# Phase 4 Double-blinded, Randomized, Active Comparator-controlled Clinical Trial to Study the Efficacy, Safety, and Pharmacokinetics of Sugammadex (MK-8616) for Reversal of Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years

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The current trial aims to demonstrate that sugammadex is generally safe and effective for reversing both moderate and deep block after rocuronium or vecuronium induced NMB in term neonates and young children.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON49696

**Source**
ToetsingOnline

**Brief title**
MK8616-169

## Condition

- Other condition

**Synonym**
Reversal of moderate to deep Neuromuscular Blockade in Pediatric Participants Aged Birth to <2 Years

**Health condition**

Opheffing van neuromusculaire blokkade (NMB)

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Merck Sharp & Dohme (MSD)
**Source(s) of monetary or material Support:** Industrie

## Intervention

**Keyword:** Efficacy, Neuromuscular Blockade, Safety, Sugammadex

## Outcome measures

**Primary outcome**

1. Part A. Pharmacokinetic parameters: Area under the plasma concentration-time

curve (AUC), clearance (CL), apparent volume of distribution (Vz and Vss),

maximum plasma concentration (Cmax), and half-life (t1/2)

2. Part B. Time to neuromuscular recovery

3. Part A and B. Number of participants experiencing adverse events.

**Secondary outcome**

1. Part B. Time to extubation

# Study description

## Background summary

Neuromuscular blockade is an important component of many surgical and medical procedures, as it provides muscle relaxation and reduces patient movement. In current anesthesia practice, reversal agents of NMB are often administered at the end of the procedure to aid the recovery of muscle function and prevent residual NMB after the procedure. Prior to the availability of sugammadex, all clinically used reversal agents (eg,
neostigmine, edrophonium) were acetylcholinesterase inhibitors. These agents achieved reversal of NMB, but at the cost of multiple side effects due to their nonselective potentiation of cholinergic neurotransmission. Moreover, these agents are only able to reverse moderate NMB, a degree of block that requires partial spontaneous recovery of neuromuscular transmission, which limits their utility. Reversal of deep NMB is a unique benefit of sugammadex compared to other current treatments, which can only reverse moderate block. From a risk perspective, sugammadex has been shown to be generally safe and well tolerated. The use of sugammadex at recommended doses is associated with a low risk of residual NMB or recurrence of NMB compared with current treatment. At this timepoint clinical trial data in children is limited. The Sponsor considers that the currently approved adult doses are appropriate for assessment to provide the optimal benefit/risk ratio in this trial, based on the adult Phase 3 trials, subsequent post marketing data, and the pediatric information collected to date in prior sugammadex trials.

## Study objective

The current trial aims to demonstrate that sugammadex is generally safe and effective for reversing both moderate and deep block after rocuronium or vecuronium induced NMB in term neonates and young children.

## Study design

This is a randomized, active comparator-controlled, parallel-group, multi-site, double-blinded
trial to evaluate the PK, safety, and efficacy of sugammadex in pediatric participants aged
birth to <2 years for the reversal of moderate and deep NMB.

The design of this trial consists of a 2-part structure (Part A and Part B). Part A will be openlabel, while Part B will be double-blinded. Part A will evaluate safety and confirm the doses of sugammadex that will produce similar exposure in children from birth to <2 years of age when compared to systemic exposure noted in adults following administration of the 2 mg/kg and 4 mg/kg doses. In Part B of this trial, the safety and efficacy parameters of sugammadex 2 mg/kg and 4 mg/kg will be assessed. Potential trial participants will have a planned nonemergent

surgical procedure or clinical situation that can be conducted under both moderate and/or deep NMB.

Enrollment into the trial will begin with Part A, which is further divided into Panel 1 and Panel 2. First, Panel 1 will evaluate the PK and safety of sugammadex 2 mg/kg in the setting of moderate block; next, Panel 2 will evaluate the PK and safety of sugammadex 4 mg/kg in the deep block setting. Panels 1 and 2 will run in succession and consecutively within each age cohort.

Participants will be enrolled within 1 of the following 4 age cohorts in a sequential approach (within each Part), beginning with the eldest age cohort. Enrollment within each age cohort will be based on the participant*s age at time of treatment allocation (age will be defined as the anniversary date of the participant*s actual birthdate):
* 6 months to <2 years
* 3 months to <6 months
* 28 days to <3 months
* Birth to 27 days

**Intervention**

There are 5 intervention groups:
Treatment allocation/randomization will occur centrally using interactive response technology (IRT). Participants will be allocated to 1 treatment group. Participants in Part A will be assigned the following treatment regimen:
* Panel 1: Moderate block and reversal with sugammadex 2 mg/kg
* Panel 2: Deep block and reversal with sugammadex 4 mg/kg

Participants in Part B of the study will be assigned randomly in a 1:1:1 ratio to 1 of the following treatment groups:
* Moderate block and reversal with sugammadex 2 mg/kg; or
* Moderate block and reversal with neostigmine 50 mcg/kg; or
* Deep block and reversal with sugammadex 4 mg/kg

**Study burden and risks**

For this study, patients will be exposed to invasive procedures such as blood collection, infusion line, physical examination, ECG monitoring, study medication administration, parents or guardians will be asked to answer questions about medication and the health status of their child and will be requested to visit the hospital for check-up visits and / or a final telephone contact.

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed

to provide information about the safety and effectiveness of an investigational medicine. However, data from clinical studies in children are limited. Current research aims to demonstrate that sugammadex is generally safe and effective for eliminating both moderate and deep blockages following rocuronium or vecuronium-induced NMB in full-term newborns and young children undergoing surgery or clinical procedure.

The Sponsor considers that the currently approved adult doses are appropriate for assessment to provide the optimal benefit/risk ratio in this trial, based on the adult Phase 3 trials, subsequent post marketing data, and the pediatric information collected to date in prior sugammadex trials.

Sugammadex has a positive benefit-risk profile and is well tolerated in the approved indications as described in the IB. It has specifically been shown to be superior (faster recovery as well as effective in a higher proportion of treated participants) to both placebo and neostigmine for reversal of moderate and deep NMB. Reversal of deep NMB is a unique benefit of sugammadex compared to other current treatments, which can only reverse moderate block. From a risk perspective, sugammadex has been shown to be generally safe and well tolerated. The use of sugammadex at recommended doses is associated with a low risk of residual NMB or recurrence of NMB compared with current treatment.

## Contacts

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NL
**Scientific**
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031BN
NL

## Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Children (2-11 years)

## Inclusion criteria

1. Is categorized as ASA Physical Status Class 1, 2, or 3 as determined by the investigator
2. Has a planned non-emergent surgical procedure or clinical situation (eg, intubation) that requires moderate or deep NMB with either rocuronium or vecuronium
3. Has a surgical procedure or clinical situation that would allow neuromuscular monitoring techniques to be applied for neuromuscular transmission monitoring
4. Is male or female, between birth and <2 years of age at Visit 2
5. The legally acceptable representative for the study participant provides written informed consent/assent for the trial

## Exclusion criteria

1. Is a preterm infant or neonate <36 weeks gestational age at birth
2. Has any clinically significant condition or situation (eg, anatomical malformation that complicates intubation) other than the condition requiring the use of NMBA that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial
3. Has a neuromuscular disorder that may affect NMB and/or trial assessments
4. Is dialysis-dependent or has (or is suspected of having) severe renal insufficiency (defined as estimated glomerular filtration rate [eGFR] <30 ml/min; using revised Schwartz estimate as method of calculation)
5. Has or is suspected of having a family or personal history of malignant hyperthermia
6. Has or is suspected of having an allergy to study treatments or its/their excipients, to opioids/opiates, muscle relaxants or their excipients, or other medication(s) used during general anesthesia
7. Is expected to require mechanical ventilation after the procedure
8. Has received or is planned to receive toremifene and/or fusidic acid via IV administration within 24 hours before or within 24 hours after administration

of study treatment
9. Use of medication expected to interfere with study treatments given in this trial, as per prescribing information. Rocuronium or vecuronium are concomitant medications to be used per label as adjunct to general anesthesia. Besides rocuronium or vecuronium, a participant must not be administered any other NMBA during the trial, including:
*Other steroidal NMBAs, such as pancuronium
*Nonsteroidal NMBAs such as succinylcholine or benzylisoquinolinium compound (eg, cisatracurium). (Except in the circumstance that renewed muscle relaxation is needed after administration of study treatment, in which case a non-steroidal NMBA should be administered)
10. Has been previously treated with sugammadex or has participated in a sugammadex clinical trial withi 30 days of signing the informed consent form of this current trial
11. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days of signing the informed consent/assent for this current trial
12. Is or has an immediate family member (eg, parent/legal guardian, or sibling) who is investigational site or Sponsor staff directly involved with this study

# Study design

## Design

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| Study phase: | 4 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 13-01-2021 |
| Enrollment: | 11 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Atropine sulfate injection |
| Generic name: | Atropine Sulfate |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Bridion |
| Generic name: | Sugammadex |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Prostigmin |
| Generic name: | Neostigmine Methylsulfate |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Robinul |
| Generic name: | Glucopyrrolate |
| Registration: | Yes - NL intended use |

# Ethics review

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| Approved WMO Date: | 02-12-2019 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-01-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 03-04-2020 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

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| Approved WMO Date: | 18-05-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 27-08-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 28-09-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-10-2020 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 11-02-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 01-04-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 07-06-2021 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 17-09-2021 |
| Application type: | Amendment |

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| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 04-02-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 04-11-2022 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 25-02-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 14-03-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
| --- | --- |
| EudraCT | EUCTR2017-000693-11-NL |
| ClinicalTrials.gov | NCT03909165 |
| CCMO | NL71143.078.19 |