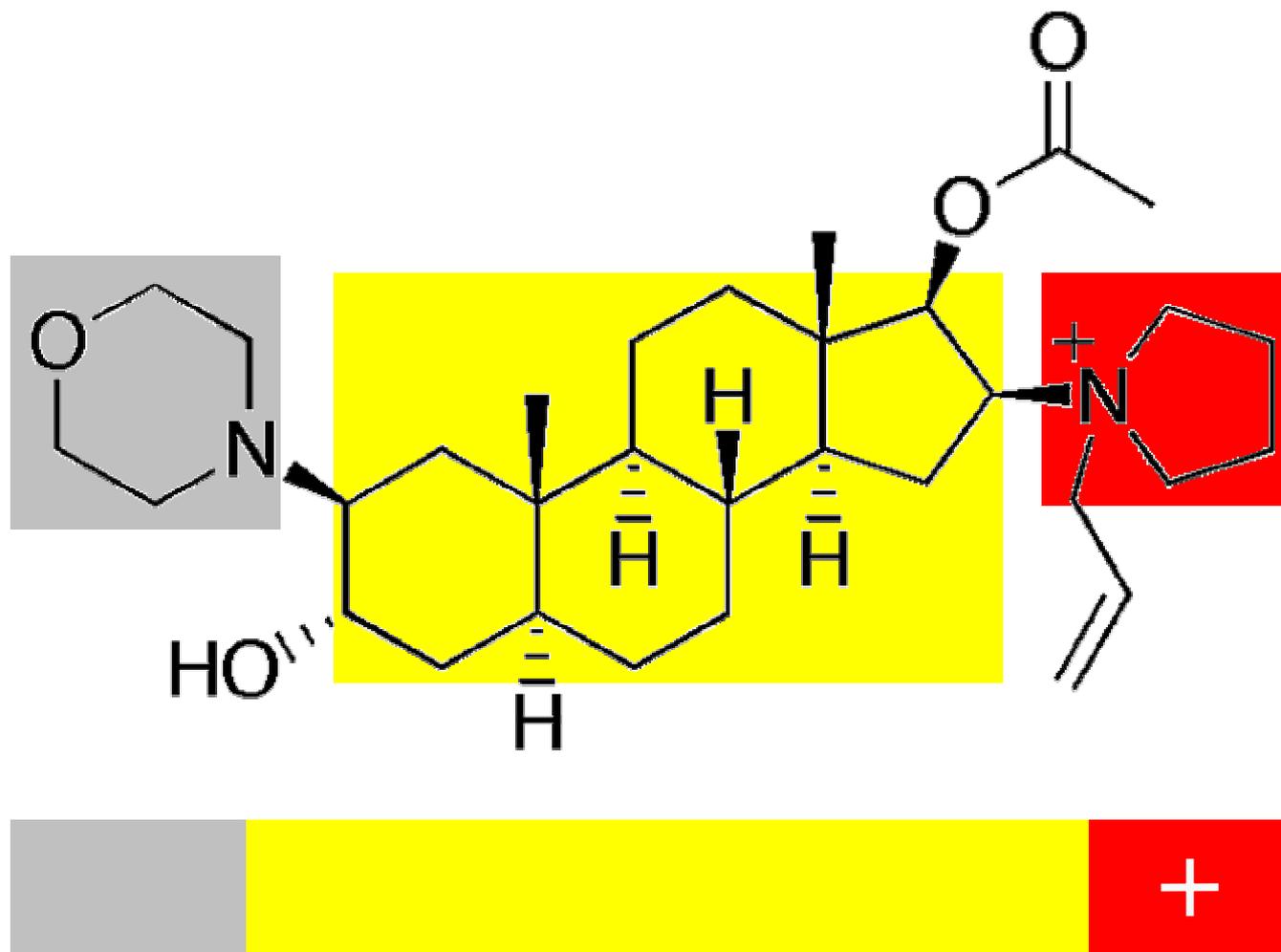
$\gamma$ -cyclodextrin: 8 sugar molecules forming a rigid ring with a central lipophilic cavity



# Properties of Cyclodextrins

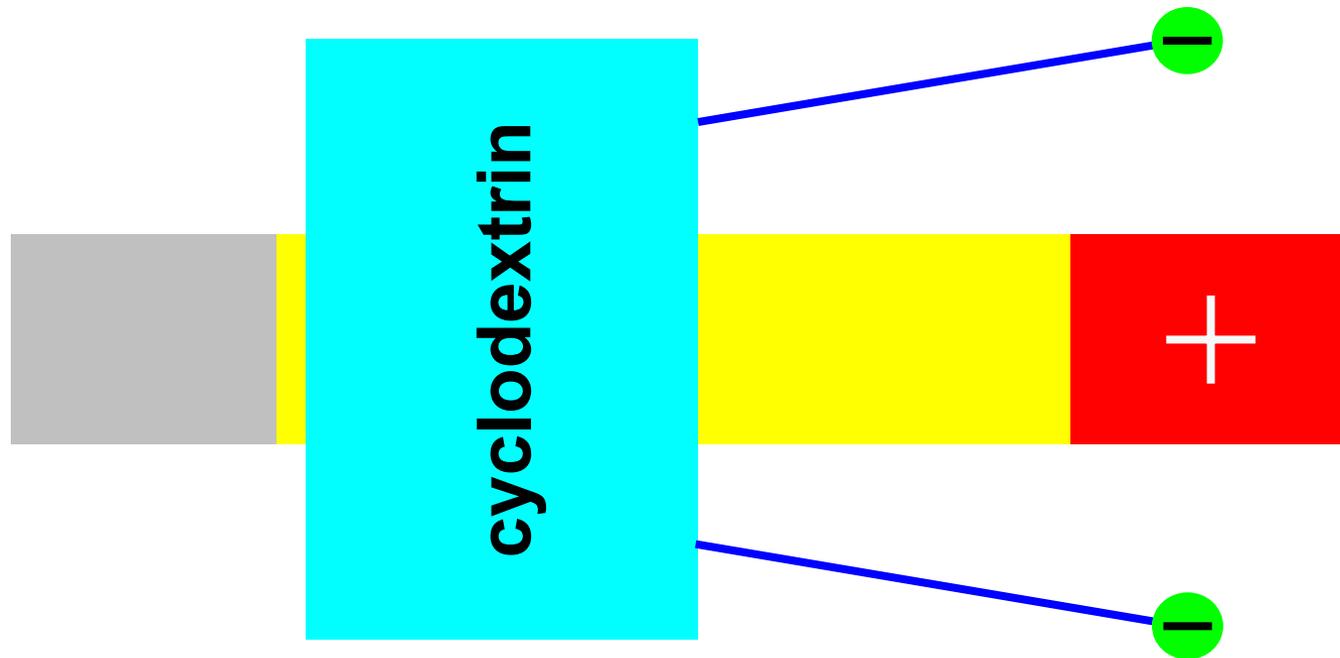
- **Very water-soluble**
- **Not metabolized**
- **Renally excreted**

# Properties of Rocuronium

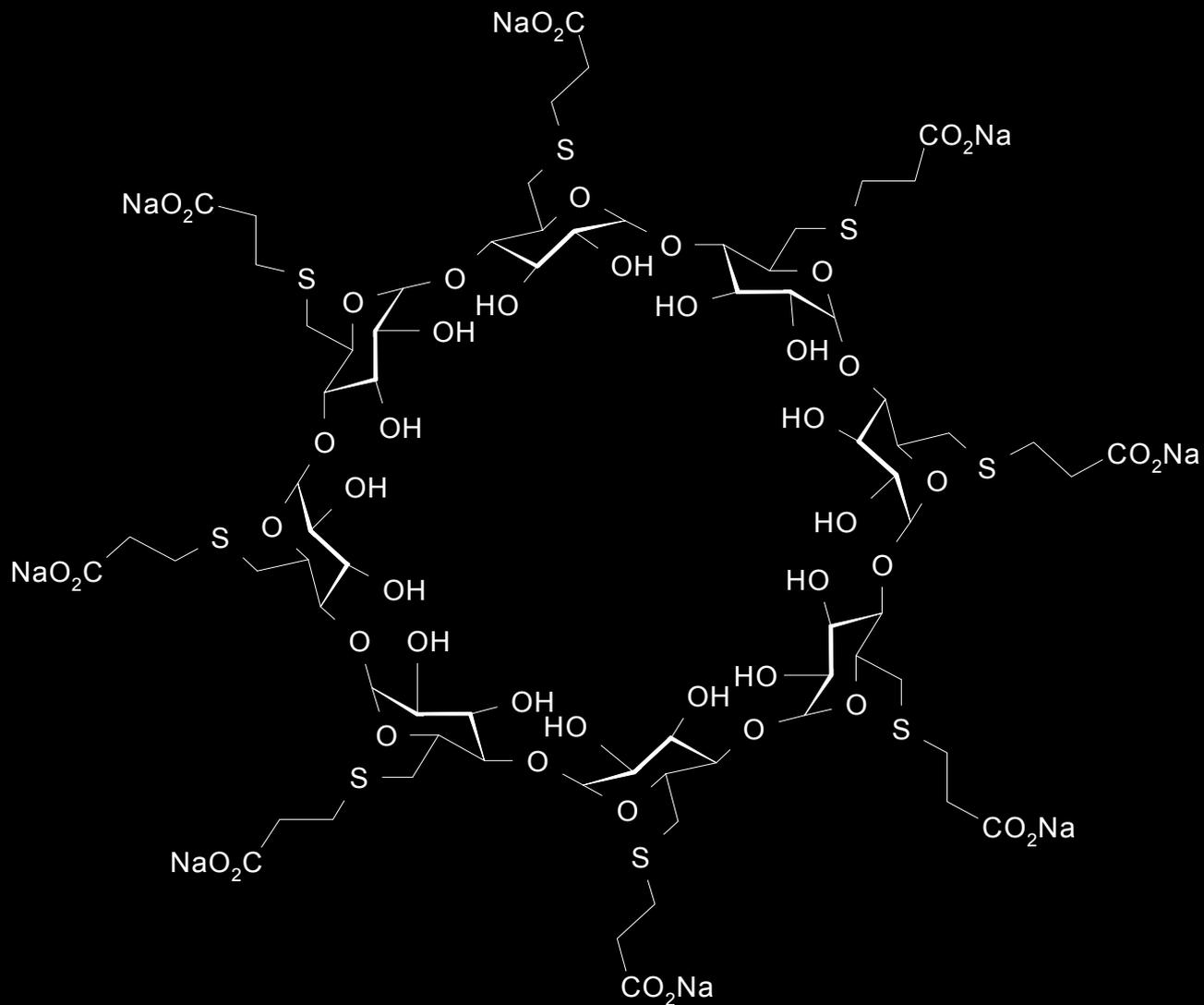


# Design of Reversal Agent

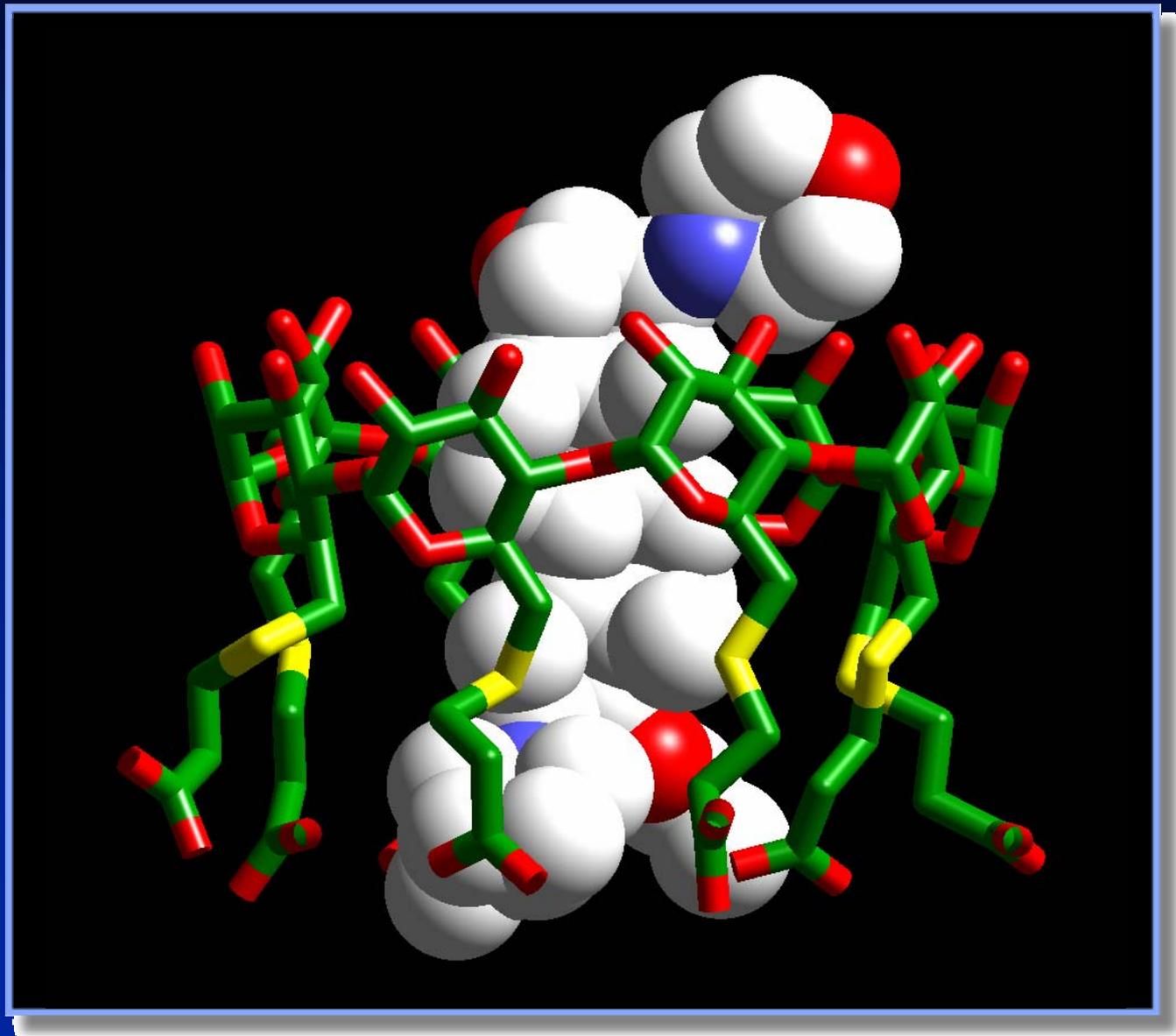
$\gamma$ -cyclodextrins can be modified to increase affinity for rocuronium



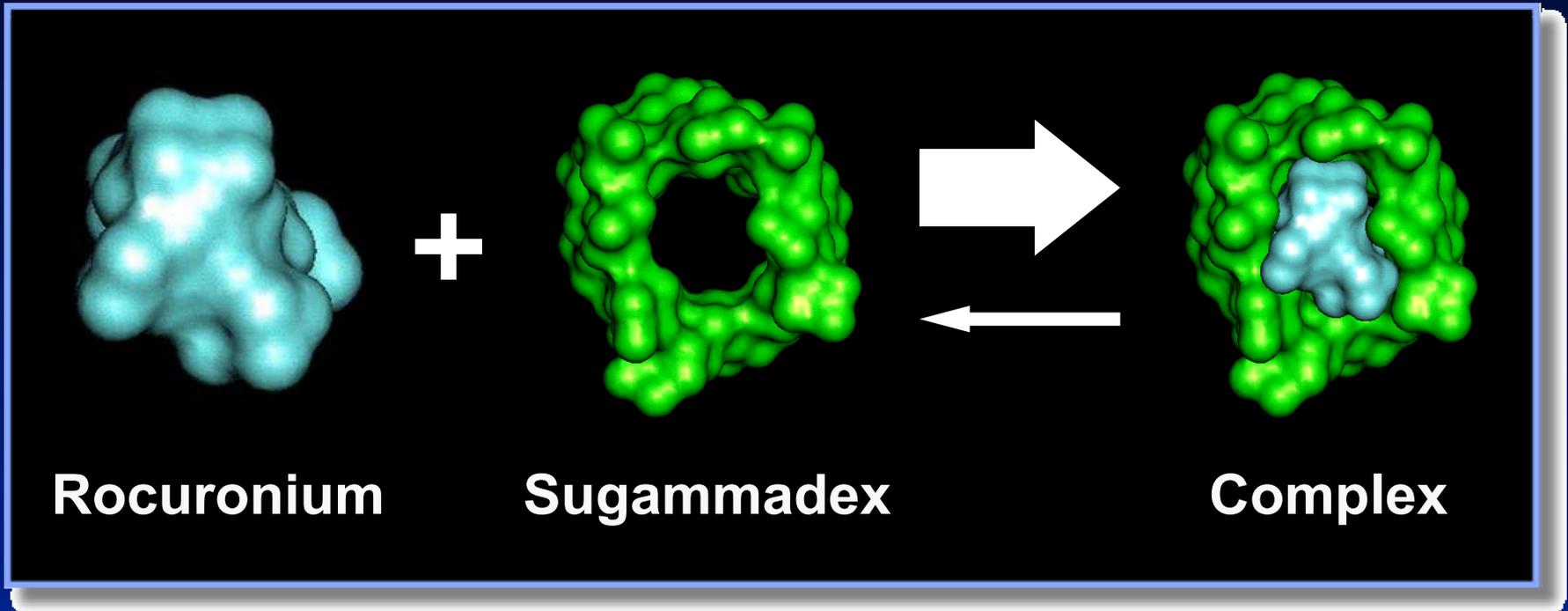
# Sugammadex



# Rocuronium – Sugammadex Complex



# Mechanism of Action

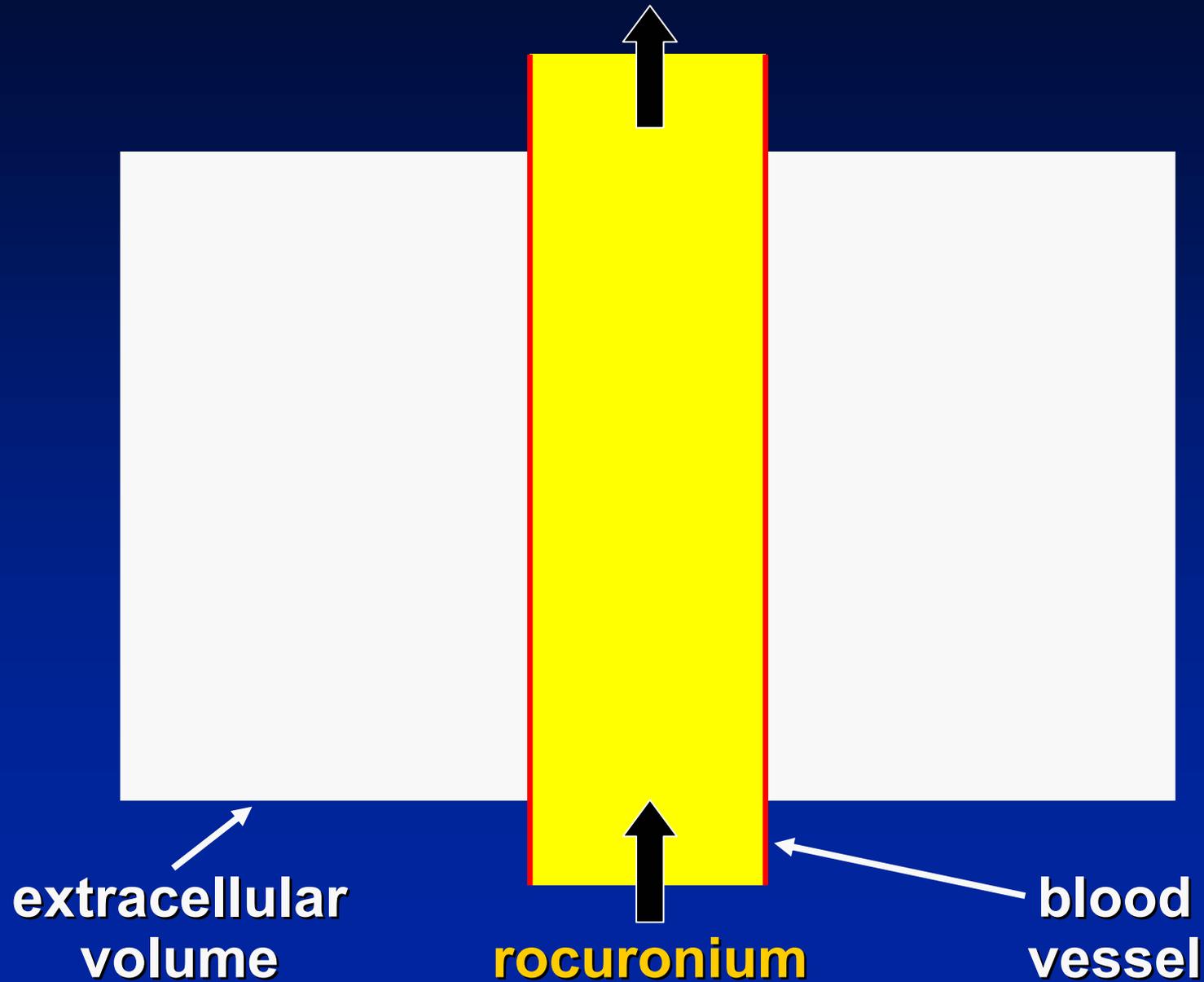


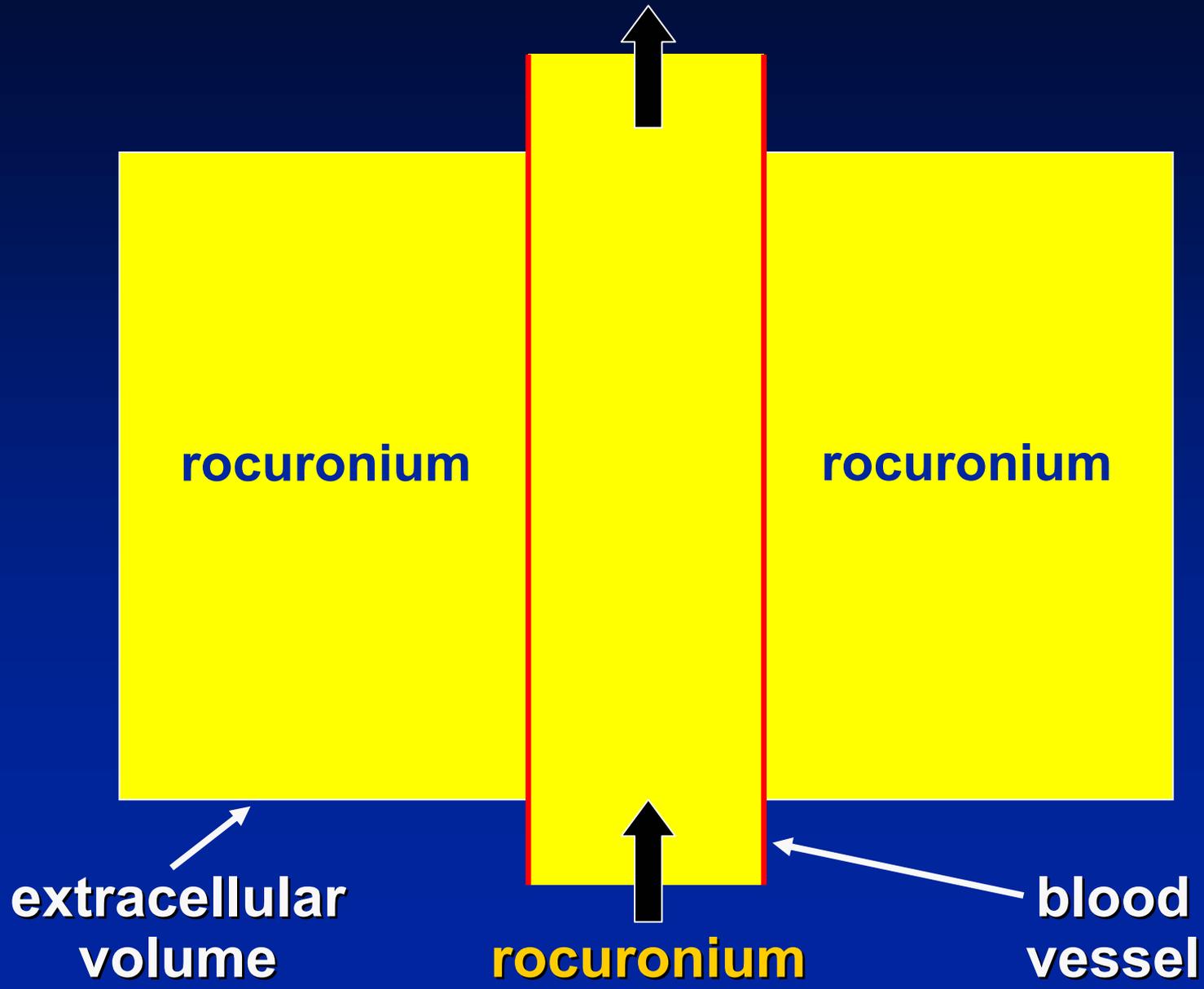
affinity ( $K_A$ M <sup>-1</sup> )	rocuronium	vecuronium
$\gamma$ -cyclodextrin	13,200	1,176
sugammadex	25,000,000	10,000,000

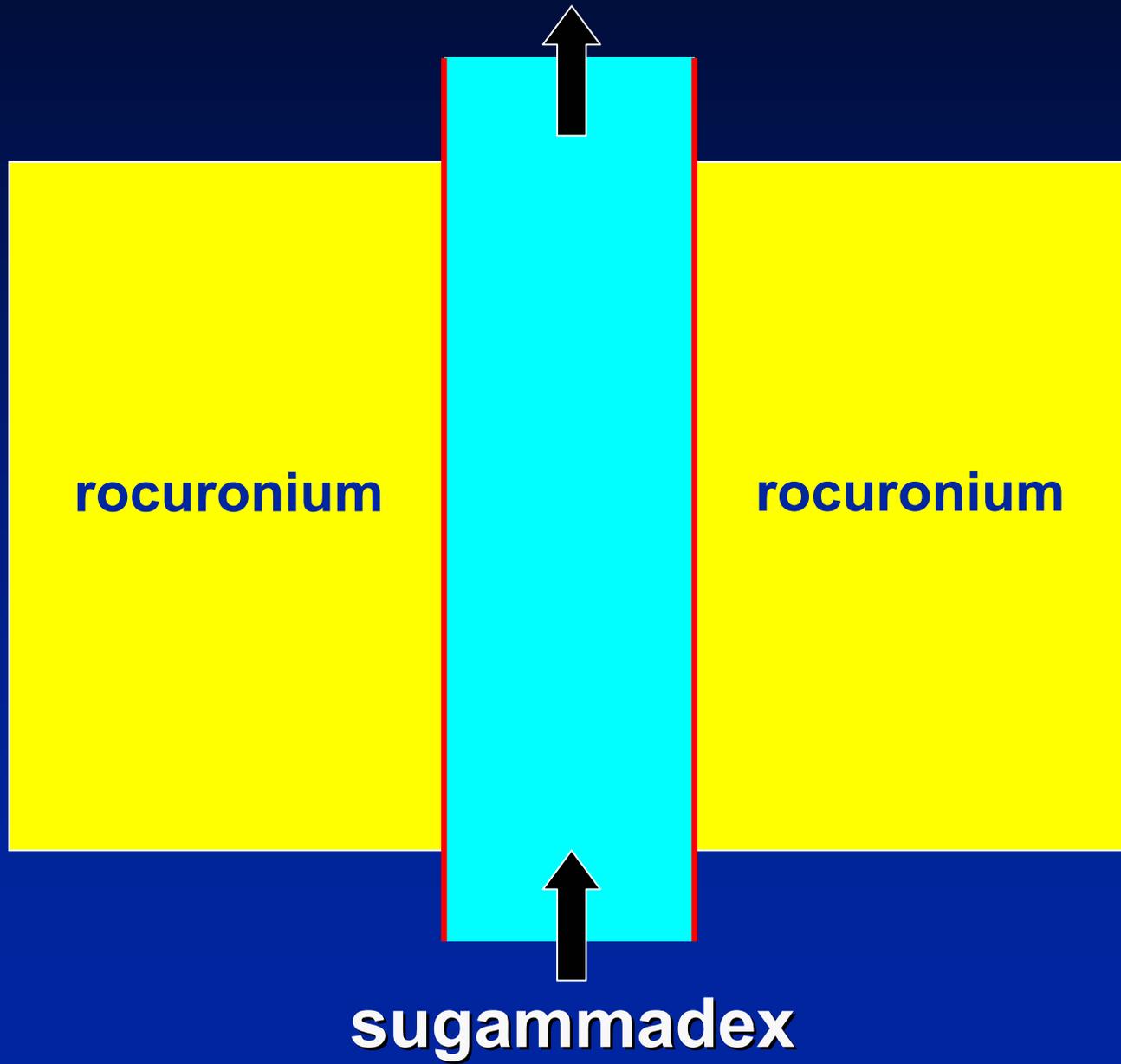
# Selectivity

<b>NMBA</b>	<b><math>K_A</math> value (megaM<sup>-1</sup>)</b>
<b>Rocuronium</b>	<b>25.0</b>
<b>Vecuronium</b>	<b>10.0</b>
<b>Pancuronium</b>	<b>2.6</b>
<b>Cisatracurium</b>	<b>0.005</b>
<b>Succinylcholine</b>	<b>0.000</b>

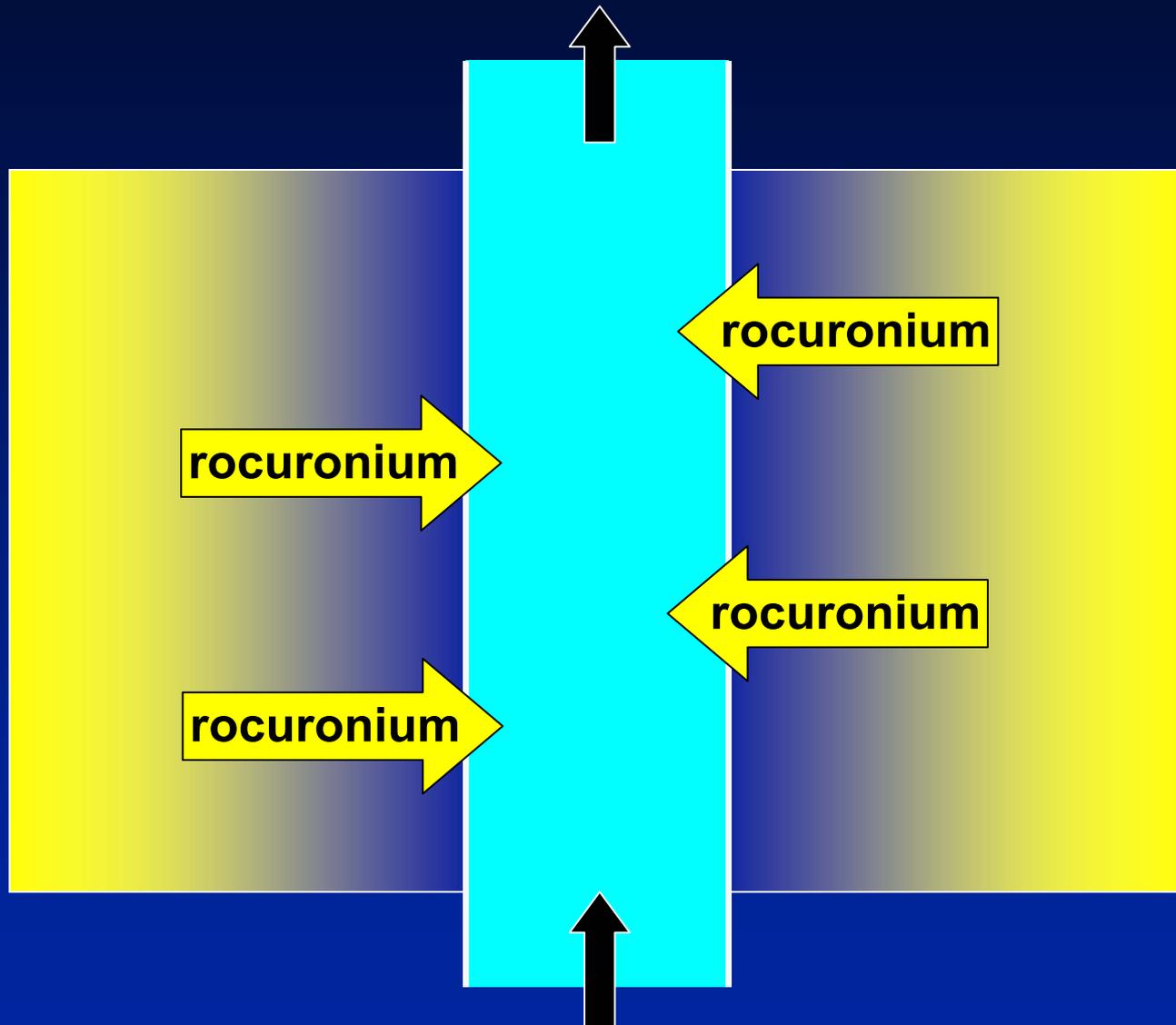
# Speed of Reversal



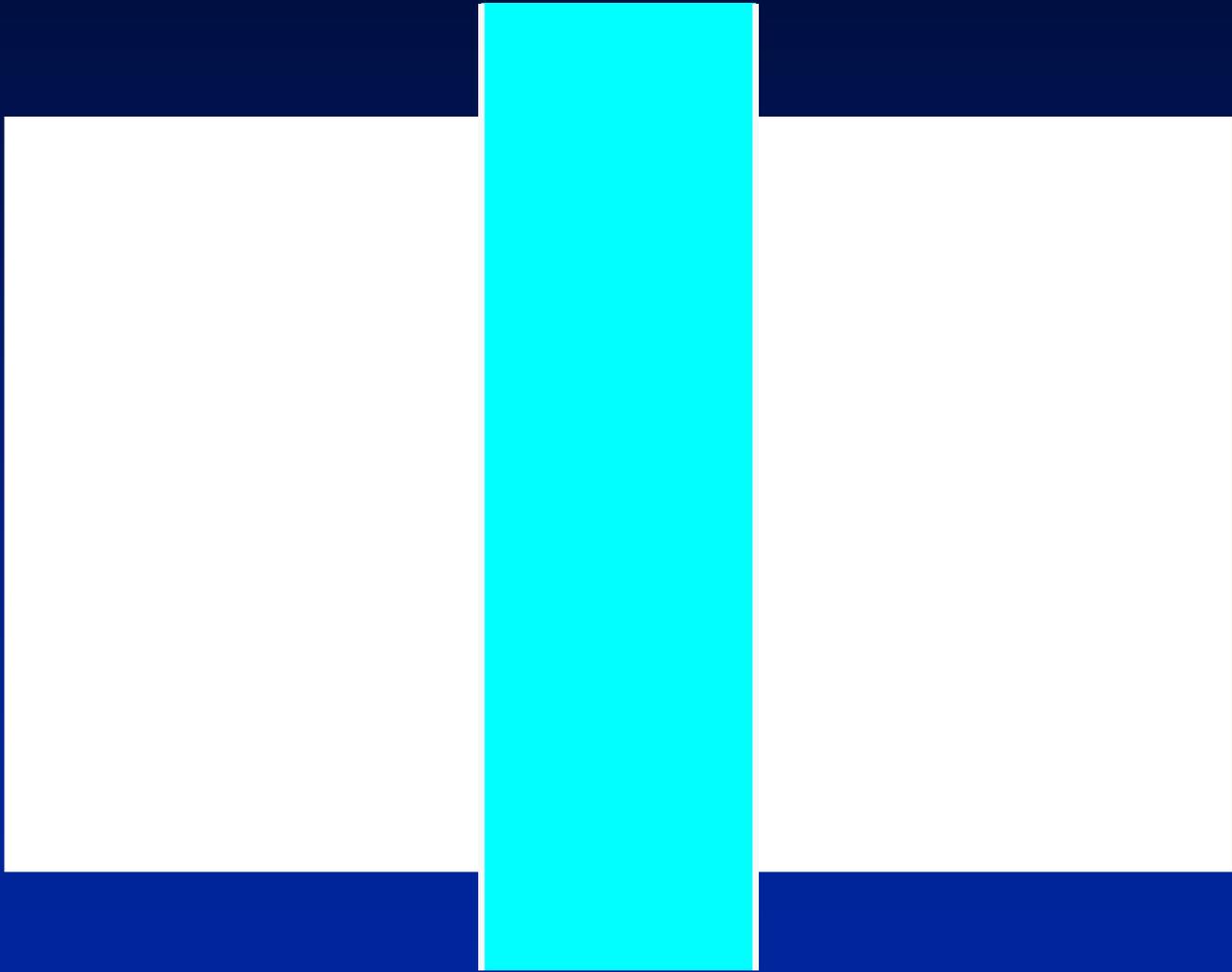




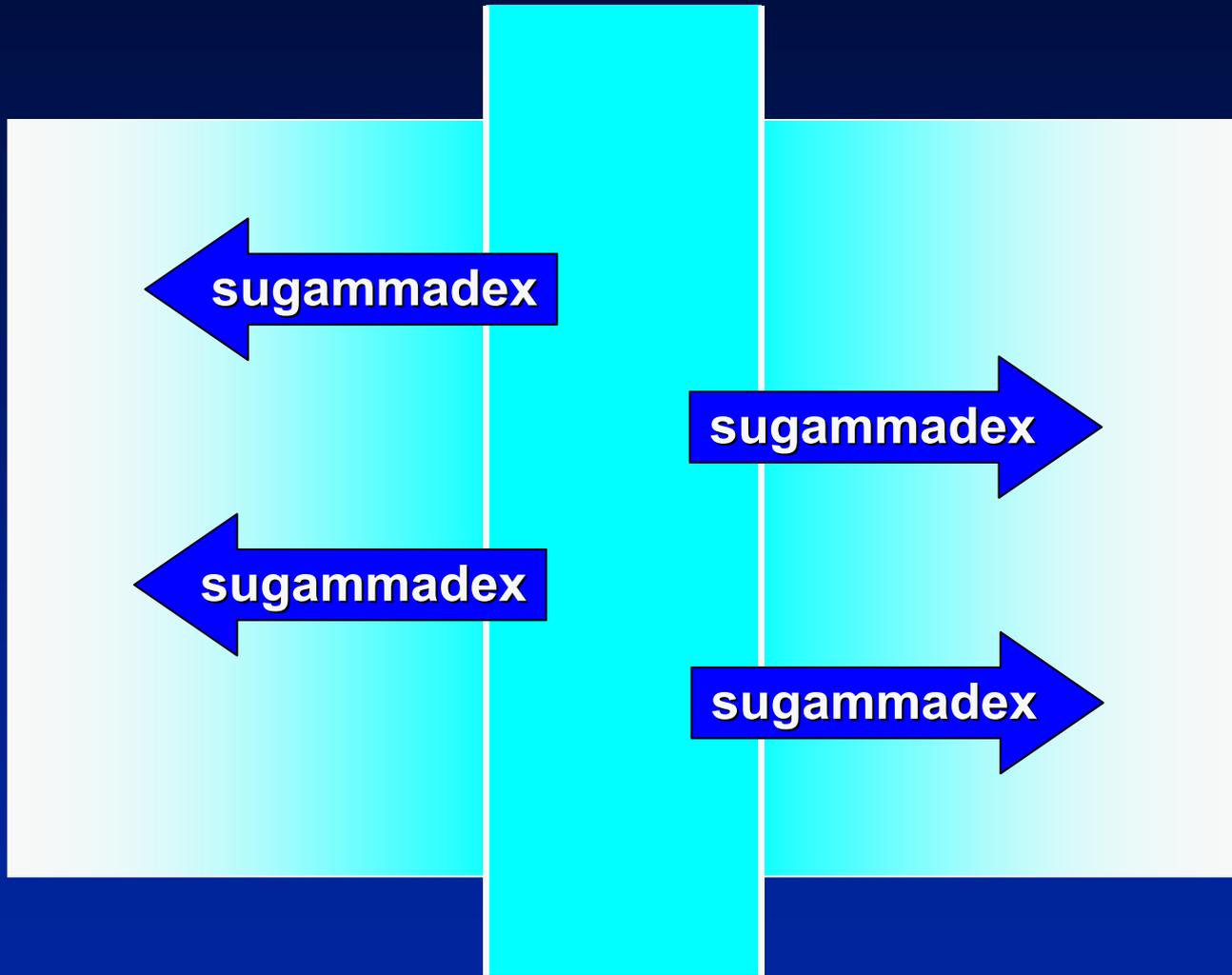
**sugammadex**



sugammadex

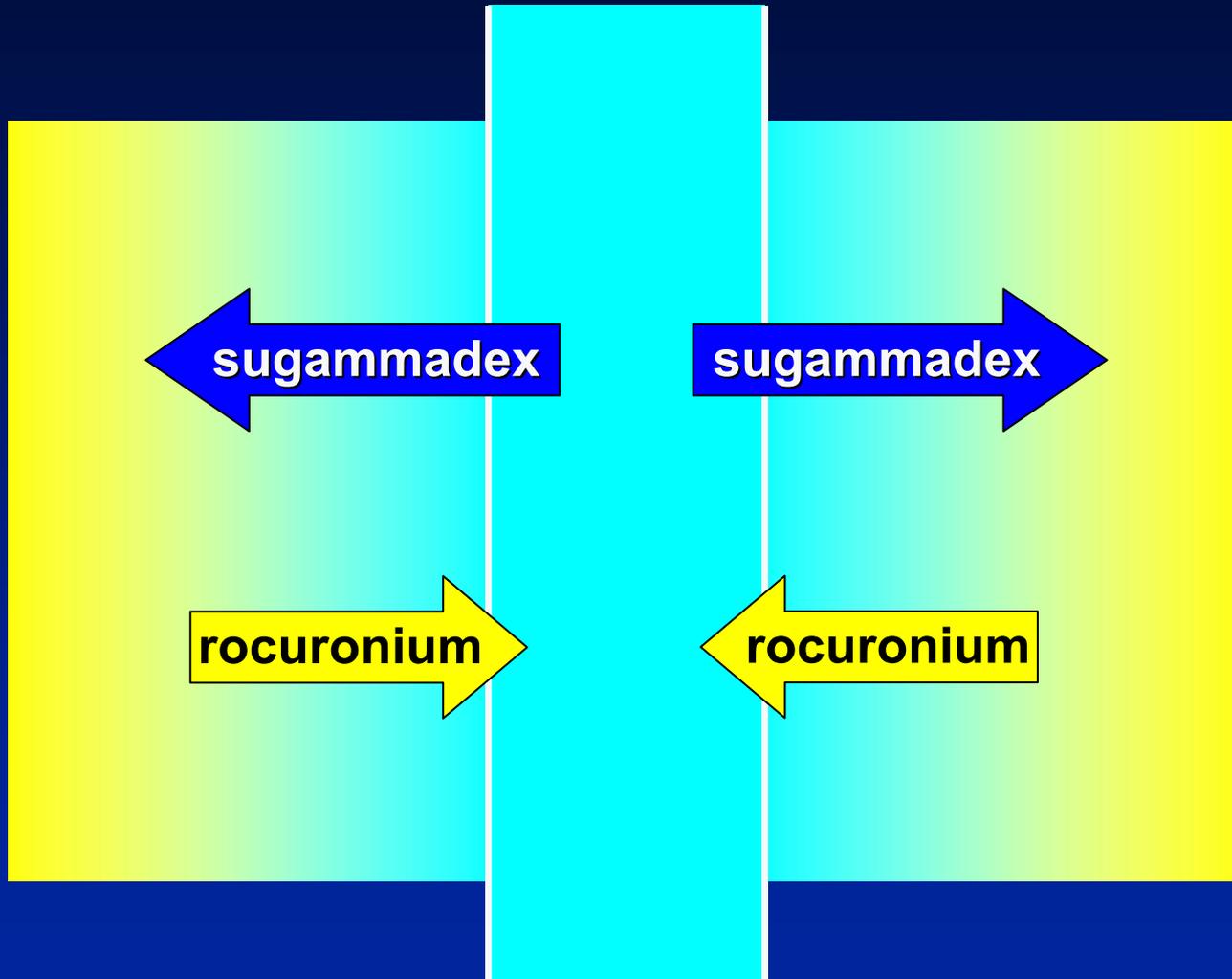


**sugammadex**



**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

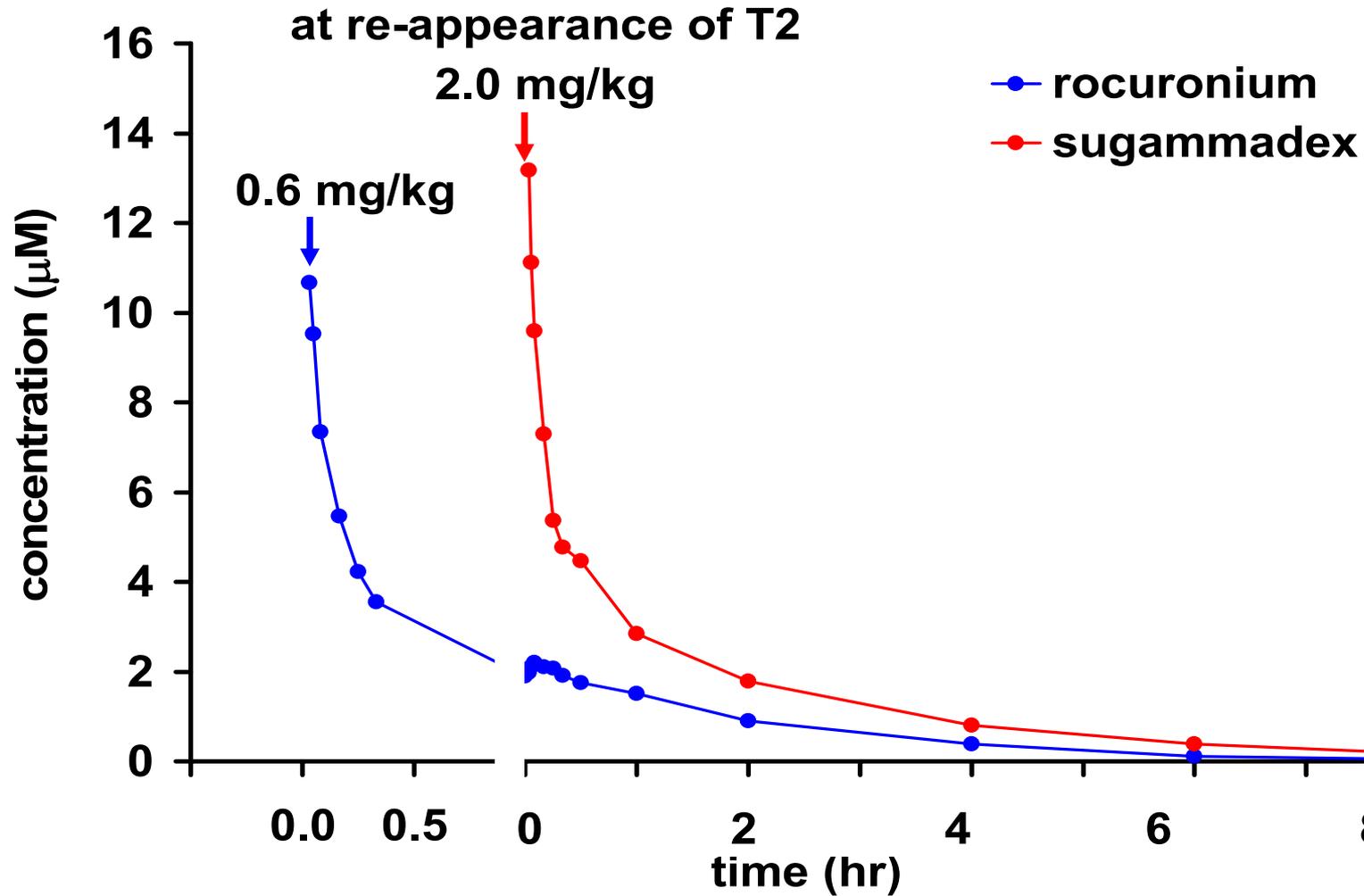
## Basic PK of Sugammadex

- **Volume of distribution:  $\approx 12-15$  L**
- **Plasma half-life:  $\approx 2.2$  h**
- **Clearance:  $\approx 91$  mL/min ( $\approx$  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 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 Dobbelen, 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-<math>\beta</math>-CD in Vfend<sup>®</sup></i>	<i>Hydroxypropyl-<math>\beta</math>-CD in Sporanox<sup>®</sup></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 ( $\mu$ 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:

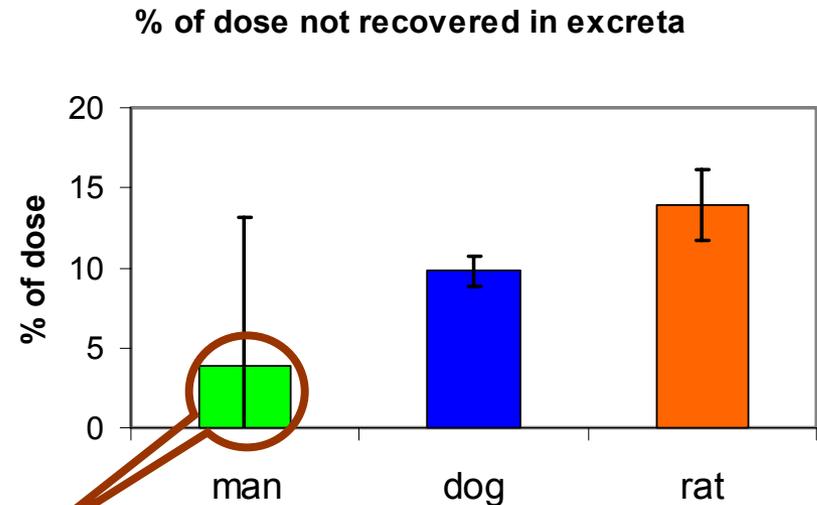
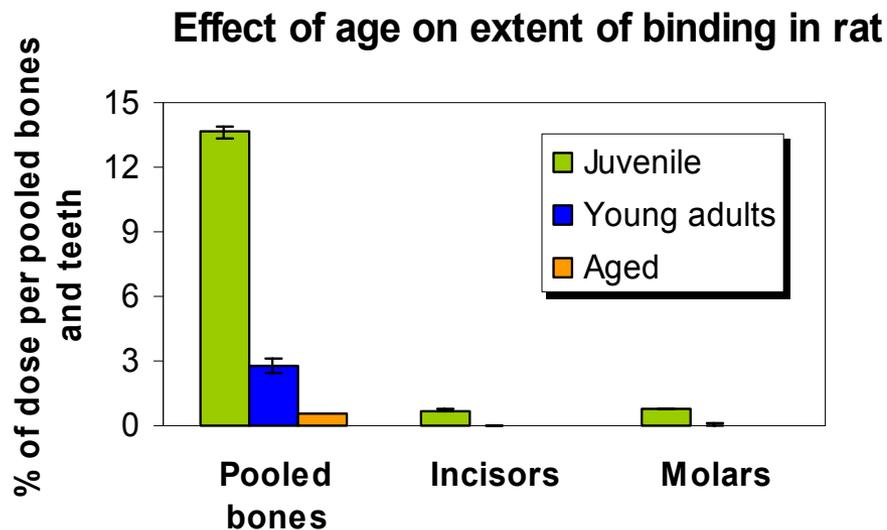
- Reversible (terminal  $t_{1/2}$  rat bone: 70-250 days)
- To rat teeth is 3-5 fold less compared to bone
- Extracellular at site of mineralization:  
hydroxy apatite
- Significantly reduced by presence of NMBA
- Not to epiphyseal disc & (joint) cartilage

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  $\mu\text{g}$  per gram bone/teeth

# Young Adult Rat: No Adverse Effects

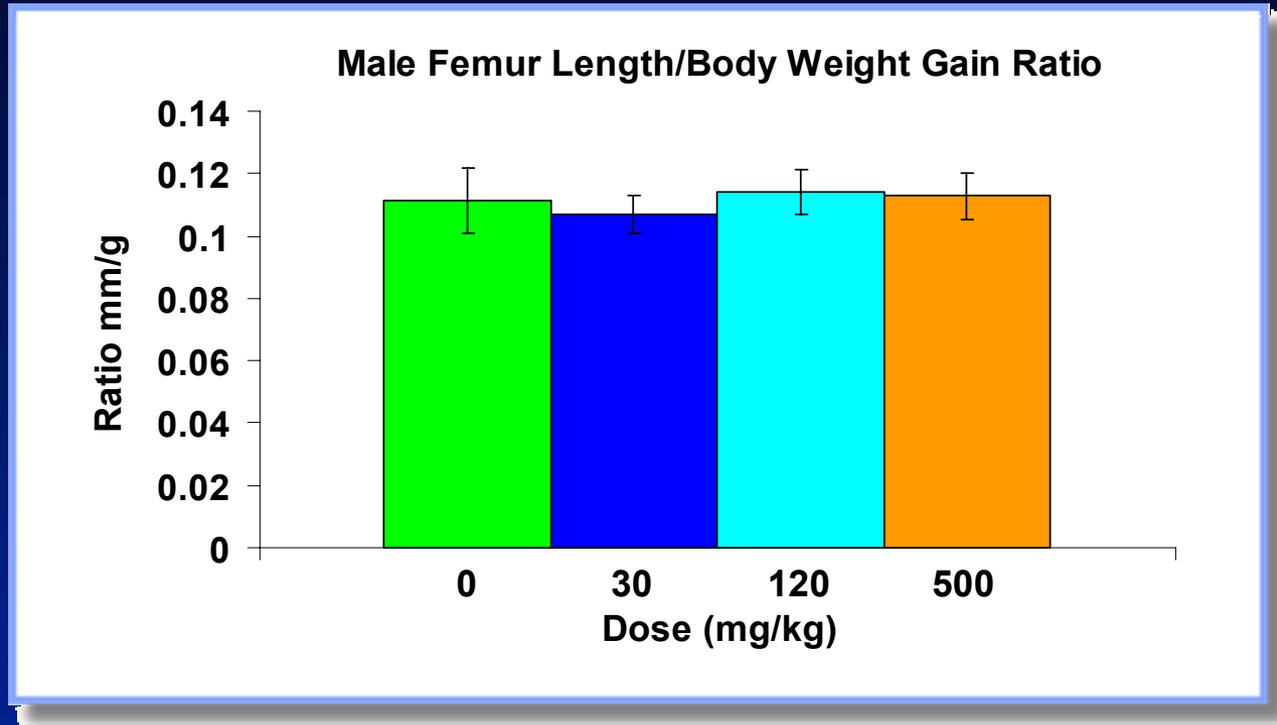
- No effect on bone at single dose  $\leq 500$  mg/kg
- Bone concentration rat : human = 313 : 4.5  $\mu\text{g/g}$

➔ ***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  $\leq 500$  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  $\leq 120$  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  $\mu\text{g/g}$**
  - Worst case human fetus bone/teeth concentration:  
**4.5  $\mu\text{g/g}$**  (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

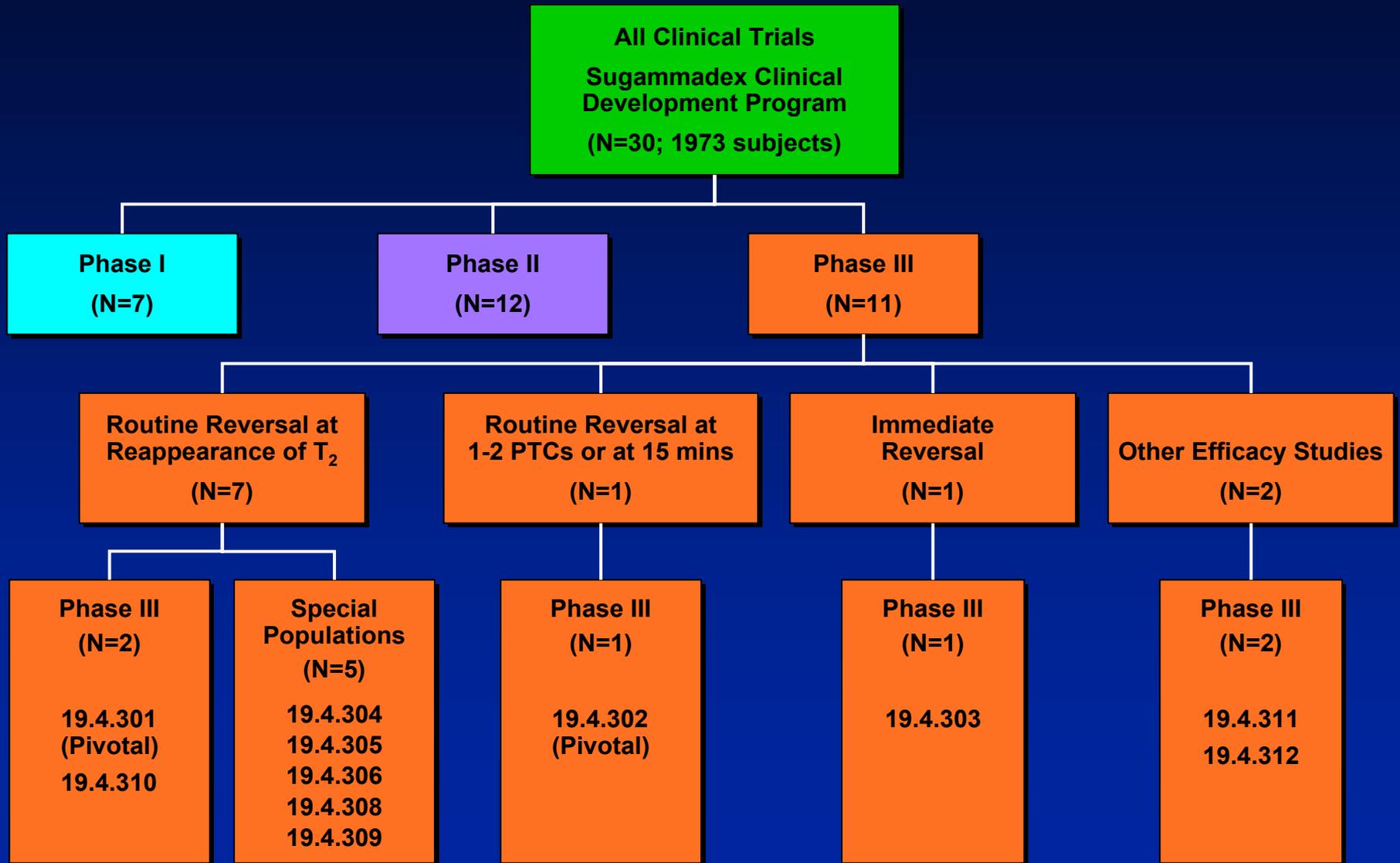
## Routine Reversal

- **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***

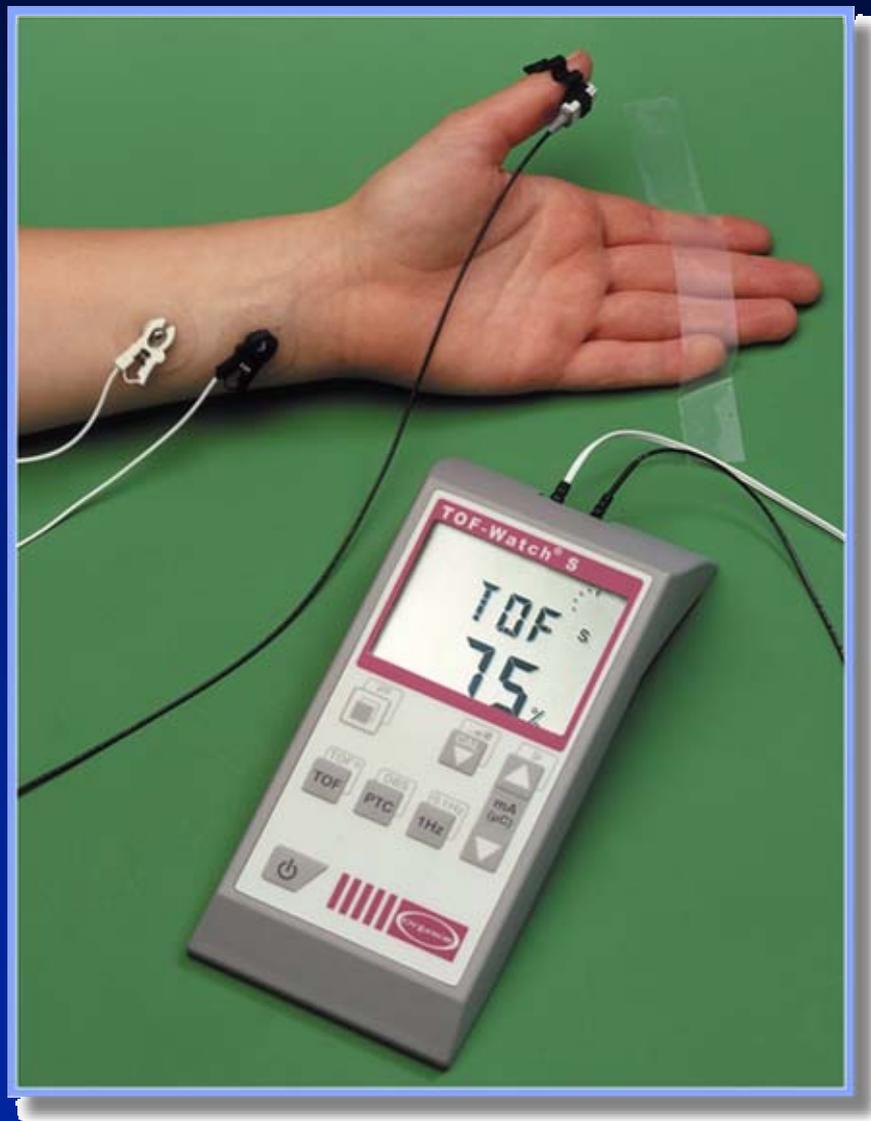
- **Neuromuscular disorders, significant renal dysfunction (except for Trial 19.4.304), history of malignant hyperthermia**
- **Allergy to narcotics, muscle relaxants or other medication used during general anesthesia**
- **Medications known to interfere with the NMBA**
- **Contraindications for the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

# Exclusion Criteria

## *Phase II and III Trials*

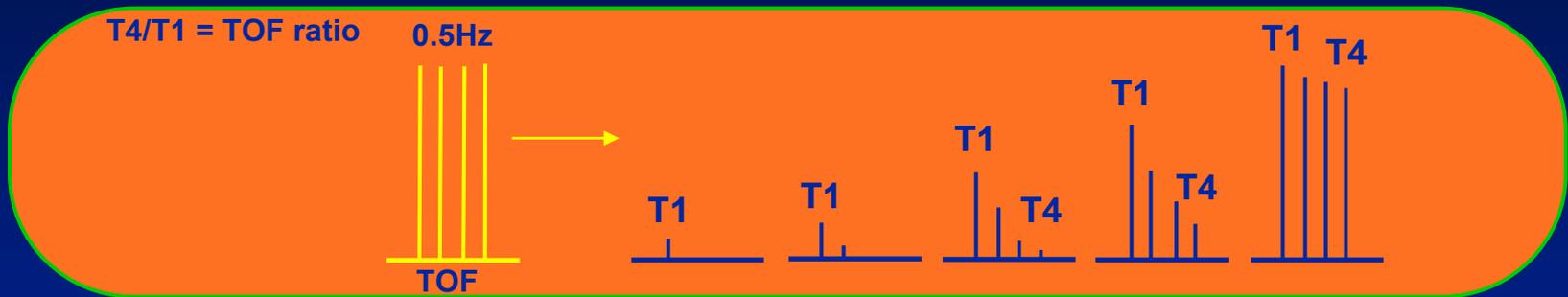
- **Pregnancy**
  - **Childbearing potential not using appropriate methods of birth control**
  - **Breast-feeding**
- **Prior participation in the trial**
- **Participation in another clinical trial, not pre-approved by Organon, part of Schering-Plough Corp**

# Neuromuscular Monitoring

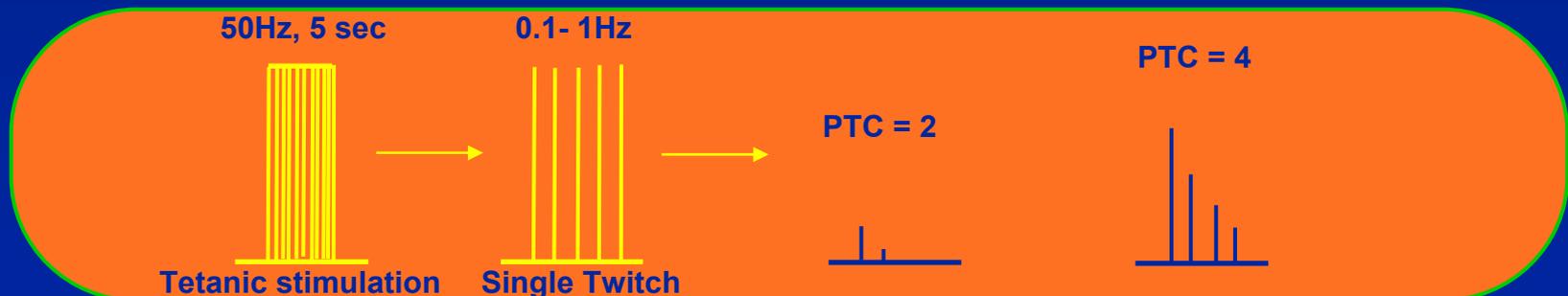


# Methods of Stimulation

- 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



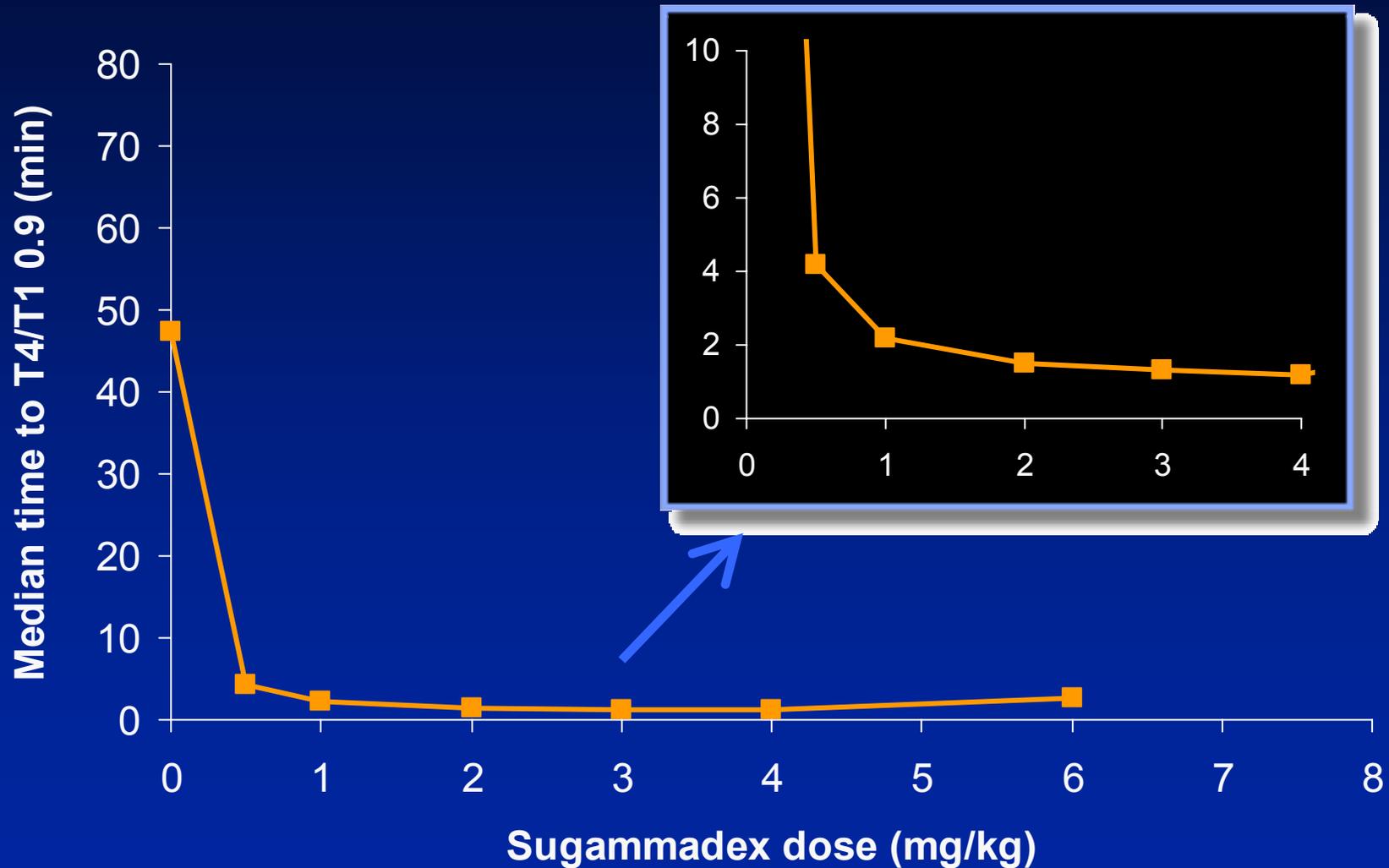
# **Dose Finding Trials – Phase II**

# 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**

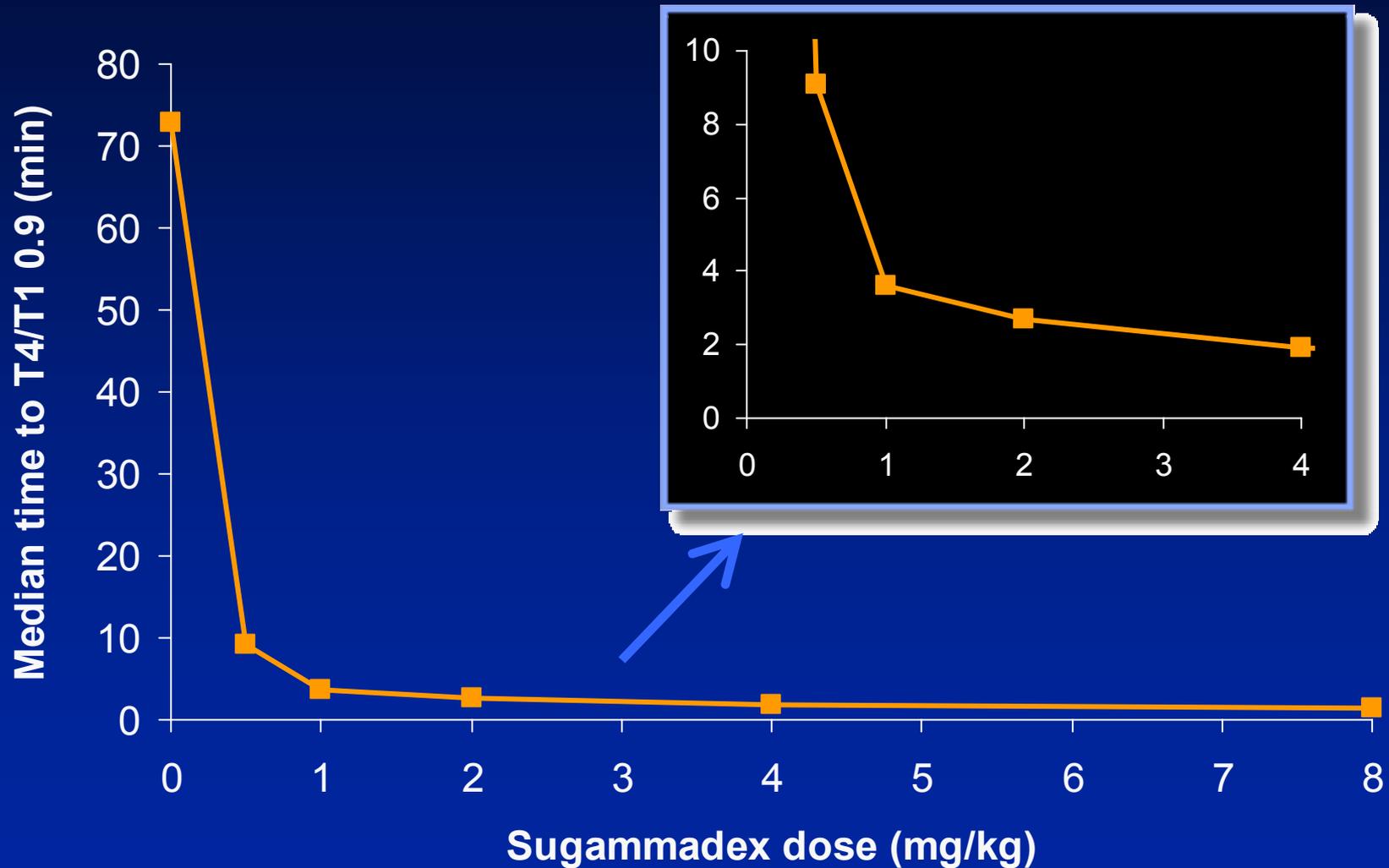
# Time to Recovery $T_4/T_1$ to 0.9

## *Sugammadex at $T_2$ after Rocuronium – Phase II*



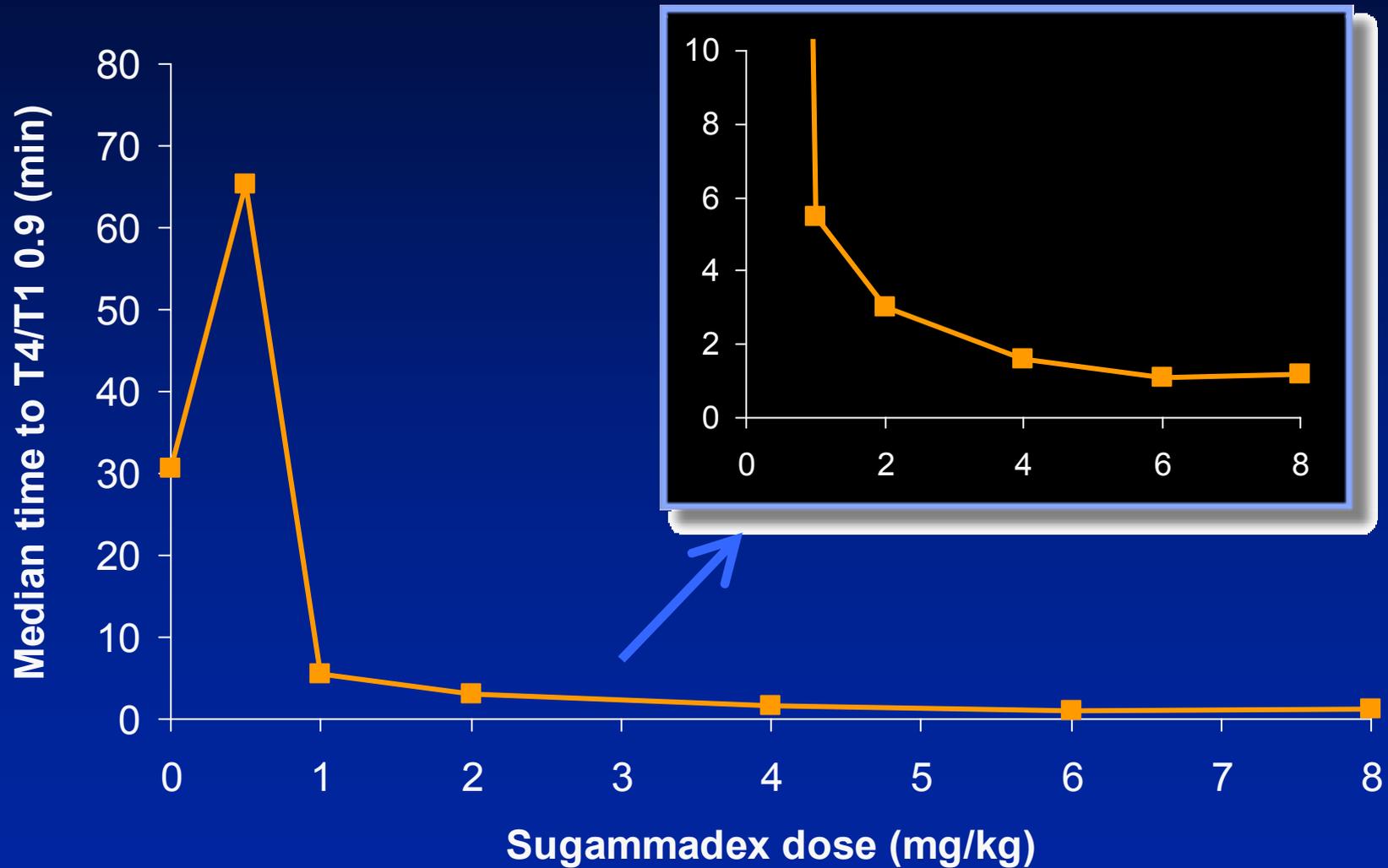
# Time to Recovery $T_4/T_1$ to 0.9

## *Sugammadex at $T_2$ after Vecuronium – Phase II*



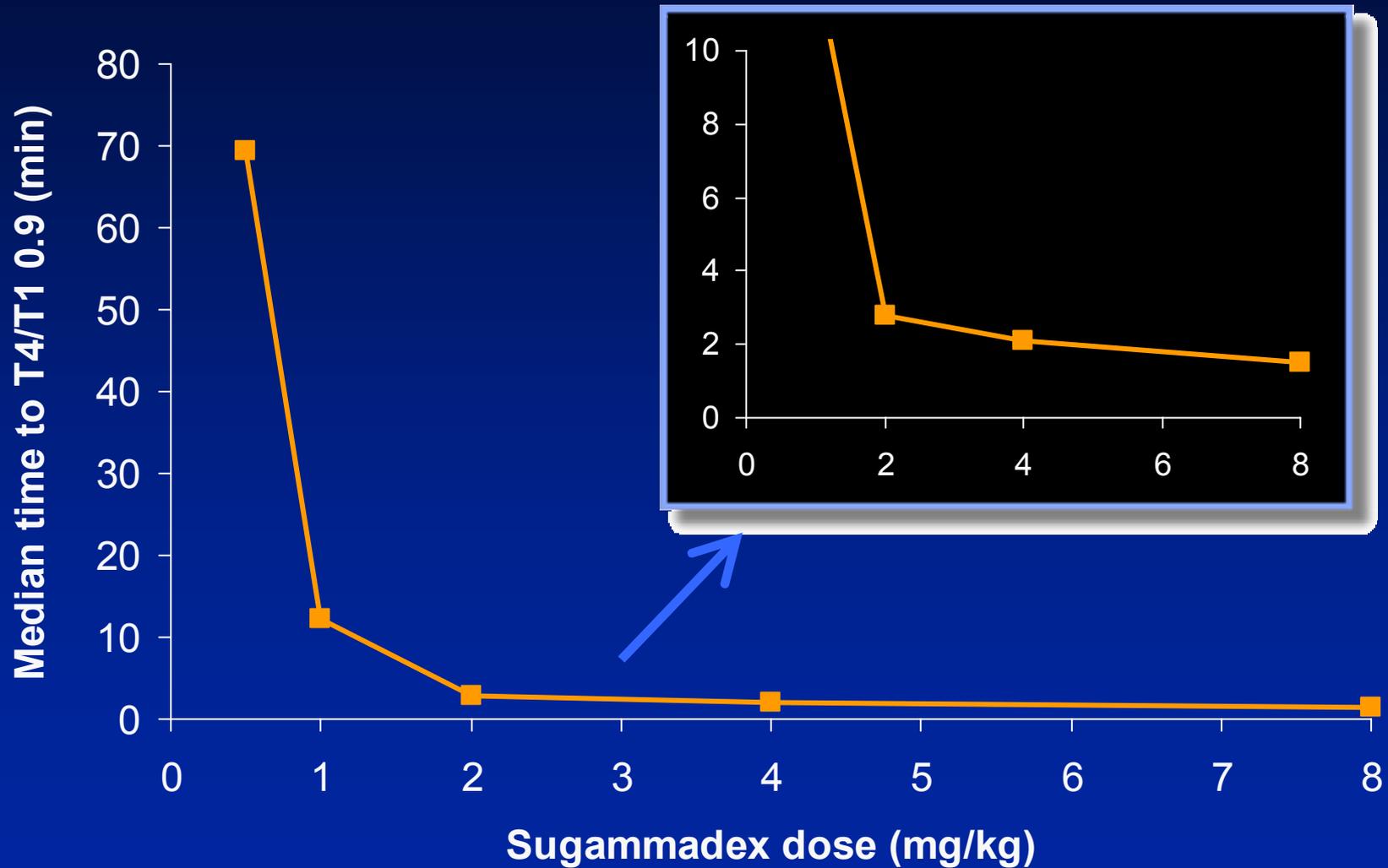
# Time to Recovery $T_4/T_1$ to 0.9

*Sugammadex at 1-2 PTC after Rocuronium – Phase II*



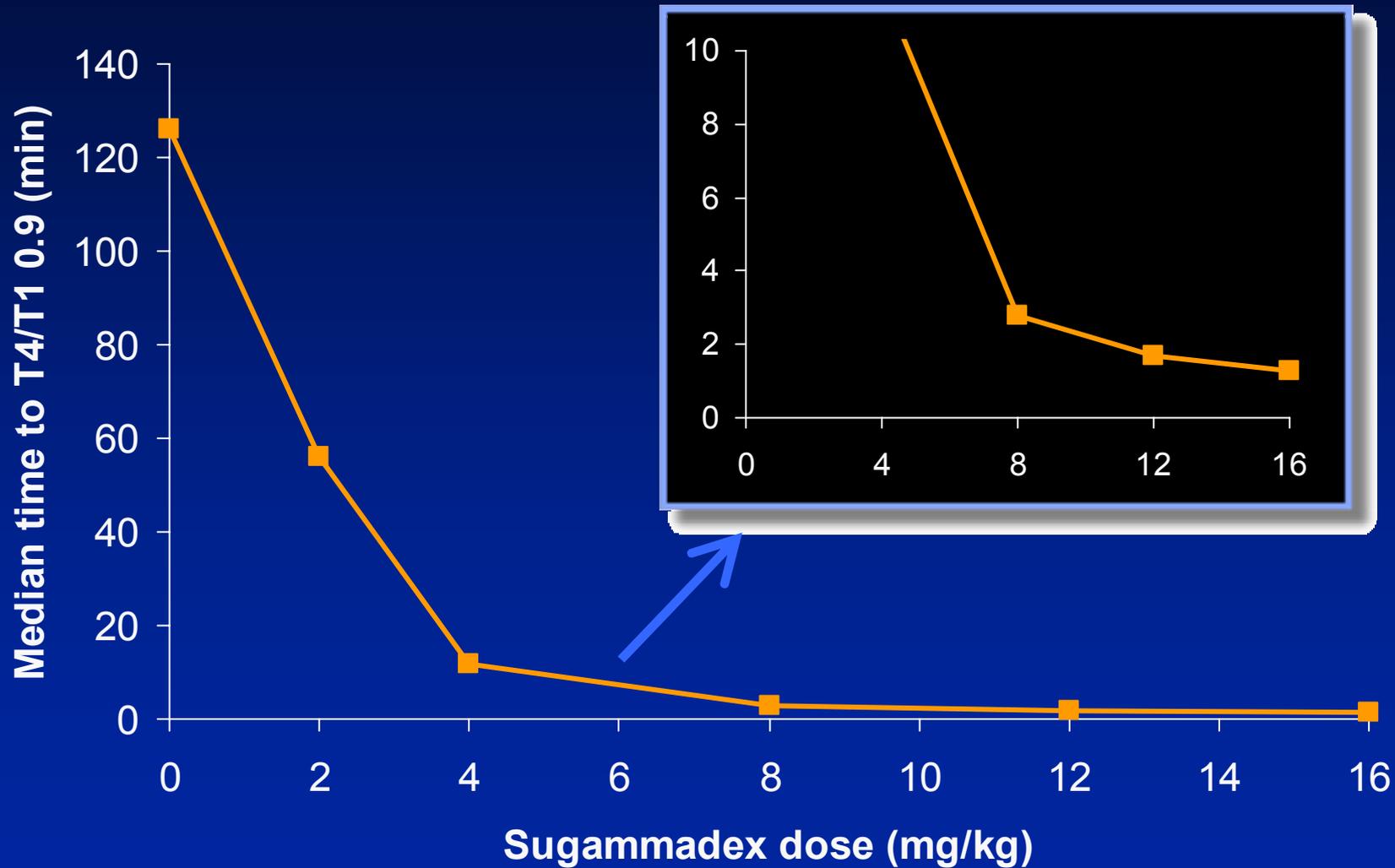
# Time to Recovery $T_4/T_1$ to 0.9

*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

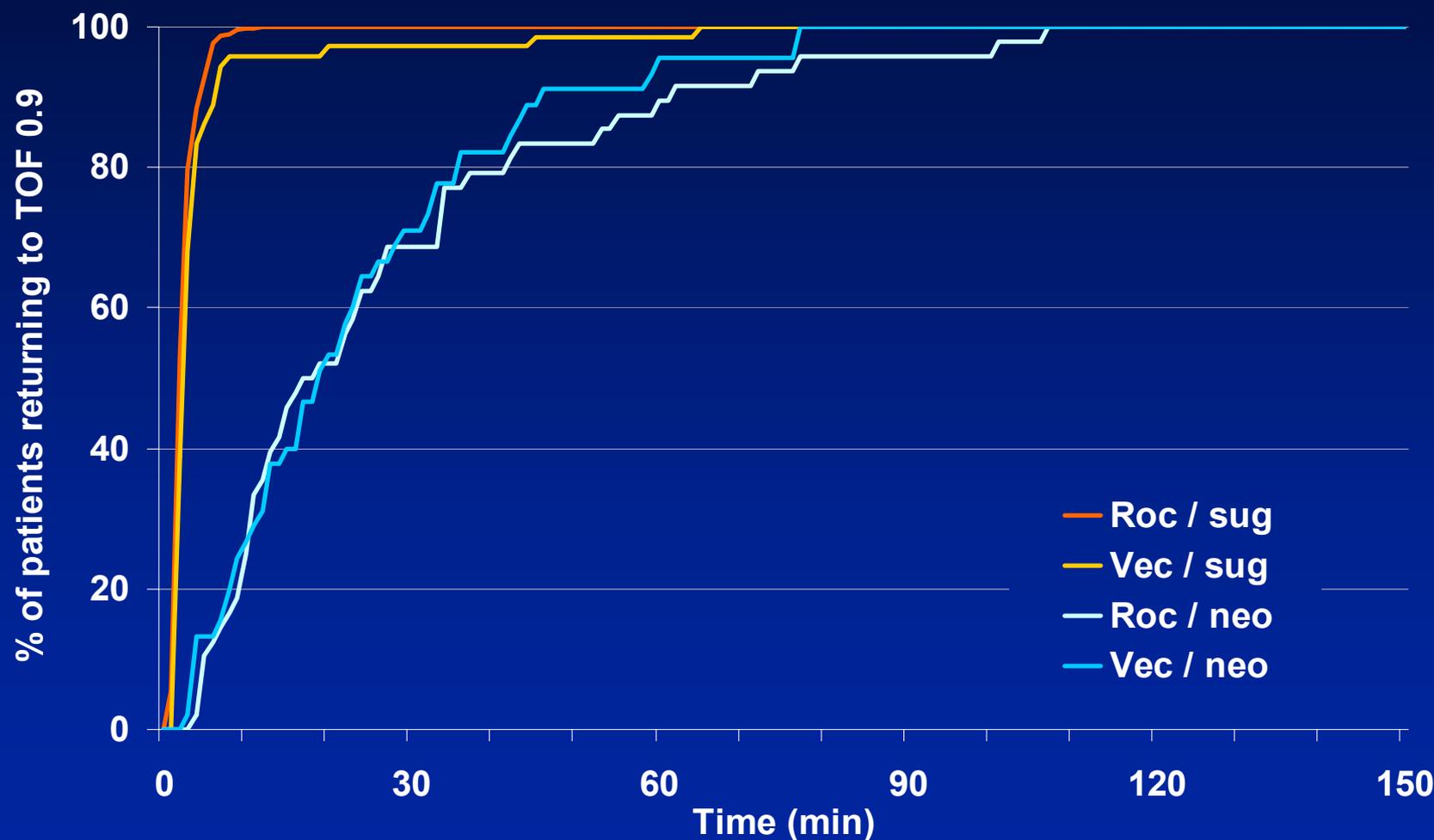
# Recovery of TOF Ratio to 0.9\*

*Trial 19.4.301*

<b>Neuromuscular Blocking Agent</b>	<b>Sugammadex 2.0 mg/kg</b>	<b>Neostigmine 50 mcg/kg</b>
<b><u>Rocuronium</u></b>		
n	48	48
Median (minutes)	<b>1.4*</b>	17.6
Range	0.9-5.4	3.7-106.9
<b><u>Vecuronium</u></b>		
n	48	45
Median (minutes)	<b>2.1*</b>	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 T<sub>2</sub>



# Recovery of TOF Ratio to 0.9\*

Trial 19.4.302

Neuromuscular Blocking Agent	Sugammadex 4.0 mg/kg	Neostigmine 70 mcg/kg
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## Rocuronium

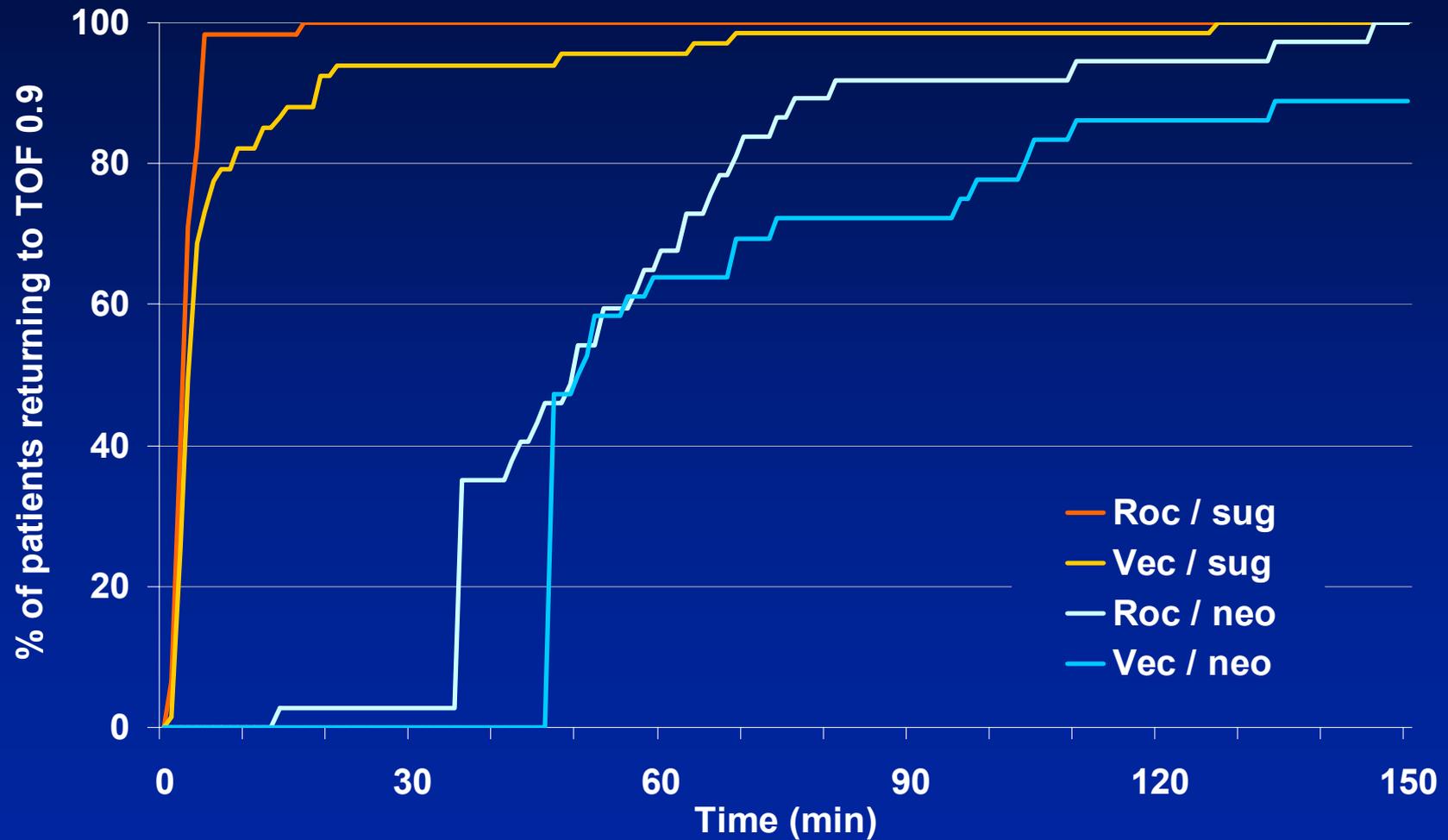
n	37	37
Median (minutes)	2.7*	49.0
Range	1.2-16.1	13.3-145.7

## Vecuronium

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**

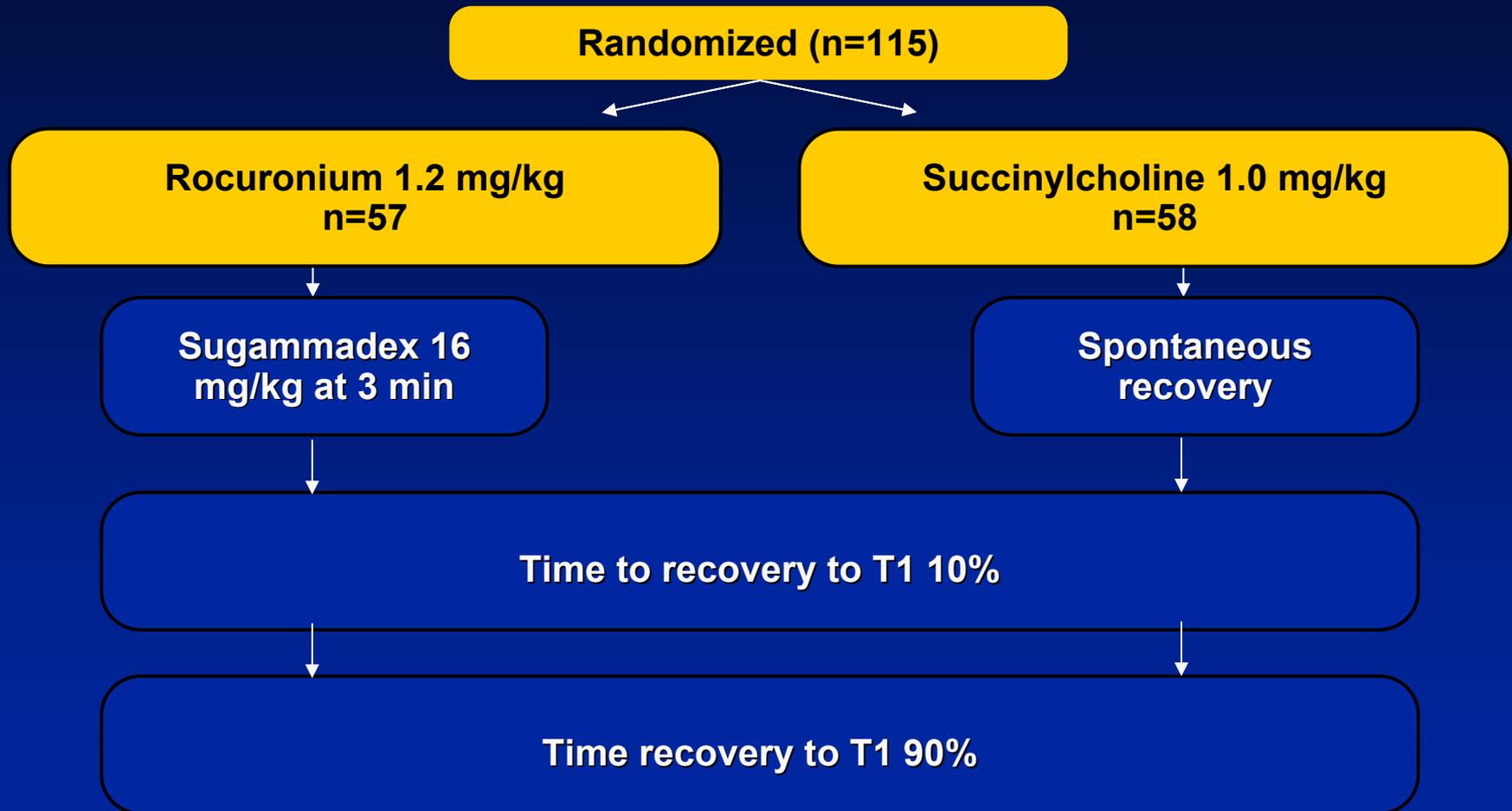
# Efficacy Variables

- **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

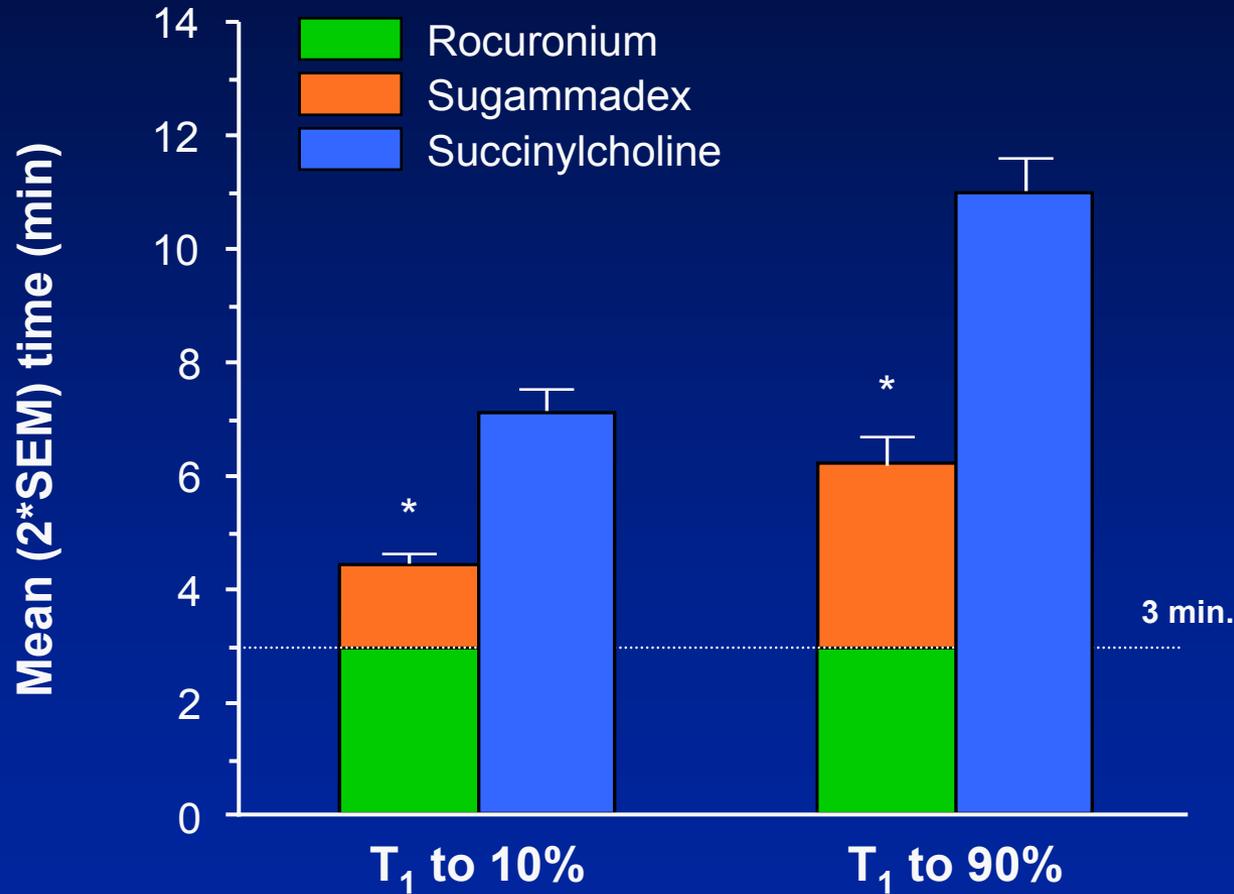
# Design Elements

- **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

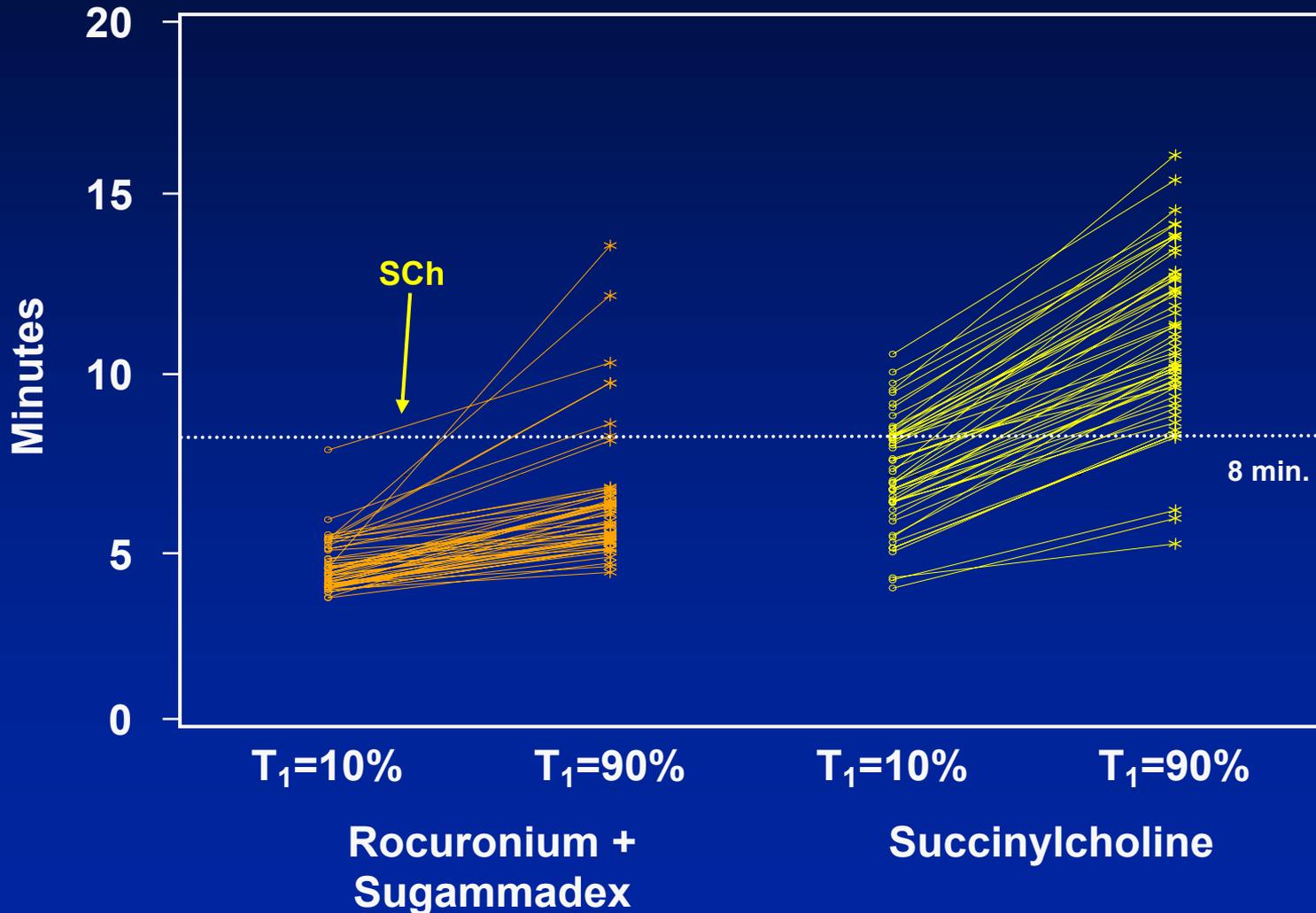


# Trial 19.4.303, Mean (2xSEM) Times to T<sub>1</sub> 10% and 90%



\* 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)*

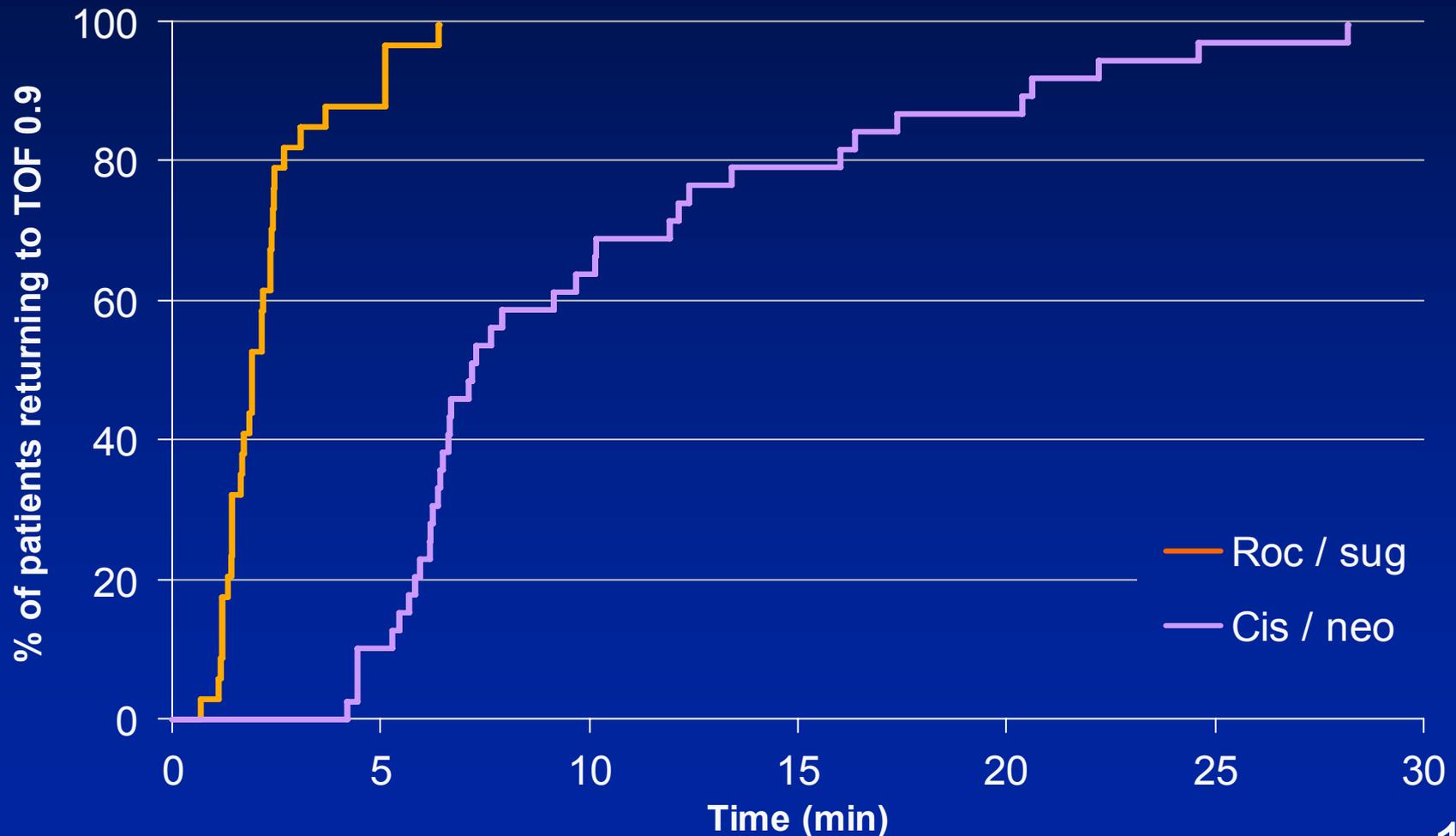
## Objective:

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

<b>Neuromuscular Blocking Agent</b>	<b>Rocuronium and Sugammadex 2.0 mg/kg</b>	<b>Cisatracurium and Neostigmine 50 mcg/kg</b>
n	34	39
Median (minutes)	<b>1.9*</b>	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 T<sub>2</sub>



# 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

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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*

<b>Group</b>	<b>Impaired Renal Function</b>	<b>Normal Renal Function</b>
	<b>CR<sub>CL</sub> &lt; 30 ml/min</b>	<b>CR<sub>CL</sub> ≥ 80 ml/min</b>
<b>n</b>	<b>15</b>	<b>14</b>
<b>Median (minutes)</b>	<b>1.6</b>	<b>1.4</b>
<b>Range</b>	<b>1.2-3.7</b>	<b>0.9-3.1</b>

# 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)*

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

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

## **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*

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

# Exposure to Sugammadex

*Phase I-III*

## *In Association with Rocuronium or Vecuronium*

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	<b>Subjects</b>	
	<b>Rocuronium</b>	<b>Vecuronium</b>
<b>Total</b>	<b>1509</b>	<b>398</b>

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## *Sugammadex Only (Volunteer Studies)*

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	<b>Exposures (subjects)</b>
<b>Total</b>	<b>443 (196)</b>

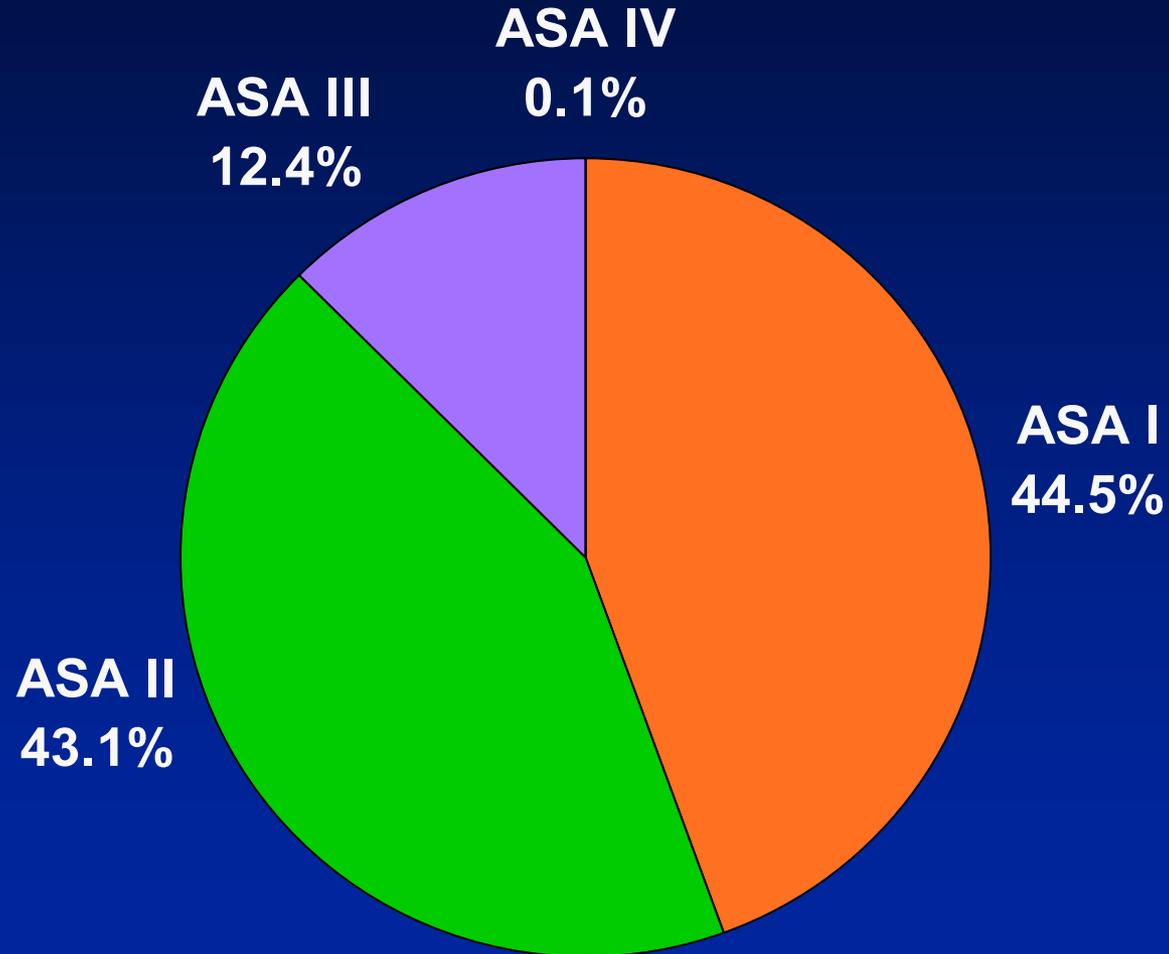
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# Exposure to Sugammadex

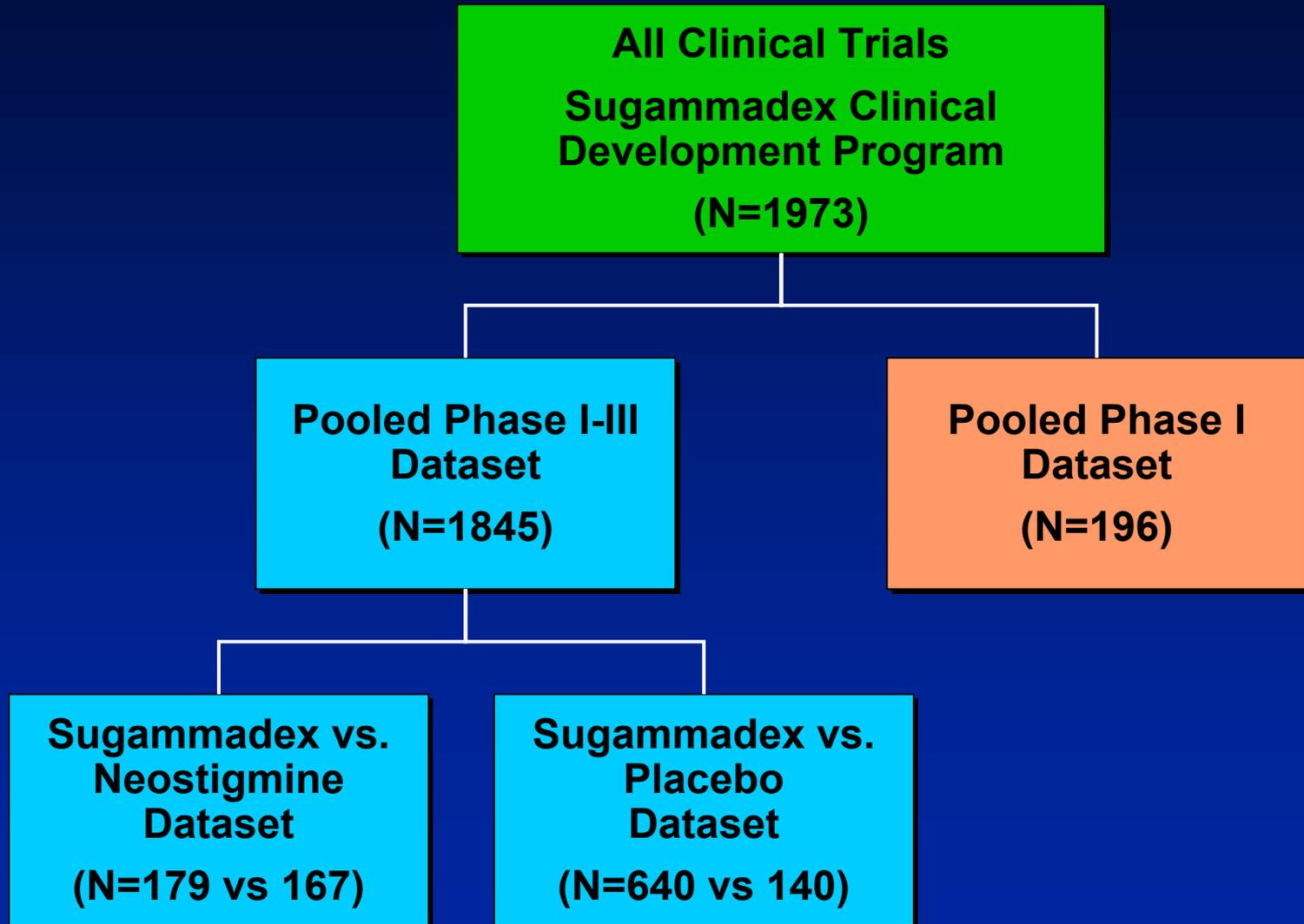
## *Special Populations*

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

# 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  $\geq 80$  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**

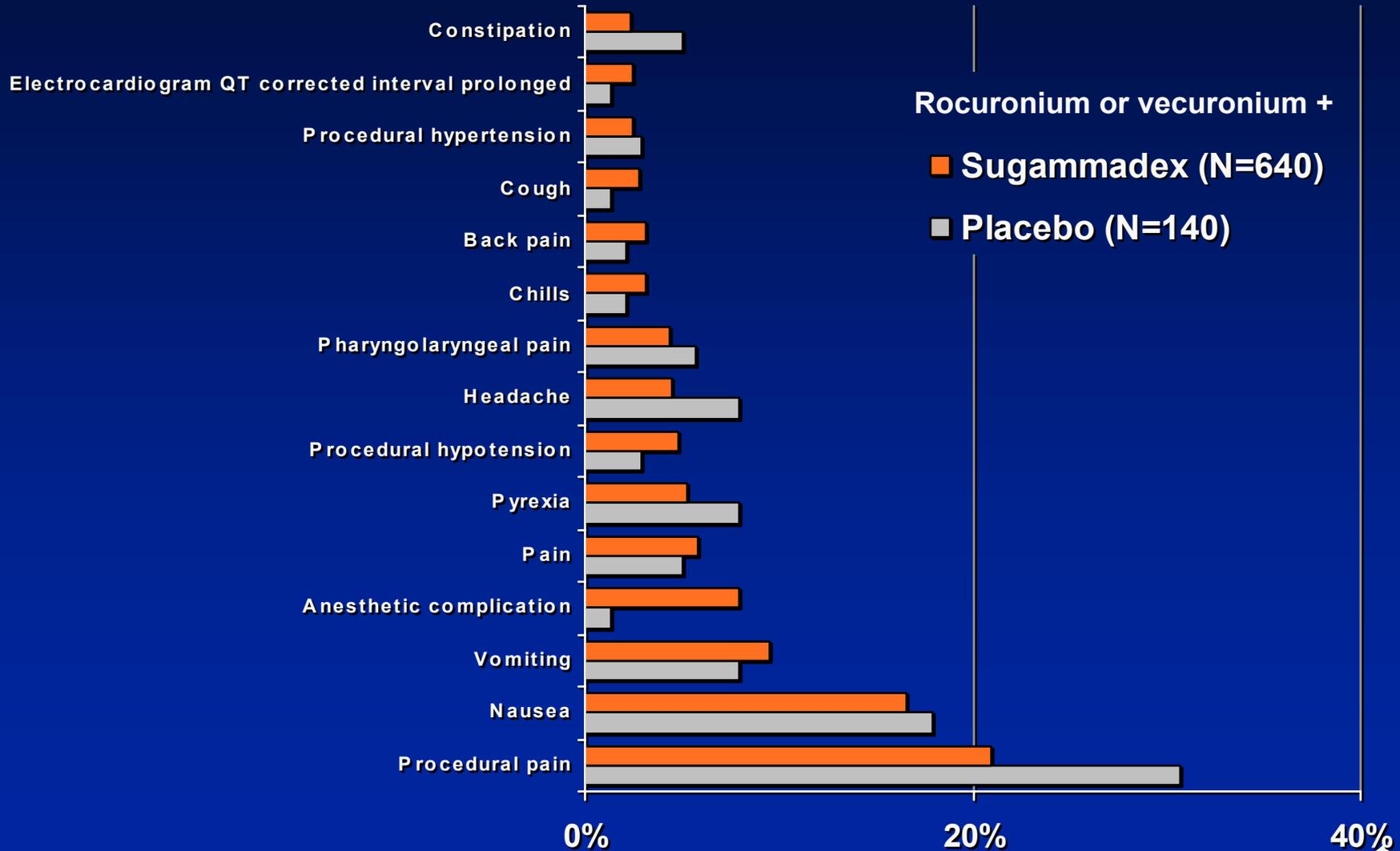
**AEs and SAEs**

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

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

\* 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**

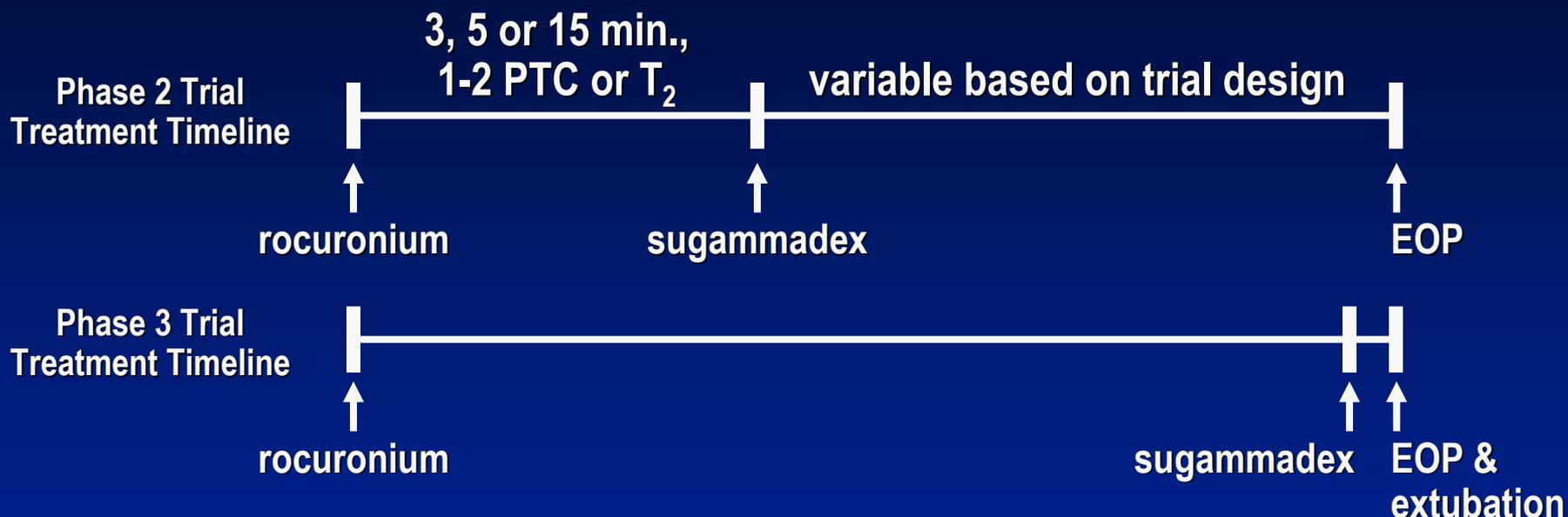
- **Anesthetic complication**
- **Dysgeusia**
- **Hypersensitivity**

# 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**

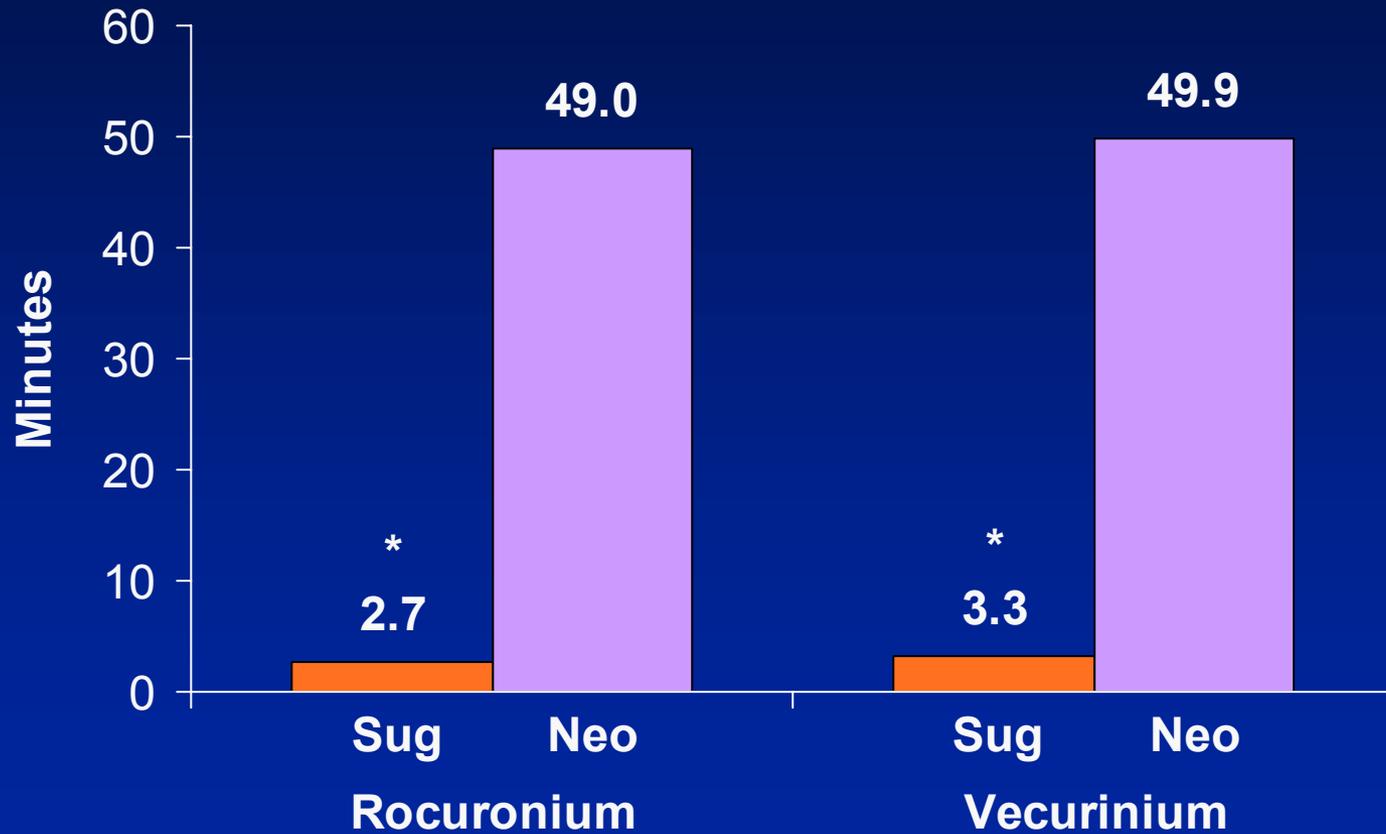
# Summary

**Ronald D. Miller, M.D.**

# Are We Meeting an Unmet Need?

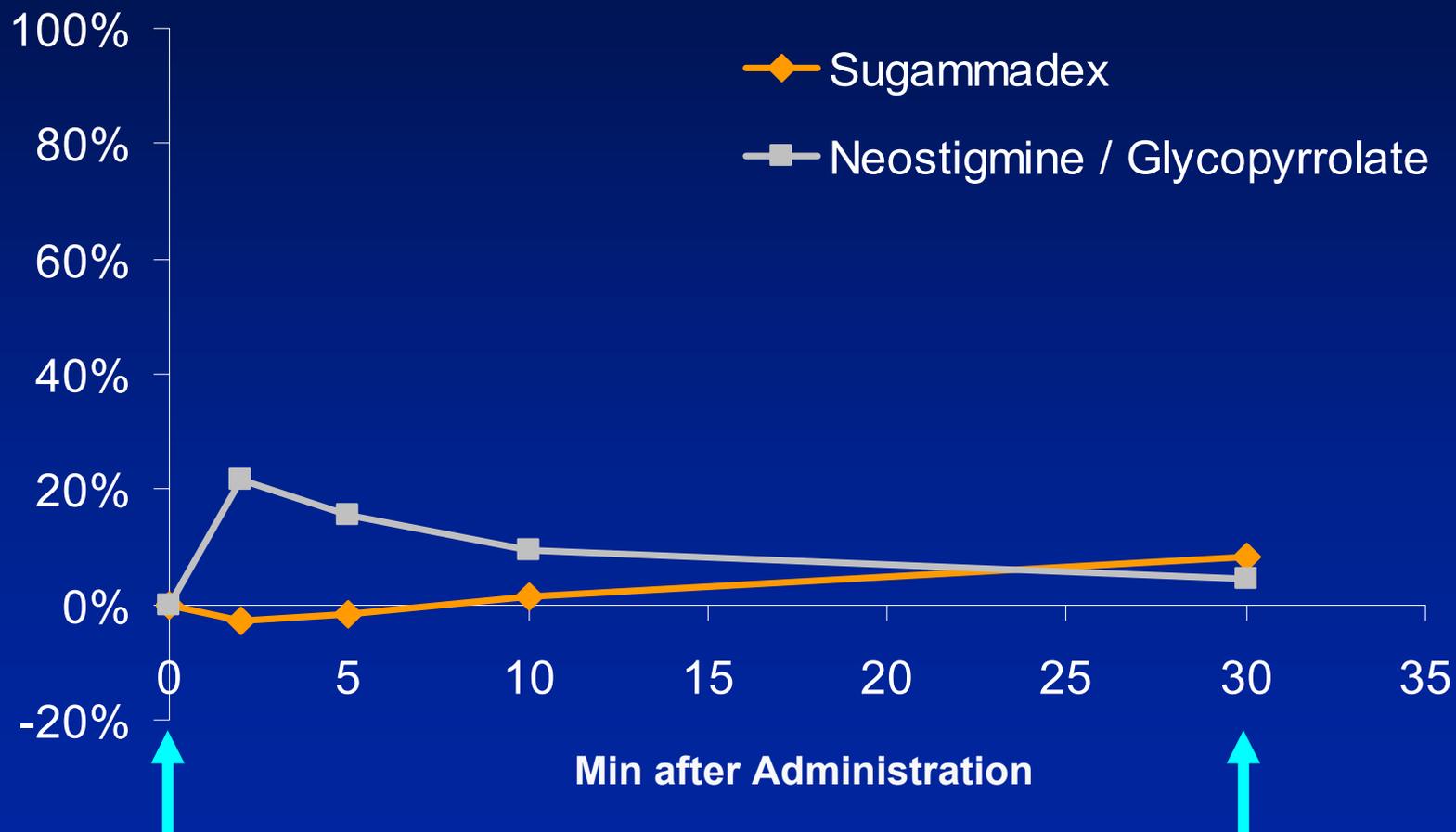
- **Minimize or eliminate neostigmine**
- **Minimize or eliminate succinylcholine**
- **Residual Postoperative Paralysis**
- **Increase Intraoperative Flexibility**
- **Increase Perioperative Safety**

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

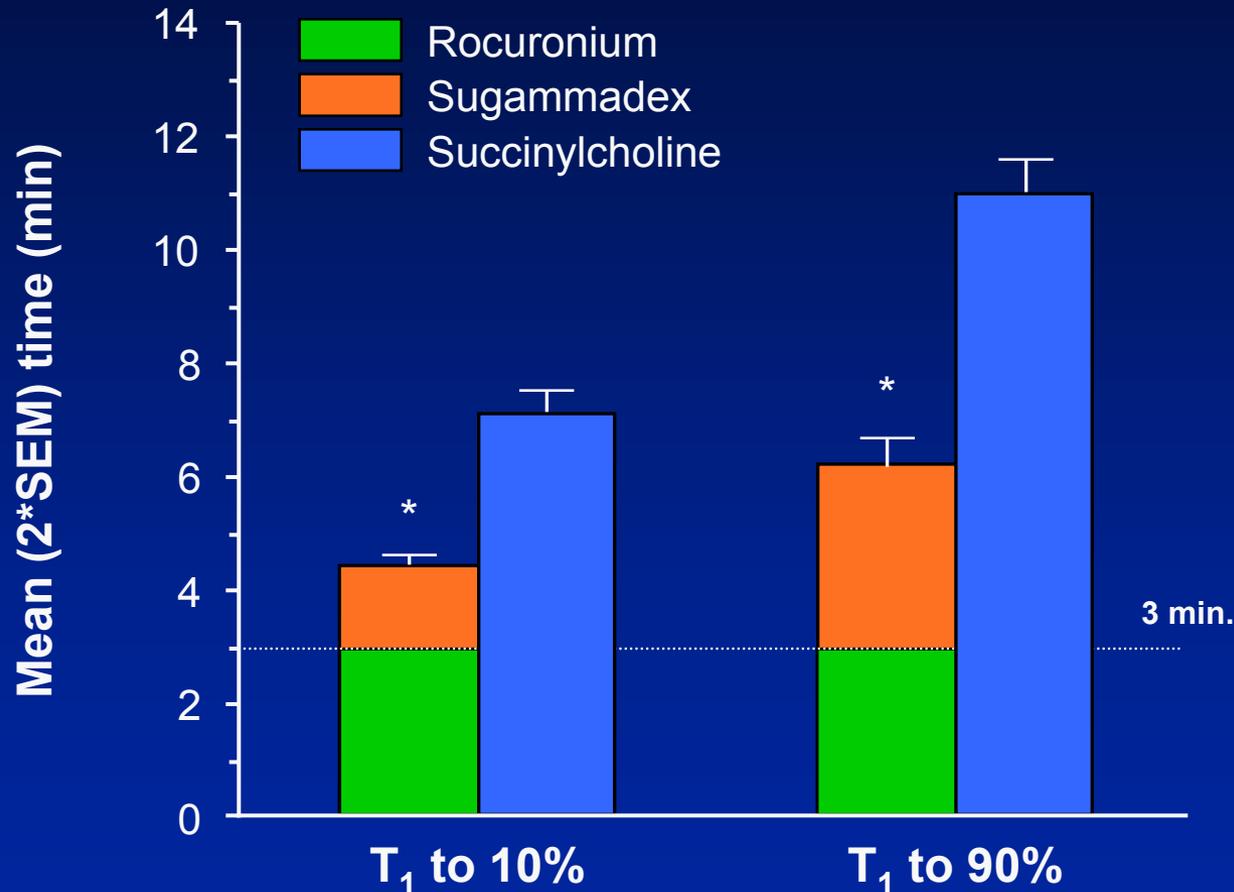


\* P<0.0001 versus neostigmine treatment group

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



# Rocuronium/Sugammadex vs. Succinylcholine, Mean (2xSEM) Times to T<sub>1</sub> 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**