Sugammadex
Introduction and Background

Presenter:

David Michelson, MD

Merck Research Laboratories

Agenda

Introduction and Overview	**David Michelson, MD** *Vice President, Clinical Neuroscience* *Merck*
Unmet Medical Need	**Glenn Murphy, MD** *Director, Clinical Research,* *NorthShore University HealthSystem* *Clinical Professor,* *University of Chicago* *Pritzker School of Medicine*
Summary of Pharmacological Profile and Overview of Clinical Efficacy	**W. Joseph Herring, MD, PhD** *Executive Director, Clinical Neuroscience* *Merck*
Overview of Clinical Safety and Tolerability	**K. Chris Min, MD, PhD** *Director, Translational Medicine* *Merck*
Benefit-Risk Assessment	**David Michelson, MD** *Vice President, Clinical Neuroscience* *Merck*

Introduction of External Consultants

Lene Heise Garvey, MD	*Specialist in Anaesthesiology with subspecialization in Allergology* *Danish Anaesthesia Allergy Centre* *Copenhagen University Hospital* *Gentofte, Denmark*
Scott Groudine, MD	*Professor of Anesthesiology and Surgery* *Albany Medical Center and College* *Albany, NY*
Glenn Murphy, MD	*Director, Clinical Research* *NorthShore University HealthSystem* *Clinical Professor* *University of Chicago* *Pritzker School of Medicine* *Evanston, IL*
Gillian Shepherd, MD	*Clinical Associate Professor of Medicine* *Weill Medical College of Cornell University*

Neuromuscular Blockade

- Neuromuscular blockade is important for the care of anesthetized surgical patients
- Reversal of neuromuscular blockade is also important
  - A requirement for extubation
  - Residual neuromuscular blockade increases risk for poorer postoperative outcomes
- Current options to actively reverse neuromuscular blockade
  - Restricted to acetylcholinesterase inhibitors
  - Limitations in efficacy restrict use
  - Common and problematic unwanted effects
  - Require co-administration of anticholinergic agents
- Taken together, these constrain the flexibility of depth and duration of neuromuscular blockade in general anesthesia

Sugammadex Is a Novel Drug Designed to Reverse Neuromuscular Blockade

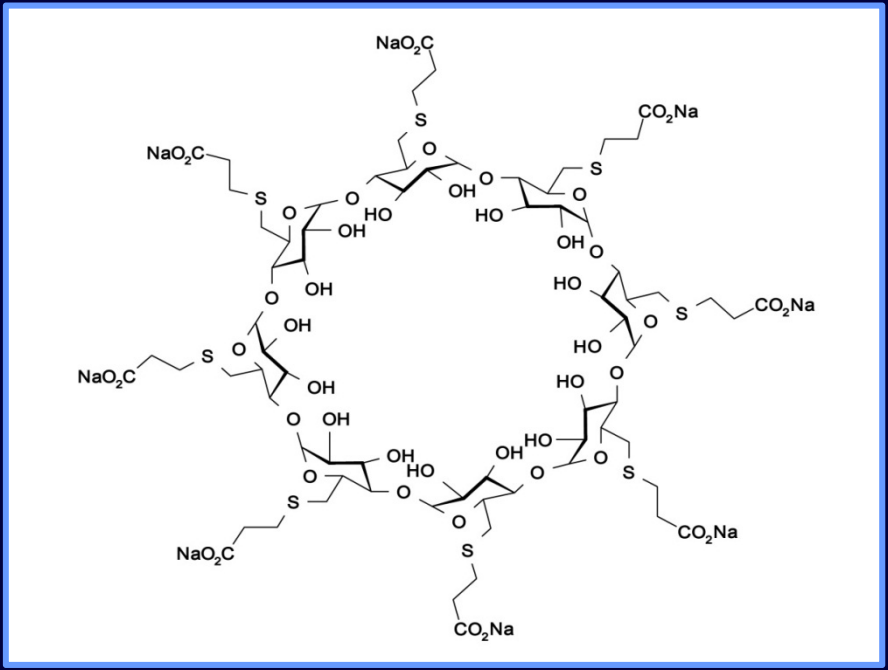
- Intended to provide a new option for reversal of rocuronium- or vecuronium-induced neuromuscular blockade
- May provide advantages over current standard of care
  - Rapid and complete reversal at any depth of blockade
  - No cholinergic side effects
- Currently approved and marketed in 57 countries

Sugammadex Proposed Indication

Sugammadex is indicated for the reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium

Sugammadex Acts by Complexing With Rocuronium or Vecuronium

Sugammadex acts by encapsulating rocuronium or vecuronium, removing them from the neuromuscular junction, and thus restoring muscle function. The complex is eliminated renally.



Gijsenbergh, et al. Anesthesiology. 2005;103:695-703.

Sugammadex Development History

- Cyclodextrins
  - Lipophilic central cavities that can complex with drug molecules
  - No intrinsic biological activity, thus less prone to off-target effects
- Sugammadex: γ-cyclodextrin modified to increase affinity for rocuronium/vecuronium
  - Extended central cavity depth
  - Anionic functional groups interact with positively charged groups on rocuronium/vecuronium
- First human dosed: 2001
- First regulatory approval: European Union 2008

Sugammadex US Regulatory History

- 2007: NDA first submitted to FDA for review
- 2008: FDA Advisory Committee recommended approval; FDA Not Approvable Letter requested further characterization of:
  - Safety of sugammadex on repeat exposure
  - Potential to affect coagulation and bleeding risk
- 2012: NDA resubmitted
  - Hypersensitivity and coagulation studies
  - Focused analysis of cardiac safety
- 2013: FDA Complete Response Letter
  - Protocol violations in hypersensitivity study raised data reliability issues
  - FDA noted that bleeding risk had been addressed

NDA=new drug application.

Sugammadex US Regulatory History

- 2014: NDA resubmitted with a new hypersensitivity study
  - FDA inspection observations during NDA review:
    - At one site, staff who dosed subjects in one cohort performed AE assessment in a different cohort; no staff dosed and assessed the same subject
    - Inadvertent unmasked variable in statistical database; no statisticians/programmers unblinded
    - Both observations summarized in CSR
- 2015: FDA Complete Response Letter
  - Requested sensitivity analyses
  - Additional site inspections
- 2015: Resubmission in June

NDA=new drug application; CSR=clinical study report.

Today's Presentation

- Address questions raised by FDA in 2008, particularly characterization of the safety of sugammadex on repeat exposure and the risk for anaphylaxis and hypersensitivity
- Review efficacy and safety of sugammadex based on
  - Core registration trials supporting efficacy
  - Current updated clinical trial database
  - Post-marketing safety data derived from use in 57 countries where sugammadex is currently approved
- Provide an overview of benefit-risk related to sugammadex

Sugammadex Summary of Key Characteristics

- The data to be reviewed today provide evidence that sugammadex
  - Rapidly and completely reverses moderate and deep neuromuscular blockade after rocuronium or vecuronium
  - Is generally safe and well tolerated
  - Is not associated with sensitization after repeat administration, and its potential to cause serious hypersensitivity reactions including anaphylaxis is limited and manageable in the surgical setting
  - Has the potential to fill important unmet needs related to the use of neuromuscular blockade

Unmet Medical Need

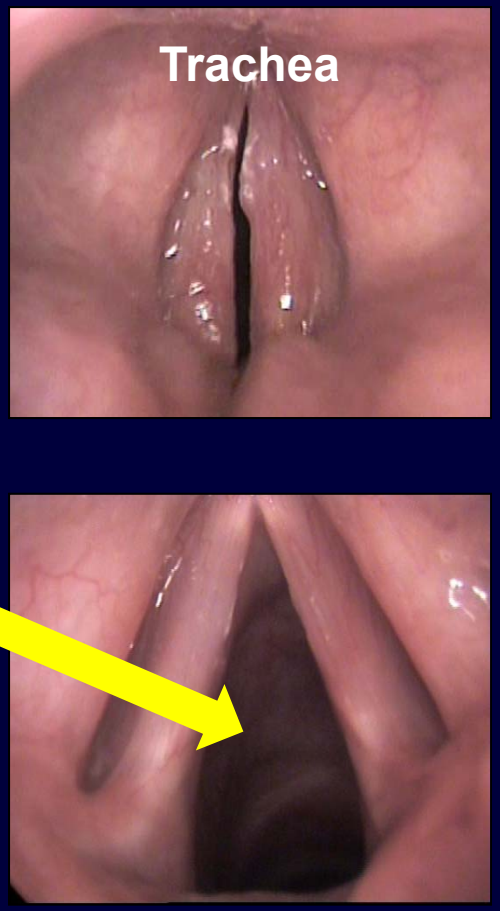
Presenter:

Glenn Murphy, MD

NorthShore University HealthSystem
Evanston, IL

Neuromuscular Blocking Agents in General Anesthesia: Why Are They Used?

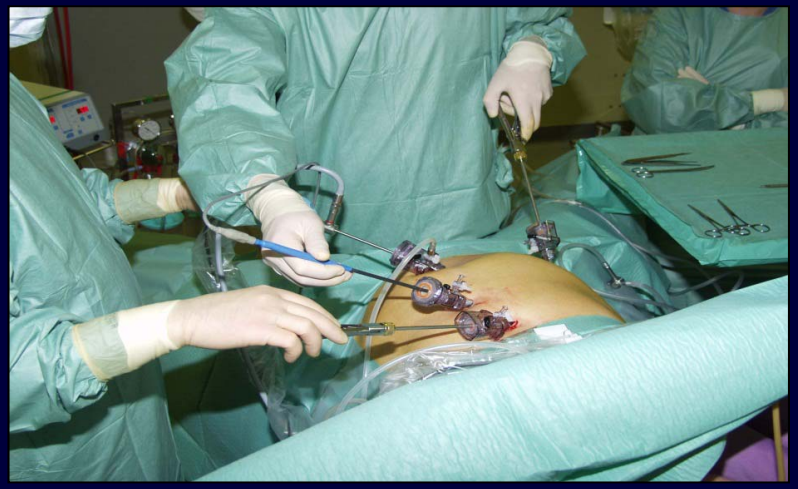
- Triad of general anesthesia
  - Hypnosis
  - Analgesia
  - Relaxation
- For anesthesiologists: neuromuscular blocking agents (NMBA)
  - Facilitate endotracheal intubation
  - Reduce laryngeal morbidity
- Full recovery from the effects of NMBAs should be present at the end of surgery
  - Incomplete recovery results in postoperative residual neuromuscular blockade (NMB)

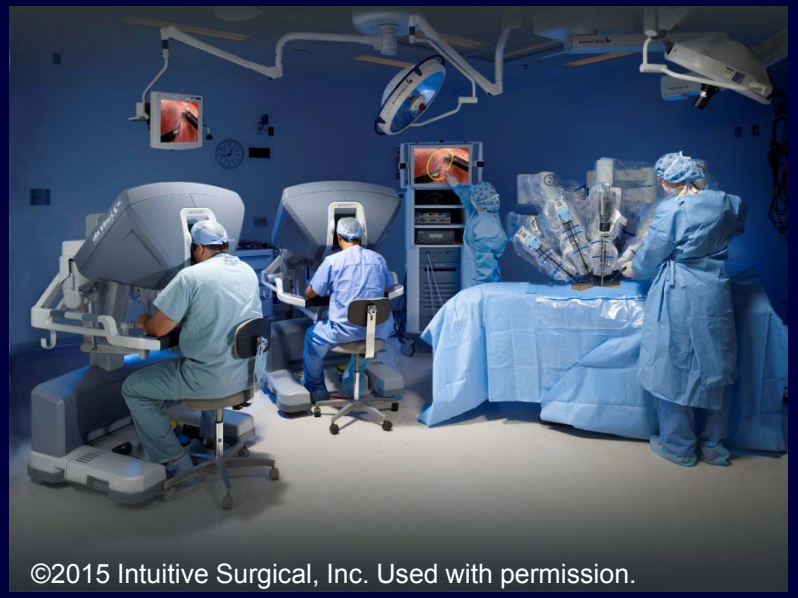


Intubating conditions without NMB (top) and with NMB (bottom)

Benefits of Neuromuscular Block

- For surgery in general
  - Facilitate surgical procedures
  - Minimize involuntary movements
- For laparoscopy/robotic surgery
  - Enable laparoscopic field of view
  - No coughing/sudden contractions
  - Facilitate extraction of excised tissue





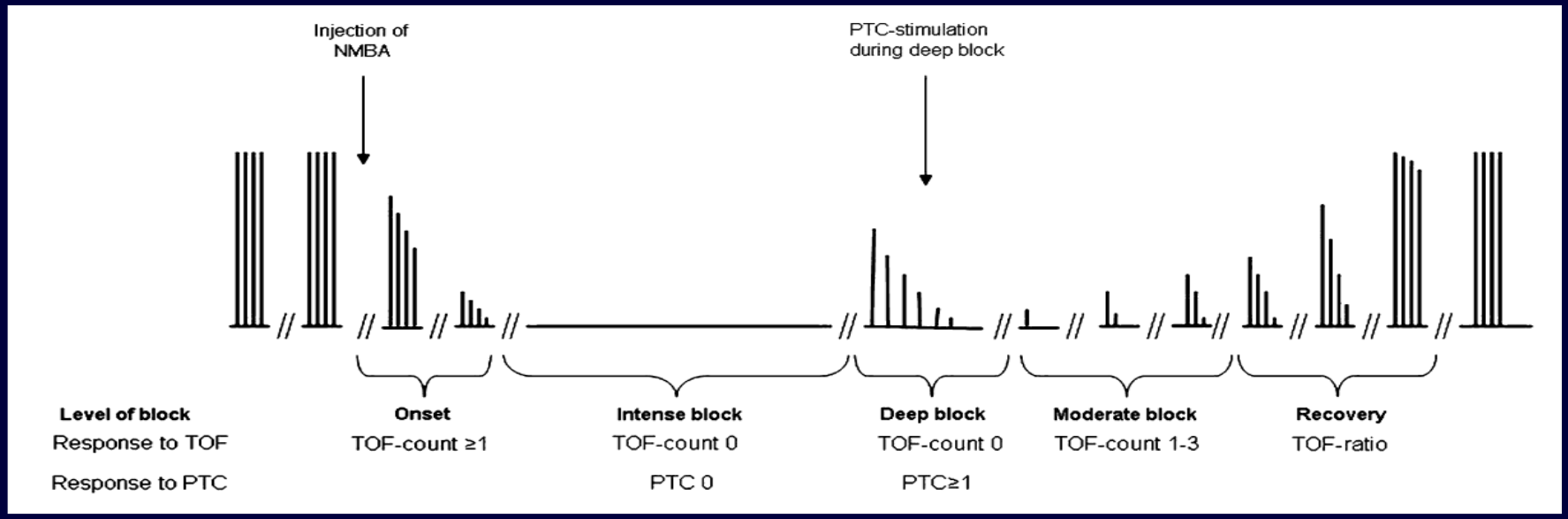
Limited Options for Reversal Currently Drive Compromises in Management

- Intraoperative
  - Deeper levels of neuromuscular blockade are desirable
    - Improved surgical field
    - No dangerous patient movement
    - But...long reversal times cause delays in extubation
  - Lighter levels of neuromuscular blockade
    - Faster reversal
    - But...surgical conditions may be compromised and patients may endanger themselves by moving

- Postoperative
  - Deeper/long neuromuscular blockade is associated with residual neuromuscular blockade and may lead to adverse clinical outcomes
  - Some patients may be at particularly high risk (elderly, obese, cardiac, and pulmonary)

Neuromuscular Monitoring

- Qualitative
  - Peripheral nerve stimulator (PNS)
  - Train-of-four (TOF) count
  - Reappearance of T2
  - TOF fade
  - Post-tetanic count (PTC)
- Quantitative
  - TOF-Watch®
  - TOF ratio
  - TOF ratio: 0-1.0
  - Residual block: TOF ratio <0.9
  - T1 (first twitch) ratio



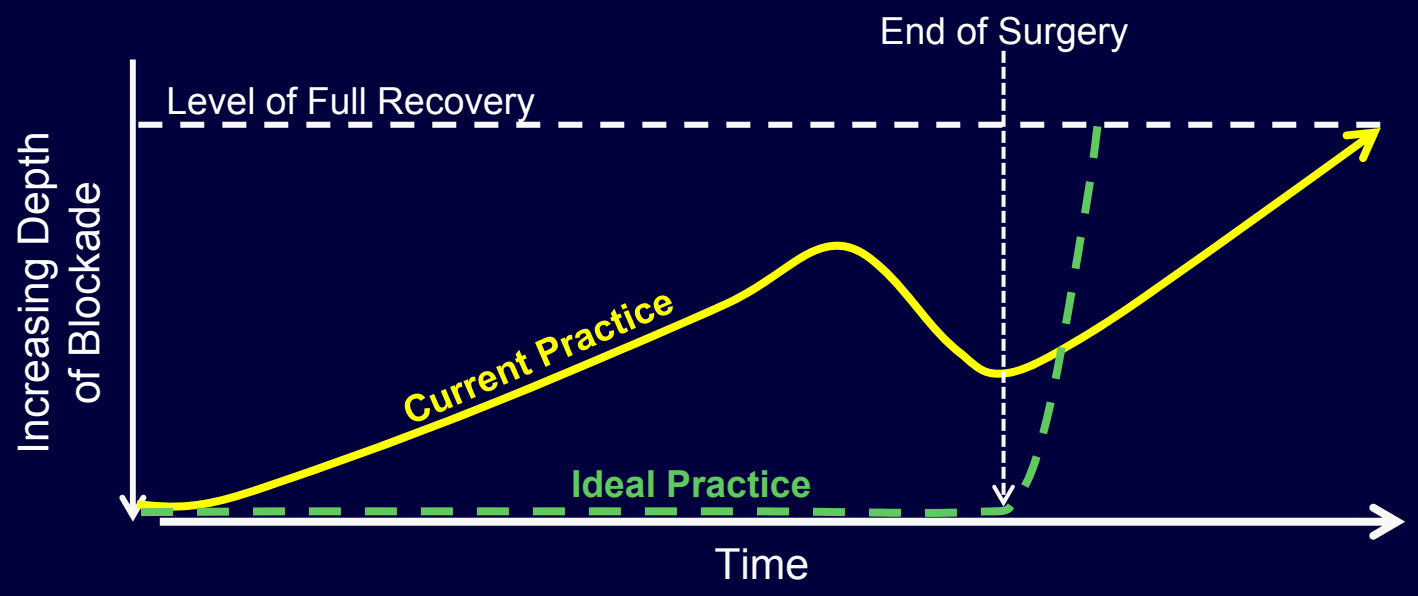
Fuchs-Buder, et al. Acta Anaesthesiol Scand. 2007;51:789-808.
NMBA=neuromuscular blocking agent.

Strategies for Reversal of Neuromuscular Blockade

Spontaneous Recovery
and
Pharmacological Reversal

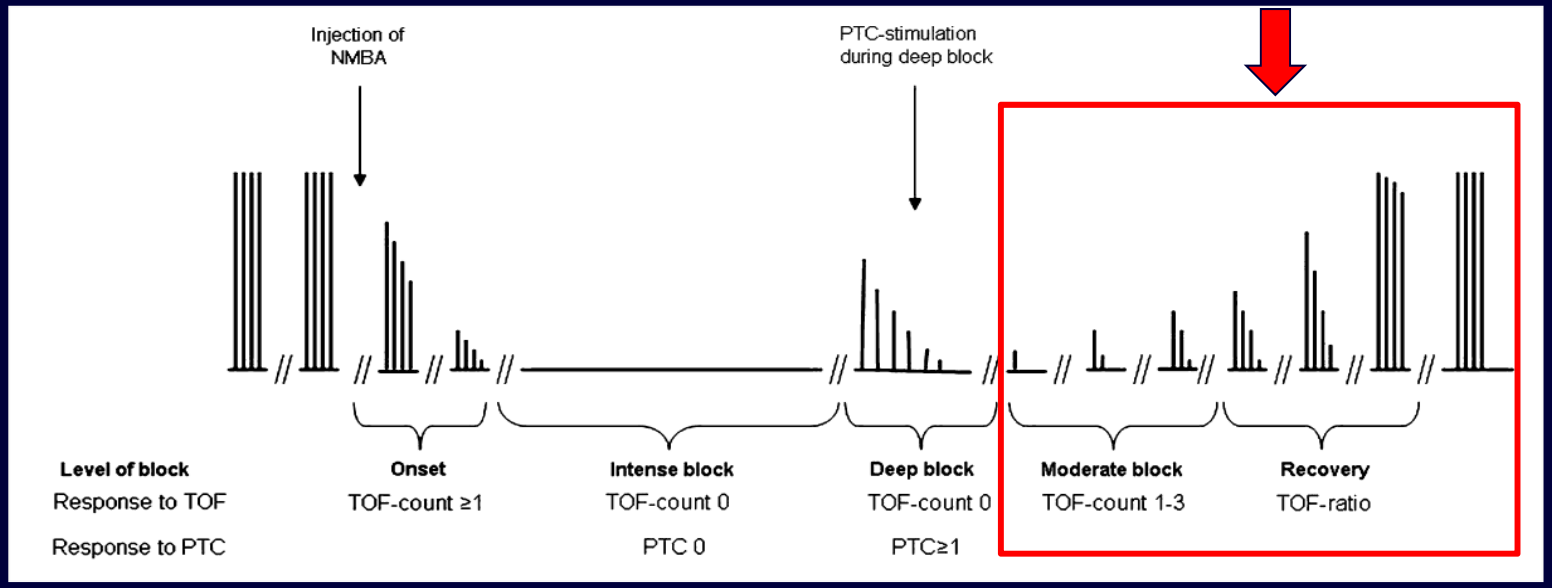
Spontaneous Recovery From Neuromuscular Blockade

- After neuromuscular blocking agent (NMBA) administration, the anesthesiologist waits for the NMBA to wear off
- Duration depends on many factors, (e.g., type and dose of NMBA)
- Limitations
  - Patient only partially relaxed throughout the procedure (compromised surgical conditions, moving, coughing)
  - Spontaneous recovery frequently takes several hours; highly variable



Pharmacological Reversal of Neuromuscular Blockade

- Only available class of agents: acetylcholinesterase inhibitors (e.g., neostigmine)
- Indirect mechanism of action: inhibits metabolism of acetylcholine (ACh)
- Increased ACh in the neuromuscular junction competes with NMBA at the nicotinic ACh receptor
- Ineffective at deeper levels of blockade (TOF count of 0)



Fuchs-Buder, et al. Acta Anaesthesiol Scand. 2007;51:789-808.
NMBA=neuromuscular blocking agent; TOF=train-of-four; PTC=post-tetanic count.

Acetylcholinesterase Inhibitors Have Important Limitations

- Muscarinic side effects are common
- Require co-administration of muscarinic antagonists
- Slow onset of effect
- Highly variable time to completely reverse NMB
- <u>High rates of residual blockade</u>

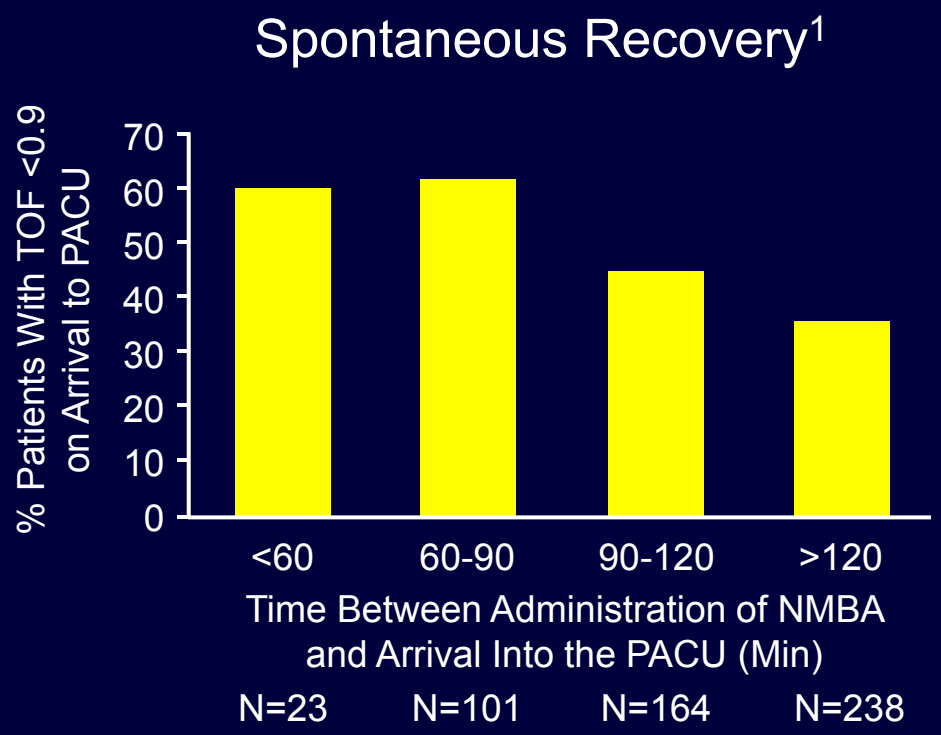
Reversal Times With Neostigmine
(0.07 mg/kg After Rocuronium) to Recovery (TOF >0.9)

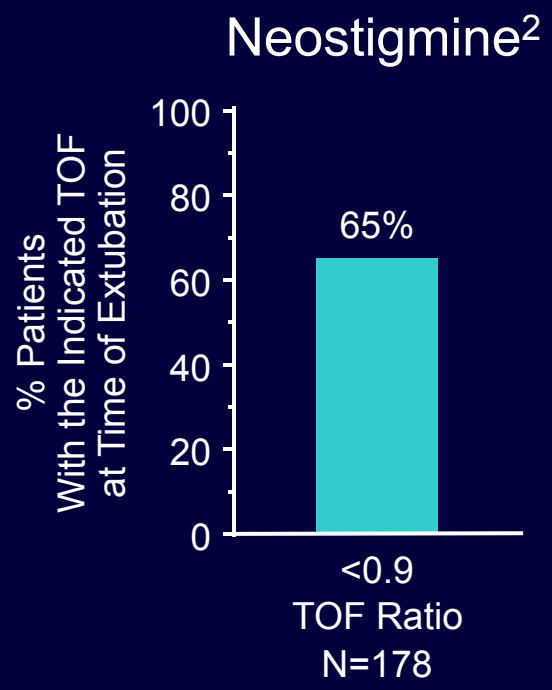
	Median	Range
From TOF count 1 - to recovery	29 min	9 - 76 min
From TOF count 2 - to recovery	23 min	8 - 57 min
From TOF count 3 - to recovery	16 min	7 - 44 min
From TOF count 4 - to recovery	10 min	5 - 26 min

Kim KS. Anesth Analg. 2004.
NMB=neuromuscular blockade; TOF=train-of-four.

Residual Neuromuscular Block Common

Residual Block After Extubation





- Residual neuromuscular block is usually undetected
- Incidence unchanged over past 4 decades[3,4]

N=total number of patients in the group.
[1] Adapted from Debaene, et al. Anesthesiology. 2003;98:1042-1048; [2] Adapted from Fortier, et al. Anesth Analg. 2015;
[3] Murphy & Brull. Anesth Analg. 2010; [4] Naguib, et al. BJA. 2007.
TOF=train-of-four; PACU=Post-Anesthesia Care Unit; NMBA=neuromuscular blocking agent.

Residual Blockade Is Associated With Adverse Physiologic Effects: Awake Volunteers

- TOF ratios <0.9 are associated with:
  - Reduced upper airway tone, increased risk for airway obstruction[1]
  - Reduced upper esophageal muscle tone, increased risk for aspiration[2]
  - Impaired hypoxic ventilatory response[3]
  - Higher incidence of unpleasant symptoms of muscle weakness[4]

[1] Eikermann, et al. Am J Respir Crit Care Med. 2007; [2] Kopman, et al. Anesthesiology. 1997; [3] Eriksson LI. Anesth Analg. 1999; [4] Murphy, et al. Anesth Analg. 2013.
TOF=train-of-four.

Residual Blockade Is Associated With Poorer Clinical Outcomes

- TOF ratios <0.9 are associated with:
  - Increased postoperative hypoxemic events[1]
  - Higher risk of airway obstruction following extubation[1]
  - Prolonged PACU admission[2]
  - Poorer patient perceived quality of recovery[3]
- Residual blockade† is associated with a higher incidence of postoperative pulmonary complications (incidence of 16.9% vs. 4.9%*)[4]

*$p<0.05$.
† Defined in this study as TOF <0.7 at time of extubation.
[1] Murphy, et al. Anesth Analg. 2004; [2] Butterly, et al. BJA. 2010; [3] Murphy, et al. Anesth Analg. 2013;
[4] Berg H, et al. Acta Anesthesiol Scand. 1997.
TOF=train-of-four; PACU=Post-Anesthesia Care Unit.

Residual Blockade Is Associated With Increased Morbidity and Mortality

- Critical respiratory events (CRE)
  - In a study of patients arriving in the PACU with CREs over a 1 year period, 90.5% of patients experiencing a CRE had residual neuromuscular block (vs. 9.5% of matched controls)[1]
- Case-control study (N=869,483)[2] to identify risk factors related to anesthetic management for mortality and coma within 24 hours of surgery
  - Failure to reverse neuromuscular blockade was associated with a 90% increase in mortality and coma risk

[1] Murphy, et al. Anesth Analg. 2008; [2] Arbous, et al. Anesthesiology. 2005.
PACU=Post-Anesthesia Care Unit.

Current Reversal Options: Summary

- Efficacy of anticholinesterase reversal agents is not optimal
  - Inability to rapidly reverse deeper levels of blockade
  - Variable and often prolonged times to recovery
  - High rate of incomplete neuromuscular recovery
- Current pharmacologic reversal agents have unwanted effects
  - Cholinergic side effects
  - Need for co-administration of anticholinergics
- The high risk for residual blockade increases risks for:
  - Upper airway obstruction
  - Pharyngeal dysfunction
  - Increased risk of aspiration
  - Impairment of the hypoxic ventilatory drive
  - Postoperative hypoxemic events
  - Prolonged PACU length of stay
  - Unpleasant symptoms of muscle weakness
  - Increased pulmonary complications

PACU=Post-Anesthesia Care Unit.

Attributes of a Better Reversal Agent

- Reverse any level of neuromuscular blockade rapidly
  - Allows flexible use of neuromuscular block intraoperatively
  - Optimizes the surgical conditions
  - Reduces risks related to patient movement
- Be free of unwanted cholinergic side effects
- Minimize risk for postoperative residual block

Sugammadex
Summary of Pharmacological Profile

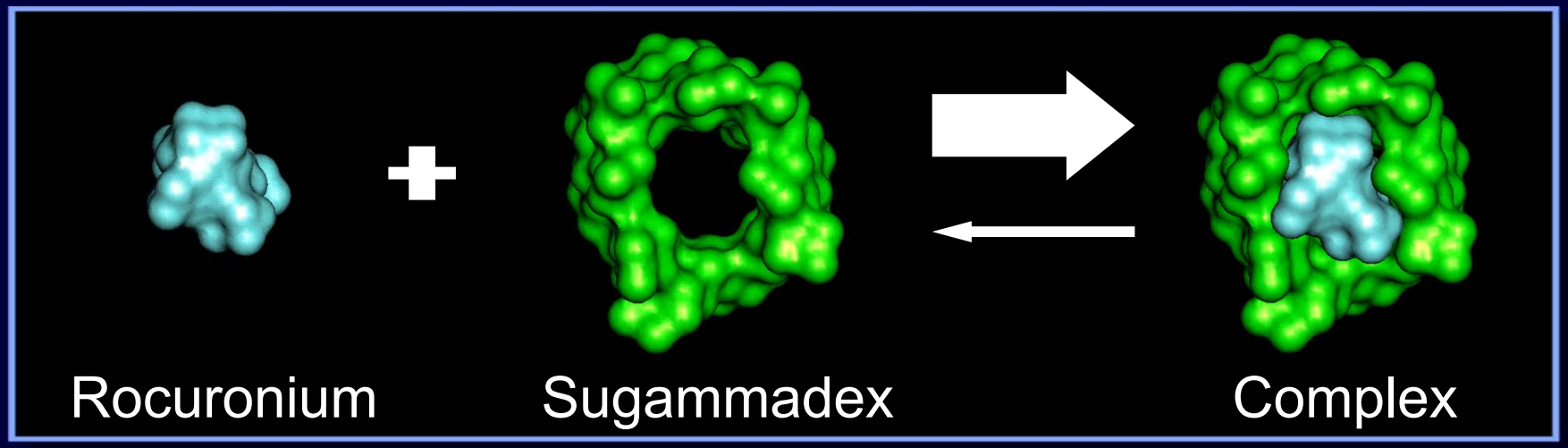
Presenter:

W. Joseph Herring, MD, PhD

Merck Research Laboratories

Sugammadex Is a Novel Drug Designed to Reverse Neuromuscular Blockade

- Sugammadex is a modified γ-cyclodextrin
- Sugammadex encapsulates the neuromuscular blocking agents rocuronium and vecuronium into a high affinity complex, such that these agents can no longer bind at the neuromuscular junction
- The complex is then eliminated, leading to reversal of their neuromuscular blocking effects



Gijsenbergh, et al. Anesthesiology. 2005;103:695-703.

Characteristics of Sugammadex

- No metabolism; no penetration across blood-brain barrier
- Renal clearance approximates glomerular filtration rate
- Plasma elimination half-life of ~2 hours
- Linear PK (range 0.1 - 96 mg/kg)
- Low potential for drug-drug interactions
- Similar PK for anesthetized surgical patients and non-anesthetized healthy subjects
- No dose adjustments based upon most intrinsic factors (e.g., age, gender, BMI and race); except, sugammadex is not recommended in severe renal impairment

PK=pharmacokinetics; BMI=body mass index.

Sugammadex Is Differentiated From Currently Available Reversal Agents

- No direct interaction with cholinergic neurotransmission and therefore no intrinsic cholinergic effects
- Can rapidly reverse deep, as well as moderate, neuromuscular blockade (NMB)
- Deep NMB can be maintained up to the very end of the surgical procedure
- Low risk of postoperative residual neuromuscular blockade

Approach to Clinical Development

- Criteria used in dose-finding studies:
  - Optimize recovery time to a train-of-four (TOF) ratio of 0.9
  - Minimize the likelihood of residual and recurrent neuromuscular blockade (NMB)
- Efficacy and safety of 2 sugammadex doses studied for routine reversal of neuromuscular blockade following administration of rocuronium or vecuronium:
  - 2 mg/kg for reversal of moderate NMB
  - 4 mg/kg for reversal of deep NMB
- Efficacy and safety of 16 mg/kg studied for urgent or emergent reversal after rocuronium

Comprehensive Clinical Trial Experience

Clinical Trial Data	Current Submission
Total subject exposures to i.v. sugammadex	5999
Number unique subjects exposed to i.v. sugammadex	4453
Studies conducted with i.v. sugammadex	56
Efficacy studies	26
Routine use studies (moderate and/or deep NMB)	24
Urgent/emergent use studies	2
Pooled Phase 1 studies – without neuromuscular blockade or anesthesia	14
Pooled Phase 1-3 studies – with neuromuscular blockade and/or anesthesia	42

- Post-marketing experience: currently approved and marketed in 57 countries, with ~11.5 million patients who have received sugammadex as of 31 Mar 2015 cutoff†

† Based on the availability of monthly drug distribution figures; hence, this cumulative estimate has been calculated to 31 Mar 2015 rather than to the post-marketing data lock point of the submission (22 Apr 2015).
NMB=neuromuscular blockade.

Sugammadex
Overview of Clinical Efficacy

Overview of Efficacy

- Reversal of neuromuscular blockade
  - Routine use
    - For moderate neuromuscular blockade
    - For deep neuromuscular blockade
  - Urgent or emergent use
- Postoperative residual neuromuscular blockade

Studies to Assess Efficacy in Routine Use

- Neuromuscular blockade induced by either rocuronium or vecuronium
- Sugammadex dose and timing of administration
  - Moderate block: 2 mg/kg at reappearance of T2
  - Deep block: 4 mg/kg at 1-2 post-tetanic counts (PTC)
- Comparators were placebo or neostigmine
- The train-of-four (TOF) ratio of 0.9 was the prespecified primary endpoint

T2=second twitch.

Registration Studies in Moderate and Deep Block: Patient Characteristics

- Patients studied were undergoing open abdominal or laparoscopic surgeries

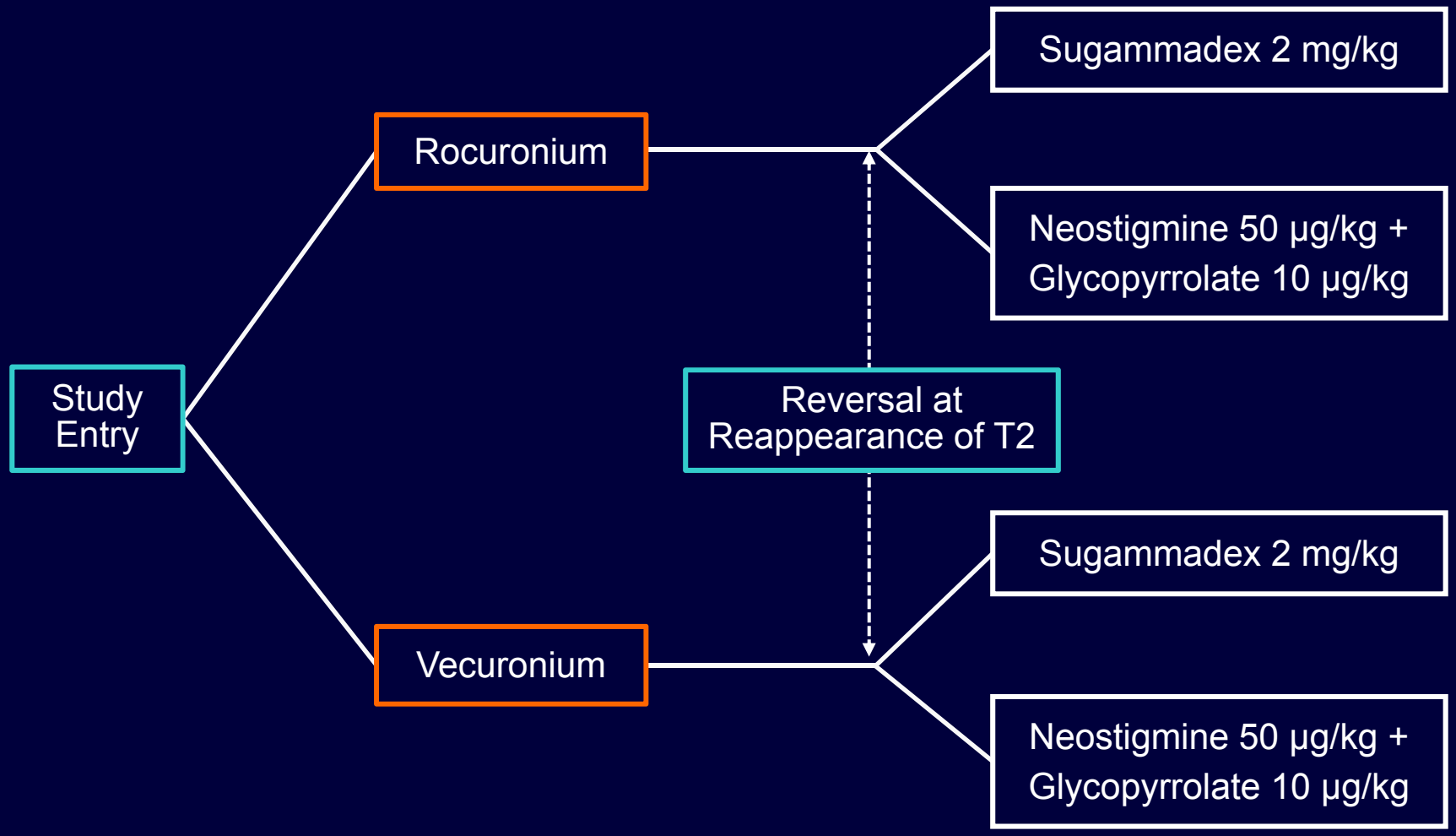
Parameter	Statistic/Class	Moderate Block Total (N=189)	Deep Block Total (N=157)
Age (years)	Mean (SD)	50 (15)	53 (14)
	Range	18 - 83	19 - 85
Gender, n (%)	Male	102 (54)	71 (45)
	Female	87 (46)	86 (55)
American Society of Anesthesiologists (ASA) Class, n (%)	Class 1	80 (42)	13 (8)
	Class 2	99 (52)	111 (71)
	Class 3	10 (5)	33 (21)
	Class 4	0	0

Sugammadex 2 mg/kg for moderate neuromuscular blockade (NMB); 4 mg/kg for deep NMB. Intent-to-treat population.

Registration Study of Sugammadex for Reversal of Moderate Neuromuscular Blockade

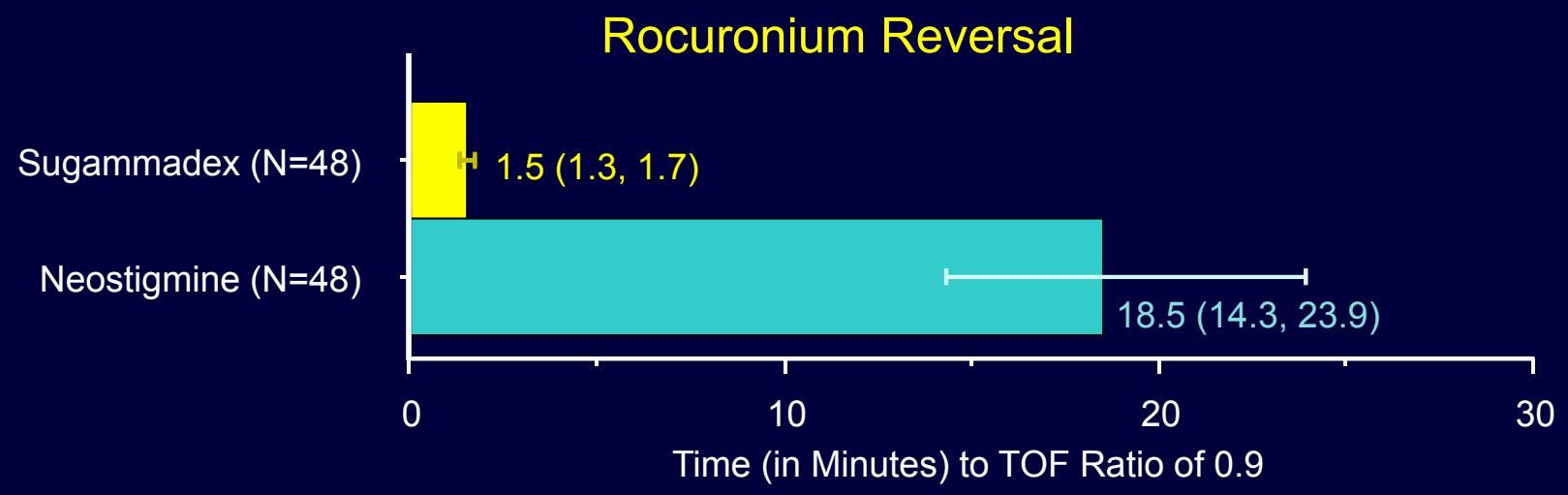
Trial 301

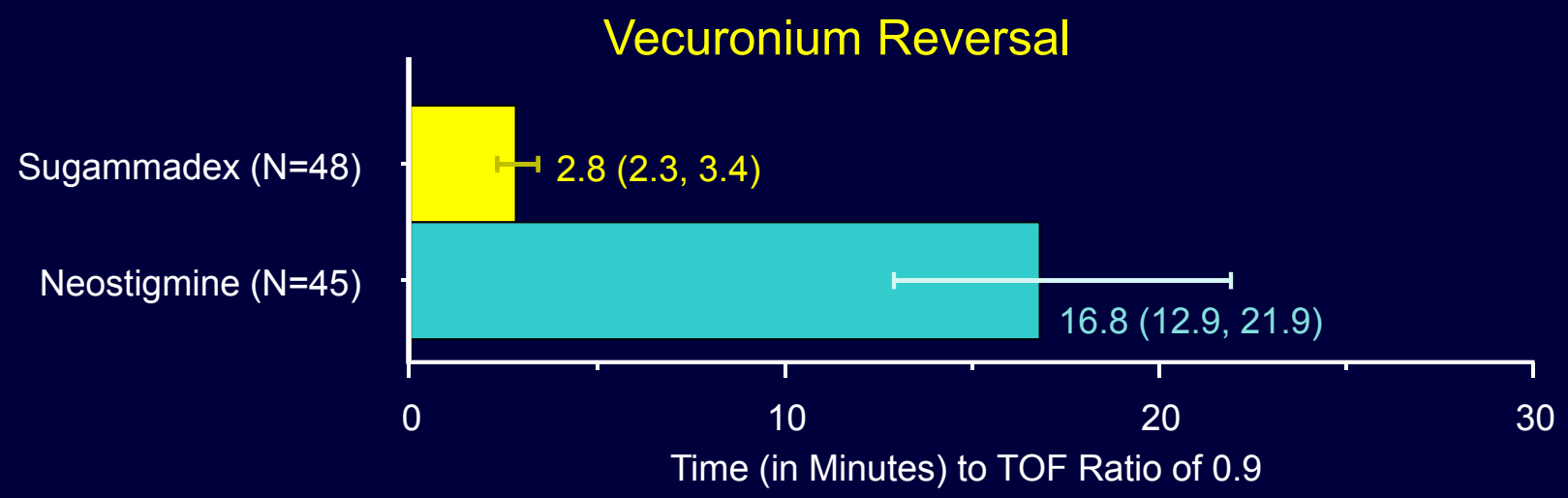
Moderate Neuromuscular Blockade Reversal Study Design: Trial 301



Patients were randomized to combination of neuromuscular blocking agent and reversal agent at time of study entry.
Blobner, et al. Eur J Anaesthesiol. 2010;27:874-881.
T2=second twitch.

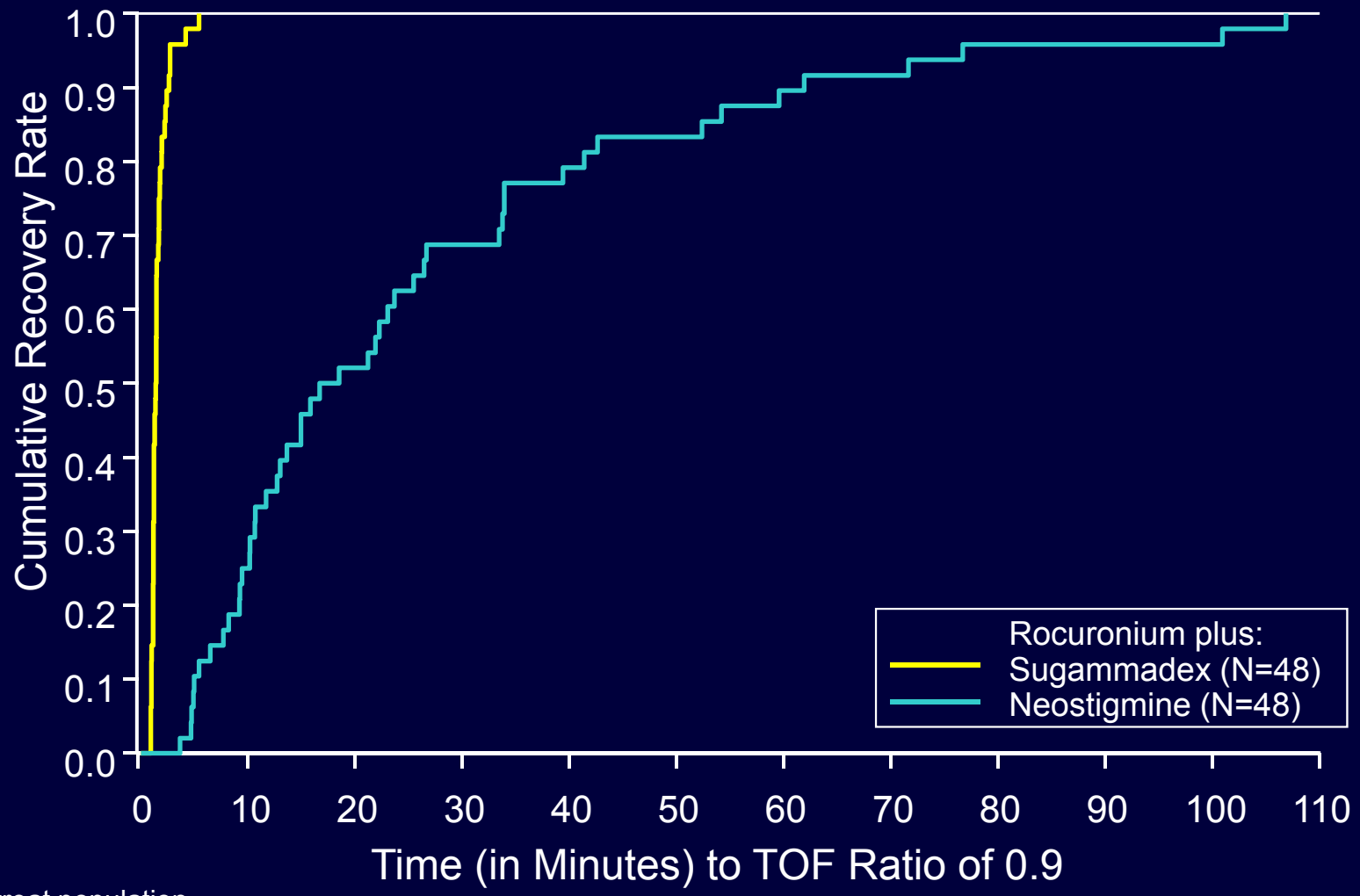
Sugammadex 2 mg/kg Superior to Neostigmine in Reversal of Moderate Blockade: Trial 301





Intent-to-treat population. Results presented as Geometric Mean (95% CI). TOF=train-of-four.

Moderate Blockade With Rocuronium: Most Patients Recover Within 5 Minutes After Sugammadex 2 mg/kg: Trial 301

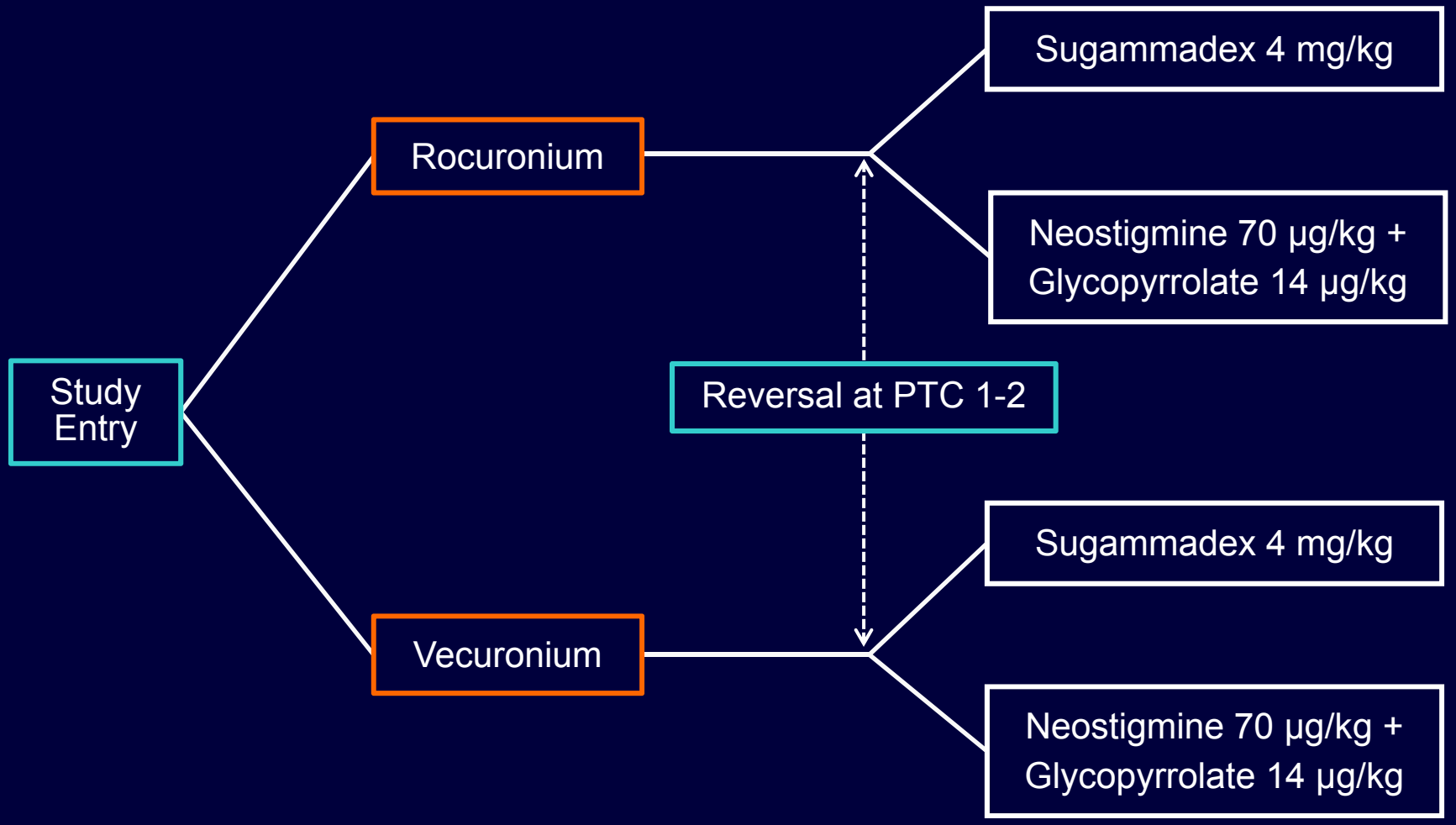


Intent-to-treat population.
TOF=train-of-four.

Registration Study of Sugammadex for Reversal of Deep Neuromuscular Blockade

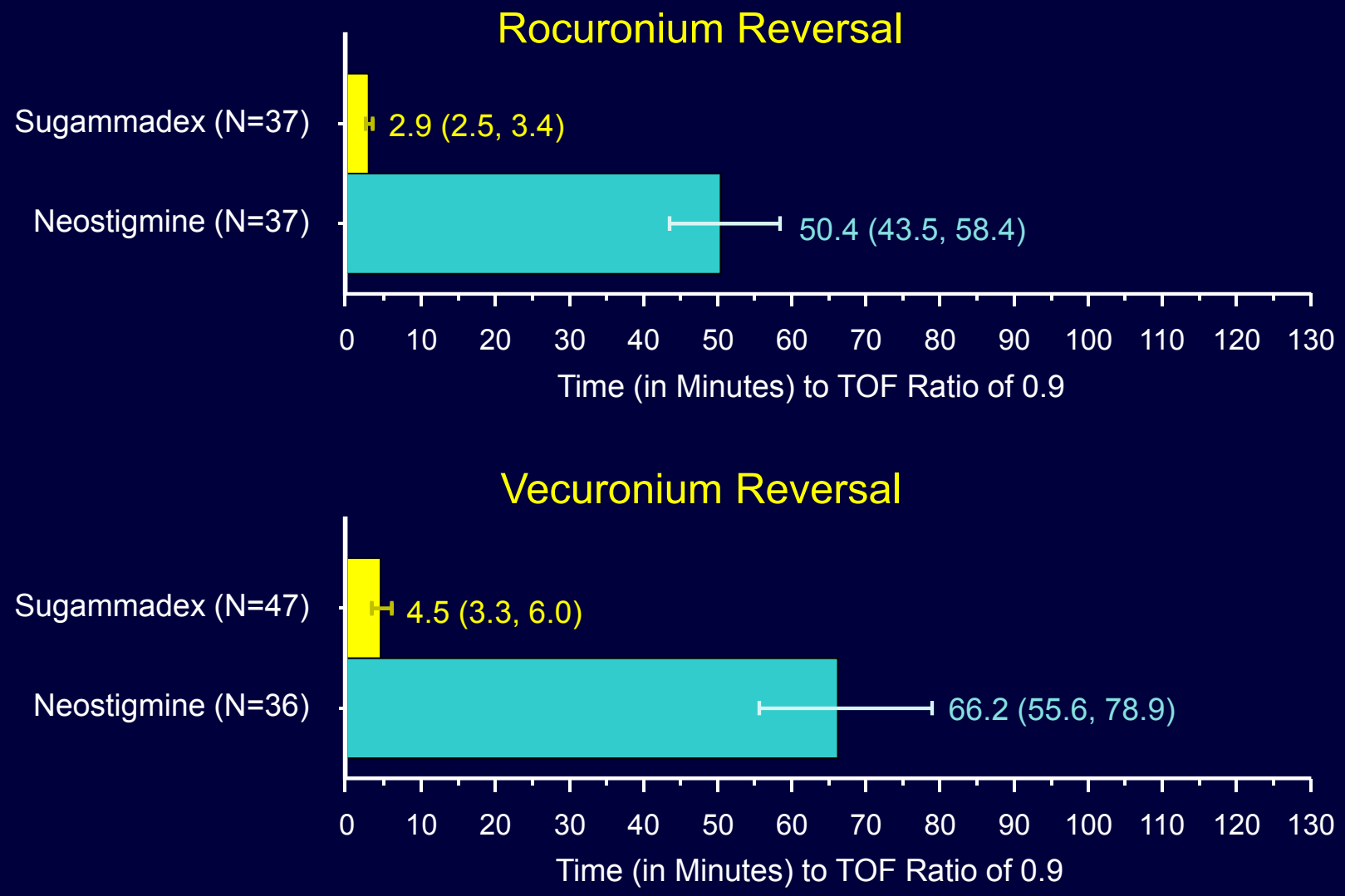
Trial 302

Deep Neuromuscular Blockade Reversal Study Design: Trial 302



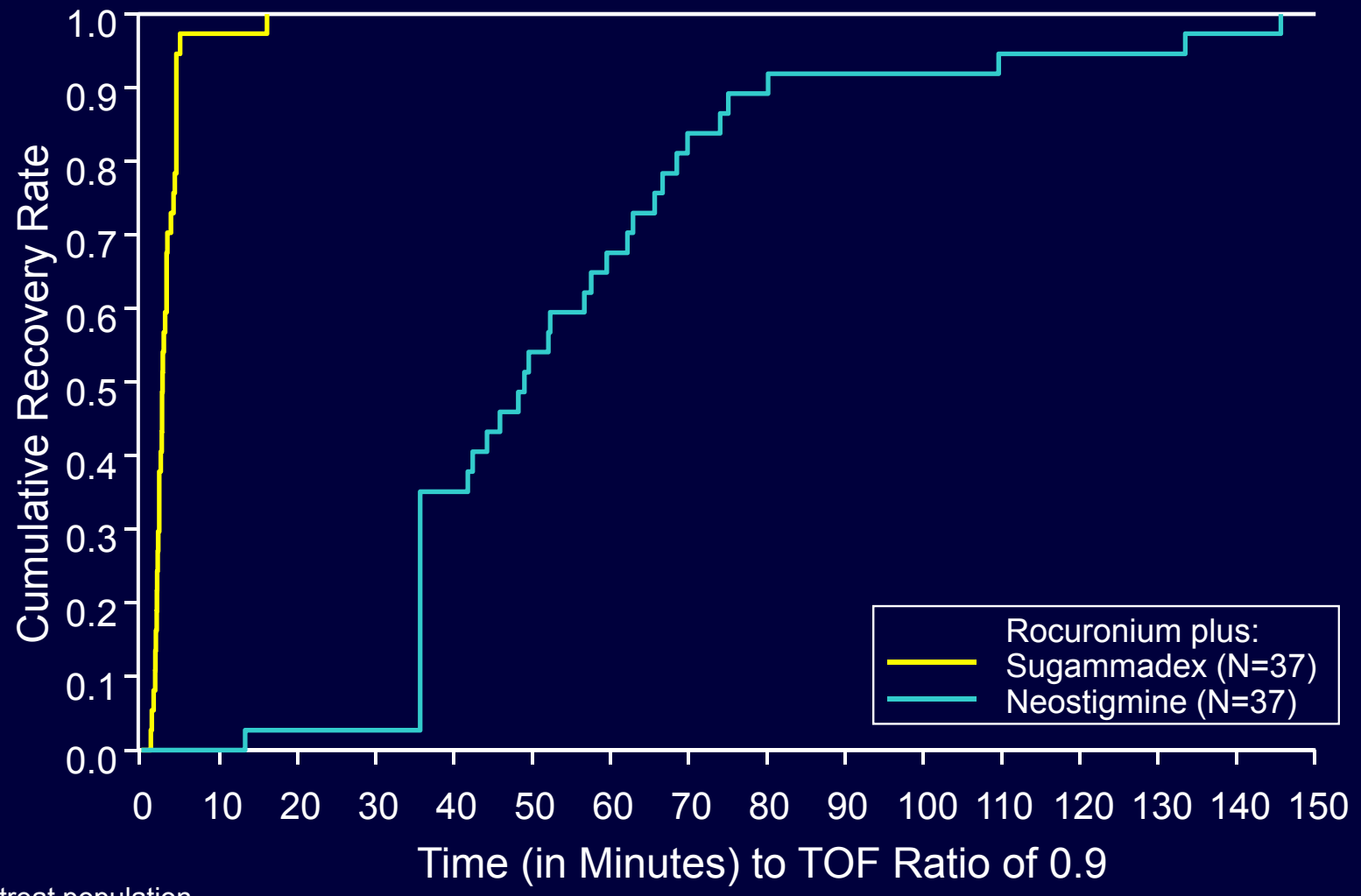
Patients were randomized to combination of neuromuscular blocking agent and reversal agent at time of study entry.
Jones, et al. Anesthesiology. 2008;109:816-824.
PTC=post-tetanic count.

Sugammadex 4 mg/kg Superior to Neostigmine in Reversal of Deep Blockade: Trial 302



Intent-to-treat population. Results presented as Geometric Mean (95% CI). TOF=train-of-four.

Deep Blockade With Rocuronium: Most Patients Recover Within 5 Minutes After Sugammadex 4 mg/kg: Trial 302



Intent-to-treat population.
TOF=train-of-four.

Reversal of Rocuronium-Induced Neuromuscular Blockade in Urgent or Emergent Situations

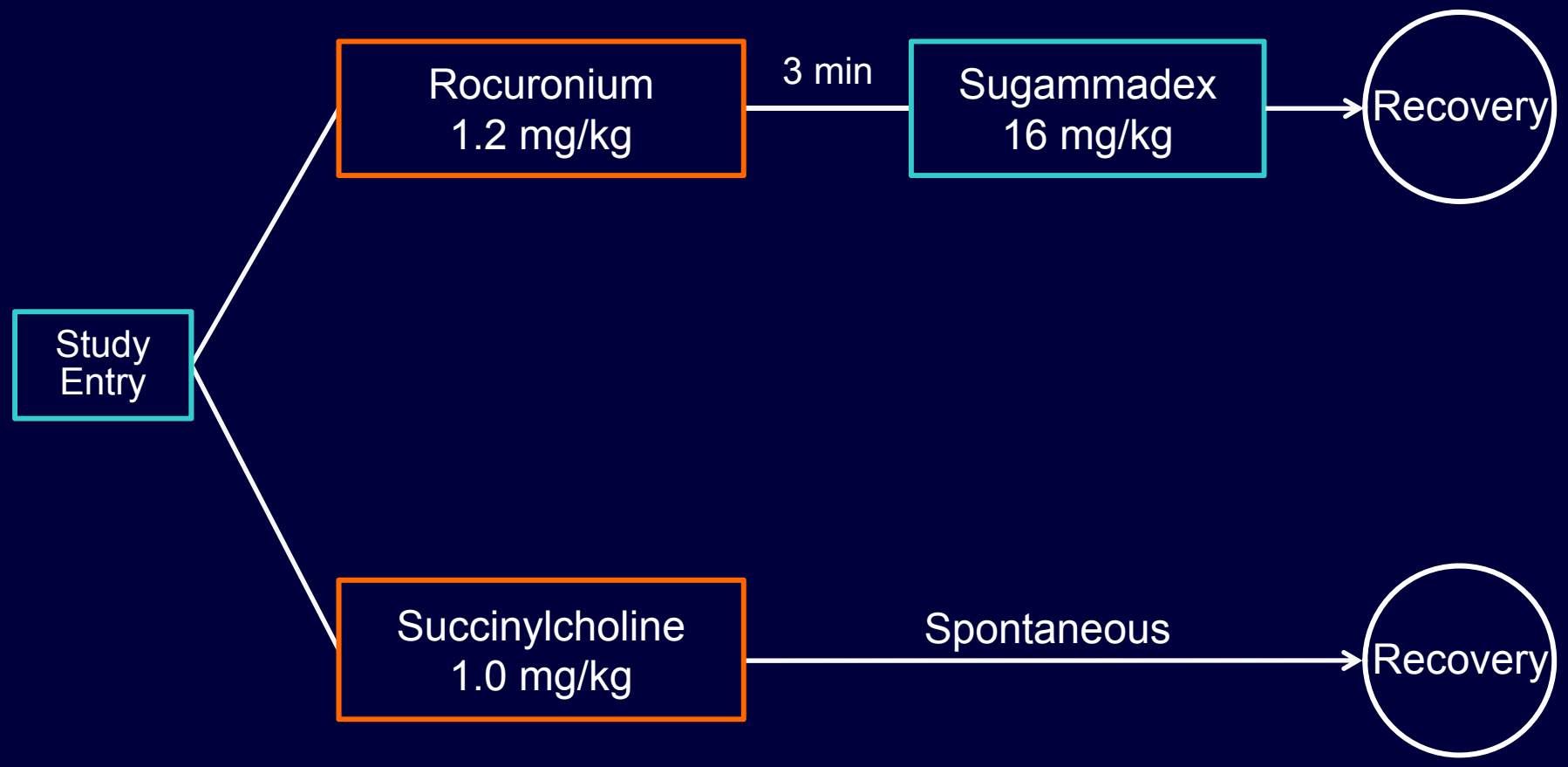
Trial 303

Sugammadex 16 mg/kg for Reversal of Neuromuscular Blockade in Urgent or Emergent Situations: Trial 303

- The 16 mg/kg sugammadex dose is intended for use in urgent or emergent situations when rapid and reliable reversal of neuromuscular blockade of rocuronium is required
- Such situations are rare, but life-threatening
- Not possible to study them directly in a clinical trial
- Instead, Study 303 was designed to simulate these emergent situations[1] and assess the efficacy of sugammadex

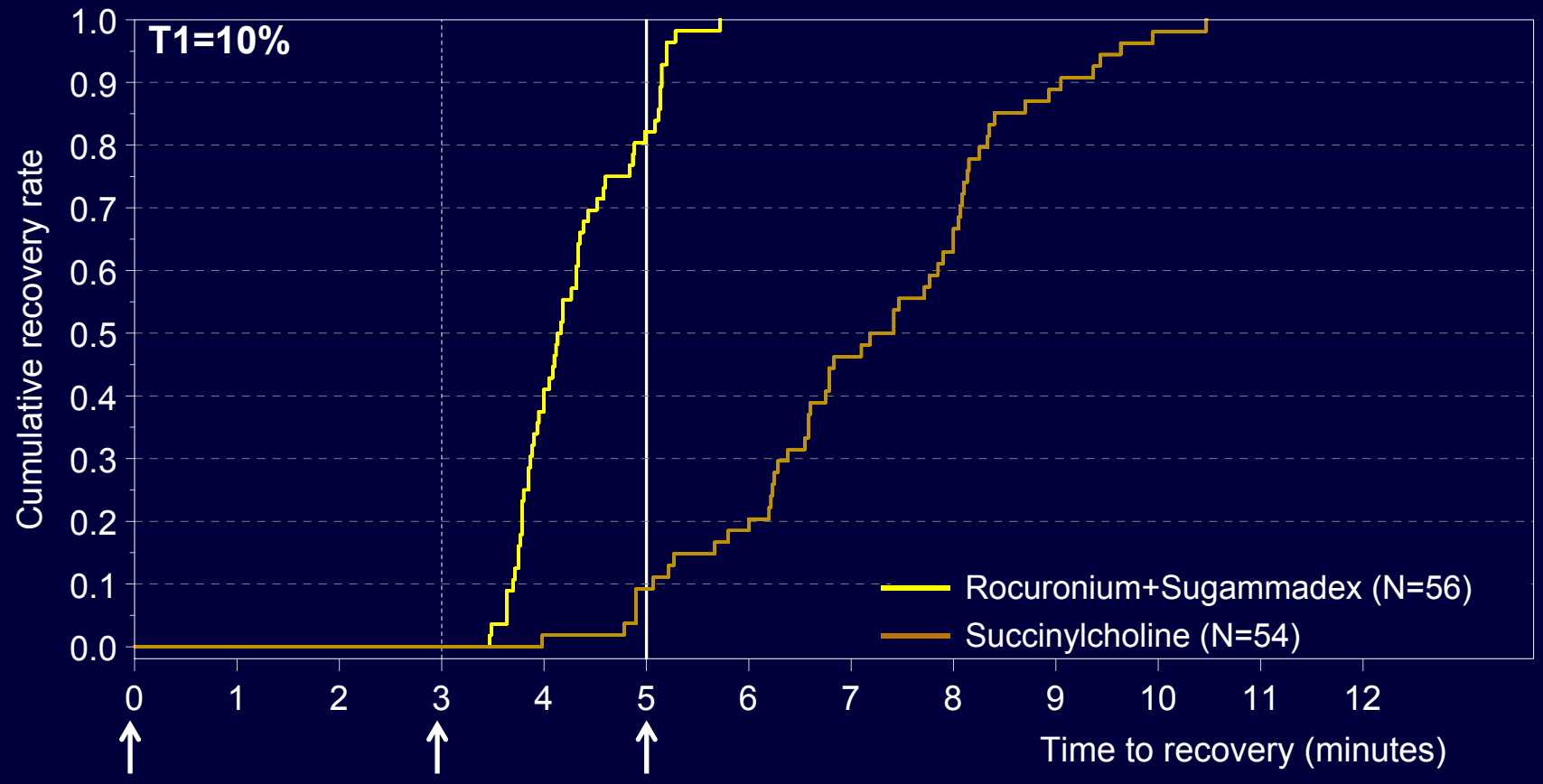
[1] Lee, et al. Anesthesiology. 2009;110:1020-1025.

Urgent or Emergent Reversal of Rocuronium-Induced Neuromuscular Blockade Study Design: Trial 303



Patients were randomized to either rocuronium/sugammadex or the succinylcholine only treatment arm.
Lee, et al. Anesthesiology. 2009;110:1020-1025.

Sugammadex 16 mg/kg Reverses Blockade Within Critical Window for Anoxia: Trial 303



Rocuronium/ Succinylcholine administered

Sugammadex administered

Onset increased risk anoxia

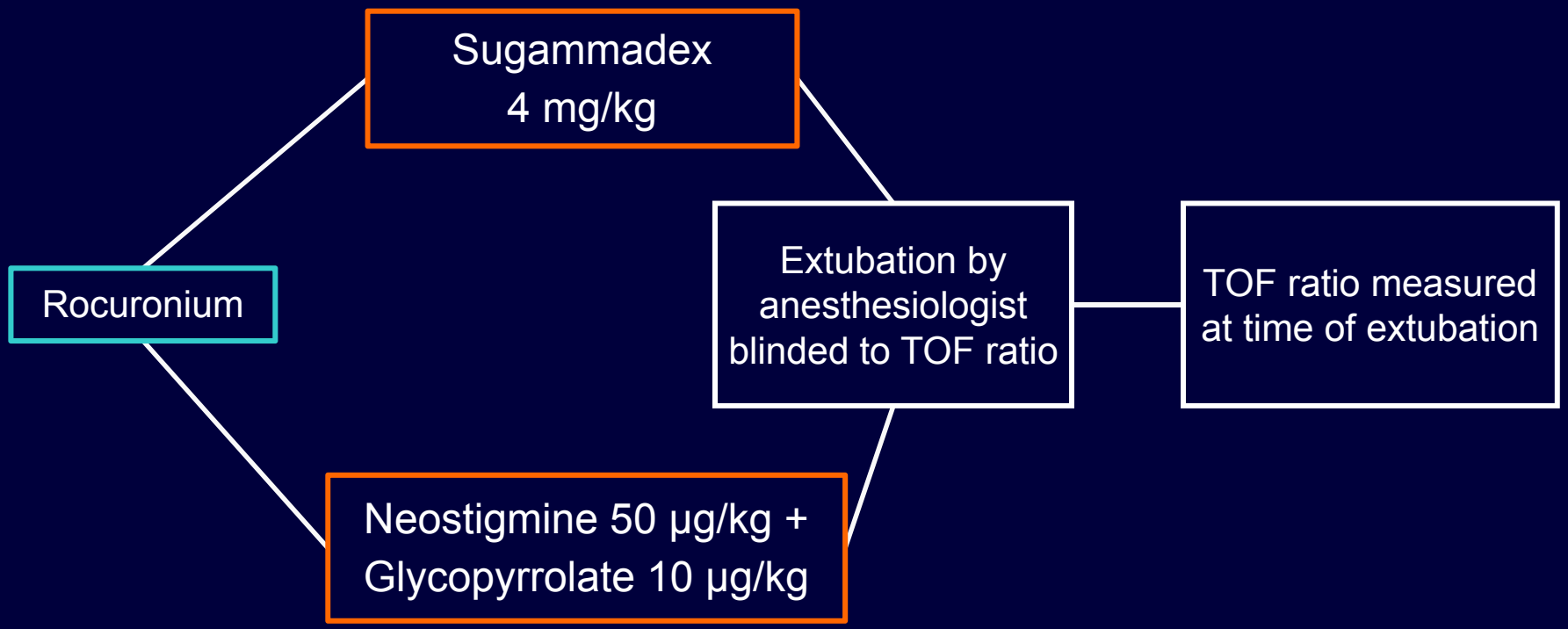
Geometric Mean Time to Recovery† (T1=10%)
Rocuronium + Sugammadex: 4.3 min
Succinylcholine: 7.1 min $p<0.001$

† As-treated population.
T1=first twitch.

Risk for Residual Block After Extubation

Trial 334

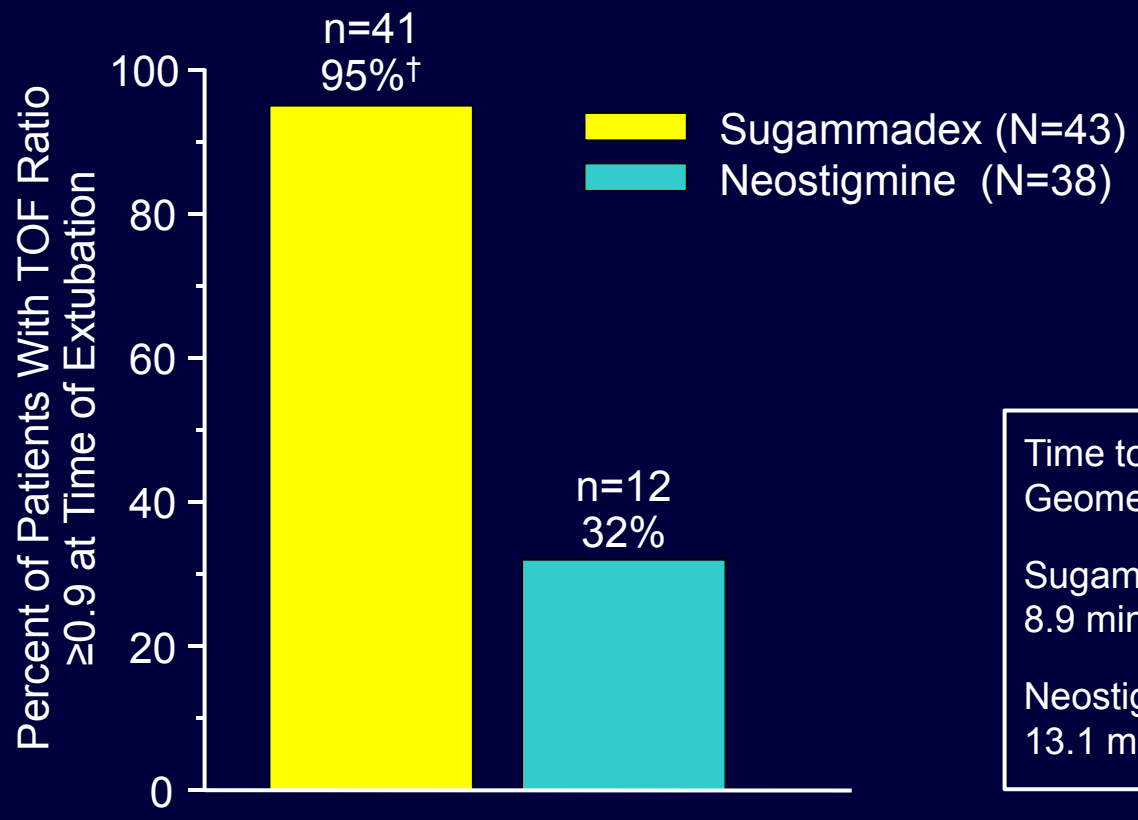
Study Design Examining Residual Blockade After Extubation: Trial 334



Patients were randomized to either sugammadex or neostigmine for reversal agent at time of study entry.
Sabo, et al. J Anesthe Clinic Res. 2011;2:6.
TOF=train-of-four.

Less Residual Blockade at Extubation After Reversal With Sugammadex vs. Neostigmine

Trial 334



Time to Extubation
Geometric Mean (95% CI)

Sugammadex (N=51):
8.9 min (7.1, 11.2)‡

Neostigmine/Glycopyrrolate (N=46):
13.1 min (11.0, 15.7)

- The majority of sugammadex-treated patients are fully recovered at the time of tracheal extubation (defined as TOF ratio ≥0.9) versus neostigmine

† p<0.0001 vs. neostigmine (completers analysis); ‡ p=0.009 vs. neostigmine (intent-to-treat analysis).
TOF=train-of-four.

Efficacy Conclusions

- Sugammadex reverses neuromuscular blockade rapidly
  - Superior to neostigmine and to spontaneous recovery
  - Efficacious for moderate and deep neuromuscular blockade
  - Efficacious for rapid reversal after rocuronium in emergent situations
- Sugammadex reverses neuromuscular blockade reliably
  - The great majority of patients recover within 5 minutes in routine use
- Residual neuromuscular blockade is infrequent with sugammadex

Sugammadex
Overview of Clinical Safety

Presenter:

K. Chris Min, MD, PhD

Merck Research Laboratories

Overview of Clinical Safety

- Overview of general safety
- Characterization of hypersensitivity
- Analysis of cardiac arrhythmias

Risk Profile of Sugammadex

- Main risks
  - Hypersensitivity, including anaphylaxis/anaphylactic shock
  - Bradycardia
- Identified in clinical trials and post-marketing experience

Sugammadex Clinical Trial Safety Database

Clinical Database Divided Into 2 Datasets

- Pooled Phase 1-3 (42 trials) [with NMBA ± anesthesia]
  - Placebo-controlled (13 trials†)
  - Neostigmine-controlled (8 trials†)
  - Other trials (22‡)
- Pooled Phase 1 (14 trials) [without NMBA/anesthesia]
  - Includes dedicated hypersensitivity Study P101

† Different arms of P07038 split into both placebo-controlled and neostigmine-controlled datasets.
‡ Other trials: Includes 4 Phase 1 trials, 4 Phase 2 dose finding trials, 6 special population studies, 3 trials using NMBA other than rocuronium or vecuronium, and 5 miscellaneous studies comparing anesthesia regimens.
NMBA=neuromuscular blocking agent.

Sugammadex Clinical Trial Safety Database

Subjects Receiving Anesthesia/Neuromuscular Blocking Agent

Pooled Phase 1-3

42 Trials

Sugammadex: N=3519

Placebo: N=544

Neostigmine: N=930

Succinylcholine: N=134†

Placebo-Controlled Subset

13 Trials

Sugammadex: N=1078

Placebo: N=544

† Succinylcholine was comparator to combination of rocuronium/sugammadex in Study #303.

Overall Adverse Event Profile

Sugammadex Generally Comparable to Placebo

Placebo-Controlled Trials in Pooled Phase 1-3 Dataset

	Placebo N=544	Sugammadex N=1078
Subjects with adverse events (AEs)	82.2%	73.6%
Subjects with serious AEs	7.0%	6.2%
Subjects with AE with severe intensity	8.5%	5.5%
Subjects with drug related AEs	9.4%	11.7%
Deaths	0.6%	0.1%
Discontinued due to AEs	0.2%	0.1%

N=unique subjects.

Most Common Adverse Events†

Sugammadex Generally Comparable to Placebo

Placebo-Controlled Trials in Pooled Phase 1-3 Dataset

	Placebo N=544	Sugammadex N=1078
At least one adverse event	82.2%	73.6%
Procedural pain	35.1%	24.9%
Nausea	17.6%	15.7%
Vomiting	7.9%	9.3%
Constipation	13.4%	6.9%
Wound complication	5.9%	6.6%
Anemia postoperative	9.4%	5.0%

Sorted by incidence in the sugammadex group. All subjects treated group.
† Any adverse event with incidence ≥5% in sugammadex group.
N=unique subjects.

Overview of Clinical Safety

- Overview of general safety
- Characterization of hypersensitivity
- Analysis of cardiac arrhythmias

Assessment of Hypersensitivity With Sugammadex

- Hypersensitivity and anaphylaxis in healthy subjects after repeat exposure in Study P101
- Hypersensitivity and anaphylaxis in the clinical database
- Anaphylaxis in the post-marketing database

Definitions of Hypersensitivity and Anaphylaxis

- World Allergy Organization[†]:
  - Hypersensitivity: used to describe objectively reproducible symptoms and signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons
  - Anaphylaxis: a severe, life-threatening, generalized or systemic hypersensitivity reaction

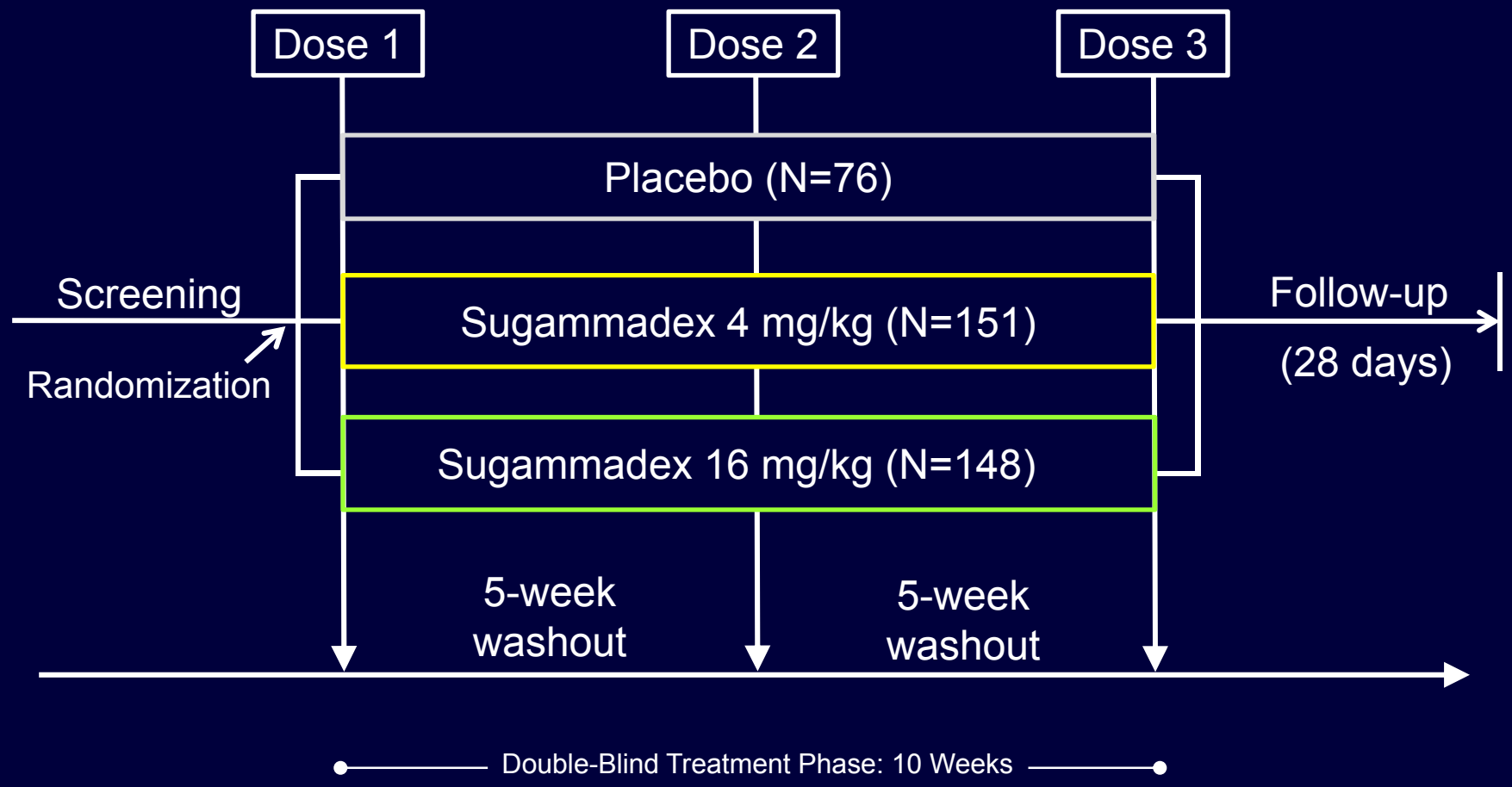
- For consistency across the program and in agreement with FDA, Sampson Criterion 1[‡] was used to diagnose anaphylaxis

[†] Johansson SGO, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, Oct. 2003. J Allergy Clin Immunol. 2004;113(5):832-836.
[‡] Sampson H, et al. Second symposium on the definition and management of anaphylaxis: summary report – second NIAID/FAAN symposium. J Allergy Clin Immunol. 2006;117(2), 391-397. Also referred to as NIAID/FAAN criteria.
NIAID=National Institute of Allergy and Infectious Disease; FAAN=Food Allergy and Anaphylaxis Network.

Dedicated Hypersensitivity Study: P101

Trial Design: 375 Healthy Subjects, 3-Arm, 3-Dose

(Randomization 1:2:2 for Placebo:4 mg/kg:16 mg/kg Sugammadex alone, no NMBAs and no anesthesia)



Identification and Adjudication of Hypersensitivity and Anaphylaxis in P101

- Step 1. Targeted Hypersensitivity Assessments (THA) were performed at 0.5, 4 and 24 hours after each dose of study drug
- Step 2. THA findings resulted in referral of the case to the blinded, independent adjudication committee (AC)
  - Sponsor also reviewed adverse events and could request referral to AC
- Step 3. AC reviewed all available data and adjudicated each event to determine whether it was
  - Hypersensitivity reaction (also rated severity and relatedness to study medication)
  - Anaphylactic reaction according to Sampson Criterion 1

Adjudication Results in P101

	Placebo	Sugammadex 4 mg/kg	Sugammadex 16 mg/kg
Subjects in population	N=76	N=151	N=148
Referred for adjudication, n (%)	14 (18.4)	35 (23.2)	45 (30.4)
Adjudicated as hypersensitivity, n (%) [95% CI][†]	1 (1.3) [0.0, 7.1]	10[‡] (6.6) [3.2, 11.8]	14 (9.5) [5.3, 15.4]
Adjudicated as anaphylaxis, n (%) [95% CI][†]	0 (0.0) [0.0, 4.7]	0 (0.0) [0.0, 2.4]	1 (0.7)[§] [0.0, 3.7]

n=number of unique subjects.
[†] Based on exact binomial method by Clopper & Pearson.
[‡] One case was considered by the independent, blinded adjudication committee as not related to study drug.
[§] The case of anaphylaxis was one of the 14 cases of hypersensitivity.
CI=confidence interval.

Characteristics of Hypersensitivity Related to Sugammadex in P101

- Onset of events shortly after dose
  - Two thirds of cases within 10 minutes, and all within 60 minutes
- Manifestations
  - Cutaneous: urticaria, pruritus, erythema
  - Upper respiratory symptoms: sneezing, rhinorrhea
  - No lower respiratory symptoms
  - Gastrointestinal symptoms: nausea, vomiting
  - No hypotension
- One case of anaphylaxis (1st dose of 16 mg/kg) with conjunctival oedema, urticaria, enlarged uvula, nasal congestion, sneezing, transient decrease in peak expiratory flow
  - Resolution with steroids and antihistamines (no epinephrine)

No Evidence for Sensitization With Repeated Dosing of Sugammadex in P101

- No increase in frequency or severity of hypersensitivity
- No subject had anaphylaxis after 2nd or 3rd dose
- In the 24 subjects with hypersensitivity
  - 21 received all 3 doses
    - All events in these subjects resolved spontaneously
    - 7 had hypersensitivity events with all 3 doses, with each event similar in severity, timing, and characteristics
  - 3 treated for symptoms (discontinued per protocol)
    - All with 1st dose of 16 mg/kg including anaphylaxis case
    - Resolution with antihistamine ± steroid (no epinephrine)

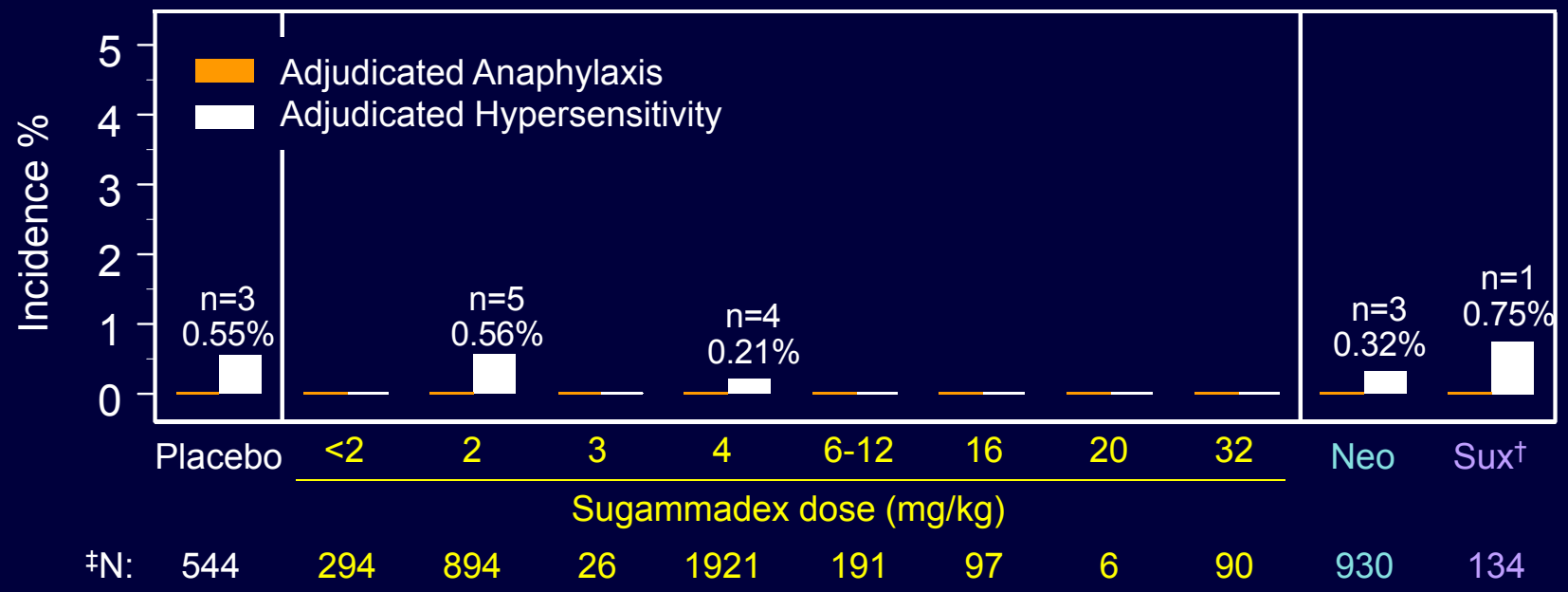
Mechanistic Investigation of Hypersensitivity

- Hypersensitivity events observed in dedicated studies not likely to be Type 1 reactions
  - No evidence of mast cell degranulation (serum tryptase)
  - Skin testing was not consistent with Type 1 hypersensitivity
  - No sugammadex-specific IgE detected
- Investigations also included
  - Ex vivo histamine release by basophils, measurements of serum and urine markers related to complement and contact system, endothelial and neutrophil activation
- Underlying mechanism for the observed hypersensitivity reactions not known

IgE=immunoglobulin E.

Hypersensitivity/Anaphylaxis in Pooled Phase 1-3 Database

- Low incidence (0.26%) of hypersensitivity and no case of anaphylaxis with sugammadex (N=3519)
  - Estimated risk of anaphylaxis is ≤0.1%†



† The upper limit of the 95% confidence interval is 0.1%.
‡ Data present unique subjects by dose group. The 3 subjects with exposures to multiple dose levels of sugammadex were counted in the higher dose group. None of the 9 cases of hypersensitivity occurred in any of these 3 subjects.
Neo=neostigmine; Sux=succinylcholine.

Sugammadex Post-marketing Experience: Anaphylaxis

- Extensive post-marketing experience with sugammadex
  - 11.5 million patient exposures as of 31 Mar 2015, assuming 95% of vials sold are used
  - Spontaneous reports entered into the company database using verbatim adverse event terms
- 273 reports of anaphylaxis†
  - Where outcome reported, most (237 of 241) recovered
  - 4 deaths in patients with complex medical conditions

† Based on review of 259 reports of anaphylaxis and 14 reports of serious hypersensitivity adjudicated as anaphylaxis up through 22 Apr 2015.

Frequency of Anaphylaxis in the Post-marketing Environment

- Post-marketing frequency for anaphylaxis with sugammadex:
  - 24 per 100,000 exposures† (0.024%)
- Anaphylaxis occurs in the perioperative setting in presence of neuromuscular blockade:
  - 15-34 per 100,000 surgeries[1,2,3,4,5] (0.015% to 0.034%)

† Assumes 95% of distributed vials sold were used and 10% of cases are reported.
[1] Laxenaire Ann. Fr Anesth Reanim. 1999;18:796-809; [2] Fasting & Gisvold. Can J Anaesth. 2002;49(6):545-553; [3] Harboe, et al. Anesthesiology. 2005;102(5):897-903; [4] Mertes PM, et al. J Investig Allergol Clin Immunol. 2011;21(6):442-453; [5] Saager L, et al. Anesthesiology. 2015.

Frequency of Anaphylaxis in Three Sugammadex Databases

- Estimated risk for anaphylaxis in surgical patients
  - Pooled Phase 1-3: ≤0.1%† (0/3519)
  - Post-marketing: 0.024%‡
- Estimated risk for anaphylaxis in P101
  - Healthy, awake subjects: 0.33%§ (1/299)

† The upper limit of the 95% confidence interval is 0.1%.
‡ Estimated risk based on assumption of 11.5 million exposures and 10% of anaphylaxis cases reported.
§ The upper limit of the 95% confidence interval 1.9%.

Summary of Hypersensitivity Including Anaphylaxis

- Sugammadex is associated with hypersensitivity, including anaphylaxis
  - Onset in minutes and responds to usual treatment
  - No sensitization with repeated dosing
- Incremental risk for anaphylaxis attributable to sugammadex in surgical patients is small
- Administered in a monitored setting where anaphylaxis can be identified quickly and treated effectively
- Risk of hypersensitivity, including anaphylaxis, can be communicated through labeling

Overview of Clinical Safety

- Overview of general safety
- Characterization of hypersensitivity
- Analysis of cardiac arrhythmias

Cardiac Arrhythmias

A focused analysis of cardiac arrhythmias was performed in the updated safety database:

- Review of pooled clinical database
- Review of post-marketing experience
- Dedicated QT studies

Arrhythmia-Related Adverse Events

Placebo-Controlled Trials in Pooled Phase 1-3 Dataset

Arrhythmia-Related Investigations, Signs and Symptoms†	Placebo N=544 n (%)	Sugammadex N=1078 n (%)
Overall	12 (2.2)‡	35 (3.2)
Bradycardia	4 (0.7)	14 (1.3)
Cardiac arrest	0	1 (0.1)
Electrocardiogram abnormal	0	1 (0.1)
Heart rate decreased	1 (0.2)	2 (0.2)
Heart rate increased	0	3 (0.3)
Palpitations	1 (0.2)	1 (0.1)
Syncope	3 (0.6)	3 (0.3)
Tachycardia	4 (0.7)	10 (0.9)

- One non-fatal cardiac arrest after sugammadex 4 mg/kg likely induced by accidental triggering of oculocardiac reflex
- No cases of Torsade de Pointes

† Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query: broad search.
‡ One patient had two different adverse events, therefore total is 12 instead of 13.

Arrhythmia-Related Adverse Events

Neostigmine-Controlled Trials in Pooled Phase 1-3 Dataset

Arrhythmia-Related Investigations, Signs and Symptoms†	Sugammadex N=871 n (%)	Neostigmine N=881 n (%)
Overall	25 (2.9)	69 (7.8)
Bradycardia	4 (0.5)	42 (4.8)
Heart rate decreased	0 (0.0)	1 (0.1)
Heart rate increased	0 (0.0)	4 (0.5)
Palpitations	3 (0.3)	4 (0.5)
Syncope	5 (0.6)	3 (0.3)
Tachycardia	16 (1.8)	20 (2.3)

† Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query: broad search.

Post-marketing Experience: Cardiac Arrhythmia AEs Reported Infrequently

There were 145 reports of arrhythmia in the post-marketing database

- 72 reports of arrhythmia other than bradycardia
  - 29 tachycardia reports in association with reported anaphylaxis
- 73 bradycardia-related reports
  - 32 reports had features suggesting a relationship to sugammadex
    - Patients hemodynamically stable prior to sugammadex
    - Onset shortly after sugammadex administration
    - No other explanation for bradycardia
    - Most were responsive to usual anticholinergic therapy
    - All recovered from initial bradyarrhythmia, including 6 cases that reported cardiac arrest

AE=adverse events.

Cardiac Arrhythmia Summary

- Bradycardia requiring intervention is rarely associated with sugammadex
- Sugammadex is administered in a monitored setting where bradycardia can be appropriately managed with usual treatment
- The risk of bradycardia including isolated cases of cardiac arrest can be effectively communicated through labeling

Safety Conclusions

- Sugammadex is generally safe and well tolerated
- Hypersensitivity/anaphylaxis
  - Risk does not appear to increase with repeat doses
  - Anaphylaxis is infrequent and responds to usual treatment
- Cardiac arrhythmias
  - Bradycardia can occur but is readily detectable and manageable in the monitored setting in which sugammadex is used

Sugammadex
Benefit-Risk Assessment

Presenter:

David Michelson, MD

Merck Research Laboratories

Sugammadex Clinical Experience

- After its initial review in 2008, the FDA requested further characterization of potential for risks related to repeated administration and hypersensitivity
- The clinical database and experience has expanded since the initial FDA review, and now includes
  - 4453 unique subjects in 56 clinical trials
  - Post-marketing experience derived from an estimated 11.5 million patients in 57 countries
  - A new safety study (P101) in 375 healthy, awake subjects characterized hypersensitivity after repeated dosing

Sugammadex Summary of Key Characteristics

- The data reviewed today provide evidence that sugammadex
  - Rapidly and completely reverses moderate and deep neuromuscular blockade after rocuronium or vecuronium
  - Is generally safe and well tolerated
  - Is not associated with sensitization after repeat administration, and its potential to cause serious hypersensitivity reactions, including anaphylaxis, is limited and manageable in the surgical setting
  - Has the potential to fill important unmet needs related to the use of neuromuscular blockade

The Benefits of Sugammadex: Routine Use

- Rapid, reliable, complete reversal of rocuronium- and vecuronium-induced neuromuscular blockade (NMB)
  - No cholinergic side effects
  - Among available options for reversal of NMB, only sugammadex rapidly reverses deep block
  - Allows deep block to be maintained throughout surgical procedures
- Deep block has, in turn, the potential to
  - Optimize surgical conditions
  - Reduce risk of injury related to patient movement
- Sugammadex reduces risk for residual block (TOF <0.9) at the time of extubation

TOF=train-of-four.

Risks Associated With Sugammadex: Routine Use

- In healthy, awake subjects
  - Hypersensitivity reactions can occur with sugammadex
  - Sensitization not observed after repeated administration
- Anaphylaxis
  - Clinical trials and post-marketing safety databases suggest risk for anaphylaxis is small
  - Responsive to usual treatment
- Bradycardia requiring intervention is rare and responsive to usual treatment

Benefit-Risk: Urgent or Emergent Use (16 mg/kg)

- Sugammadex 16 mg/kg is intended only for reversal of rocuronium-induced NMB in urgent or emergent situations
- The ability of sugammadex to reverse NMB rapidly is potentially life saving and brain sparing in the setting of anoxia due to rocuronium-induced NMB
  - No pharmacological alternative
  - May avert emergency surgery in some patients
- At the 16 mg/kg dose, data suggest an increased risk for anaphylaxis in healthy volunteers; data in patients are limited
- Overall, the benefit-risk assessment for sugammadex for reversal in urgent or emergent situations is positive

NMB=neuromuscular blockade.

Summary and Conclusion

- Sugammadex is a new treatment option providing greater flexibility to manage neuromuscular blockade
  - Allows use of deep block throughout the entire surgery with the option to rapidly reverse at any point
  - Reduces the risk of residual neuromuscular blockade associated with current standard of care
  - Provides a pharmacological option when reversal of rocuronium-induced neuromuscular blockade is urgently or emergently indicated
- Sugammadex provides these previously unavailable benefits in the setting of an acceptable safety and tolerability profile

Q&A Response Slides

Trial 306: Efficacy in Pediatrics Similar to Adults

Recovery of the TOF Ratio to 0.9 by Age Group and Dose

Age Group	Placebo	Median Time to TOF Ratio 0.9 (min)			
		Sugammadex			
		0.5 mg/kg	1.0 mg/kg	2 mg/kg	4 mg/kg
Infants (n=8) 28 days-23 months inclusive	21.0	3.7	2.4	0.6	0.7
Children (n=24) 2-11 years inclusive	19.0	3.7	2.7	1.2	0.6
Adolescents (n=31) 12-17 years inclusive	23.4	4.6	1.7	1.1	1.1
Adults (n=28) 18-65 years inclusive	28.5	4.2	1.7	1.2	1.4

Plaud, et al. Anesthesiology. 2009;110:284-294.
TOF=train-of-four.

Estimating Rate of Spontaneous Reports

- Observed reporting frequency must be adjusted because not all doses are used and not all events are reported
- Usage: assumed 95% of vials distributed were used
  - 3 months stockpile over 80 months sales gives a 95% usage rate
  - Most hospitals have <3 month stockpile
  - Few doses returned to suppliers (1%-2%)
- Adjusted reporting rate = observed rate/0.95
- Included sensitivity analyses over the range from 90%-100% usage
  - Adjusted reporting rate would be within the background rate even if the usage rate was as low as 70%

Additional Risk of Anaphylaxis Associated With Sugammadex is Small Regardless of Assumptions on Usage and Reporting

- Background rate of 15-34 per 100,000 shows that other factors in the surgical setting have a risk of anaphylaxis[a-e]
- Extensive post-marketing experience with sugammadex
  - Over 12.1 million vials distributed
  - Observed anaphylaxis frequency = 2.26 per 100,000 (0.002%)

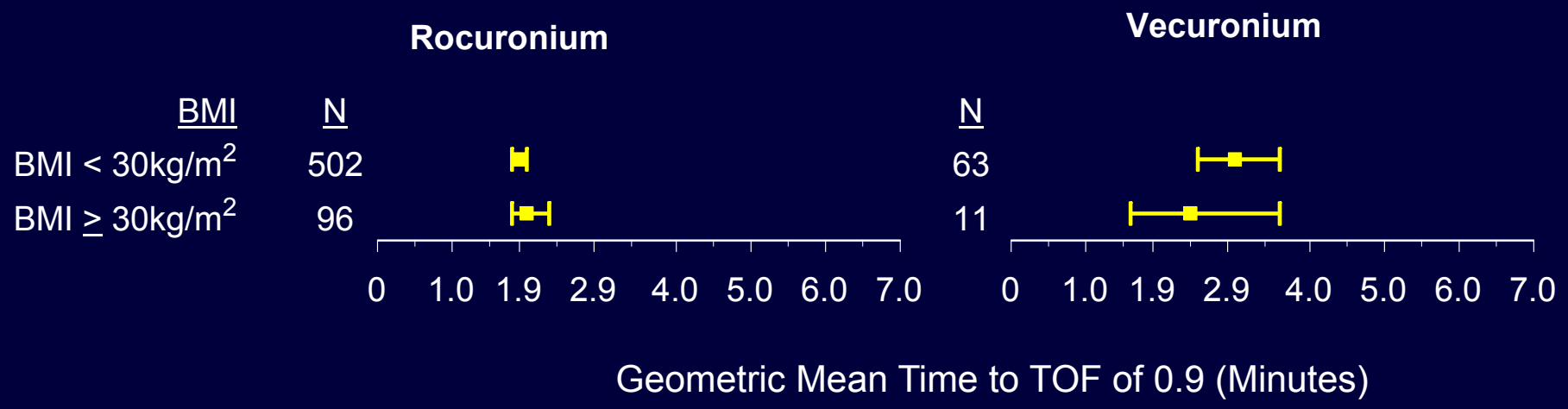
273 Total Anaphylaxis Cases as of 22 April 2015

Assumed Usage of Doses Distributed	Assumed Reporting Rates	
	25%	10%
100%	9.0 (8.5; 9.6)	22.6 (21.7; 23.4)
95%	9.5 (8.9; 10.1)	23.7 (22.8; 24.6)
90%	10.0 (9.4; 10.6)	25.1 (24.1; 26.0)

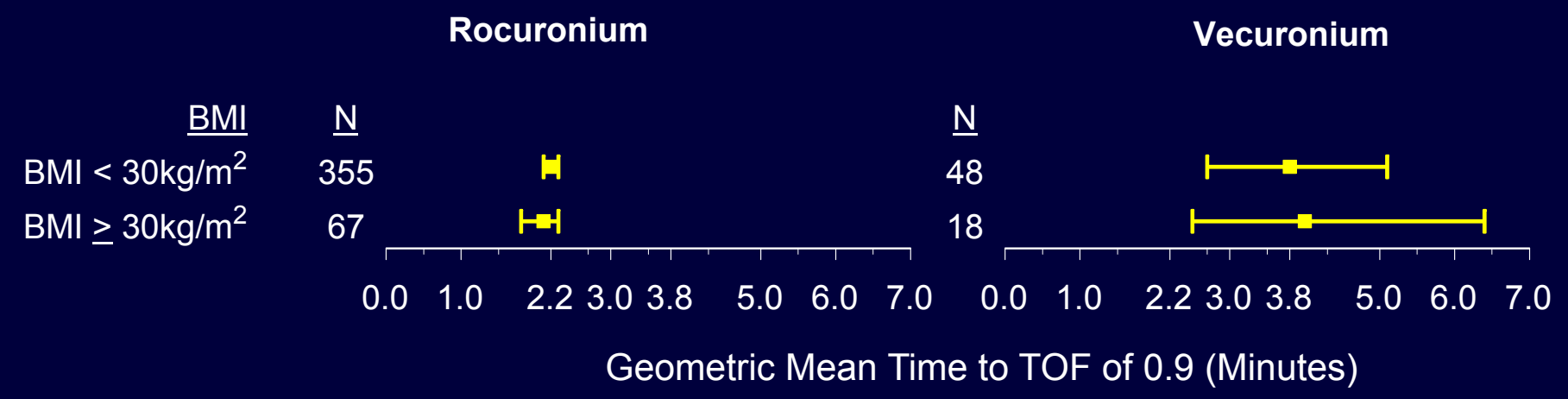
[a] Laxenaire Ann. Fr Anesth Reanim. 1999;18:796-809; [b] Fasting & Gisvold. Can J Anaesth. 2002;49(6):545-53;
[c] Harboe, et al. Anesthesiology. 2005;102(5):897-903; [d] Mertes PM, et al. J Investig Allergol Clin Immunol. 2011;21(6):442-453.
[e] Saager L, et al. Anesthesiology. 2015.

Efficacy and BMI

Moderate Block, 2 mg/kg



Deep Block, 4 mg/kg



BMI=body mass index; TOF=train-of-four.

Adverse Event Summary by BMI

Pooled Phase 1-3 Placebo-Controlled Trials

	BMI <30 kg/m^2		BMI ≥30 kg/m^2	
	Placebo N=426	SGDX N=908	Placebo N=118	SGDX N=157
Subjects with AE	80.8%	72.6%	87.3%	79.6%
Subjects with serious AE (SAE)	6.3%	6.2%	9.3%	7.0%
Subjects with AE with severe intensity	8.2%	5.5%	9.3%	5.7%
Subjects with drug related AEs	9.4%	11.7%	9.3%	12.7%
Deaths†	0.7%	0.1%	0	0
Discontinued due to AEs‡	0.2%	0.1%	0	0

† Irrespective of time point of death.
‡ Relationship specified as 'Definite', 'Probable', 'Possible'.
BMI=body mass index; SGDX=sugammadex.

Exposure by Race/Ethnicity

Pooled Phase 1-3 Placebo-Controlled Trials

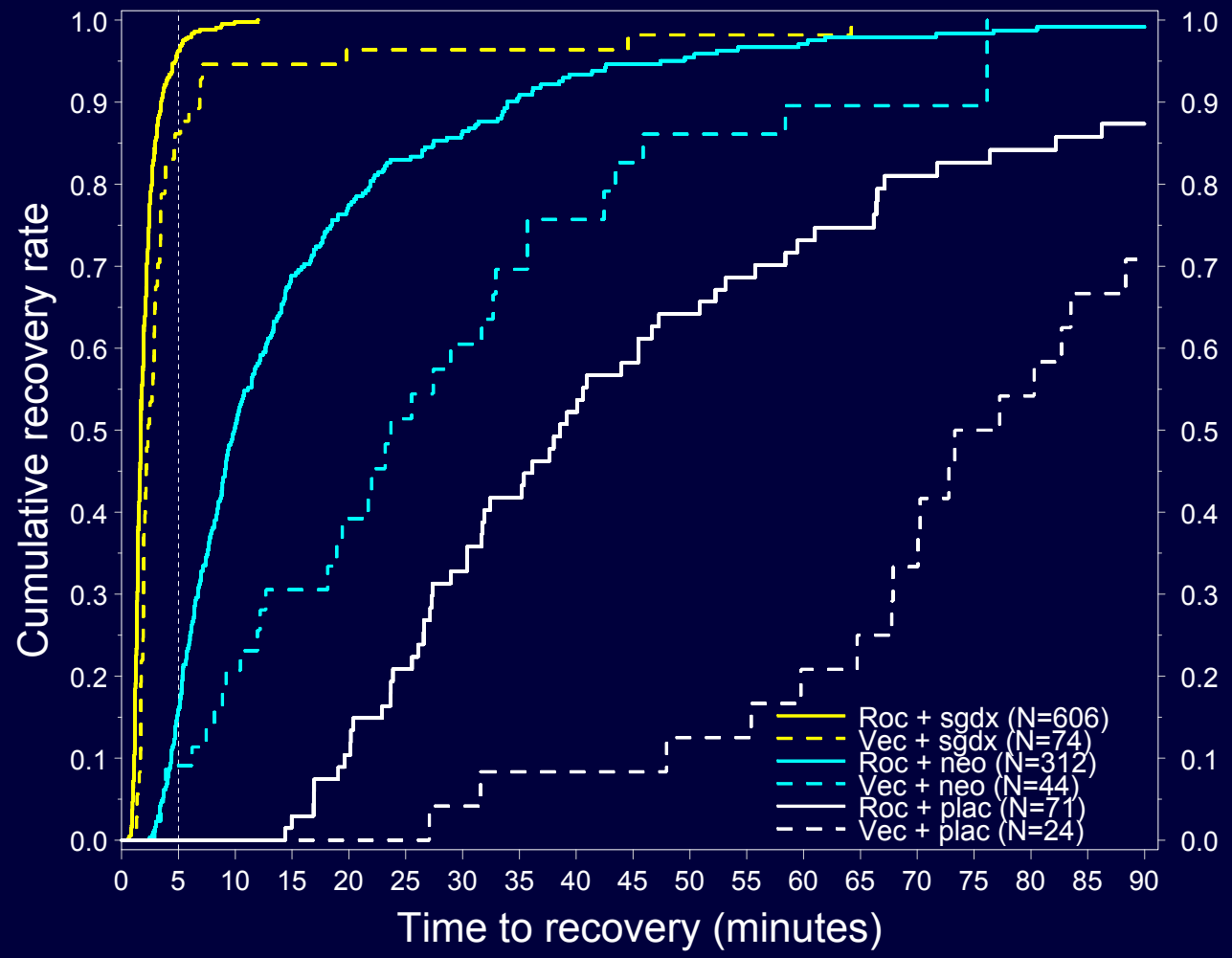
	Placebo N=544 n (%)	Total Sugammadex N=1078 n (%)
Race		
Asian	25 (5)	80 (7)
Black/African American	0 (0)	2 (0)
White	513 (94)	992 (92)
Other	6 (1)	4 (0)
Ethnicity Hispanic or Latino		
Yes	5 (1)	8 (1)
No	485 (99)	684 (99)

Exposure by Race/Ethnicity

Pooled Phase 1-3 Trials

	Placebo N=544 n (%)	Total Sugammadex N=3601 n (%)
Race		
Asian	25 (5)	503 (14)
Black/African American	0 (0)	99 (3)
White	513 (94)	2975 (83)
Other	6 (1)	23 (1)
Ethnicity Hispanic or Latino		
Yes	5 (1)	86 (3)
No	485 (99)	2993 (97)

Sugammadex 2 mg/kg Reverses Moderate NMB Rapidly and Reliably



ITT population.
NMB=neuromuscular blockade; roc=rocuronium; sgdx=sugammadex; plac=placebo; vec=vecuronium; neo=neostigmine.

Relevant History
Past Medical Conditions – P101

Subjects in Population	Preferred Term	Placebo N=76	Sugammadex 4 mg/kg N=151	Sugammadex 16 mg/kg N=148	Total N=375
With one or more conditions		62	123	113	298
With no conditions		12	28	35	77
Respiratory disorders	Total	3	4	7	14
	Asthma	0	1	2	3
Skin and subcutaneous tissues disorders	Total	5	14	16	35
	Dermatitis allergic	0	0	1	1
	Dermatitis atopic	0	0	1	1
	Eczema	1	2	3†	6
	Erythema	0	0	1	1
	Erythema nodosum	1	0	0	1
	Rash	2	0	0	2
	Urticaria	0	2	1	3

† One subject with confirmed hypersensitivity had a past medical history of eczema.