

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022225Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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NDA: 022225 SDN99	Submission Date(s): 10/22/2014
Brand Name	Bridion
Generic Name	Sugammadex Sodium Injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	Atul V. Bhattaram, Ph.D.
Pharmacometrics Team Leader	Kevin Krudys, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Organon USA Inc., a subsidiary of Merck & Co., Inc.
Relevant IND(s)	68,029
Submission Type; Code	Class 2, Resubmission: 505(b)(1)
Formulation; Strength(s)	Solution for Injection; 100 mg/mL
Indication	Reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.
Proposed Dosage Regimen	4 mg/kg or 16 mg/kg IV bolus Injection

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### Executive Summary:

Organon USA, a subsidiary of Merck & Co submitted response to Agency's complete response action taken on 9/30/2014. From a clinical pharmacology perspective the submission has one study assessing pharmacokinetics of Sugammadex in patients with renal impairment. The results of the renal impairment study (P105) are discussed below briefly.

This study (P105) was a 2-center, 2-part, open-label, single-dose (sugammadex 4 mg/kg) study evaluating the effect of chronic renal impairment on sugammadex PK in subjects with severe or moderate renal impairment compared to healthy matched control subjects. Part 1 (n=24) of this study included eight (8) subjects with severe (CLCr <30 mL/min), eight (8) subjects with moderate (CLCr 30 - <50 mL/min) renal impairment and eight (8) healthy control subjects (CLCr ≥80 mL/min). The sponsor utilized previously established (and reviewed) bioanalytical methodology for assessing sugammadex plasma levels. The sponsor indicated that a preliminary review of the sugammadex concentration data from Part 1 of the study combined with dosing irregularities reported from the clinical research units indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue. Substantial delays in Tmax (range: 1 to 4 hours) and an apparent absorption phase in the pharmacokinetic (concentration-time)

profiles provided additional evidence of dosing issues. Given the apparent dosing irregularities in Part 1, the pharmacokinetic data from Part 1 are considered to be uninterpretable; therefore, the study was subsequently amended to include a Part 2 in order to achieve the original pharmacokinetic objectives of the study. Part 2 provided clarification on the dosing procedures in order to ensure that bolus IV administration was achieved (a direct stick method of administration through a fixed needle was used in Part 1) and the duration of pharmacokinetic collection was reduced to 10 days postdose in subjects with moderate and severe renal impairment with flexibility to extend the pharmacokinetic collection in subjects with severe renal impairment, if warranted. This reduction in collection time was based on Part 1 data indicating that, despite the dosing irregularities, none of the subjects with severe or moderate renal impairment had measurable sugammadex concentrations (all were < lower limit of quantitation [LLOQ]) on Day 7 (144 hours) and Day 4 (72 hours), respectively. In Part 2 (n=18) of this study, six (6) subjects with severe (CLcr <30 mL/min), six (6) subjects with moderate (CLcr 30 - < 50 mL/min) renal impairment and six (6) healthy control subjects (CLcr > 80 mL/min) received single doses of IV sugammadex (4 mg/kg). The total enrollment in this study was N=33. Eligible subjects from Part 1 could enroll in Part 2 (n=9 subjects participated in both parts).

**Results and Conclusions:** As a result of the dosing issues in Part 1, the final pharmacokinetic and subsequent statistical analyses were not conducted for Part 1 of the study. Based on data from Part 2, sugammadex exposure (AUC<sub>0-∞</sub>) was higher in subjects with moderate and severe renal impairment compared to healthy control subjects. Specifically, the GMR (90% CI) of AUC<sub>0-∞</sub> in subjects with moderate and severe renal impairment compared to healthy subjects was 2.42 (1.84, 3.17) and 5.42 (4.12, 7.11), respectively. By comparison, the GMR (90% CI) of C<sub>max</sub> in subjects with moderate and severe renal impairment compared to healthy subjects was 0.92 (0.72, 1.18) and 0.94 (0.73, 1.21), respectively. Clearance progressively decreased and apparent half-life (t<sub>1/2</sub>) was progressively prolonged with increased levels of renal dysfunction.

**Table: Statistical summary and comparison of plasma sugammadex PK parameters following IV dose of 4 mg/kg to subjects with varying degrees of renal insufficiency (Part 2 only).**

Pharmacokinetic Parameter	Severe Renal Insufficiency Subjects			Moderate Renal Insufficiency Subjects			Healthy Control Subjects		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
AUC <sub>0-∞</sub> <sup>2</sup> (ug•hr/mL)	6	339	(268, 428)	6	151	(120, 191)	6	62.5	(49.5, 79.0)
AUC <sub>0-last</sub> <sup>2</sup> (ug•hr/mL)	6	335	(265, 424)	6	148	(117, 187)	6	61.1	(48.3, 77.3)
C <sub>max</sub> <sup>2</sup> (ug/mL)	6	62.2	(50.2, 77.1)	6	60.6	(49.0, 75.1)	6	66.1	(53.3, 81.8)
AUC%extrap <sup>3</sup> (%)	6	0.850	43.5	6	2.14	29.2	6	2.10	45.3
CL <sup>3</sup> (L/hr)	6	0.961	26.8	6	2.27	39.6	6	5.70	16.0
V <sub>z</sub> <sup>3</sup> (L)	6	18.3	24.8	6	18.8	24.2	6	20.4	25.7
MRT <sup>3</sup> (hr)	6	15.7	26.2	6	7.02	30.8	6	2.48	13.4
V <sub>ss</sub> <sup>3</sup> (L)	6	15.1	19.7	6	15.9	21.9	6	14.1	20.4
T <sub>max</sub> <sup>1</sup> (hr)	6	0.03	(0.03, 0.08)	6	0.03	(0.02, 0.08)	6	0.03	(0.03, 0.08)
T <sub>last</sub> <sup>1</sup> (hr)	6	72.00	(71.99, 143.99)	6	24.00	(23.99, 47.99)	6	12.00	(11.99, 12.00)
Apparent terminal t <sub>1/2</sub> <sup>5</sup> (hr)	6	13.24	35.50	6	5.73	29.79	6	2.47	13.49
t <sub>1/2,eff</sub> <sup>6</sup> (hr)	6	10.89	26.15	6	4.87	30.84	6	1.72	13.36
λ <sub>z</sub> <sup>7</sup> (1/hr)	6	0.0524	35.5	6	0.121	29.8	6	0.280	13.5
Pharmacokinetic Parameter	Severe Renal Insufficiency/Healthy Control		Moderate Renal Insufficiency/Healthy Control		rMSE <sup>7</sup>				
	GMR	90% CI	GMR	90% CI					
AUC <sub>0-∞</sub> <sup>2</sup> (ug•hr/mL)	5.42	(4.12, 7.11)	2.42	(1.84, 3.17)	0.269				
AUC <sub>0-last</sub> <sup>2</sup> (ug•hr/mL)	5.49	(4.18, 7.22)	2.42	(1.84, 3.18)	0.270				
C <sub>max</sub> <sup>2</sup> (ug/mL)	0.94	(0.73, 1.21)	0.92	(0.72, 1.18)	0.246				

Re-evaluation of population PK model of sugammadex including newly available data in the renally impaired population

Sponsor submitted a modeling and simulation report (Dated August 14<sup>th</sup>, 2014) that

1. Re-evaluated the original 2-compartment population PK model for its appropriateness to describe sugammadex with newly generated PK data from the renally impaired population
2. Simulated PK parameters of sugammadex in various typical populations based on the updated population PK model.

The original 2-compartment population PK model for sugammadex was able to adequately described additional renally impaired data. Renal function, as determined by creatinine clearance, continued to be a major predictor of sugammadex pharmacokinetics.

*Reviewer's Comments : The findings from the analyses are similar to those from previous review cycle. No new labeling statements are being proposed based on updated population pharmacokinetic analyses.*

The submission is acceptable from a clinical pharmacology perspective.

## **Labeling**

A number of labeling changes were recommended in the previous clinical pharmacology reviews by this reviewer and the previous reviewers. All labeling changes should be conveyed to the sponsor.

As it relates to the current submission of a new renal impairment study, a slight modification in renal impairment section of the label was made by the sponsor. The sponsor's proposal is indicated as regular text and the reviewers edits are marked as strike through text for deletions or as bold font text for additions.

### *Renal Impairment and Geriatric Patients*

(b) (4)



16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Synopsis of Study P105 (Renal Impairment study):**

<b>SPONSOR:</b>	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.	
<b>COMPOUND NAME:</b>	MK-8616, Sugammadex, Intravenous	
<b>INDICATION:</b>	Selective Relaxant Binding Agent (SRBA) for the Reversal of Neuromuscular Blockade Induced by Rocuronium or Vecuronium	
<b>PROTOCOL TITLE:</b>	An Open-Label, Single-Dose Study to Investigate the Pharmacokinetics of MK-8616 in Subjects With Moderate and Severe Renal Insufficiency	
<b>TRIAL IDENTIFIERS:</b>	Protocol Number:	MK-8616-105
	Clinical Phase:	1
<b>TRIAL CENTERS:</b>	Kenneth Lasseter, MD Clinical Pharmacology of Miami, Inc. 550 West 84 <sup>th</sup> Street Miami, Florida 33014 Thomas Marbury, MD Orlando Clinical Research Center 5055 South Orange Avenue Orlando, Florida 32809	
<b>DESIGN:</b>	<p><b>STUDY DESIGN:</b> This was a 2-center, 2-part, open-label, single-dose study to evaluate the plasma pharmacokinetics of a single 4 mg/kg dose of sugammadex (MK-8616) in subjects with moderate and severe renal insufficiency compared with healthy control subjects.</p> <p><b>Part 1:</b> Eight (8) subjects with severe renal insufficiency (Panel A) and 8 subjects with moderate renal insufficiency (Panel B) were enrolled. Eight (8) healthy control subjects (Panel C) matched to the mean age of subjects in Panels A and B with renal insufficiency were enrolled in parallel. On Day 1, each subject received a single 4 mg/kg dose of MK-8616 administered as an intravenous (IV) bolus (within 10 seconds) through a straight needle directly into a peripheral vein. The protocol was amended to add a second part (Part 2) to the study as a preliminary review of the concentration data from the original study (now Part 1) indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue based on substantial delays in Tmax and an apparent absorption phase.</p>	

<p><b>DESIGN (Continued):</b></p>	<p><b>STUDY DESIGN (Continued):</b></p> <p><b>Part 2:</b></p> <p>Six (6) subjects with severe renal insufficiency (Panel D) and 6 subjects with moderate renal insufficiency (Panel E) were enrolled. Six (6) healthy control subjects (Panel F) matched to the mean age of subjects in Panels D and E were enrolled in parallel. On Day 1, each subject received a single 4 mg/kg dose of MK-8616 administered as an IV bolus (within 10 seconds) through an IV catheter into which free-flowing access to a peripheral vein was confirmed immediately prior to dose administration, followed by saline flush.</p> <p><b>DIAGNOSIS/INCLUSION CRITERIA:</b> Male or female adult subjects with varying degrees of renal impairment (see table below) along with matched healthy control subjects (for mean age only [<math>\pm 15</math> years]) with normal renal function who met all the inclusion and none of the exclusion criteria were selected for the study. The following table summarizes creatinine clearance (CrCL) ranges for each panel.</p> <table border="1" data-bbox="532 825 1325 993"> <thead> <tr> <th>Panel (Part 1/Part 2)</th> <th>Stage</th> <th>N (Part 1/Part 2)</th> <th>CrCL (mL/min)<sup>†</sup></th> </tr> </thead> <tbody> <tr> <td>A/D</td> <td>Severe</td> <td>8/6</td> <td>&lt; 30, not on dialysis</td> </tr> <tr> <td>B/E</td> <td>Moderate</td> <td>8/6</td> <td>30 - &lt; 50</td> </tr> <tr> <td>C/F</td> <td>Normal</td> <td>8/6</td> <td>&gt; 80<sup>‡</sup></td> </tr> </tbody> </table> <p><sup>†</sup>CrCL based on Cockcroft-Gault equation. Baseline CrCL was obtained twice (at screening and check-in) and the mean of the 2 values was used for group assignment.</p> <p><sup>‡</sup>The age of the individual healthy subjects was aimed to be within the range of the mean age <math>\pm</math> ~15 years of all subjects with renal impairment combined in each part of this study.</p> <p>Subjects who participated in Part 1 of this study were considered eligible to participate in Part 2 of this study.</p>	Panel (Part 1/Part 2)	Stage	N (Part 1/Part 2)	CrCL (mL/min) <sup>†</sup>	A/D	Severe	8/6	< 30, not on dialysis	B/E	Moderate	8/6	30 - < 50	C/F	Normal	8/6	> 80 <sup>‡</sup>
Panel (Part 1/Part 2)	Stage	N (Part 1/Part 2)	CrCL (mL/min) <sup>†</sup>														
A/D	Severe	8/6	< 30, not on dialysis														
B/E	Moderate	8/6	30 - < 50														
C/F	Normal	8/6	> 80 <sup>‡</sup>														
<p>Actual duration of main phase:</p>	<p><b>Panel A:</b> Approximately 5 to 7 weeks from screening to Day 35</p> <p><b>Panel B:</b> Approximately 4 to 5 weeks from screening to Day 28</p> <p><b>Panels D and E:</b> Approximately 3 - 4 weeks from screening to follow-up</p> <p><b>Panels C and F:</b> Approximately 2 - 3 weeks from screening to follow-up (Day 15)</p>																

<b>OBJECTIVES:</b>	<p><b>Primary:</b> To evaluate the plasma pharmacokinetics of a single 4 mg/kg dose of MK-8616 administered to subjects with moderate and severe renal insufficiency compared to subjects with normal renal function.</p> <p><b>Secondary:</b> To evaluate the safety and tolerability of MK-8616 in subjects with moderate and severe renal insufficiency.</p>	
<b>HYPOTHESIS:</b>	<p><b>Primary Estimation:</b> In subjects with moderate and severe renal insufficiency, plasma pharmacokinetic parameters (e.g., AUC<sub>0-last</sub>, AUC<sub>0-∞</sub>, AUC%extrap, C<sub>max</sub>, T<sub>max</sub>, T<sub>last</sub>, CL, V<sub>z</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, t<sub>1/2eff</sub>, MRT, and V<sub>ss</sub>) of MK-8616 following administration of a single 4 mg/kg dose will be estimated and compared to those observed in healthy control subjects.</p>	
<b>TREATMENT GROUPS:</b>	Subjects with Severe Renal Insufficiency CrCL < 30 mL/min (not on dialysis)	A single IV dose of 4 mg/kg MK-8616 administered on Day 1. 8 Subjects in Panel A (Part 1) 6 Subjects in Panel D (Part 2)
	Subjects with Moderate Renal Insufficiency CrCL 30 - < 50 mL/min	A single IV dose of 4 mg/kg MK-8616 administered on Day 1. 8 Subjects in Panel B (Part 1) 6 Subjects in Panel E (Part 2)
	Healthy Control Subjects CrCL ≥ 80 mL/min	A single IV dose of 4 mg/kg MK-8616 administered on Day 1. 8 Subjects in Panel C (Part 1) 6 Subjects in Panel F (Part 2)

The bulk product description and manufacturing lot number are provided in the table below.

#### Clinical Supplies Dispensed to Subjects

Bulk Product Description	Manufacturing Lot Number
<sup>(b) (4)</sup> MK-8616, Sugammadex, 100 mg/mL, 5 mL	WL00055458

<b>ENDPOINTS AND DEFINITIONS:</b>	<b>Primary Endpoints</b>	<b>Pharmacokinetics (Parts 1 and 2):</b> Blood samples for MK-8616 concentration in plasma were collected as follows in subjects with severe and moderate renal insufficiency and in healthy control subjects following a single 4 mg/kg dose of MK-8616 administered as an IV bolus in Parts 1 and 2:
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<b>ENDPOINTS AND DEFINITIONS (Continued):</b>	<b>Primary Endpoints (Continued)</b>	<p><b>Part 1:</b></p> <ul style="list-style-type: none"> <li>• <u>Severe renal insufficiency (Panel A):</u> Predose through Day 35</li> <li>• <u>Moderate renal insufficiency (Panel B):</u> Predose through Day 28</li> <li>• <u>Healthy control subjects (Panel C):</u> Predose through 48 hours postdose.</li> </ul> <p>Descriptive statistics were calculated for all individual MK-8616 concentration data by population and time point of collection and individual concentration-time profiles were presented for Part 1.</p> <p><b>Part 2:</b></p> <ul style="list-style-type: none"> <li>• <u>Severe renal insufficiency (Panel D):</u> Predose through Day 10 (216 hours) postdose. Flexibility was included to extend pharmacokinetic assessment as needed up to 3 additional samples (Days 14 ± 1, 18 ± 1, and Day 21) based on the presence of measurable MK-8616 on Day 7 and/or Day 10. Sampling was extended to Day 14 (312 hours postdose) for a single subject.</li> <li>• <u>Moderate renal insufficiency (Panel E):</u> Predose through Day 10 (216 hours postdose).</li> <li>• <u>Healthy control subjects (Panel F):</u> Predose through 48 hours postdose.</li> </ul> <p>Plasma MK-8616 concentrations were summarized using the following pharmacokinetic parameters calculated by non-compartmental analyses for Part 2: AUC<sub>0-last</sub>, AUC<sub>0-∞</sub>, AUC%extrap, C<sub>max</sub>, T<sub>max</sub>, T<sub>last</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, CL, V<sub>z</sub>, MRT, t<sub>1/2eff</sub>, and V<sub>ss</sub> following a single IV dose administration.</p>	
	<b>Secondary Endpoints</b>	<p><b>Safety (Parts 1 and 2):</b></p> <p>For each part, the safety and tolerability of MK-8616 was evaluated by clinical assessment of adverse events and other safety measurements. Safety and tolerability was assessed by clinical evaluation of adverse experiences and other safety measurements including vital signs, medical history, physical examination, 12-lead ECGs, and standard laboratory safety tests (hematology, chemistry, and urinalysis) that were obtained at pre-specified time points throughout the study.</p>	
<b>DATABASE LOCK:</b>	03-Jun-2014 (Part 1) 20-Jun-2014 (Part 2)	<b>TRIAL STATUS:</b>	20-Dec-2013 to 06-Jun-2014

<b>RESULTS AND ANALYSIS:</b>	Due to dosing issues, the pharmacokinetic analysis was not conducted for Part 1 of the study. Descriptive statistics were calculated for all MK-8616 concentration data by population and time point of collection. Pharmacokinetic and subsequent statistical analyses for Part 2 of the study, and safety analyses (Parts 1 and 2) were performed according to the protocol.
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<b>SUBJECT DISPOSITION:</b>	<b><u>Part 1</u></b>			
		<b><u>Panel A</u></b> <b><u>(Severe)</u></b>	<b><u>Panel B</u></b> <b><u>(Moderate)</u></b>	<b><u>Panel C</u></b> <b><u>(Healthy)</u></b>
	ENTERED: Total	8	8	8
	Male N (age range)	6 (47-76 yr)	7 (47-71 yr)	3 (53-60 yr)
	Female N (age range)	2 (59-67 yr)	1 (74 yr)	5 (50-67 yr)
	COMPLETED:	8	8	8
	DISCONTINUED:	0	0	0
	<b><u>Part 2</u></b>			
		<b><u>Panel D</u></b> <b><u>(Severe)</u></b>	<b><u>Panel E</u></b> <b><u>(Moderate)</u></b>	<b><u>Panel F</u></b> <b><u>(Healthy)</u></b>
	ENTERED: Total	6	6	6
Male N (age range)	5 (54 - 76 yr)	5 (54 - 76 yr)	4 (54 - 59 yr)	
Female N (age range)	1 (67 yr)	1 (74 yr)	2 (55 - 68 yr)	
COMPLETED:	6	6	6	
DISCONTINUED:	0	0	0	
Note: Nine (9) of the subjects enrolled in Part 1 of the study were also enrolled in Part 2. Therefore, the total number of subjects enrolled in the study was 33.				

<b>ANALYSIS DESCRIPTION:</b>	<p><b>Primary - Pharmacokinetics</b></p> <p><b>Part 1:</b> Due to the dosing issues, the protocol-specified pharmacokinetic analysis was not conducted for Part 1 of the study.</p> <p><b>Part 2:</b> The natural log (ln)-transformed plasma MK-8616 AUC<sub>0-∞</sub> following the administration of MK-8616 in renal insufficiency subjects (severe and moderate) and healthy subjects were modeled using a linear fixed-effect model with population (severe insufficiency, moderate insufficiency, and healthy control) as a fixed effect. The least-squares means (LSMs) and corresponding 95% confidence intervals (CIs) were calculated by population for AUC<sub>0-∞</sub>. The differences in population LSMs and corresponding 90% CIs were calculated for the comparisons between populations (i.e., severe insufficiency vs. healthy control, moderate insufficiency vs. healthy control) for AUC<sub>0-∞</sub>. The back-transformed summary results, i.e., the population geometric means (GMs) and corresponding 95% CIs, geometric mean ratios (GMRs) and corresponding 90% CIs were reported for AUC<sub>0-∞</sub>.</p>
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<b>ANALYSIS DESCRIPTION (Continued):</b>	<b>Primary - Pharmacokinetics</b> <b>Part 2 (Continued):</b> Similarly, AUC <sub>0-last</sub> , C <sub>max</sub> , CL, V <sub>z</sub> , MRT, and V <sub>ss</sub> were analyzed using the above model. Descriptive statistics were calculated for all plasma MK-8616 pharmacokinetic parameters (i.e., AUC <sub>0-last</sub> , AUC <sub>0-∞</sub> , AUC% <sub>extrap</sub> , C <sub>max</sub> , T <sub>max</sub> , T <sub>last</sub> , λ <sub>z</sub> , apparent terminal t <sub>1/2</sub> , CL, V <sub>z</sub> , MRT, t <sub>1/2eff</sub> , and V <sub>ss</sub> ) by population.
<b>ANALYSIS POPULATION AND TIME POINT DESCRIPTION:</b>	Data from all 24 subjects dosed in Part 1 were included in the clinical study report. Pharmacokinetic parameters and subsequent statistical analyses were not performed for subjects in Part 1 due to dosing issues experienced by some subjects. All 18 subjects dosed in Part 2 of the study were included in the pharmacokinetic and subsequent statistical analyses. Safety is reported on all subjects.
<b>SUMMARY:</b>	<b>Primary - PHARMACOKINETICS:</b> <u><b>Part 1</b></u> Preliminary review of the MK-8616 concentration data combined with dosing issues reported from the clinical research units indicated that in some subjects, doses may not have been administered directly into the vein, and likely infiltrated surrounding tissue based on substantial delays (range: 1 to 4 hours) in T <sub>max</sub> and an apparent absorption phase. As a result of these dosing issues, the protocol-specified pharmacokinetic parameters and subsequent statistical analyses were not conducted for Part 1 of the study. In Part 1, none of the subjects with severe or moderate renal insufficiency had measurable concentrations of MK-8616 (all were < LLOQ) on Day 7 (144 hours) and Day 4 (72 hours), respectively; therefore, despite the dosing issues noted above, extended pharmacokinetic collection beyond Day 10 (216 hours) did not appear to be necessary to characterize the pharmacokinetics of MK-8616 in these subjects. As a result, in Part 2 of the study, pharmacokinetic collection was reduced to Day 10 postdose in subjects with moderate and severe renal insufficiency with flexibility to extend the pharmacokinetic collection in subjects with severe renal insufficiency, if warranted, based upon the presence of measurable concentrations of MK-8616 on Day 7 and/or Day 10. <u><b>Part 2</b></u> The table below summarizes the statistical comparisons of the pharmacokinetics of plasma MK-8616 following a single IV dose of 4 mg/kg MK-8616 administered to subjects with varying degrees of renal insufficiency relative to healthy control subjects. The plasma MK-8616 AUC <sub>0-∞</sub> in subjects with severe and moderate renal insufficiency were 5.42 and 2.42 times, respectively, those calculated in healthy control subjects. The plasma MK-8616 C <sub>max</sub> in subjects with severe and moderate renal insufficiency were

<b>SUMMARY (Continued):</b>	<p><b>Primary – PHARMACOKINETICS (Continued): Part 2 (Continued):</b></p> <p>comparable to those in the healthy control subjects, and the median Tmax was 0.03 hours for all 3 panels of subjects. The Vz and Vss following a single IV administration were comparable in subjects with severe and moderate renal insufficiency, and in healthy control subjects. Clearance progressively decreased and apparent terminal t<sub>1/2</sub>, t<sub>1/2</sub>eff, MRT, and Tlast were progressively prolonged with increased levels of renal dysfunction. Although plasma concentrations were measured for a longer a duration after dosing in subjects with severe renal insufficiency compared to subjects with moderate renal insufficiency and healthy controls, generally, plasma concentrations were not measurable (&lt; LLOQ) in the majority of subjects with severe renal insufficiency 5 days postdose and in no subjects were MK-8616 concentrations measurable beyond 7 days postdose.</p>
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Statistical Summary and Comparison of Plasma Pharmacokinetic Parameters of MK-8616 Following a Single IV Dose of 4 mg/kg MK-8616 Administered to Subjects With Varying Degrees of Renal Insufficiency and to Healthy Control Subjects (Part 2)

Pharmacokinetic Parameter	Severe Renal Insufficiency Subjects			Moderate Renal Insufficiency Subjects			Healthy Control Subjects		
	N	GM	95% CI	N	GM	95% CI	N	GM	95% CI
AUC <sub>0-∞</sub> <sup>‡</sup> (ug•hr/mL)	6	339	(268, 428)	6	151	(120, 191)	6	62.5	(49.5, 79.0)
AUC <sub>0-last</sub> <sup>‡</sup> (ug•hr/mL)	6	335	(265, 424)	6	148	(117, 187)	6	61.1	(48.3, 77.3)
C <sub>max</sub> <sup>‡</sup> (ug/mL)	6	62.2	(50.2, 77.1)	6	60.6	(49.0, 75.1)	6	66.1	(53.3, 81.8)
AUC% <sub>extrap</sub> <sup>§</sup> (%)	6	0.850	43.5	6	2.14	29.2	6	2.10	45.3
CL <sup>§</sup> (L/hr)	6	0.961	26.8	6	2.27	39.6	6	5.70	16.0
Vz <sup>§</sup> (L)	6	18.3	24.8	6	18.8	24.2	6	20.4	25.7
MRT <sup>§</sup> (hr)	6	15.7	26.2	6	7.02	30.8	6	2.48	13.4
V <sub>ss</sub> <sup>§</sup> (L)	6	15.1	19.7	6	15.9	21.9	6	14.1	20.4
T <sub>max</sub> <sup>  </sup> (hr)	6	0.03	(0.03, 0.08)	6	0.03	(0.02, 0.08)	6	0.03	(0.03, 0.08)
T <sub>last</sub> <sup>  </sup> (hr)	6	72.00	(71.99, 143.99)	6	24.00	(23.99, 47.99)	6	12.00	(11.99, 12.00)
Apparent terminal t <sub>s</sub> <sup>§</sup> (hr)	6	13.24	35.50	6	5.73	29.79	6	2.47	13.49
t <sub>s,eff</sub> <sup>§</sup> (hr)	6	10.89	26.15	6	4.87	30.84	6	1.72	13.36
λ <sub>z</sub> <sup>§</sup> (1/hr)	6	0.0524	35.5	6	0.121	29.8	6	0.280	13.5
Pharmacokinetic Parameter	Severe Renal Insufficiency/Healthy Control			Moderate Renal Insufficiency/Healthy Control			rMSE <sup>†</sup>		
	GMR	90% CI		GMR	90% CI				
AUC <sub>0-∞</sub> <sup>‡</sup> (ug•hr/mL)	5.42	(4.12, 7.11)		2.42	(1.84, 3.17)		0.269		
AUC <sub>0-last</sub> <sup>‡</sup> (ug•hr/mL)	5.49	(4.18, 7.22)		2.42	(1.84, 3.18)		0.270		
C <sub>max</sub> <sup>‡</sup> (ug/mL)	0.94	(0.73, 1.21)		0.92	(0.72, 1.18)		0.246		

A single IV dose of 4 mg/kg MK-8616 administered on Day 1.  
<sup>†</sup>rMSE: Square root of conditional mean squared error (residual error) from the ANOVA model. rMSE×100% approximates the %CV on the normal scale.  
<sup>‡</sup>Back-transformed least-squares mean and confidence interval from the ANOVA linear fixed-effect model performed on natural log-transformed values.  
<sup>§</sup>Geometric mean and geometric coefficient of variation reported for AUC%<sub>extrap</sub>, CL, Vz, MRT, V<sub>ss</sub>, apparent terminal t<sub>s</sub>, t<sub>s,eff</sub>, and λ<sub>z</sub>.  
<sup>||</sup>Median and (Minimum, Maximum) reported for T<sub>max</sub> and T<sub>last</sub>.  
GM = Geometric least-squares mean; CI = Confidence interval; GMR = Geometric least-squares mean ratio.  
Program: /CB13254/sas\_prg/pksas/stats-it-MK\_primary.sas 19AUG2014 16:21

<b>CONCLUSIONS:</b>	<ol style="list-style-type: none"> <li>1. Exposure (AUC<sub>0-∞</sub>) to MK-8616 increased approximately 5.42 times and 2.42 times in subjects with severe and moderate renal insufficiency, respectively, relative to healthy control subjects.</li> <li>2. Clearance progressively decreased and apparent terminal t<sub>1/2</sub>, t<sub>1/2</sub>eff, MRT, and Tlast were progressively prolonged with increased levels of renal dysfunction. Although measurable plasma concentrations were detected for a longer duration after dosing in subjects with severe renal insufficiency compared to subjects with moderate renal insufficiency and healthy controls, plasma concentrations were not measurable (&lt; LLOQ) in the majority of subjects 5 days postdose and in any subject with severe renal insufficiency beyond 7 days postdose.</li> <li>3. C<sub>max</sub>, T<sub>max</sub>, V<sub>z</sub>, and V<sub>ss</sub> values in subjects with severe and moderate renal insufficiency were comparable to those in the healthy control subjects.</li> <li>4. Administration of a single 4 mg/kg IV dose of MK-8616 was generally well tolerated in male and female subjects with moderate to severe renal insufficiency and matched healthy control subjects.</li> </ol>
<b>PUBLICATION(S):</b>	None
<b>REPORT DATE:</b>	Final: 21-Aug-2014

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/s/  
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03/25/2015

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03/25/2015

## CLINICAL PHARMACOLOGY REVIEW

NDA: 22-225 SDN 51	Submission Date(s): 12/21/2012
Brand Name	(b) (4)
Generic Name	Sugammadex Sodium
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Team Leader	Atul V. Bhattaram, Ph.D.
Clinical Pharmacology Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia and Analgesia Products
Sponsor	Merck/Organon USA
Submission Type; Code	Response to CR action
Formulation; Strength(s)	IV Injection; 100 mg/mL
Indication	Routine reversal of moderate or deep neuromuscular blockade (NMB) by rocuronium or vecuronium, and immediate reversal of NMB at 3 minutes after administration of rocuronium.
Proposed Dosage Regimen	2 – 4 mg/kg for Routine reversal of moderate to deep NMB. 16 mg/kg for immediate reversal of NMB.

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## **1 Executive Summary**

### **1.1 Recommendation**

The application is acceptable from a clinical pharmacology perspective provided that a mutually satisfactory agreement can be reached between the Agency and the Sponsor regarding the labeling changes.

### **1.2 Phase IV Commitments**

None.

### **1.3 Summary of Clinical Pharmacology Findings**

Originally, Organon (now acquired by Merck) sought Agency's approval of its product, Sugammadex for two indications: a) routine reversal of shallow or profound neuromuscular blockade (NMB) induced by rocuronium or vecuronium, and b) immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

Sugammadex, if approved, will be the first in a new class of NMB reversing agent. This is a resubmission by Merck in response to the Not Approvable letter issued by the Agency on July 31, 2008 for NDA 22-225 mainly due to the lack of adequate characterization of (1) hypersensitivity reactions and (2) effect on coagulation of the product. Additional clinical pharmacology studies were also submitted to support labeling claims.

Clinical study (P07044) was conducted in healthy subjects to assess sugammadex-anticoagulant (enoxaparin or heparin) interaction. There was no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin.

Clinical study (P07025) was conducted in healthy subjects to assess sugammadex-aspirin interaction. There was no effect of 4 mg/kg of platelet aggregation effects of aspirin.

Second TQT study (Study 19.4.116 or P06315) was conducted to evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers. No significant QTc prolongation effect of sugammadex was detected in this TQT study.

In three clinical studies (19.4.304 (already previously reviewed by Dr. Lei K. Zhang in 2008), 19.4.328, and 19.4.333), PK of sugammadex and removal of sugammadex from plasma circulation of patients with severe renal impairment by hemodialysis was investigated. In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment. Using high-flux dialysis filter, compared to low-

flux filter, results in a more efficient clearance of sugammadex (and sugammadex+ rocuronium) from plasma.

Clinical study 19.4.112 or P05861 was conducted to assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by diclofenac or flucloxacillin 5 minutes after reversal of NMB by sugammadex. Diclofenac or flucloxacillin did not alter pharmacokinetic disposition of rocuronium or vecuronium in plasma. No reoccurrence of neuromuscular block was observed after the administration of the administration of diclofenac or flucloxacillin based on TOF Watch SX monitoring during anesthesia.

Clinical Study 19.4.113 or P05861 evaluated re-use of rocuronium and vecuronium after NMB with Sugammadex. This was an open-label study to assess the safety of re-use of 1.2 mg/kg rocuronium and 0.1 mg/kg vecuronium after reversal of neuromuscular blockade by 4 mg/kg sugammadex in anesthetized healthy volunteers.

- After re-use of rocuronium, subjects showed neuromuscular block after the shortest reuse time at 5 minutes following sugammadex reversal.
  - NMB onset time ranged from 1.92 to 4.72 min (arithmetic mean: 3.06).
  - For later re-use time points (30 min onwards) NMB onset times decreased, ranging between 1.23 and 1.43 min.
- Clinical duration of the NMB with rocuronium re-use time-point at 5 minutes, ranged from 17.8-41.0 min.
- After re-use of vecuronium, neuromuscular block with onset times below 3 minutes was only observed with a wait time of 3.5 hours onwards.
  - Complete NMB did not occur after vecuronium re-use at 2 hours and 2.5 hours after sugammadex administration. Therefore, it was decided not to proceed with earlier time-points of re-use of vecuronium.
  - Onset times of neuromuscular block at re-use times  $\geq 3.5$  hours ranged from 1.68 minutes (re-use at 3.5 h) to 3.15 minutes (re-use at 4 h) with NMB durations between 24.2 minutes (reuse at 4 h) and 31.4 minutes.

## 2 Clinical Pharmacology Review

Originally, Organon sought Agency's approval of its product, Sugammadex for two indications: a) routine reversal of shallow or profound neuromuscular blockade (NMB) induced by rocuronium or vecuronium, and b) immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium. Merck acquired Organon and Scherring Plough since 2008 and hence the studies make reference to different study number classification and different drug ID's.

Sugammadex, if approved, will be the first in a new class of NMB reversing agent. This is a resubmission by Merck in response to the Not Approvable letter issued by the Agency on July 31, 2008 for NDA 22-225 mainly due to the lack of adequate characterization of (1) hypersensitivity reactions and (2) effect on coagulation of the product. Merck considers this to be a complete response to the deficiencies outlined in the Not Approvable letter cited above for NDA 22-225. Clinical safety and clinical pharmacology studies were submitted in response to deficiency #2 described below.

2. Studies evaluating the effects of sugammadex on coagulation in patients undergoing surgical procedures. The studies should be designed to evaluate the magnitude and duration of sugammadex's effect, the mechanism by which it occurs, and its clinical relevance in the perioperative setting.

In addition to the deficiencies, Agency issued various comments (not required for approval) in the not approvable letter which were relevant to the clinical pharmacology discipline.

2. A study of the frequency and severity of cardiac arrhythmias and QTc prolongation occurring in patients receiving sugammadex versus those receiving other NMBA reversal agents and those not receiving reversal agents but who were administered an NMBA during their surgical procedure. The study should be powered to detect differences for these adverse events based on findings from the clinical trials submitted in the NDA.

3. A study to assess clearance of sugammadex-rocuronium complexes in patients with renal failure who undergo hemodialysis using high flux filtration.

4. Studies to assess safety, efficacy, and dosing requirements for sugammadex when used in patients with hepatic impairment. The studies should characterize the pharmacokinetics and pharmacodynamics of rocuronium and vecuronium in these patients following the administration of sugammadex.

5. Studies to assess safety and efficacy and appropriate dosing regimens in pediatric patients. Such studies should not be started until the safety issues for the adult population have been fully vetted by the Agency.

The following clinical pharmacology studies were submitted and reviewed in the current review cycle. In addition, original clinical pharmacology review was also reviewed to reconcile labeling recommendations.

**Studies conducted to address the deficiency 2, in part, as described above:**

The following two clinical pharmacology studies were conducted in healthy volunteers as a randomized, double-blind, placebo-controlled, 4-period, crossover trials.

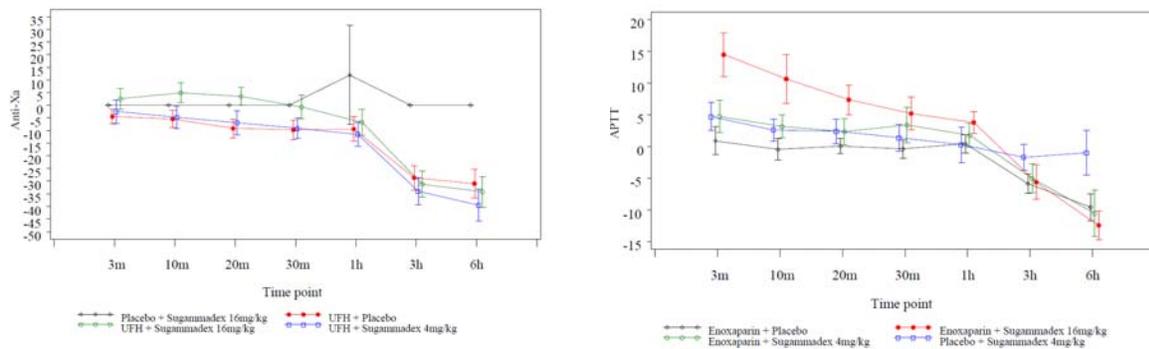
- Clinical study (P07044) in healthy subjects to assess sugammadex-anticoagulant (enoxaparin or heparin) interaction. There was no effect of 4 mg/kg and 16 mg/kg sugammadex on anti-Xa and APTT effects of enoxaparin 40 mg SC or 5000 units of unfractionated heparin (See details in attached study synopsis or review by Dr. George Shashaty).

The results of the primary and secondary analysis can be summarized as follows:

No interaction on Anti-Xa activity was observed, exceeding the pre-specified non-inferiority margin after the addition of 4 mg/kg or 16 mg/kg sugammadex to background prophylactic enoxaparin dosing (Part 1).

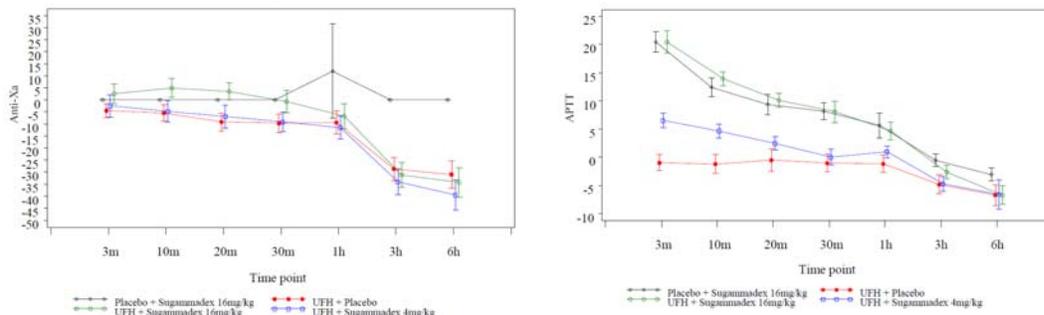
The two sided 90% upper confidence limits of the GMRs representing the anti-Xa effect of sugammadex in combination with enoxaparin versus enoxaparin alone were 1.07 and 1.08 for 4 mg/kg and 16 mg/kg sugammadex respectively, i.e. below the pre-specified non-inferiority margin of 1.50.

**Figure: Mean and 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for anti-Xa/APTT (Part 1).**



□ No interaction on APTT was observed, exceeding the pre-specified non-inferiority margin after the addition of 4 mg/kg or 16 mg/kg sugammadex to background prophylactic UFH dosing (Part 2).

**Figure: Mean and 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for anti-Xa/APTT (Part 2).**



The two sided 90% upper confidence limits of the GMRs representing the APTT effect of sugammadex in combination with UFH versus UFH alone were 1.06 and 1.15 for 4 mg/kg and 16 mg/kg sugammadex respectively, i.e. below the pre-specified non-inferiority margin of 1.50.

- Clinical study (P07025) in healthy subjects to assess sugammadex-aspirin interaction. There was no effect of 4 mg/kg of platelet aggregation effects of aspirin (See details in attached study synopsis or review by Dr. George Shashaty).

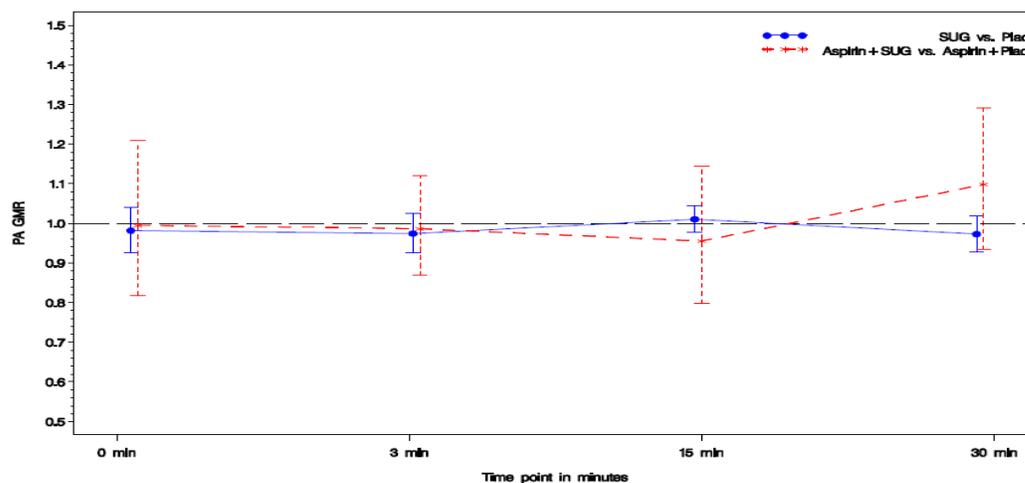
The area under effect curve (AUEC) 3-30min geometric mean ratio (GMR) for platelet aggregation of aspirin in combination with sugammadex versus aspirin alone was 1.01 and the corresponding two sided 90% lower confidence limit was 0.91, which was above the pre-specified non-inferiority margin of 0.75.

**Table: Treatment GMRs and corresponding lower limits of 90% CI's for the AUEC3 -30 min of platelet aggregation (PA).**

Treatment comparison	Geometric mean ratio	Lower limit of the 90% CI
Aspirin+Sug. vs Aspirin	1.01	0.91
Sug. vs placebo	0.99	0.96
Sug*Aspirin interaction	1.02	0.91

The GMR for bleeding time of aspirin in combination with sugammadex versus aspirin alone was 1.20 and the corresponding two sided 90% upper confidence limit was 1.45, which was below the pre-specified non-inferiority margin 1.5.

**Figure: Unadjusted GMR of sugammadex alone to placebo and aspirin with sugammadex + aspirin and corresponding 90% CI of platelet aggregation, by time point.**



**Studies conducted to address comments (2 -5) provided by the Agency (as described above):**

***Response to comment 2:***

- TQT study to evaluate the potential for QT/QTc prolongation after administration of 4 mg/kg sugammadex as compared to placebo in the presence of the maintenance anesthetic agents, propofol or sevoflurane in healthy volunteers (Study 19.4.116 or P06315). See the review by QT - Integrated Review Team dated March 21, 2013.

**Summary:** No significant QTc prolongation effect of sugammadex was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between propofol/sugammadex and placebo and sevoflurane/ sugammadex were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. In this randomized, blinded, four-treatment parallel study, 132 healthy subjects received sugammadex with propofol or sevoflurane, or placebo with propofol or sevoflurane. The overall summary of findings is presented in the table below:

**The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Sugammadex (FDA Analysis)**

Treatment	Time (min)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Propofol/Sugammadex	120	2.7	(-3.1, 8.5)
Sevoflurane/Sugammadex	30	2.0	(-1.6, 5.7)

There was no significant concentration-QT relationship observed for the studied sugammadex dose of 4 mg/kg. In addition, there was no suprathreshold dose evaluated in this study, and the evaluated dose is not sufficient to address the high exposure scenario (e.g., elderly subject with moderate renal impairment treated with 16 mg/kg for immediate reversal), which would result in an 8.8-fold increase in AUC compared to sugammadex 4 mg/kg. However; a previous submission evaluated a suprathreshold dose of sugammadex 32 mg/kg, and the mean QT prolongation was less 10 ms. The combination of the previous study results where an appropriate suprathreshold dose was evaluated and the current study results, which demonstrate no significant concentration-QT relationship support that substantial QT prolongation under the high exposure scenario is unlikely with the proposed maintenance regimens.

***Response to comment 3:***

- Clinical study to evaluate the dialyzability of the sugammadex-rocuronium complex in vivo in subjects with renal impairment (Study 19.4.333 or P05773).
- Clinical study evaluating effectiveness of sugammadex in subjects with normal or severely impaired renal function (Study 19.4.328 or P05769).
- Clinical study evaluating effectiveness, PK, and safety of sugammadex after rocuronium in subjects with normal or impaired renal function (updated Study 19.4.304 or P05948, previously reviewed in the original NDA review cycle).

**Summary:** Previous studies indicate that sugammadex is eliminated unchanged via renal excretion and accordingly, increased exposure is noted in patients with mild, moderate or severe renal impairment. In three clinical studies in the program (19.4.304 (already previously reviewed by Dr. Lei K. Zhang in 2008), 19.4.328, and 19.4.333), removal of sugammadex from plasma circulation by hemodialysis was investigated. In study 19.4.333 (or P05773), over an average six hours of dialysis episode a mean reduction in plasma sugammadex and rocuronium concentration was about 70% and 75% during the first episode and about 50% during the sequential episodes. Study 19.4.328 was conducted as a Follow-up Measure (FUM) at the request of the European Medicines Agency (EMA) and was an open-label, multicenter, parallel-group, comparative Phase 3 trial investigating the PK, and safety of sugammadex to reverse deep NMB (at 1-2 PTC) in subjects with severe renal impairment compared with subjects with normal renal function. In subjects with severe renal impairment, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold, and volume of distribution increased by a factor of approximately 2 compared to the control group. This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher in subjects with severe renal impairment. In this study (19.4.328), the median reduction in sugammadex plasma concentrations after a 3 to 4 hours of dialysis for the high-flux filter (n=5) was 70.2% and for the low-flux filter (n=5) the reduction was only 29.8%. In addition, the sponsor indicated that a high-flux filter in study 19.4.304 instead of the reported low flux dialysis filters. Results of this study were already reviewed in the original review cycle. In conclusion, using high-flux dialysis filter, compared to low-flux filter, results in a more efficient clearance of sugammadex (and sugammadex+rocuronium) from plasma.

#### ***Response to comment 4***

- Sponsor does not plan to propose specific recovery times of T4/T1 ratio to 0.9 in the label in patients with hepatic impairment. Therefore, a dedicated PK-PD trial in subjects with hepatic impairment has not been conducted. The Sponsor states that hepatic impairment is unlikely to affect PK of sugammadex, as it is predominantly, if not exclusively, eliminated via renal excretion of the unchanged product. The Sponsor also states that it cannot be entirely excluded that in some individuals with severe hepatic impairment (especially in cases of ascites or general edema in severe hepatic impairment with significantly impaired protein synthesis function) the time of distribution of sugammadex and/or rocuronium/vecuronium may be altered, potentially resulting in some delay in the recovery time from NMBA effects. A recent publication of 3 cases with hepatic impairment, in whom variable and somewhat prolonged recovery times from NMB were reported, supports this note of caution.[Ref. 5.4: 160]

Therefore, the Sponsor proposes a general statement in the label stating that sugammadex should be used with caution in subjects with severe hepatic impairment with coagulopathy or severe edema. This is an acceptable approach, as the caution is meant towards the use of NMB's rocuronium and vecuronium that may be cleared by the hepatic route and not meant towards use of renally cleared sugammadex.

**Response to comment 5**

- Pediatric study plan proposal was submitted during the course of the NDA review.

**Rationale for proposed pediatric plan:** The new proposed plan aims to leverage the results from the pediatric clinical trial 19.4.306 (conducted previously outside of the US) and the extensive adult clinical trial data base. Trial 19.4.306 was designed as a dose-finding trial investigating 4 doses of sugammadex (0.5, 1.0., 2.0 and 4.0 mg/kg) and placebo for the reversal of rocuronium induced moderate NMB (“at the reappearance of T2”) at different age groups of pediatric subjects.

The trial also investigated a cohort of adult subjects. The full CSR for this trial was included in Module 5.3.4.2 of the original NDA for sugammadex. Table below summarizes the efficacy data by dose and age group and also presents an overview of the number of evaluated pediatric and adult subjects in Trial 19.4.306.

**Table: Summary of the recovery times (min:sec) from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 by dose and age group (PP group).**

Age class	Statistic	Dose group				
		Placebo (N=12)	0.5 mg/kg Org 25969 (N=12)	1.0 mg/kg Org 25969 (N=13)	2.0 mg/kg Org 25969 (N=11)	4.0 mg/kg Org 25969 (N=11)
Infants (28 days - 23 months)	n	2	2	2	1	1
	Mean (SD)	20:59 (11:18)	3:43 (0:38)	2:25 (0:42)	0:35 (-)	0:40 (-)
	Median	20:59	3:43	2:25	0:35	0:40
	Min. – max.	12:59 – 28:58	3:16 – 4:10	1:55 – 2:54	0:35 – 0:35	0:40 – 0:40
Children (2 - 11 years)	n	4	5	5	4	4
	Mean (SD)	19:34 (10:58)	5:13 (3:30)	3:57 (3:14)	1:12 (0:21)	1:34 (1:54)
	Median	19:02	3:42	2:39	1:09	0:38
	Min. – max.	8:25 – 31:47	2:22 – 10:56	1:54 – 9:36	0:51 – 1:37	0:36 – 4:25
Adolescents (12 - 17 years)	n	5 <sup>1)</sup>	5	6	6	6
	Mean (SD)	22:46 (13:06)	11:58 (17:39)	1:46 (0:22)	1:52 (1:42)	1:05 (0:15)
	Median	23:22	4:37	1:40	1:08	1:05
	Min. – max.	6:50 – 41:40	1:56 – 43:27	1:28 – 2:27	0:42 – 5:14	0:44 – 1:26
Adults (18 - 65 years)	n	6	5	5	5	5
	Mean (SD)	29:29 (8:26)	3:46 (1:07)	1:37 (0:18)	1:16 (0:16)	1:22 (0:23)
	Median	28:30	4:13	1:44	1:13	1:24
	Min. – max.	19:37 – 43:57	2:15 – 4:45	1:11 – 1:57	0:54 – 1:34	0:57 – 1:57

<sup>1)</sup> One adolescent had missing times with respect to the recovery of the T4/T1 ratio to 0.9

The dose of 2 mg/kg was considered also to provide adequate reversal of moderate block in children and adolescents, where higher doses did not provide a relevant clinical benefit. For infants there was insufficient data to fit a dose response curve, but the observed data do reveal a clear dose response and rapid reversal at 2 mg/kg (see Table above).

Nevertheless, the current data base does not cover all pediatric age groups (so far no data on neonates are available), there are no pediatric data in the reversal of deep block, and the current number of pediatric subjects is still limited.

(b) (4)  
 (b) (4)  
 In addition, the plan  
 (b) (4)  
 proposes

### ***Other studies***

- Clinical study to assess the potential for recurrence of NMB through displacement of rocuronium or vecuronium by diclofenac or flucloxacillin 5 minutes after reversal of NMB by sugammadex (Study 19.4.112 or P05861).

**Summary:** Diclofenac or flucloxacillin did not alter pharmacokinetic disposition of rocuronium or vecuronium in plasma. No reoccurrence of neuromuscular block was observed after the administration of the administration of diclofenac or flucloxacillin based on TOF Watch SX monitoring during anesthesia.

- Clinical study to evaluate re-use of rocuronium and vecuronium after NMB with Sugammadex (Study 19.4.113 or P05861). This was an open-label study to assess the safety of re-use of 1.2 mg/kg rocuronium and 0.1 mg/kg vecuronium after reversal of neuromuscular blockade by 4 mg/kg sugammadex in anesthetized healthy volunteers.

### ***Summary:***

***Rocuronium re-use:*** After re-use of rocuronium, subjects showed fast onset times of neuromuscular block already after the shortest reuse time at 5 minutes following sugammadex reversal. For the 6 subjects with rocuronium re-use at 5 min, NMB onset time ranged from 1.92 to 4.72 min (arithmetic mean: 3.06). For later re-use time points (30 min onwards) NMB onset times decreased, ranging between 1.23 and 1.43 min. Clinical duration of the NMB among the 6 subjects with rocuronium re-use time-point at 5 minutes, ranged from 17.8-41.0 min (arithmetic mean 25.3 minutes) and was around 30 min and longer for subjects with rocuronium re-use time points from 22 minutes (N=7) onwards.

*Vecuronium re-use:* In Part 2, six subjects received the second dose of vecuronium with re-use time points between 2 hours and 5 hours after sugammadex administration. A complete neuromuscular block with onset times below 3 minutes was only observed for vecuronium re-use times from 3.5 hours onwards. No complete NMB occurred after vecuronium re-use at 2 hours and 2.5 hours after sugammadex administration. Therefore, it was decided not to proceed with earlier time-points of re-use of vecuronium. Onset times of neuromuscular block at re-use times  $\geq 3.5$  hours ranged from 1.68 minutes (re-use at 3.5 h) to 3.15 minutes (re-use at 4 h) with NMB durations between 24.2 minutes (reuse at 4 h) and 31.4 minutes.

## 2.1 Bioanalytical methods used

Assays 1, 2, and 3 (determination of sugammadex, rocuronium [Org 9426], and vecuronium [Org NC 45], respectively, in human plasma) were the same as applied in clinical trials described in the original NDA submission. A modified liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) assay for the determination of sugammadex in human plasma (Assay 6) was developed, validated, and applied in Trials P07044 and P07038 (validation report DM-1011A/AMR DM-1011A). The major modifications of this assay compared with the assay previously used (Assay 1) are:



Furthermore, 2 new assays (Assays 4 and 5) were developed and validated for the determination of sugammadex and rocuronium, respectively, in dialysate (Trial 19.4.333; validation reports 080064/INT00077119 and 080101/INT00082710, respectively).

### ***Anti-Activated Coagulation Factor Xa (Anti-Xa)***

Anti-Xa was analyzed in **Trials P07044** and **P07038**. The anti-Xa assay was performed using a commercially available amidolytic chromogenic assay for the determination of heparin(s). The principle of the test was to determine in human plasma the capacity to neutralize added bovine Factor Xa activity. The residual Factor Xa activity is inversely proportional to the heparin concentration. After a reaction with substrate, the amount of heparin was determined spectrophotometrically. The results were to be recorded in international units (IU)/mL.

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## 3.2 Individual Study Reviews

### 3.2.1 Synopsis of Clinical Study P07044

**Study Title:** A randomized, double-blind, placebo-controlled, 4-period, two part cross-over study to evaluate the potential interaction effect between 4 mg/kg and 16 mg/kg sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity in young healthy male volunteers (Protocol No. P07044).

#### **OBJECTIVES:**

##### **Part 1: Enoxaparin**

##### **Primary Objective:**

To investigate the potential effect of 4 mg/kg and 16 mg/kg sugammadex on the Anti-Xa anticoagulant activity of enoxaparin.

##### **Primary Hypotheses:**

1. Administration of a single subcutaneous (SC) dose of 40 mg enoxaparin in combination with 4 mg/kg sugammadex does not increase the Anti-Xa activity AUEC3-30 min to a ratio exceeding 1.5 as compared to enoxaparin alone.
2. Administration of a single SC dose of 40 mg enoxaparin in combination with 16 mg/kg sugammadex does not increase the Anti-Xa activity AUEC3-30 min to a ratio exceeding 1.5 as compared to enoxaparin alone.

##### **Secondary Objectives:**

- To investigate the potential effect of 4 mg/kg and 16 mg/kg sugammadex on the APTT anticoagulant activity of enoxaparin.
- To evaluate the effect of enoxaparin on the potential APTT anticoagulant activity of 4 mg/kg sugammadex.
- To evaluate the potential anticoagulant activity of 4 mg/kg sugammadex as compared to baseline. Anti-Xa activity and APTT will be the secondary endpoint measures.
- To evaluate the safety and tolerability of sugammadex alone or in combination with enoxaparin.

##### **Part 2: Unfractionated Heparin (UFH)**

##### **Primary Objective:**

To investigate the potential effect of 4 mg/kg and 16 mg/kg sugammadex on the APTT anticoagulant activity of UFH.

##### **Secondary Objectives:**

- To evaluate the effect of UFH on the potential APTT anticoagulant activity of 16 mg/kg sugammadex.
- To evaluate the potential anticoagulant activity of 16 mg/kg sugammadex as compared to baseline. APTT and Anti-Xa activity will be the secondary endpoint measures.
- To evaluate the safety and tolerability of sugammadex alone or in combination with UFH.

##### **STUDY DESIGN:**

This study was conducted as a randomized, double-blind, placebo-controlled, 4-period, two part cross-over study to evaluate the potential interaction between 4 mg/kg and 16 mg/kg sugammadex and enoxaparin or unfractionated heparin on anticoagulant activity in young healthy male volunteers. A double-blind design for sugammadex and placebo was used to avoid biases in (subjective) safety reporting. Furthermore, the

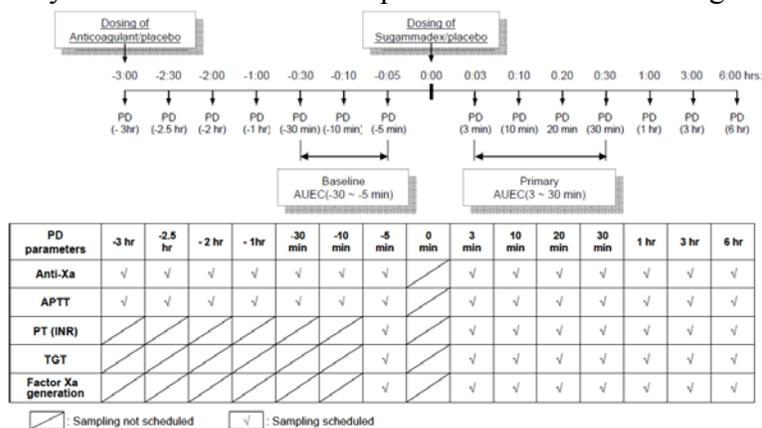
anticoagulant/placebo was administered in a double-blind fashion to avoid the unblinding of the randomization sequence (i.e. after placebo anticoagulant sugammadex is always administered). A 4-period cross-over study to be performed in 2 parts was considered to be an efficient and powerful design for the evaluation of the potential interaction of 4 mg/kg and 16 mg/kg sugammadex on the anticoagulant activity of enoxaparin (Part 1) and UFH (Part 2), in both parts applying a within-subject comparison. Part 1 and Part 2 consisted of the following treatments:

Part 1								
Treatment sequence	Period 1	Wash-out	Period 2	Wash-out	Period 3	Wash-out	Period 4	F/U visit
1	P-S4		E-P		E-S4			
2	E-S16		P-S4		E-P			
3	E-S4		E-S16		P-S4			
4	E-P		E-S4		E-S16			
P-S4: Placebo SC, after 3 hours followed by 4 mg/kg sugammadex IV E-P: Enoxaparin 40 mg SC, after 3 hours followed by placebo IV E-S4: Enoxaparin 40 mg SC, after 3 hours followed by 4 mg/kg sugammadex IV E-S16: Enoxaparin 40 mg SC, after 3 hours followed by 16 mg/kg sugammadex IV								
Part 2								
Treatment sequence	Period 1	Wash-out	Period 2	Wash-out	Period 3	Wash-out	Period 4	F/U visit
1	P-S16		U-P		U-S4			
2	U-S16		P-S16		U-P			
3	U-S4		U-S16		P-S16			
4	U-P		U-S4		U-S16			
P-S16: Placebo SC, after 3 hours followed by 16 mg/kg sugammadex IV U-P: UFH 5000 units SC, after 3 hours followed by placebo IV U-S4: UFH 5000 units SC, after 3 hours followed by 4 mg/kg sugammadex IV U-S16: UFH 5000 units SC, after 3 hours followed by 16 mg/kg sugammadex IV								

### Pharmacodynamics:

Blood sampling for Anti-Xa activity and APTT was to be performed at - 3:00 (i.e. pre-dose anticoagulant (-3 h 00 min), -2:30, -2:00, - 1:00, -0:30, -0:10, -0:05 hrs:min (i.e. pre-dose sugammadex/placebo), and 0:03, 0:10, 0:20, 0:30, 1:00, 3:00 and 6:00 hrs:min post sugammadex/placebo for both Part 1 and Part 2.

For other PD parameters (i.e. PT(INR)), TGT and Factor Xa generation), samples were to be collected at - 0:05 (i.e. pre-dose sugammadex/placebo) and 0:03, 0:10, 0:20, 0:30, 1:00, 3:00 and 6:00 hrs:min post sugammadex/placebo for both Part 1 and 2. All PD blood samples were to be taken from the arm opposite to the arm used for sugammadex/placebo administration. PD parameters were to be assessed using validated assays. Details of the PD sample collection schedule is given below.



## Part 1: Enoxaparin

### Primary objective:

#### Endpoint: AUEC3-30min of Anti-Xa

- The AUEC3-30min GMR for Anti-Xa of enoxaparin in combination with sugammadex 4 mg/kg versus enoxaparin alone was 1.02 and the corresponding two sided 90% upper confidence limit was 1.07, which was below the prespecified non-inferiority margin of 1.50.
- The AUEC3-30min GMR for Anti-Xa of enoxaparin in combination with sugammadex 16 mg/kg versus enoxaparin alone was 1.04 and the corresponding two sided 90% upper confidence limit was 1.08, which was below the prespecified non-inferiority margin of 1.50.

## Part 2: Unfractionated Heparin

### Primary objective

#### Endpoint: AUEC3-30min of APTT

- The AUEC3-30min GMR for APTT of UFH in combination with sugammadex 4 mg/kg versus UFH alone was 1.04 and the corresponding two sided 90% upper confidence limit was 1.06, which was below the prespecified non-inferiority margin of 1.50.
- The AUEC3-30min GMR for APTT of UFH in combination with sugammadex 16 mg/kg versus UFH alone was 1.13 and the corresponding two sided 90% upper confidence limit was 1.15, which was below the prespecified non-inferiority margin of 1.50.

## Pharmacokinetics

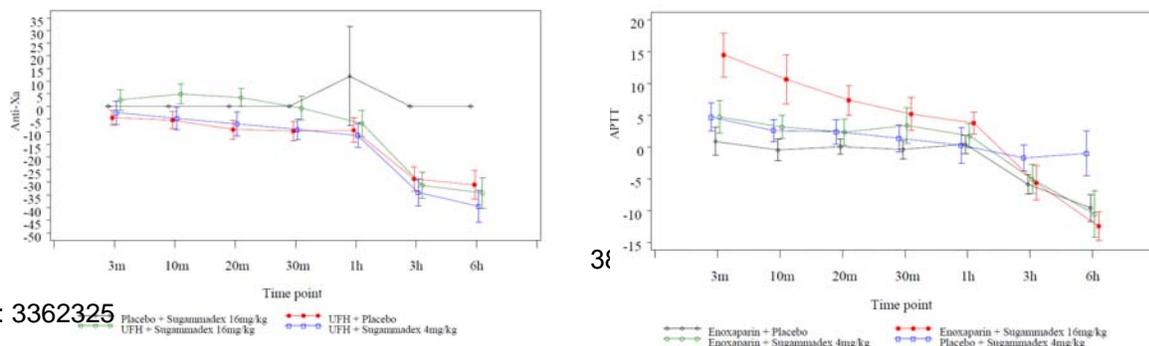
The plasma concentration profiles of sugammadex during the period of pharmacokinetic measurements (3 minutes to 6 hours) after treatment with 4 mg/kg sugammadex alone and after treatment with 4 mg/kg sugammadex on top of enoxaparin treatment are similar. Likewise, the plasma concentration profiles of sugammadex during the same period after treatment with 16 mg/kg sugammadex alone and after treatment with 16 mg/kg sugammadex on top of UFH treatment are similar.

### Summary of Results:

The results of the primary and secondary analysis can be summarized as follows:

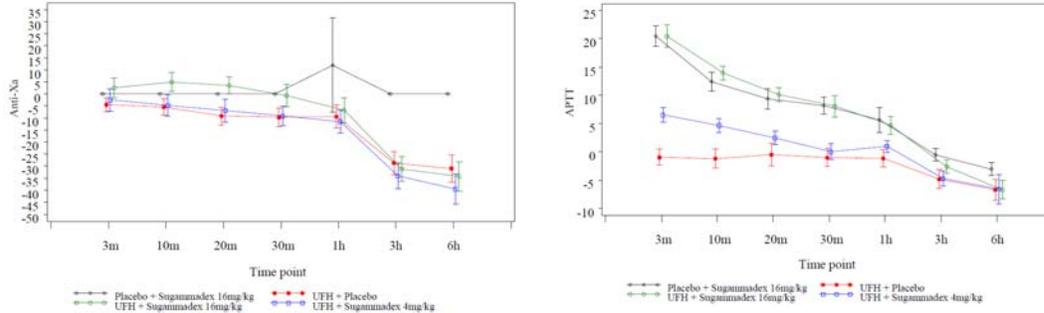
- No interaction on Anti-Xa activity was observed, exceeding the pre-specified non-inferiority margin after the addition of 4 mg/kg or 16 mg/kg sugammadex to background prophylactic enoxaparin dosing (Part 1).
- The two sided 90% upper confidence limits of the GMRs representing the anti-Xa effect of sugammadex in combination with enoxaparin versus enoxaparin alone were 1.07 and 1.08 for 4 mg/kg and 16 mg/kg sugammadex respectively, i.e. below the pre-specified non-inferiority margin of 1.50.

**Figure: Mean and 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for anti-Xa/APTT (Part 1).**



□ No interaction on APTT was observed, exceeding the pre-specified non-inferiority margin after the addition of 4 mg/kg or 16 mg/kg sugammadex to background prophylactic UFH dosing (Part 2).

**Figure: Mean and 90% CI percentage change from pre-dose sugammadex/placebo by treatment group for anti-Xa/APTT (Part 2).**



□ The two sided 90% upper confidence limits of the GMRs representing the APTT effect of sugammadex in combination with UFH versus UFH alone were 1.06 and 1.15 for 4 mg/kg and 16 mg/kg sugammadex respectively, i.e. below the pre-specified non-inferiority margin of 1.50.

□ Sugammadex treatment alone resulted in similar limited APTT increases, with two sided 90% upper confidence limits of the GMRs 1.08 and 1.15 for 4 mg/kg and 16 mg/kg sugammadex respectively.

### 3.2.2 Synopsis of Clinical Study P07025

**Study Title:** A Randomized, Double-Blind, Placebo-Controlled, 4-Period Cross-Over Drug-Drug Interaction Study to Evaluate the Effect Of Sugammadex and Aspirin on Platelet Aggregation and Coagulation Parameters in Young Healthy Male Volunteers.

**Primary Objective:**

To investigate the potential of an interaction between 4 mg/kg sugammadex and aspirin on platelet aggregation (PA) using collagen-induced whole blood aggregometry in young healthy male volunteers.

**Secondary Objectives:**

1 To investigate the potential of an interaction between 4 mg/kg sugammadex and aspirin on activated partial thromboplastin time (APTT).

2 To compare the effect of single intravenous doses of 4 mg/kg sugammadex on APTT with placebo.

3 To investigate the potential interaction between 4 mg/kg sugammadex and aspirin on cutaneous bleeding time.

**Treatment:** The study consisted of 4 cross-over treatment periods and each treatment period consisted of three confinement days (i.e. Day -1, Day 1 and Day 2). In each period, subjects received a single intravenous injection of placebo or of 4 mg/kg sugammadex, according to a sponsor provided randomization schedule. In periods 1 and 2, subjects received placebo or sugammadex with an in-between washout period of at least 4 days, without a co-administration of 75 mg aspirin. After the washout period following treatment period 2, once daily oral administration of 75 mg aspirin was started and continued until period 4, for maximally 16 days. A single intravenous injection of placebo or sugammadex was administered after at least 7 and 11 consecutive days of once daily treatment of 75 mg aspirin in periods 3 and 4 respectively.

In the occasion that aspirin treatment was interrupted temporarily after sugammadex/placebo dosing in period 3, intake of at least 7 consecutive daily doses of aspirin was required prior to sugammadex/placebo dosing in Period 4.

**EVALUATION CRITERIA:**

**Pharmacodynamics:**

Platelet aggregation, APTT, PT/INR, ACT, TGT and the factor Xa generation test were evaluated at pre-dose (i.e. -5 minutes) and 3, 15 and 30 minutes and 1, 3 and 6 hours post-dose. All pharmacodynamic blood samples were to be taken from the arm opposite to the arm used for drug infusion. For the bleeding time, evaluations were conducted at pre-dose (i.e. -15 minutes) and 5 minutes and 6 hours post-dose. The bleeding time assessment was performed in the same arm as used for drug infusion.

**Pharmacokinetics:**

Plasma concentrations of sugammadex were determined at pre-dose (i.e. -5 minutes) and 3, 15 and 30 minutes and 1, 3 and 6 hours post-dose using a validated assay. All pharmacokinetic blood samples were taken from the arm opposite to the arm used for drug infusion. Samples drawn after placebo treatment were not analyzed.

## RESULTS:

### Pharmacodynamics:

□ The AUEC3-30min GMR for platelet aggregation of aspirin in combination with sugammadex versus aspirin alone was 1.01 and the corresponding two sided 90% lower confidence limit was 0.91, which was above the pre-specified non-inferiority margin of 0.75.

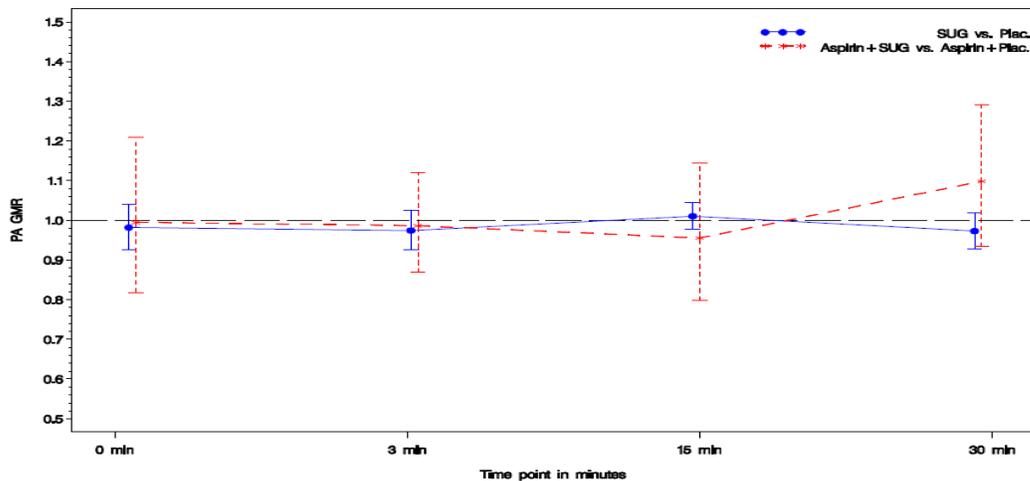
**Table 9 Treatment geometric mean ratios and corresponding lower limits of 90% CI's for the AUEC<sub>3-30min</sub> of PA**

Treatment comparison	Geometric mean ratio	Lower limit of the 90% CI
Aspirin+Sug. vs Aspirin	1.01	0.91
Sug. vs placebo	0.99	0.96
Sug*Aspirin interaction	1.02	0.91

□ The AUEC3-30min GMR of the statistical interaction between sugammadex and aspirin on APTT was 1.01 and the corresponding two sided 90% upper confidence limit was 1.04, which was below the prespecified non-inferiority margin 1.50.

□ The AUEC3-30min GMR for APTT of sugammadex alone versus placebo was 1.06 and the corresponding two sided 90% upper confidence limit was 1.07, which was below the pre-specified non-inferiority margin 1.5.

□ The GMR for bleeding time of aspirin in combination with sugammadex versus aspirin alone was 1.20 and the corresponding two sided 90% upper confidence limit was 1.45, which was below the prespecified non-inferiority margin 1.5.



**Figure 2 Unadjusted geometric mean ratios of sugammadex alone to placebo alone and aspirin with sugammadex combination to aspirin alone, and corresponding 90% CI's of PA, by time point**

### Pharmacokinetics:

□ The plasma concentration profiles of SCH 900616 during the period of pharmacokinetic measurements (3 minutes to 6 hours) after treatment with sugammadex alone and after treatment with sugammadex on aspirin medication background were similar.

### 3.2.3 Synopsis of Clinical Study P05773 or 19.4.333

**Title of Study:** A Single Center, Open-Label Trial In Subjects With Severe Renal Impairment Evaluating The Dialysability Of The Sugammadex (Sch 900616, Org 25969) - Rocuronium Complex (Protocol No. P05773, Formerly 19.4.333)

**Objective(s):** The clinical trial objectives were:

To evaluate the dialysability of the sugammadex-rocuronium complex in subjects with severe renal impairment;

To evaluate the safety of sugammadex in subjects with severe renal impairment;

To evaluate the efficacy of sugammadex in subjects with severe renal impairment.

**Methodology:**

This was a single center, exploratory, open label trial. It was designed to evaluate the dialysability of the sugammadex-rocuronium complex *in vivo* in subjects with severe renal impairment. At day 1, the subjects with severe renal impairment were to receive a single dose of 4.0 mg.kg<sup>-1</sup> sugammadex at 15 minutes after administration of rocuronium. From day 1 on, the dialysability of the sugammadex-rocuronium complex was evaluated. Dialysis was done using the Fresenius 4008H hemodialyzer, with a hemodiafilter standard helixone membrane FX 600. Plasma samples taken 15 minutes and 6 hours after end of dialysis were used for determining rebound by comparison to arterial concentrations just before end of dialysis. For neuromuscular monitoring a TOF-Watch® SX was used.

This study was performed in compliance with good clinical practice, including the archiving of essential documents.

**Number of Subjects:**

In total, six subjects were treated with sugammadex in this study, four males and two females. Their mean age was 76 years. Five subjects were American Society of Anesthesiologists (ASA) class 3, one was ASA class 4.

**Diagnosis and Criteria for Inclusion:**

Males or females of at least 18 years of age; who were ASA class  $\leq 4$ ; had creatinine clearance  $< 30$  mL/min and clinical indication for dialysis; were hospitalized at the intensive care unit (ICU) and scheduled for a (surgical) procedure under general anesthesia requiring neuromuscular relaxation with the use of rocuronium; scheduled for a (surgical) procedure in supine position; and had provided written informed consent (of the legal representative).

**Test Product, Dose, Mode of Administration, Batch No(s):**

Esmeron® (rocuronium bromide); supplied in colorless 10-mL vials containing 100 mg (ie, 10 mg.mL<sup>-1</sup>) of rocuronium bromide (further referred to as rocuronium), batch number CB040. Each subject received an intravenous (IV) single bolus dose of 0.6 mg.kg<sup>-1</sup> rocuronium. Rocuronium was considered trial medication, not test product, in this study.

Sugammadex (investigational medicinal product, IMP); supplied in 5-mL vials containing 500 mg active entity (ie, 100 mg.mL<sup>-1</sup>) of sugammadex, batch numbers CA050 and CB133. At 15 minutes after administration of rocuronium, a single IV bolus dose of 4.0 mg.kg<sup>-1</sup> sugammadex was administered.

The bolus doses of rocuronium and sugammadex were administered within 10 seconds into a fast running infusion. Rocuronium and sugammadex were dosed on the actual body weight.

**Duration of Treatment:** Full recovery from neuromuscular blockade is expected at the end of anesthesia. The trial period consisted of four major periods: a screening period of maximally 7 days, a 1-day peri-procedural period, a post-procedural visit, and a 7-day follow-up period.

**Criteria for Evaluation:**

*Pharmacokinetic variables:* Rocuronium and sugammadex concentrations were measured in plasma and dialysate at several time points before, during and (until 6 hours) after dialysis. The following pharmacokinetic parameters were calculated for each dialysis episode: the dialysis clearance in plasma and dialysate (CL<sub>blood</sub> and CL<sub>dialysate</sub>) and the reduction ratio (RR).

*Safety variables:* (Serious) Adverse Events (from signing informed consent until follow-up visit), Medical Device (near) Incidents (during neuromuscular monitoring), vital signs, ie, blood pressure and heart rate (at screening, before rocuronium, before sugammadex, at 2, 5, 10, and 30 minutes after sugammadex at the post-procedural visit and at the follow-up visit), physical examination (at screening, at the post-procedural visit and at the follow-up visit).

*Other safety variables:* Recurrence of neuromuscular blockade based on the TOF-Watch SX recording or based on clinical evidence (until the post-procedural visit), events due to a possible interaction of sugammadex with an endogenous or exogenous compound other than rocuronium (until the post-procedural visit), pregnancy follow-up (7th post-procedural day) according to regulatory requirements.

*Efficacy variables:* Time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.7, 0.8, and 0.9.

**Statistical Methods:**

Descriptive statistics were presented for the concentrations and pharmacokinetic parameters of rocuronium and sugammadex.

For the primary analysis of the efficacy parameters, the summary statistics of the times from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.7, 0.8 and 0.9, were calculated for the ITT group. The summary statistics included among others geometric mean, 95% confidence interval of the geometric mean, median, minimum and maximum values.

**SUMMARY-CONCLUSIONS:**

**RESULTS:**

**Pharmacokinetics:**

Descriptive statistics of the pharmacokinetic parameters for sugammadex and rocuronium are given in the following table.

	Parameter (unit)	First dialysis (n=5)	Second dialysis (n=6)	Third dialysis (n=4)	Fourth dialysis (n=4)
Sugammadex	Reduction ratio <sup>a</sup>	0.687 (0.113)	0.566 (0.150)	0.516 (0.232)	0.532 (0.144)
	CLblood (mL/min)	79.1 (19.0)	76.5 (19.6)	72.4 (18.4)	83.4 (16.5)
	CLdialysate (mL/min)	63.0 (8.74)	65.1 (7.06)	66.8 (13.2)	Not calculable
Rocuronium	Reduction ratio <sup>a</sup>	0.750 (0.0786)	0.625 (0.144)	0.521 (0.0489)	0.458 (0.115)
	CLblood (mL/min)	80.2 (15.2)	86.3 (14.1)	94.1 (14.8)	94.8 <sup>b</sup> (9.68)
	CLdialysate (mL/min)	75.1 (5.81)	97.2 (32.4)	110 (36.4)	95.3 (19.2)

Presented are arithmetic mean (SD). a: Reduction ratios pertain to an average duration of dialysis of 6 hours. b: n=3.

The concentrations in plasma entering the dialyzer (C<sub>in</sub>) as well as the concentrations in plasma leaving the dialyzer (C<sub>out</sub>) showed a decreasing trend in time for sugammadex as well as rocuronium.

The reduction ratios which reflect the extent of reduction of the concentrations in plasma before dialysis compared to the end of a dialysis episode (average duration: 6 hours) indicate a mean reduction of the plasma concentration of about 70% and 75% during the first episode and mostly more than 50% during the sequential episodes for sugammadex and rocuronium, respectively.

On average blood clearance of sugammadex was approximately 78 mL/min and dialysate clearance 65 mL/min over two to four dialysis episodes.

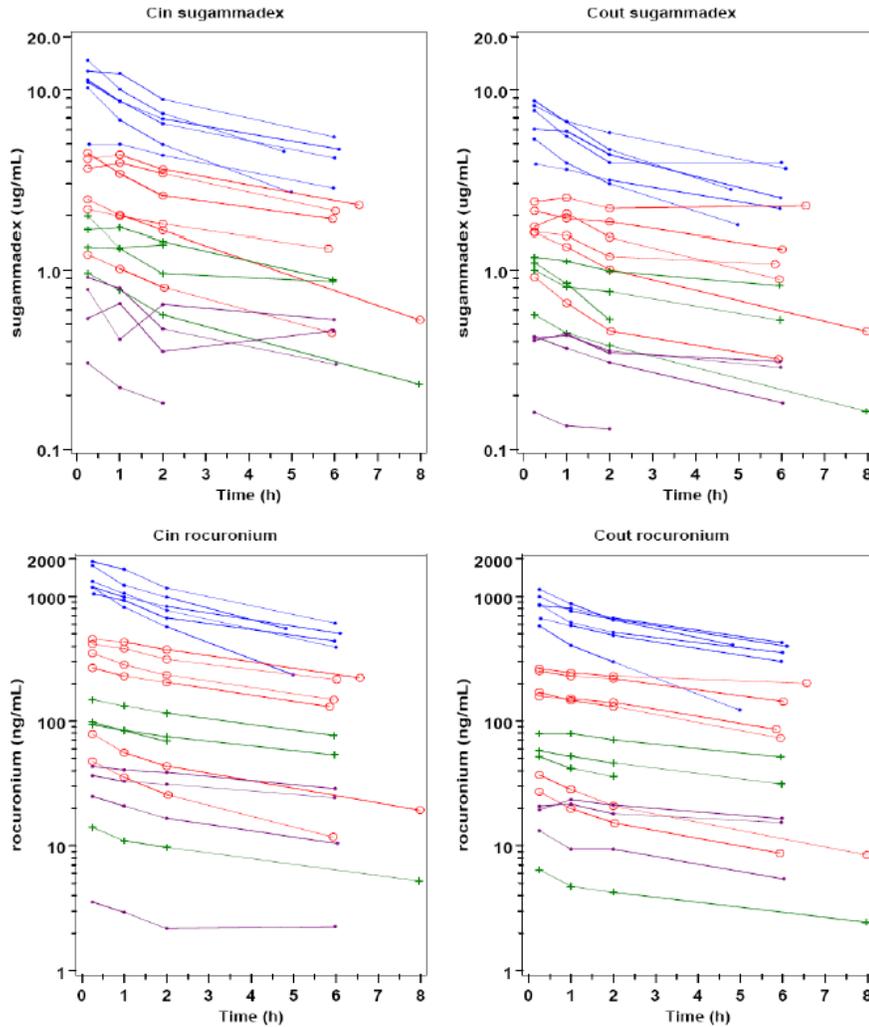
On average blood clearance of rocuronium was approximately 89 mL/min and dialysate clearance 94 mL/min over two to four dialysis episodes.

#### **Effectiveness:**

The times from the start of the administration of sugammadex to recovery of the T4/T1 ratio to 0.9 ranged from 3 min: 26 sec to 9 min: 49 sec, with a median of 4 min: 9 sec. The geometric mean of the time from administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was 5 min: 7 sec (95% CI: 3 min: 4 sec – 8 min: 32 sec). These recovery times seem somewhat prolonged in comparison to results from previous deep block studies.

For none of the subjects a possible interaction of sugammadex with endogenous or with exogenous compounds, other than rocuronium, was reported.

**Figure : Overlay Plots of Concentrations in Plasma Entering the Dialyzer (Cin) and Leaving the Dialyzer (Cout) versus Time for the Sequential Dialysis Episodes**



Each single line represents the measurements of one subject. Blue lines: first dialysis episodes, Red lines: second dialysis episodes, Green lines: third dialysis episodes, Purple lines: fourth dialysis episodes. Note: concentrations pertain to total sugammadex and total rocuronium. Source

### 3.2.4 Synopsis of Clinical Study P05769 (or 19.4.328)

**Title of Study:** A Multi-Center, Parallel-Group, Comparative Trial Evaluating The Efficacy, Pharmacokinetics And Safety Of 4.0 Mg.Kg-1 Sugammadex (Sch900616, Org 25969) Administered At 1-2 Ptc In Subjects With Normal Or Severely Impaired Renal Function (Protocol No. P05769, Formerly 19.4.328)

**Objective(s):**

Primary objective: To show equivalence with respect to the efficacy of sugammadex in subjects with normal or severely impaired renal (SRI) function.

Secondary objectives: To evaluate the safety of sugammadex in subjects with normal or severely impaired renal function, and to compare the pharmacokinetics of sugammadex in subjects with normal or severely impaired renal function.

**Methodology:**

This was an open-label, multicenter, parallel-group, comparative study in subjects with normal and severely impaired renal function. Each subject received an intravenous (IV) single bolus dose of 0.6 mg.kg-1 rocuronium. After this dose, maintenance doses of 0.1 - 0.2 mg.kg-1 rocuronium could be given. After the last dose of rocuronium had been administered, the subject received a single bolus dose of 4.0 mg.kg-1 sugammadex at a target depth of neuromuscular blockade of 1-2 post tetanic counts (PTC). For neuromuscular monitoring a TOFWatch SX was used.

**Number of Subjects:**

In total, 69 subjects were enrolled, but one subject discontinued before treatment with sugammadex. Hence, 68 subjects were treated with sugammadex in this study, 35 subjects with SRI and 33 control subjects.

**Diagnosis and Criteria for Inclusion:**

Males or females of at least 18 years of age; who are ASA class 1-3 (classification of physical status established by the American Society of Anesthesiologists); have creatinine clearance (CLcr) < 30 mL.min-1 and no anticipated clinical indication for high flux hemodialysis during first 24 hours after sugammadex administration (for SRI group) or CLcr ≥ 80 mL.min-1 (for control group); are scheduled for a surgical procedure under general anesthesia with propofol requiring neuromuscular relaxation with the use of rocuronium; are scheduled for a surgical procedure in supine position; and have provided written informed consent.

**Test Product, Dose, Mode of Administration, Batch No(s):**

Esmeron® (rocuronium bromide); supplied in colorless vials containing 100 mg in 10 mL (ie, 10 mg.mL-1) of rocuronium bromide (further referred to as rocuronium), batch numbers CB040 and CB135. Each subject received rocuronium as a single IV intubation dose (0.6 mg.kg-1) and, if necessary, as maintenance bolus dosages of 0.1 to 0.2 mg.kg-1. Rocuronium was considered trial medication, not test product, in this study.

Sugammadex (investigational medicinal product, (IMP)); supplied in vials containing 500 mg active entity in 5 mL (ie, 100 mg.mL-1) of sugammadex, batch numbers CA050 and CB133. After the last dose of rocuronium had been administered, the subject received a single bolus dose of 4.0 mg.kg-1 sugammadex at a target depth of blockade of 1-2 PTC. The bolus doses of sugammadex and rocuronium were administered within 10 seconds into a fast running venous infusion. Sugammadex and rocuronium were dosed on the actual body weight.

**Duration of Treatment:** The study period consisted of four major periods: a screening period of maximally 7 days, a 1-day peri-procedural period, a post-procedural visit, and a follow-up period with 2 visits.

**Criteria for Evaluation:**

*Efficacy variables:* Time from start of administration of sugammadex to recovery of the T4/T1 ratio (ie, ratio of fourth response over first response to TOF stimulation) to 0.9, 0.8 and 0.7.

*Other neuromuscular variable:* Number of PTCs at the time point of administration of sugammadex.

*Safety variables:* Pre-treatment events (from signing informed consent until administration of IMP), (Serious) Adverse Events (from administration of IMP up to end of trial), Medical Device (near) Incidents (during neuromuscular transmission monitoring), laboratory parameters (at screening [CLcr only], pre-rocuronium, at 20 minutes and 4-6 hours post-IMP, at the post-anesthetic visit, and at the follow-up visits), physical examination (at screening, at the post-anesthetic visit, and at the follow-up visits), vital signs (ie, blood pressure and heart rate, at screening, pre-rocuronium, pre-IMP, at 2, 5, 10, and 30 minutes post-IMP, at the post-anesthetic visit, and at the follow-up visits).

*Other safety variables:* Recurrence of neuromuscular blockade based on the TOF-Watch SX recording (ie, a decline in T4/T1 ratio from  $\geq 0.9$  to  $< 0.8$  in at least three consecutive T4/T1 values), clinical evidence of recurrence of neuromuscular blockade or residual neuromuscular blockade (as assessed by routine oxygen saturation by pulse oximetry, breath frequency measurement, etc.), events due to a possible interaction of sugammadex with an endogenous or exogenous compound other than rocuronium, pregnancy follow-up at last visit (28 days after IMP administration) according to regulatory requirements.

*Pharmacokinetic variables:* Sugammadex and rocuronium concentrations in plasma, pharmacokinetic variables clearance (CL), volume of distribution (Vss) and t1/2 for sugammadex.

**Statistical Methods:**

The primary and secondary efficacy variables (times from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.7, 0.8 and 0.9) are analyzed using a non-parametric confidence interval (CI) approach. The estimated difference between the two subject groups with the corresponding two-sided 95% CI is calculated by using the methods of Hodges-Lehmann and Moses. The primary efficacy analysis is performed for the Intent-to-Treat (ITT) group using, in case of missing data, imputed data. Supportive efficacy analyses are performed for the ITT and Per Protocol groups on the complete cases (only available data were used).

Safety data, demographic and baseline characteristics data, and data related to the study-medication (sugammadex and rocuronium) and anesthetics are analyzed using descriptive statistics. No statistical tests are performed for these data. Descriptive statistics were used for sugammadex and rocuronium concentrations in plasma and PK variables for sugammadex

**SUMMARY-CONCLUSIONS:**

**RESULTS:** In total, 68 subjects were treated with sugammadex in this study, 35 subjects with SRI (18 males and 17 females) and 33 control subjects (20 males and 13 females). Their mean age (range) was 57 (27-79) years and 45 (18-73) years in SRI and control

subjects, respectively. The majority of subjects in the SRI group were classified as ASA class 3 (91%), and in the control group as ASA class 1 or 2 (48% and 42%, respectively).

**Efficacy:** The geometric mean time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was 3 min: 25 sec (95% CI: 2 min: 49 sec – 4 min: 08 sec) for the SRI group and 1 min: 52 sec (95% CI: 1 min: 32 sec – 2 min: 18 sec) for the control group.

The estimated median treatment difference in the time from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.9 was 78 seconds with corresponding 95% CI ranging from 36 to 143 seconds for the ITT group, using imputation of missing data. Therefore, the primary endpoint, recovery of the T4/T1 ratio to 0.9, does not meet the pre-specified bounds for equivalence of +/- 60 seconds in subjects with severe renal impairment and normal renal function. Data from the ITT group, using completed cases, and data from the PP group support this statement. With respect to the times from start of administration of sugammadex to recovery of the T4/T1 ratio to 0.7 and 0.8 the estimated median differences (95% CI) were 60 seconds (31-103 seconds) and 68 seconds (36-120 seconds), respectively, for the ITT population using imputation for missing data. The results for the ITT and PP populations were similar, considering both completed cases as well as results using imputed TOF ratios.

#### **Pharmacokinetics:**

Five minutes after sugammadex administration, plasma levels of sugammadex were about 50 µg.mL<sup>-1</sup> for both groups. Thereafter, sugammadex levels decreased faster in the control group than in the SRI group, reflective of the difference in renal function between groups. At 10 h after dosing, median sugammadex levels were about 14 µg.mL<sup>-1</sup> in the SRI group and about 0.5 µg.mL<sup>-1</sup> in the control group.

On follow-up Day 28, nine SRI subjects still had measurable sugammadex levels (ie, above LLOQ of 0.1 µg.mL<sup>-1</sup>) up to 0.252 µg.mL<sup>-1</sup> for eight subjects and 1.95 µg.mL<sup>-1</sup> for one subject.

In SRI patients, clearance of sugammadex was reduced approximately 10-fold, terminal half-life increased 13-fold and volume of distribution (V<sub>ss</sub>) was increased by a factor of approximately 2 compared to the control group.

This resulted in prolonged exposure to sugammadex, with AUC being 8-fold higher, in severely renally impaired patients. Twelve subjects received hemodialysis within the first 48 h after dosing. In general, high flux filters appeared to be more effective for removing sugammadex from circulation, as the median reduction in sugammadex plasma concentrations after a 3-4 hour dialysis for the high flux filter (n=5) was 70.2% and for the low flux filter (n=5) was 29.8%.

**Table: Summary of sugammadex pharmacokinetics following administration in patients with normal renal function and severe renal impairment.**

Protocol No. P05769

		Subject Group	
		SRI	Control
		CLcr <30 mL.min <sup>-1</sup> (n=33)	CLcr ≥80 mL.min <sup>-1</sup> (n=26) <sup>a</sup>
t <sub>1/2</sub> (min)	Mean	1752	136
	CV (%)	113	49
t <sub>1/2,eff</sub> (min)	Mean	1365	70.4
	CV (%)	85	58
AUC <sub>∞</sub> (µg·min·mL <sup>-1</sup> )	Mean	43430	5444
	CV (%)	83	40
dn-AUC <sub>∞</sub> (µg·min·mL <sup>-1</sup> ·mg <sup>-1</sup> )	Mean	151	15.8
	CV (%)	83	33
AUC-extrapolated (%)	Median	6.72	1.13
	Range	0.596-62.3	0.387-20.9
CL (mL·min <sup>-1</sup> )	Mean	6.62	63.3
	CV (%)	83	33
wn-CL (mL·min <sup>-1</sup> ·kg <sup>-1</sup> )	Mean	0.0922	0.736
	CV (%)	84	40
V <sub>ss</sub> (mL)	Mean	13032	6423
	CV (%)	52	49
wn-V <sub>ss</sub> (mL·kg <sup>-1</sup> )	Mean	182	74.8
	CV (%)	49	42
MRT (min)	Mean	1969	102
	CV (%)	85	58

AUC = area under the curve; CLcr = creatinine clearance; CV = coefficient of variance; dn = dose-normalized; wn = weight-normalized; Mean = geometric mean and CV(%) = geometric CV(%); MRT = mean residence time.

a: For two subjects in the control group only three or four measurable sugammadex levels were available, allowing only calculation of AUC<sub>last</sub> (not presented here).

Source Data: Section 14.2.2, Table 4.2.1.

**Table: Dialysis Parameters for Sugammadex in Severe Renally Impaired Subjects Receiving Hemodialysis (All-Subjects-Pharmacokinetically-Evaluable Group)**

Protocol No. P05769

Filter type	Subject	Membrane (machine)	Dialysis half-life (min)	Reduction rate (%)
High flux	101008	Polyflux 140H (Gambro AK 200S)	124	73.2
	101012	Crystal 3400 (Gambro AK 200)	269	46.2
	101014	Helixone FX80 (Gambro AK 200)	137	70.2
	101022	Polyflux 170H (Gambro AK 200S)	100	74.1
	110008	Polyflux 21L (Fresenius 4008)	358	37.2
Low flux	106003	Helixone FX8 (Fresenius 5008)	159	60.1
	106004	Helixone FX8 (Fresenius 4008)	578	25.0
	106014	Helixone FX8 (Fresenius 4008)	248	48.8
	106015	Helixone FX8 (Gambro AK 200)	352	29.8
	108001	Polyflux 14L (Gambro AK 200 ULTRA S)	686	18.0

Source Data: Section 14.2.2, Tables 4.1.2 and 4.1.3

### 3.2.5 Synopsis of Clinical Study 19.4.112

A randomized, open-label, parallel study to assess the potential for re-occurrence of neuromuscular blockade through displacement of rocuronium or vecuronium by diclofenac or flucloxacillin, administered 5 minutes after reversal of neuromuscular block by 2 mg/kg Org 25969 in anesthetized healthy volunteers.

#### **Objectives**

Primary:

- To evaluate reoccurrence of neuromuscular blockade (TOF<0.8) through displacement of rocuronium or vecuronium after administration of diclofenac or flucloxacillin following successful reversal (TOF>0.9) of neuromuscular block by 2 mg/kg sugammadex in anesthetized healthy volunteers

Secondary:

- To evaluate plasma pharmacokinetics of rocuronium, vecuronium and sugammadex
- To evaluate plasma pharmacokinetics of diclofenac or flucloxacillin in case of reoccurrence of neuromuscular block
- To evaluate re-use of sugammadex in case of reoccurrence of neuromuscular block
- To evaluate general safety and tolerability for the four treatment groups

#### **Methodology**

This trial was performed as a single center, randomized, open-label, parallel phase 1 trial during phase 3B study in 24 healthy anesthetized volunteers and consisted of a diclofenac displacement part (Part A) and a flucloxacillin displacement part (Part B).

#### **Number of subjects (total and for each treatment)**

24 subjects (12 men and 12 women) were enrolled, randomized and treated, 3 men and 3 women in each of the 4 treatment groups:

- Treatment A1: 0.6 mg/kg rocuronium, 2.0 mg/kg sugammadex, 75 mg diclofenac
- Treatment A2: 0.1 mg/kg vecuronium, 2.0 mg/kg sugammadex, 75 mg diclofenac
- Treatment B1: 0.6 mg/kg rocuronium, 2.0 mg/kg sugammadex, 2 g flucloxacillin
- Treatment B2: 0.1 mg/kg vecuronium, 2.0 mg/kg sugammadex, 2 g flucloxacillin

#### **Duration of treatment**

Subjects were randomized to one of four treatment groups. All trial medication was administered intravenously.

Subjects' body weight assessed at admission was used for i.v. dosing volume of rocuronium, vecuronium and

sugammadex. Rocuronium, vecuronium and sugammadex were administered as a bolus in 10 seconds into a fast running venous infusion in the forearm.

#### **Reference therapy, dose and mode of administration, batch No.**

Not applicable.

#### **Criteria for evaluation**

##### **Pharmacokinetics:**

Based on the total plasma sugammadex, rocuronium and vecuronium concentrations pharmacokinetic parameters as Area-Under-the-Curve (AUC), terminal half-life (t<sub>1/2</sub>), clearance (CL) and weight-normalized clearance (wn-CL) were calculated.

**Safety:** Clinical safety assessment included physical examination, vital signs (blood pressure, heart rate, respiratory rate and temperature), ECG oxygen saturation by pulse

oximetry (SpO<sub>2</sub>), documentation of (serious) adverse events and laboratory safety parameters (hematology, biochemistry and urinalysis) during the study.

**Special safety measurements (neuromuscular blocking):** Neuromuscular functioning was monitored with acceleromyography (TOF Watch® SX) at the adductor pollicis muscle according to the ‘Schering-Plough NMT Monitoring Guidelines for Clinical Studies, Version 4.0’.

## Summary

After initial successful reversal of rocuronium/vecuronium induced neuromuscular blocking (NMB) by sugammadex, rocuronium or vecuronium could theoretically be displaced from sugammadex by drugs commonly used in anesthesia and a reoccurrence of NMB might be observed, requiring immediate ventilation. In case reoccurrence of NMB in such situations would be unnoticed, this may result in life-threatening situations. Displacement of rocuronium or vecuronium by diclofenac or flucloxacillin after reversal of NM block by sugammadex:

No reoccurrence of neuromuscular blocking was observed after administration of either of the diclofenac/flucloxacillin based on TOF Watch SX® monitoring during anesthesia (i.e. no decline in T<sub>4</sub>/T<sub>1</sub> ratio <0.8 in at least three consecutive TOF values during approximately 90 minutes after administration of displacement drugs). Furthermore, there was no clinical evidence of residual blockade after anesthesia.

Pharmacokinetics:

Individual concentration-versus-time curves for Org 25969, rocuronium and vecuronium showed minor fluctuations in total (complex-bound plus free) concentrations during administration of the potential displacement drugs diclofenac and flucloxacillin, within the typical level of bioanalytical variation.

In Part A, the mean exposure (AUC<sub>0-∞</sub>) to sugammadex was 30.9 µg\*h/mL for the six subjects treated with rocuronium and 33.2 µg\*h/mL for the six subjects treated with vecuronium in combination with an intravenous dose of 75 mg diclofenac (Part A).

The (geometric) mean peak concentration of diclofenac in plasma (Part A) was 7830 ng/mL for the subjects with NMBA rocuronium and 8547 ng/mL for the subjects with NMBA vecuronium at the end of a 15-minute infusion of 75 mg diclofenac (individual maximum value of 10500 ng/mL).

**The sponsor indicated that for the flucloxacillin groups (Part B) no sugammadex PK parameters could be calculated, as no plasma concentrations were available due to interference of flucloxacillin on the Org 25969 assay, which could not be resolved. The concentrations of flucloxacillin were unreliable as flucloxacillin appeared not to be stable in human plasma during storage.**

### 3.2.6 Synopsis of Clinical Study 19.4.113 or P05861

**Title:** An open-label study to assess the safety of re-use of 1.2 mg/kg rocuronium and 0.1 mg/kg vecuronium after reversal of neuromuscular blockade by 4 mg/kg sugammadex in anesthetized healthy volunteers.

#### **Objectives**

This study consisted of two parts, a rocuronium re-use part (Part 1) and a vecuronium re-use part (Part 2). The objectives were defined separately for Part 1 and Part 2.

##### Part 1

###### *Primary:*

- To evaluate the onset of neuromuscular blockade at variable times of re-use of 1.2 mg/kg rocuronium in healthy volunteers

###### *Secondary:*

- To evaluate the duration of action after re-use of 1.2 mg/kg rocuronium
- To evaluate the relation between the pharmacokinetics, onset times and duration of action of neuromuscular blockade after re-use of 1.2 mg/kg rocuronium
- To evaluate the safety and tolerability with respect to re-use of rocuronium

Based on the on-line safety results, one additional secondary objective was added, introduced by Amendment 1:

- To evaluate the onset times of neuromuscular blockade at 5 minutes of re-use of 1.2 mg/kg rocuronium in healthy volunteers

##### Part 2

###### *Primary:*

- To evaluate the onset of neuromuscular blockade at variable times of re-use of 0.1 mg/kg vecuronium in healthy volunteers

###### *Secondary:*

- To evaluate the duration of action after re-use of 0.1 mg/kg vecuronium
- To evaluate the relation between the pharmacokinetics, onset times and duration of action of neuromuscular blockade after re-use of 0.1 mg/kg vecuronium
- To evaluate the safety and tolerability with respect to re-use of vecuronium

#### **Methodology**

This study was performed as a single center, open-label, parallel study in healthy anesthetized volunteers and consisted of two parts with variable times of re-use of rocuronium (Part 1) and variable times of re-use of vecuronium (Part 2) after reversal of sugammadex-induced reversal of neuromuscular blockade. Part 2 was initiated after Part 1.

#### **Number of subjects (total and for each treatment)**

23 subjects (11 men and 12 women) were enrolled; 17 (9 men and 8 women) enrolled in Part 1 and 6 (4 men and 2 women) in Part 2.

- Treatment A (Part 1): 0.6 mg/kg rocuronium, 4.0 mg/kg sugammadex, 1.2 mg/kg rocuronium

- Treatment B (Part 2): 0.1 mg/kg vecuronium, 4.0 mg/kg sugammadex, 0.1 mg/kg vecuronium

#### **Criteria for evaluation**

##### **Pharmacokinetics:**

Based on the sugammadex and rocuronium concentrations in plasma of Part 1, pharmacokinetic parameters as maximum concentration (C<sub>max</sub>), Area-Under-the-Curve

(AUC), terminal half-life ( $t_{1/2}$ ), Clearance (CL) and weight normalized Clearance (wn-CL) were calculated, next to concentration-versus-time plots. For Part 2 only concentration-versus-time plots were made.

**Safety:** Clinical safety assessment included physical examination, vital signs (blood pressure, heart rate, respiratory rate and temperature), ECG, oxygen saturation by pulse oximetry (SpO<sub>2</sub>), documentation of (serious) adverse events and laboratory safety parameters (hematology, biochemistry and urinalysis) during the study.

**Special safety measurements (neuromuscular blocking):** Neuromuscular functioning was monitored with acceleromyography (TOF Watch® SX) at the adductor pollicis muscle according to the Schering-Plough 'NMT Monitoring Guidelines for Clinical Studies. Schering-Plough provided guidance on the set-up of the TOF Watch® SX. The monitored arm was immobilized with an arm board. Following the induction of anesthesia the TOF Watch® SX was stabilized and calibrated. Repetitive Train of Four (TOF) stimulation was applied by the TOF Watch® SX every 15 seconds at the ulnar nerve until the end of anesthesia. Neuromuscular data were collected via a transducer affixed to the top of the thumb and transferred on-line via an interface to a computer by means of the TOF Watch® SX monitoring program.

Evaluation of the neuromuscular data:

After the treatment of each subject, the file containing the TOF Watch® SX data was sent as soon as possible to Schering-Plough for quality checks of the TOF Watch® SX registration and adherence to the protocol and guidelines. Deviations from the guidelines were communicated to the site for correction or explanation.

### **Summary**

The current study was conducted to obtain information about re-use of rocuronium and vecuronium after sugammadex administration in a clinical setting.

Overall, 16 of 17 subjects enrolled in Part 1 received [0.6 mg/kg rocuronium – 4 mg/kg sugammadex - 1.2 mg/kg rocuronium] and all six subjects enrolled in Part 2 received [0.1 mg/kg vecuronium - 4 mg/kg sugammadex - 0.1 mg/kg vecuronium]. A total of 22 subjects were included in the safety analysis.

Neuromuscular monitoring:

Neuromuscular analysis was performed for both the ASE group and the PP group. In the rocuronium re-use part of this study 16 of the 17 enrolled subjects were included in ASE and PP group. For vecuronium re-use, all six enrolled subjects were included in the ASE group and four of the six enrolled subjects were included in the PP group.

A relationship between the NMBA re-use time point after sugammadex administration and neuromuscular onset times as well as the clinical duration was observed.

#### *Rocuronium:*

After re-use of rocuronium, subjects showed fast onset times of neuromuscular block already after the shortest reuse time at 5 minutes following sugammadex reversal. For the 6 subjects with rocuronium re-use at 5 min, NMB onset time ranged from 1.92 to 4.72 min (arithmetic mean: 3.06). For later re-use time points (30 min onwards) NMB onset times decreased, ranging between 1.23 and 1.43 min. Clinical duration of the NMB among the 6 subjects with rocuronium re-use time-point at 5 minutes, ranged from 17.8-41.0 min (arithmetic mean 25.3 minutes) and was around 30 min and longer for subjects with rocuronium re-use time points from 22 minutes (N=7) onwards.

**Table 14 Part 1: Individual onset times of NMB relative to rocuronium administration and NMB duration (lowest T<sub>1</sub>-25% recovery), All-Subject-Evaluable (ASE) group = Per-Protocol (PP) group, N=16**

Relative re-use time-points <sup>1</sup> [mm:ss]	Subject Number	Relative NMB onset time <sup>2</sup> [min]	Clinical duration of NMB <sup>3</sup> [min]
59:59	101001	1.32	43.6
45:00	101007	1.23	46.0
30:00	101002	1.43	29.9
27:30	101012	2.60	34.4
25:00	101006	2.05	37.3
22:30	101011	3.83	29.1
20:00	101003	3.15	21.4
15:00	101008	2.80	26.6
09:57	101004	3.48	19.7
07:30	101010	2.35	24.6
05:00	101005	3.57	17.8
05:00	101013	2.73	22.7
05:00	101014 <sup>4</sup>	2.75	41.0
05:00	101016	1.92	22.4
05:00	101017	2.68	17.7
04:59	101015	4.72	30.0

Note: Subject 101009 was not dosed with sugammadex due to technical issues with the monitoring of neuromuscular transmission, which prevented adequate timing of sugammadex dosing. Subsequently, no rocuronium re-use took place.

<sup>1</sup> relative to start of sugammadex administration

<sup>2</sup> relative to start of rocuronium administration

<sup>3</sup> time to recovery to T<sub>1</sub>=25%

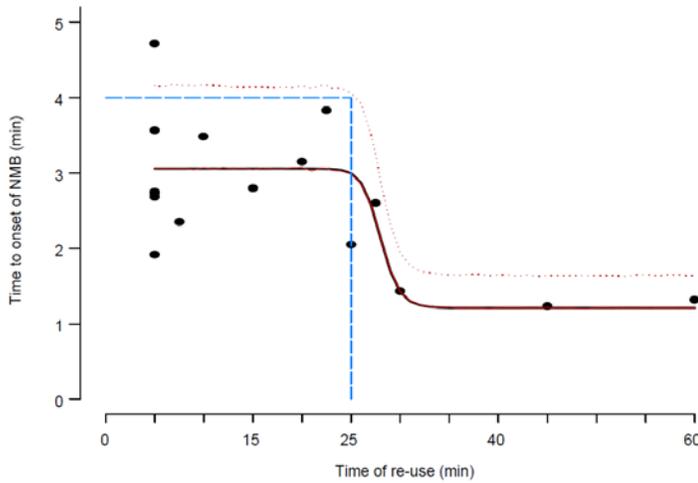
<sup>4</sup> Subject 101014 received a second i.v. dose of sugammadex (2 mg/kg) because recovery times after re-use of rocuronium exceeded 2 hours.

Source: Table 14.3.7-1

Simulations showed that if re-use of 1.2 mg/kg rocuronium is initiated >25 minutes after 4 mg/kg sugammadex reversal, NMB onset times are achieved which are with 95% confidence below 4 minutes. Moreover, if in this setting re-use of 1.2 mg/kg rocuronium is initiated <25 minutes after reversal of sugammadex, NMB onset times are with 95% confidence below 4.25 minutes. Furthermore, subgroup analysis, performed in the six subjects with rocuronium re-use time-point 5 minutes after sugammadex, revealed that complete neuromuscular block can be expected to be achieved within 4 minutes with 95% confidence, which is about 1 minute above the geometric mean onset time of 2.94 minutes observed in this study.

The estimated geometric mean duration of NMB was 24.1 minutes and the lower limit of the 95% C.I. was 17.2 minutes for subjects receiving 1.2 mg/kg rocuronium 5 minutes after reversal with 4 mg/kg sugammadex.

**Figure 7** Simulations with 5000 replicates from the final rocuronium model to determine the mean time to onset of NMB (red solid line) and one-sided upper 95% confidence limits of the individual predictions (red dotted line)



*Vecuronium:*

In Part 2, six subjects received the second dose of vecuronium with re-use time points between 2 hours and 5 hours after sugammadex administration. A complete neuromuscular block with onset times below 3 minutes was only observed for vecuronium re-use times from 3.5 hours onwards. **No complete NMB occurred after vecuronium re-use at 2 hours and 2.5 hours after sugammadex administration. Therefore, it was decided not to proceed with earlier time-points of re-use of vecuronium.** Onset times of neuromuscular block at re-use times  $\geq 3.5$  hours ranged from 1.68 minutes (re-use at 3.5 h) to 3.15 minutes (re-use at 4 h) with NMB durations between 24.2 minutes (reuse at 4 h) and 31.4 minutes.

**Table 15** Part 2: Individual onset times of NMB relative to vecuronium administration and NMB duration (lowest  $T_1$ -25% recovery), Per-Protocol (PP) group, N=4 and All-Subject-Evaluable (ASE) group, N=6

Relative re-use time-points <sup>1</sup> [hh:mm]	Subject Number	Relative NMB onset time-point <sup>2</sup> [min]	Duration of NMB <sup>3</sup> [min]
05:00	101101	2.03	31.3
04:00	101104	3.15	24.2
03:30	101105	1.68	31.4
03:00	101103	7.35	20.6
Subjects excluded from the Per-Protocol group (no complete neuromuscular block appeared)			
02:30	101106	5.68	Not possible
02:00	101102	5.45	10.5

Subjects 101102 and Subject 101106 were excluded from the Per-Protocol (PP) group because no complete neuromuscular block ( $T_1=0\%$ ) occurred after re-use of vecuronium.

<sup>1</sup> relative to start of sugammadex administration

<sup>2</sup> relative to start of vecuronium administration

<sup>3</sup> time to recovery to  $T_1=25\%$

Source: Table 14.3.7-1

**Pharmacokinetics:**

After intravenous administration of 4 mg/kg sugammadex at 1-2 PTC after 0.6 mg/kg rocuronium, the mean exposure ( $AUC_{0-\infty}$ ) to sugammadex was comparable between the five subjects with re-use time 5 minutes (60.1  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) and all subjects, including those with re-use times up to 1 hour (61.7  $\mu\text{g}\cdot\text{h}/\text{mL}$ ). This finding, supported by the individual data, indicates that the timing of rocuronium re-use after sugammadex reversal has limited influence on total sugammadex exposure.

In subjects with re-use times of rocuronium varying between 7.5 and 60 min. after successful sugammadex reversal, some temporary flattening and/or a slight increase in (total) sugammadex concentration was observed just after re-use of rocuronium, followed by a further decrease. For the rocuronium concentrations the same flattening/increasing could be observed after administration of sugammadex, which can be explained by a distribution effect, and has also previously been reported in trials applying this combination.

Also for Part 2 with re-use times of vecuronium varying between 2 and 5 hours after sugammadex, a slight increase in sugammadex concentration just after re-use of vecuronium and a temporary slowdown in decrease of sugammadex concentration could be observed.

**Conclusion:**

Rocuronium: Re-use of 1.2 mg/kg rocuronium initiated >25 minutes after 4 mg/kg sugammadex reversal resulted in NMB onset times <4 minutes. Moreover, when rocuronium re-use is initiated  $\leq 25$  minutes after sugammadex reversal, NMB onset times <4.25 minutes are achieved. In this setting, the average duration of NMB was 25.3 minutes (range 18-41 min).

Vecuronium: Following re-use of 0.1 mg/kg vecuronium, complete neuromuscular block with adequate onset times (<3 minutes) was only observed 3.5 hours after 4 mg/kg sugammadex reversal onwards with NMB durations between 24.2 and 31.4 minutes.

### 3.2.7 Synopsis of Clinical Study P05997

**Title of Study:** An Open Label Single Dose Pharmacokinetic Study with Sugammadex in Chinese Healthy Volunteers.

**Objectives:** The primary objective was to determine pharmacokinetics after single dose intravenous (iv) administration of 16 mg/kg of sugammadex (SCH 900616) in Chinese healthy male and female volunteers.

The secondary objective was to evaluate of the safety of sugammadex in Chinese healthy male and female volunteers.

**Methodology:** This study was an open label, single dose, single site study in Chinese healthy volunteers, conducted in conformance with Good Clinical Practices. Subjects were given an intravenous dose of 16 mg/kg sugammadex based on actual body weight as a 10 second bolus infusion in the forearm. Blood samples for PK evaluation were to be collected at pre-infusion (0 hour) and 2, 3, 5, 10, 15, 20, 30, 60 minutes, and 2, 4, 6, 8, 12, 18, 24 hours post infusion.

**Number of Subjects:** A total of 12 subjects was planned and enrolled in this study. All of the 12 subjects completed this study.

**Diagnosis and Criteria for Inclusion:** Chinese healthy volunteers, age between 18 and 45 with a Body Mass Index (BMI) between 18 and 30 kg/m<sup>2</sup> were selected for this study.

**Criteria for Evaluation:**

- **Pharmacokinetics (PK):** Plasma concentrations of sugammadex were measured up to 24 hours after drug administration for calculation of PK parameters: C<sub>max</sub>, t<sub>max</sub>, AUC, t<sub>1/2</sub>, V and CL.
- **Safety:** Vital signs, clinical labs, ECGs and AEs.

**Results:**

**Pharmacokinetics (PK):**

Geometric mean and CV (%) (for t<sub>max</sub>: median, min-max) of the main sugammadex PK parameters are presented in the table below.

Parameter (unit)		Overall	Female	Male
		(n=12)	(n=6)	(n=6)
t <sub>max</sub> (min)	Median	2.5	3.0	2.0
	Min-Max	2.0-3.0	2.0-3.0	2.0-3.0
C <sub>max</sub> (µg/mL)	Mean	197	182	214
	CV (%)	21.7	10.6	27.7
t <sub>1/2</sub> (min)	Mean	145	152	139
	CV (%)	17.9	18.6	17.7
AUC <sub>∞</sub> (µg·min/mL)	Mean	8971	8956	8986
	CV (%)	13.8	16.4	12.2
CL (mL/min)	Mean	99.7	95.8	104
	CV (%)	12.6	12.4	12.5
wn-CL (mL/min/kg)	Mean	1.78	1.79	1.78
	CV (%)	13.8	16.4	12.2
V <sub>ss</sub> (L)	Mean	10.5	10.3	10.7
	CV (%)	9.03	7.44	10.7
wn-V <sub>ss</sub> (mL/kg)	Mean	188	193	184
	CV (%)	8.68	8.92	8.65

There were no gender-related differences in the pharmacokinetics of sugammadex in Chinese subjects.

**Safety:** A total of 3 (25%) subjects reported at least one AE (i.e. in all cases mild dysgeusia) after administration of 16 mg/kg sugammadex. There were no deaths and no other serious and/or significant AEs were reported. In general, no clinically significant changes occurred in blood chemistry or hematological parameters, vital signs, or ECGs.

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/s/  
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SRIKANTH C NALLANI  
08/23/2013

YUN XU  
08/23/2013

Dr. Atul Bhattaram was included in all discussions with regard to the review and labeling changes. However, he cannot sign it since he is out of US now.

## **CLINICAL PHARMACOLOGY REVIEW**

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NDA	22-225
Submission Dates	10/30/2007; 11/27/2007; 2/25/2008
Proposed Brand Name	(b) (4)
Generic Name	Sugammadex Sodium (Org 25969)
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Sponsor	Organon (a part of Schering-Plough)
Relevant IND	IND 68,029
Type of Submission; Code	505 (b)(1); 1P
Formulation; Strength(s)	Injection Solution; 100 mg/mL
Proposed Indications	Routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium and for immediate reversal of neuromuscular blockade at 3 min after administration of rocuronium
Proposed Dosing Regimen	Routine Reversal: <ul style="list-style-type: none"><li>• A dose of 4.0 mg/kg (b) (4)™ is recommended if recovery has reached 1-2 post tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.</li><li>• A dose of 2.0 mg/kg (b) (4)™ is only recommended if spontaneous recovery has reached the reappearance of T2 (shallow blockade) following rocuronium or vecuronium induced blockade.</li></ul> Immediate Reversal: <ul style="list-style-type: none"><li>• If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4)™ is recommended.</li></ul>

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# 1 EXECUTIVE SUMMARY

Sugammadex sodium (also known as Organon 25969) is a new molecular entity. Structurally it is a modified  $\gamma$ -cyclodextrin which is designed to form a 1:1 inclusion complex with the neuromuscular blocking molecule, rocuronium and vecuronium. Sequestration of the free neuromuscular blocker results in reversal of the neuromuscular blockade (NMB).

The rationale for reversal of neuromuscular blockade is prevention of prolonged muscular weakness and its clinical consequences, including respiratory insufficiency and aspiration. Currently available reversal agents act through inhibition of acetyl cholinesterase. Their dose-response curve plateaus when the enzyme is fully inhibited, they are inactive when all receptors are blocked (no twitch following electrical stimulation of any type), and their half-life may be less than the neuromuscular blocking agent, leading to recurrence of neuromuscular blockade. There are clinically significant side effects attributable to the pharmacologic properties of the reversal agents as well as to the muscarinic receptor antagonists co-administered to counteract these side effects. Sugammadex, with its novel mechanism, may be devoided of these side effects.

The applicant, Organon, is seeking two indications: a) routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and b) immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

Sugammadex, if approved, will be the first in a new class of NMB reversing agent. An AC meeting was held on March 11, 2008.

## 1.1 Recommendations

From a Clinical Pharmacology point of view, the application is acceptable provided that a mutually agreeable is reached between the Agency and the Sponsor regarding the labeling language in the package insert.

## 1.2 Phase 4 Commitments

The following post marketing requirements should be carried out by the Sponsor for better understanding of the use of this product in hemodialysis and hepatic impairment patients;

1. Carry out additional study in hemodialysis patients to determine conclusively if sugammadex and rocuronium could be removed in vivo by high flux filter.
2. Carry out a study in hepatic impairment patients assessing the PK and PD of rocuronium and vecuronium when Sugammadex is administered. This will provide concrete data in terms of the delay in recovery of neuromuscular blockade induced by rocuronium or vecuronium by sugammadex in hepatic impairment subjects.

### 1.3 Summary of Important Clinical Pharmacology Findings

Sugammadex is a modified  $\gamma$ -cyclodextrin that shows high affinity to rocuronium ( $K_A$   $1.8 \times 10^6$  mol<sup>-1</sup>) and vecuronium ( $K_A$   $5.7 \times 10^5$  mol<sup>-1</sup>). The molecular weight of sugammadex is about 2178. It does not bind to plasma protein or erythrocytes *in vitro*. The final product, (b) (4)™, contains a low percentage (up to 7%) of the mono OH-derivative of sugammadex, Org 48032. Org 48302 has similar pharmacological activity and PK characteristics as sugammadex.

(b) (4) is intended for a single intravenous bolus injection. The clinical development program for (b) (4) was conducted in Europe, the U.S., Canada, and Japan and is comprised of 30 Phase 1, 2, and 3 clinical studies in support of this NDA. In addition, there are several *in vitro* study reports included to characterize protein binding, *in vitro* dialysis and interference with clinical chemistry assays of sugammadex.

The pharmacokinetics (PK) of sugammadex has been characterized in subjects who were not anesthetized and who were anesthetized after a single dose. The proposed doses for reversal of NMB were 2, 4, and 16 mg/kg based on the depth of NMB. The highest dose studied in healthy subjects was 96 mg/kg. PK was also characterized in the presence of rocuronium or vecuronium. The bioanalytical methods could not distinguish free sugammadex or rocuronium/vecuronium from those in complex with each other. Therefore, PK parameters obtained were based on total amount present in plasma or urine. Based on the molecular weight differences, a 2 mg/kg of sugammadex is approximately at the equal molar dose as 0.6 mg/kg of rocuronium or vecuronium.

The clinical pharmacology characteristics of sugammadex observed in these studies are summarized in the following sections.

#### **Pharmacokinetics (Distribution, Metabolism, Excretion)**

Human PK studies showed that clearance of sugammadex ranges from 97-138 mL/min, similar to the glomerular filtration rate in healthy humans. PK is approximately dose-proportional at the proposed doses (2 to 16 mg/kg).

The volume of distribution of sugammadex is 12-15 L indicating some extravascular distribution in the body.

The results from a single IV dose study of 4 mg/kg [<sup>14</sup>C] sugammadex given to 6 healthy male subjects indicate that the metabolism of sugammadex is limited and the compound is mainly eliminated unchanged via renal excretion. On an average, more than 90% of sugammadex was recovered in urine within 24 hours. Other PK studies also showed that 65-97% of the dose was recovered in urine. The differences in urine excretion percentage may be partly due to error associated with urine sample collection.

#### **Special Populations**

The effects of rocuronium, vecuronium, anesthetic states, renal impairment, age, gender, body weight, or race on sugammadex pharmacokinetics were assessed in Phase 1, 2, and 3 studies. The presence of rocuronium or vecuronium, or anesthetic state showed little effect on PK of

sugammadex. The intrinsic factors, gender, weight, or race (Japanese vs. Caucasian), showed little effect on sugammadex PK.

**Renal Impairment:** As expected, renal function affects sugammadex PK. Increased exposure (AUC) and terminal half-life (about 16-fold) was observed in patients with severe renal impairment (CLcr < 30 mL/min including 9 patients who were on hemodialysis) vs. patients with normal renal function (CLcr ≥ 80 mL/min) receiving 2 mg/kg sugammadex following NMB induced by 0.6 mg/kg rocuronium (shallow blockade) (Study 19.4.304). Sugammadex and rocuronium complex was not efficiently removed from plasma using low flux filter (5 subjects), consistent with the *in vitro* dialysis finding. High flux filter showed a variable effectiveness for removing sugammadex and rocuronium (4 subjects) while *in vitro* dialysis study suggested that high flux filter could efficiently remove sugammadex and rocuronium.

In the same study, it was found that renal impairment also affected PK of rocuronium (in the presence of sugammadex) but to a lesser extent. AUC and terminal half-life increased about 3 to 4-fold. The data indicate that rocuronium, even in the presence of excess sugammadex, can still be cleared hepatically to a substantial degree.

Efficacy evaluation based on a mean time from start of administration of sugammadex to recovery of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9 suggested that efficacy is comparable between the two groups: 2 minutes for the renally impaired subjects, and 1 min:39 sec for the control subjects.

The Sponsor concluded that there were no appreciable differences in terms of safety between the two groups. Per the discussion, this reviewer had with Dr. Art Simone (Clinical reviewer for safety assessment of Sugammadex), his Clinical review for safety will contain an in depth assessment of this issue.

PK and safety of sugammadex was not studied in young adult patients with mild or moderate renal impairment patients. Effect of mild or moderate renal impairment on sugammadex PK and PD was obtained from a study in elderly patients (Study 19.4.305). The study suggested that renal impairment is the main covariate that affected sugammadex PK and there was no additional effect from age.

Based on the fact that sugammadex is mainly eliminated unchanged in urine, a proportional relationship of PK with CLcr may be expected. Increase in AUC and half-life in mild or moderate renal impairment patients is expected as compared to patients with normal renal function. The Sponsor proposes no dose adjustment for mild or moderate renal impairment patients and they strongly discourage usage of sugammadex in severe renal impairment patients. We recommend contraindication in patients with severe renal impairment for the immediate reversal indication if the dose of 16 mg/kg is approved because of lack of safety database to support a 16-fold increase in AUC (equivalent to a dose of 256 mg/kg in normal patients).

PK and safety of sugammadex in hemodialysis patients need further investigation.

PK of sugammadex has not been evaluated in patients with renal impairment whose NMB are induced by vecuronium. Because vecuronium or rocuronium shows little effect on sugammadex

PK, the studies conducted with rocuronium-induced NMB (Study 19.4.304) may be extrapolable to vecuronium-induced NMB.

**Age:** Increased exposure of sugammadex was observed with increased age which is attributed to decrease in renal function. There was no additional effect for sugammadex PK from age. The mean time from administration of Org 25969 to recovery of the  $T_4/T_1$  ratio to 0.9 was 2 min:16 sec (adult group) and 2 min:56 sec (geriatric group,  $\geq 65$  years), respectively. The recovery time in patients who are 75 years and older (3 min:36 sec) is slightly longer than other age groups even though exposure of sugammadex exposure was higher in elderly.

**Gender:** The PK of sugammadex is similar in female and male subjects.

**Race:** The PK of sugammadex is similar in Caucasian and Japanese subjects. Numbers of other races including African American is too small for meaningful analysis.

**Hepatic Impairment:** No study has been conducted in patients with hepatic impairment because sugammadex is mainly eliminated in the kidney. However, hepatic impairment would affect PK of rocuronium. The Sponsor applied the population PK/PD interaction model with rocuronium to simulate the reversal of rocuronium-induced neuromuscular blockade (NMB) by sugammadex in hepatic impairment patients. A prolongation of recovery time in hepatic impaired patients was predicted. Refer to PM review (Appendix 4.3) for details.

### **Drug-Drug Interactions**

*In vitro* metabolism or transport study for sugammadex has not been conducted. Drug interactions via CYP inhibition or induction are not anticipated. Sugammadex is not likely to be metabolized by CYP enzymes and susceptible to drug interaction with CYP inhibitors or inducers because of large molecular size and 3-dimensional structure of sugammadex, limited metabolism observed *in vivo*, and limited liver distribution as suggested by the animal studies. Sugammadex is also not likely to affect other drugs' metabolism as an inhibitor or inducer because of limited liver distribution and single-use nature.

However, transport-based drug-drug interaction cannot be ruled out. Sugammadex may affect other drugs' transport in the kidney. Transport-based drug-drug interactions were not studied.

Drug interaction of sugammadex and rocuronium/vecuronium was evaluated based on PK assessments from various studies. Because of encapsulation nature of cyclodextrin, sugammadex may "trap" drugs other than rocuronium or vecuronium that have high affinity to sugammadex. The Sponsor evaluated potential drug-drug interactions based on complexation with sugammadex using a strategy that comprises of in-vitro assessments, preclinical assessment, and PK/PD modeling.

### ***Effects of Other Drugs on Sugammadex***

**Rocuronium and Vecuronium:** The presence of rocuronium or vecuronium showed little effect on PK of sugammadex.

**Other Drugs:** The displacement interaction potential caused by the presence of a third drug either before or after sugammadex administration was evaluated using a PK/PD model. Three major kinds of drugs were evaluated by the model: drugs commonly used in anesthesia; drugs that are most frequently prescribed; and steroidal molecules. The brief description of the model is described in the modeling section. Toremifene, flucloxacillin and fusidic acid were identified to carry a risk of displacement interaction with sugammadex. Only toremifene is currently marketed in the U.S. The label will need to include cautionary languages for drugs with steroidal structures. Refer to PM review (Appendix 4.3) for details.

### ***Effects of Sugammadex on Other Drugs***

**Rocuronium and Vecuronium:** Sugammadex affects PK of rocuronium and vecuronium as indicated by increased plasma concentrations, decreased elimination half-life, and decreased total clearance. With increased doses of sugammadex, increased amount of rocuronium was recovered in urine. *In vitro* assay also suggest that sugammadex decreases plasma protein binding of rocuronium or vecuronium.

**Other Drugs:** The capturing interaction potential caused by complexation between a third drug and sugammadex and thus reduces the clinical effect of the third drug was evaluated using the PK/PD model. A clinically relevant interaction cannot be ruled out for hormonal contraceptives.

### **QTc Prolongation Potential (QT-IRT)**

Results from a thorough QT study, Study 19.4.109, showed that although there was a concentration-dependent increase in QTcI, the mean increase in QTcI for the supratherapeutic dose (32 mg/kg) was below 10 msec, the regulatory threshold for concern. This dose gives 2-fold higher peak concentrations than the dose recommended for immediate reversal, 16 mg/kg, and 8- and 16-fold higher peak concentrations of the doses recommended for routine reversal. Refer to QT-IRT consult review for details.

### **Pharmacodynamics**

The reversal of rocuronium- or vecuronium-induced NMB by sugammadex is based on its capability to form an inclusion complex with rocuronium or vecuronium. Upon complexation, the amount of rocuronium or vecuronium available to bind to receptors in the neuromuscular junction is reduced, resulting in reversal of the blockade. Time to recovery of T<sub>4</sub>:T<sub>1</sub> to 0.9 was used as the pharmacodynamic endpoint.

### **Exposure-Response/ Dose Selection**

Several Phase 2 studies were conducted for dose selection for the Phase 3 studies. A clear dose-response relationship was observed in all the studies. The doses selected by the Sponsor corresponding with reversal of various depth of NMB seem acceptable.

### **PK/PD Modeling/Simulation**

A mechanism-based population PK/PD model was used to determine prognostic factors such as body weight, age, renal function, etc that may affect the clinical response and simulate conditions that were not studied clinically. For example, the reversal of rocuronium-induced NMB by sugammadex in subjects with hepatic impairment; onset time following re-

administration of rocuronium shortly after the reversal of a previous NMB by sugammadex; and potential displacement drug interactions with a third drug. Refer to PM review (Appendix 4.3) for details.

We in general agree with the modeling and simulation approach to understand PK and PD of sugammadex and rocuronium or vecuronium under the above-mentioned various scenarios.

A Clinical Pharmacology briefing (Required Office-Level) was held on May 30, 2008.

## 2 QUESTION BASED REVIEW

(Reviewer's Note: Sugammadex and Org 25969 are used interchangeably in the review.

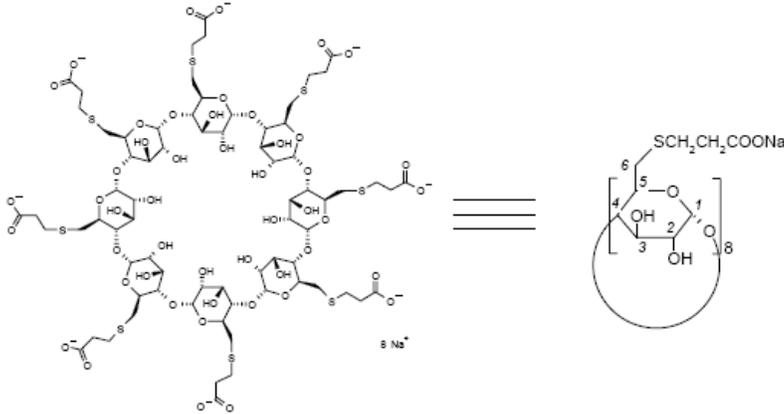
(b)(4)™ is the proposed tradename. BRIDION is an earlier proposed tradename.)

### 2.1 General Attributes

#### 2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Sugammadex is a modified  $\gamma$ -cyclodextrin (Table 2.1.1.1). (b)(4) drug product contains both sugammadex and the related  $\gamma$ -cyclodextrin compound Org 48302 (Table 2.1.1.2) that is present at concentrations up to 7% in the drug substance. (b)(4) is supplied as 100 mg/mL ready-to-use solution for injection and there are 2 vial sizes, 2 mL and 5 mL. The composition of the formulation is listed in Section 2.5.1.

**Table 2.1.1.1. Physico-Chemical Properties of Sugammadex.**

Drug Name	Sugammadex	
Chemical Name	6 <sup>A</sup> ,6 <sup>B</sup> ,6 <sup>C</sup> ,6 <sup>D</sup> ,6 <sup>E</sup> ,6 <sup>F</sup> ,6 <sup>G</sup> ,6 <sup>H</sup> –octakis- S-(2-carboxyethyl) - 6 <sup>A</sup> ,6 <sup>B</sup> ,6 <sup>C</sup> ,6 <sup>D</sup> ,6 <sup>E</sup> ,6 <sup>F</sup> ,6 <sup>G</sup> ,6 <sup>H</sup> – octathio- $\gamma$ -cyclodextrin octasodium salt	
Structure and Molecular Formula		
Molecular Weight	C <sub>72</sub> H <sub>104</sub> O <sub>48</sub> S <sub>8</sub> Na <sub>8</sub> 2178.01	
LogP	Very low	
Appearance	White to off-white powder to grainy powder	
Melting Range	Has no melting point/range. It decomposes at approximately 220°C.	
Solubility	Water (mg/mL)	≥ 500
	Phosphate buffer pH 7.4 (mg/mL)	≥ 500
	Ethanol (mg/mL)	0.65

**Table 2.1.1.2. Physico-Chemical Properties of Org 48302.**

Drug Name	Org 48302
Chemical Name	(b) (4)
Structure and Molecular Formula	(b) (4)
Molecular Weight	2067.9
LogP	(b) (4)
Appearance	(b) (4)
Melting Range	(b) (4)
Solubility	(b) (4)

Org 48302 has comparable pharmacological activity and PK characteristics as Org 25969. (b) (4)  
(b) (4) was implemented from clinical batch CY039 onwards.

**2.1.2 What is the proposed mechanism of drug action and therapeutic indications?**

**Mechanism of Action:** (b) (4)™ (sugammadex sodium) Injection is a modified gamma cyclodextrin. It forms a complex with the neuromuscular blocking agents, rocuronium and vecuronium, and it reduces the amount of neuromuscular blocking agent available to bind to nicotinic receptors in the neuromuscular junction. This results in the reversal of neuromuscular blockade (NMB) induced by rocuronium and vecuronium.

The tight binding between the cyclodextrin and rocuronium ( $K_A 1.8 \times 10^6 \text{ mol}^{-1}$ ) or vecuronium ( $K_A 5.7 \times 10^5 \text{ mol}^{-1}$ ) is a result of van der Waal's forces, hydrophobic and electrostatic interactions.

**Proposed Indications:** Routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium, and immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium.

**2.1.3 What are the proposed dosage recommendations by the Sponsor and route of administration for the proposed indication?**

***Routine Reversal:***

- A dose of 2.0 mg/kg (b) (4)™ is only recommended if spontaneous recovery has reached the reappearance of T<sub>2</sub> (shallow blockade) following rocuronium or vecuronium induced blockade.
- A dose of 4.0 mg/kg (b) (4)™ is recommended if recovery has reached 1-2 post tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.

***Immediate Reversal:***

If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4)™ is recommended.

(b) (4)™ is administered as a single bolus injection. The injection should be administered as a single dose within 10 seconds.

**2.2 General Clinical Pharmacology**

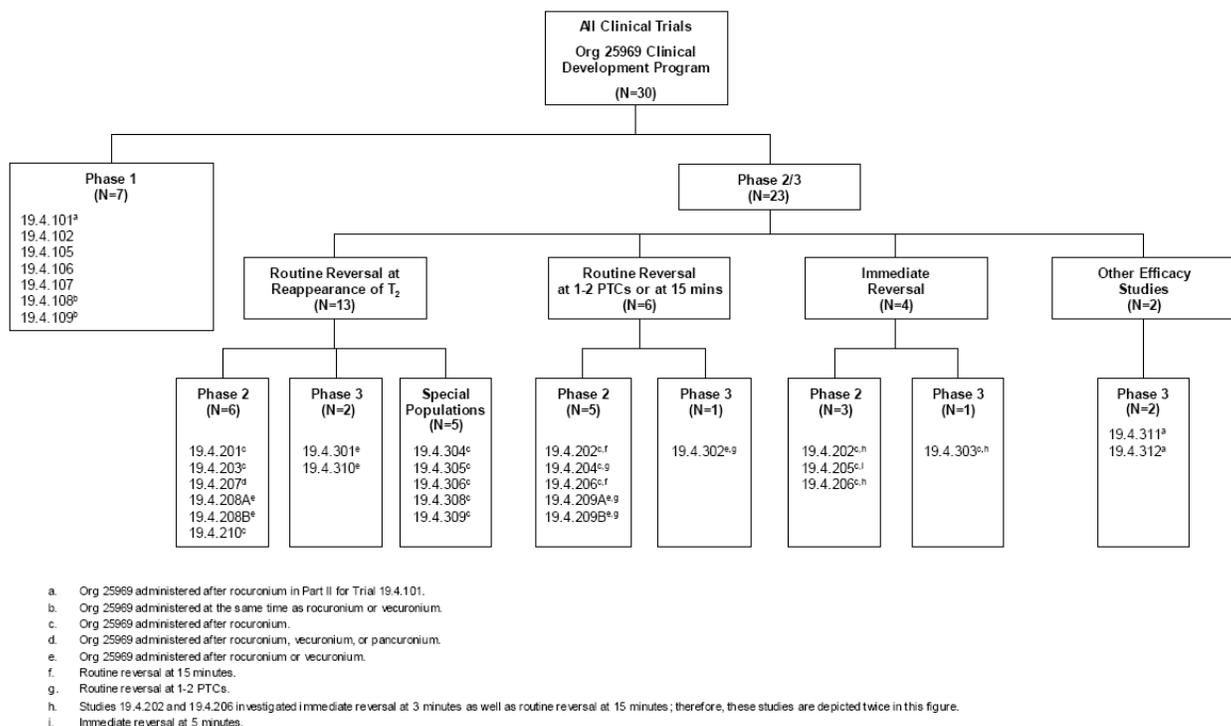
**2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?**

The sugammadex clinical development program consisted of 30 clinical trials (Figure 2.2.1.1), including 7 Phase 1 studies, 12 Phase 2 studies and 11 Phase 3 studies. It should be noted that three studies (Studies 201, 204 and 306) were terminated prematurely for logistical reasons. During the review cycle, study report for one additional Phase 1 study (Study 110) was submitted. This study is mainly to study the hypersensitivity reaction in healthy subjects.

The total study enrollment was 2128 subjects, of whom 1187 received a dose of sugammadex. Most of these studies were conducted to support the doses of (b) (4) selected for the Sponsor's pivotal studies or to study special populations such as the elderly (Study 305), patients with cardiac (Study 309) or pulmonary disorders (Study 308), or subjects with impaired renal function (Study 304).

The alignment of "pivotal" Phase 3 studies with regard to the two proposed indications is as follows:

- The routine reversal of "shallow" (Study 301; dose: 2 mg/mL) or "profound" (Study 302; dose: 4 mg/mL) neuromuscular blockade induced by rocuronium or vecuronium.
- The immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium (Study 303; dose: 16 mg/mL).



**Figure 2.2.1.1. Clinical Studies.**

**2.2.2 What are the study design and clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?**

***Efficacy:***

***Clinical Endpoints:***

The depth of neuromuscular blockade and the effect of the reversal agent were monitored via a TOF-Watch SX® accelerometer, a train-of-four (TOF) twitch monitor device, which provides an electrical stimulus to the ulnar nerve while measuring contraction of the adductor pollicis muscle.

TOF stimulation consists of four supramaximal stimuli delivered to the ulnar nerve (frequency of 2 Hz), which provoke four contractions (twitches) of the thumb. Typically the subsequent muscle contractions after a series of nerve stimulations diminish after administration of a non-depolarizing muscle relaxant like rocuronium or vecuronium (‘fading’), which is caused by a lack of readily releasable acetylcholine in response to a higher rate of stimulation in the presence of the NMBA; the response of a muscle to electrical stimulation reaches maximum fading after four twitches. Counting the number of twitches in response to TOF stimulation (TOF count) or by comparing the height of the fourth twitch with the height of the first twitch (TOF ratio, T<sub>4</sub>:T<sub>1</sub> ratio) are accepted methods of assessing the efficacy of NMBAs and reversal agents. A T<sub>4</sub>:T<sub>1</sub> ratio of < 0.9 indicates impaired pharyngeal function with the risk of aspiration in the case of regurgitation. Recovery to a T<sub>4</sub>:T<sub>1</sub> ratio of 0.9 or above has been shown to correlate well with

adequate and safe recovery from a NMB. Therefore, the primary efficacy parameter used for Studies 301 and 302 was time to recovery from neuromuscular blockade starting from the time of administration of test article (b)(4) until the return of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9 (i.e., the point where the ratio of the 4th twitch in a train-of-four (TOF) stimulation is 90% of the magnitude of the first twitch; considered clinically significant neuromuscular recovery). The T<sub>4</sub>:T<sub>1</sub> ratio was measured by acceleromyography. Secondary endpoints included intermediate levels of recovery, specifically the time from test article administration to recovery of a T<sub>4</sub>:T<sub>1</sub> ratio of 0.7 or 0.8. Other endpoints included clinical assessments of neuromuscular recovery such as the ability to maintain the head lifted from the pillow for 5 seconds and generalized weakness.

In Study 303, which investigated the efficacy of Org 25969 in an immediate reversal setting (i.e., 3 minutes after rocuronium) versus spontaneous recovery following administration of succinylcholine, the time to recovery of T<sub>1</sub> (height of the first twitch) to 10% was the primary endpoint, and the time to recovery of T<sub>1</sub> to 90% was the secondary endpoint. After administration of a depolarizing muscle relaxant like succinylcholine, fading is not observed and, therefore, the T<sub>4</sub>:T<sub>1</sub> ratio cannot be used in the evaluation of efficacy.

Study Design and Outcome:

The administration of reversal agent was timed to coincide with reappearance of T<sub>2</sub> for “shallow” NMB, 1-2 post-tetanic contractions (PTC) for “profound” NMB, and at 3 minutes after rocuronium infusion for “immediate” reversal. The doses of (b)(4) used for these paradigms was 2 mg/kg for shallow, 4 mg/kg for profound, and 16 mg/kg for immediate reversal. The reversal agent used as a comparator in the pivotal clinical trials was neostigmine 50 – 70 mcg/kg administered with glycopyrrolate 10 – 14 mcg/kg.

**Study 301**

This study was conducted to support the routine reversal claim, “shallow” neuromuscular blockade. The dose of (b)(4) assessed was 2 mg/kg. NMB was induced by rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg). All study sites were in Europe. The patient population totaled 196 randomized, 189 treated, and 185 completed. Subjects were relatively healthy adults (ASA physical status 1-3) without serious concomitant systemic conditions who were scheduled for surgery requiring general anesthesia in the supine position. Following screening, patients were randomized 1:1:1 to one of the following treatment groups:

**Study 301**

Group Number	N	Neuromuscular Blocking Agent (NBMA)	Reversal agent
1	48	Rocuronium	Sugammadex
2	48	Rocuronium	Neostigmine*
3	48	Vecuronium	Sugammadex
4	45	Vecuronium	Neostigmine*

\*Glycopyrrolate was also administered for its anti-muscarinic effects; the dose of neostigmine was 50 mcg/kg.

Patients were induced with intravenous medications including benzodiazepines, narcotics and a hypnotic agent followed by paralysis with the specified NBMA. Anesthesia was maintained

with sevoflurane and parenteral agents including propofol and fentanyl. The elapsed time between the start of administration of the reversal agent and the recovery of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9, as measured by acceleromyography, was the primary efficacy endpoint.

**Study 302**

This study was conducted to support the routine reversal claim, “profound” neuromuscular blockade. The dose of (b)(4) assessed was 4 mg/kg. NMB was induced using rocuronium (0.6 mg/kg) or vecuronium (0.1 mg/kg). Profound NMB was defined as 1-2 Post-Tetanic-Contractions (PTC). All study sites were in the US. A total of 187 patients were randomized, 157 were treated and 155 completed the study. The patients were relatively healthy adults scheduled to undergo elective surgery in the supine position (ASA 1-3).

**Study 302**

Group Number	N	Neuromuscular Blocking Agent (NBMA)	Reversal agent
1	37	Rocuronium	Sugammadex
2	37	Rocuronium	Neostigmine*
3	47	Vecuronium	Sugammadex
4	36	Vecuronium	Neostigmine*

\*Glycopyrrolate was also administered for its anti-muscarinic effects; the dose of neostigmine was 70 mcg/kg.

Anesthesia was induced and maintained as described above. The specified NMBA (rocuronium and vecuronium) was administered, and the level of neuromuscular blockade was monitored via a TOF nerve stimulator. After the final maintenance dose of NMBA, the blockade was verified as 1-2 PTC and the reversal agent was administered. The dose of Sugammadex was 4 mg/kg. The dose of neostigmine was 70 mcg/kg. The elapsed time between the start of administration of the reversal agent and the recovery of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9 was again the primary endpoint.

Below is a summary table of data from the pivotal efficacy studies 301 and 302. The efficacy data demonstrated a significant treatment effect that favored (b)(4) over the active comparator, netostigmine plus glycopyrrolate.

**Table 2.2.2.1. Summary Table of Efficacy**

Study #	NMB	Sugammadex (sec)	Neostigmine (sec)	p-value
301 shallow	Rocuronium	1:29	18:30	<0.0001
	Vecuronium	2:48	16:48	
302 profound	Rocuronium	2:50	50:22	<0.0001
	Vecuronium	4:28	66:12	

**Study 303**

This study was conducted to support the immediate reversal claim. The dose of (b)(4) assessed was 16 mg/kg. The patients were relatively healthy adults scheduled to undergo elective surgery in the supine position (ASA 1-2). Treatment arms included rocuronium 1.2

mg/kg followed in 3 minutes with (b) (4) 16 mg/kg or succinylcholine 1.0 mg/kg. The primary endpoint is time from NMBA administration to T<sub>1</sub> = 0.1.

**Table 2.2.2.2. Summary of the time (min) from start of administration of (b) (4) or succinylcholine to recovery of T<sub>1</sub> to 10%.**

	Treatment group	
	Rocuronium + Org 25969	Succinylcholine
n	55	55
Mean (SD)	4.4 (0.7)	7.1 (1.6)
Median	4.2	7.1
Range	3.5-7.7	3.8-10.5

Refer to Dr. Shibuya (Clinical) and Dr. Permutt (Statistics)'s reviews for detail evaluation of efficacy measures.

**Safety:**

The safety database from these clinical trials includes 1973 subjects who received (b) (4) Of the total (b) (4) exposures, 209 received the drug alone for purposes of safety, tolerability, and PK assessment, and 1845 subjects received a neuromuscular blocking agent (NMBA), either rocuronium, vecuronium, or pancuronium,) prior to (b) (4) 88% of the subjects were ASA 1 and 2 who are relatively healthy subjects. Doses of (b) (4) ranged from 0.5 - 32 mg/kg. Safety was assessed across treatment groups by clinical laboratory values, vital signs, ECG recordings, AEs, and serious adverse events (SAEs). There were no clinically significant changes in laboratory values attributable to study drug. There were three deaths overall during the clinical development program, two of which occurred in subjects who received (b) (4) One case may be study drug related. Refer to Dr. Simone (Clinical)'s review for detailed evaluation of safety measures.

**2.2.3 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic and pharmacodynamic parameters and exposure-response relationships?**

Yes, the Sponsor measured the appropriate moieties in plasma and urine in clinical pharmacology studies. Besides sugammadex, total rocuronium and vecuronium (bound to cyclodextrin plus unbound) concentrations were also monitored in some studies.

Please refer to Section 2.6 Analysis for analytical details.

**2.2.4 What was exposure-response relationship of sugammadex in terms of efficacy and safety? Are the doses proposed by the sponsor acceptable?**

The doses selected by the sponsor corresponding with reversal of various depth of NMB seem acceptable.

Twelve clinical studies investigated the dose-response relation of Org 25969 administered as reversal agent at various time points after administration of various doses of rocuronium or vecuronium, representing different depths of NMB (Table 2.2.4.1). Of these twelve trials, seven

were Phase 2 dose finding clinical studies (Studies 201-207), four were prospective bridging trials in Japanese and Caucasian subjects (Studies 208A, 208B, 209A and 209B) and one was a Phase 3 trial in pediatric and adult subjects (Study 306). The following situations were studied:

- Routine reversal – Reversal at reappearance of T<sub>2</sub>, representing a shallow blockade;
- Routine reversal – Reversal at 1-2 PTC or reversal at 15 minutes, representing a profound blockade;
- Reversal 3 minutes or 5 minutes after rocuronium, representing an immediate reversal situation.

**Table 2.2.4.1. Overview of the time points of administration of Org 25969, doses of rocuronium and vecuronium, and doses of Org 25969 used in the dose-response studies.**

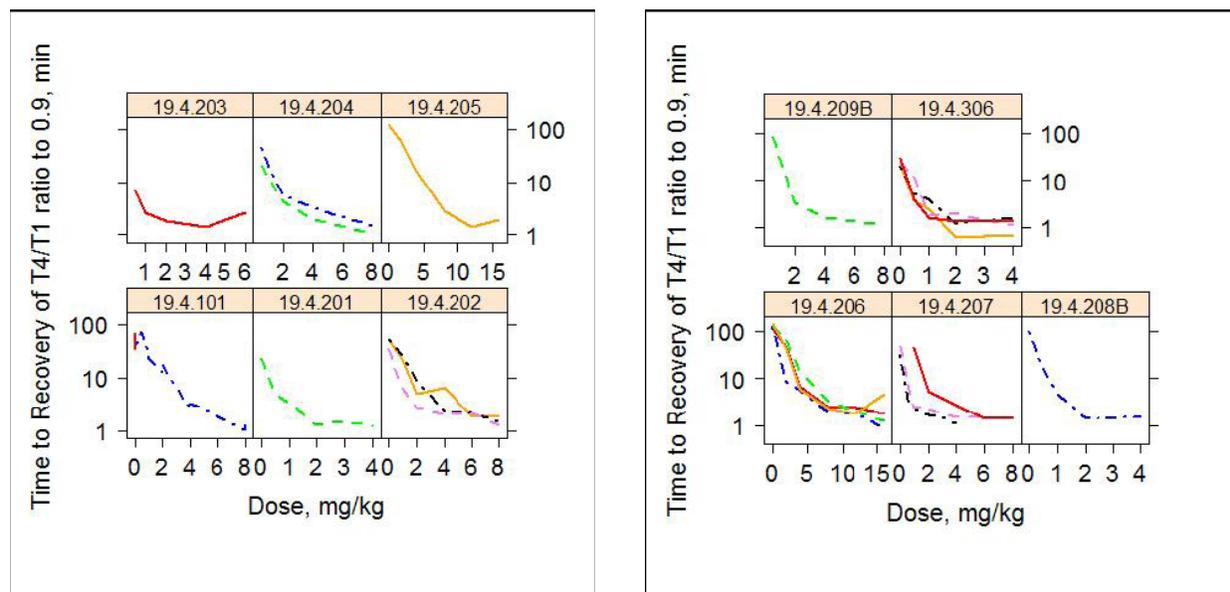
Clinical trial number	Time point of administration of Org 25969 (minutes or depth of blockade)					Dose of rocuronium (mg/kg)				Dose of vecuronium (mg/kg)	Dose of Org 25969 (mg/kg)										
	3	5	15	T <sub>2</sub>	1-2 PTC	0.6	0.9	1.0	1.2	0.1	0 <sup>a)</sup>	0.5	1	2	3	4	6	8	12	16	
19.4.201				X		X					X	X	X	X	X						
19.4.202	X	X	X			X					X		X	X	X	X	X	X			
19.4.203				X		X <sup>b)</sup>						X	X	X		X	X				
19.4.204					X	X <sup>c)</sup>			X <sup>c)</sup>			X	X	X		X			X		
19.4.205		X							X		X		X	X	X	X			X	X	X
19.4.206	X		X					X	X		X			X	X	X			X	X	X
19.4.207				X		X				X	X	X	X	X	X	X					
19.4.208A				X			X <sup>c)</sup>			X <sup>c)</sup>	X	X	X	X	X	X					
19.4.208B				X			X <sup>c)</sup>			X <sup>c)</sup>	X	X	X	X	X	X					
19.4.209A					X		X <sup>c)</sup>			X <sup>c)</sup>		X	X	X	X	X			X		
19.4.209B					X		X <sup>c)</sup>			X <sup>c)</sup>		X	X	X	X	X			X		
19.4.306				X		X					X	X	X	X	X	X					

<sup>a)</sup> Dose of 0 mg/kg Org 25969 = placebo treatment.

<sup>b)</sup> Intubating dose of NMBA followed by maintenance dosing to maintain blockade for at least 2 h.

<sup>c)</sup> Intubating dose of NMBA followed by maintenance dosing if further NMB was required.

A clear dose-response relationship was observed in all the studies (Figure 2.2.4.1).



**Figure 2.2.4.1. Dose-Response of sugammadex in Phase 1, 2, and 3 Studies.**

***Routine reversal (shallow)—Reversal at reappearance of T<sub>2</sub> after rocuronium or vecuronium:  
Rocuronium:***

Data from six clinical studies (doses of 0 to 6 mg/kg) were pooled for analysis to support the dose selection of Org 25969 for reversal at reappearance of T<sub>2</sub> of rocuronium-induced NMB (shallow). Table 2.2.4.2 presents a summary of the primary variable of efficacy by dose group, within and across studies.

The mean recovery time decreased from 60 min at spontaneous recovery (after placebo) to 1.6 min after a dose of 2.0 mg/kg Org 25969. Doubling the dose from 2.0 to 4.0 mg/kg resulted in a small further reduction of only 0.2 min in the overall mean recovery time, from 1.6 to 1.4 min. A dose of 2 mg/kg was selected to be studied in Phase 3 studies. The shortest recovery time observed in individual subjects at Org 25969 dose levels of 2 mg/kg and higher was 0.7 min and longest recovery time was 4.8 min.

**Table 2.2.4.2. Org 25969 administered at reappearance of T<sub>2</sub> following rocuronium administration: summary of the time to recovery of T<sub>4</sub>:T<sub>1</sub> to 0.9 (min) by dose, within and across studies.**

Trial		Dose of Org 25969 (mg/kg)						
		Placebo	0.5	1.0	2.0	3.0	4.0	6.0
201	n	4	5	4	3	5	3	0
	Mean (SD)	23.1 (8.8)	5.0 (2.8)	3.2 (1.7)	1.3 (0.4)	1.5 (1.0)	1.2 (0.2)	
	Median	21.0	4.3	3.3	1.3	1.2	1.1	
	Min. –max.	15.0 – 35.4	1.3 – 8.5	1.4 – 4.9	0.9 – 1.7	0.7 – 3.2	1.0 – 1.4	
203	n	0	4	4	6	0	6	4
	Mean (SD)		6.8 (3.1)	2.7 (1.0)	1.8 (0.6)		1.4 (0.6)	2.6 (1.3)
	Median		5.5	2.7	1.8		1.1	2.7
	Min. –max.		4.8 – 11.4	1.8 – 3.7	1.0 – 2.5		1.0 – 2.3	1.1 – 3.9
207	n	2	8	7	8	3	8	0
	Mean (SD)	31.8 (21.0)	3.7 (1.0)	2.3 (0.6)	1.7 (0.6)	1.9 (1.2)	1.1 (0.3)	
	Median	31.8	3.7	2.2	1.7	1.5	1.1	
	Min. –max.	17.0 – 46.7	2.1 – 4.9	1.5 – 3.4	0.9 – 2.8	1.0 – 3.2	0.7 – 1.6	
208A	n	6	5	10	7		9	0
	Mean (SD)	82.1 (27.6)	3.9 (2.5)	2.5 (1.3)	2.2 (1.2)		1.8 (1.2)	
	Median	86.0	3.2	2.3	1.6		1.6	
	Min. –max.	47.3 – 108.5	1.9 – 8.3	1.3 – 5.6	1.4 – 4.8		0.8 – 4.8	
208B	n	7	8	8	9	0	8	0
	Mean (SD)	96.3 (33.1)	16.3 (20.6)	4.6 (6.0)	1.4 (0.5)		1.5 (0.4)	
	Median	86.2	5.2	2.6	1.5		1.3	
	Min. –max.	55.7 – 153.0	1.3 – 55.5	1.5 – 19.3	0.7 – 2.4		1.2 – 2.2	
306 <sup>a</sup>	n	6	5	5	5	0	5	0
	Mean (SD)	29.5 (8.4)	3.8 (1.1)	1.6 (0.3)	1.3 (0.3)		1.4 (0.4)	
	Median	28.5	4.2	1.7	1.2		1.4	
	Min. –max.	19.6 – 44.0	2.3 – 4.8	1.2 – 2.0	0.9 – 1.6		1.0 – 2.0	
<b>Total</b>	<b>n</b>	<b>25</b>	<b>35</b>	<b>38</b>	<b>38</b>	<b>8</b>	<b>39</b>	<b>4</b>
	<b>Mean (SD)</b>	<b>60.0 (38.8)</b>	<b>7.2 (10.8)</b>	<b>2.9 (2.9)</b>	<b>1.6 (0.7)</b>	<b>1.6 (1.0)</b>	<b>1.4 (0.7)</b>	<b>2.6 (1.3)</b>
	<b>Median</b>	<b>47.3</b>	<b>4.2</b>	<b>2.2</b>	<b>1.5</b>	<b>1.3</b>	<b>1.2</b>	<b>2.7</b>
	<b>Min. –max.</b>	<b>15.0 – 153.0</b>	<b>1.3 – 55.5</b>	<b>1.2 – 19.3</b>	<b>0.7 – 4.8</b>	<b>0.7 – 3.2</b>	<b>0.7 – 4.8</b>	<b>1.1 – 3.9</b>

<sup>a</sup> Only data from the adult subjects of this trial were included in the summary.

Vecuronium:

Data from three clinical studies were pooled for analysis to support the dose selection of Org 25969 for reversal at reappearance of T<sub>2</sub> of vecuronium-induced NMB. Table 2.2.4.3 presents a summary of the primary variable of efficacy by dose group, within and across studies.

On average, the recovery time decreased from approximately 74 min at spontaneous recovery (after placebo) to within 3 min after a dose of 2.0 mg/kg or higher. The mean recovery time after administration of 2.0 mg/kg Org 25969 at reappearance of T<sub>2</sub> following vecuronium (2.8 min) was longer than the mean recovery time after administration of the same dose of Org 25969 at reappearance of T<sub>2</sub> following rocuronium (1.6 min). Taking into account the advantage in clinical practice of having one dosing instruction for routine reversal at reappearance of T<sub>2</sub> after use of both rocuronium and vecuronium, the Sponsor selected the same dose (2 mg/kg) as reversal of rocuronium-induced NMB for Phase 3 investigation of reversal of vecuronium-induced NMB at reappearance of T<sub>2</sub>. The shortest recovery time observed in individual subjects at Org 25969 dose levels of 2 mg/kg and higher was 0.8 min and longest recovery time was 8.5 min.

**Table 2.2.4.3. Org 25969 administered at reappearance of T<sub>2</sub> following vecuronium administration: summary of the time to recovery of T<sub>4</sub>:T<sub>1</sub> to 0.9 (min) by dose group, within and across studies.**

Trial		Dose of Org 25969 (mg/kg)					
		Placebo	0.5	1.0	2.0	4.0	8.0
19.4.207	n	4	6	8	8	7	4
	Mean (SD)	48.7 (27.9)	7.7 (2.6)	2.5 (0.8)	2.3 (0.8)	1.5 (0.5)	1.4 (0.5)
	Median	39.8	7.1	2.3	2.3	1.4	1.4
	Min. – max.	27.1 – 88.4	5.5 – 11.5	1.4 – 3.9	1.3 – 3.5	1.1 – 2.5	0.8 – 2.0
19.4.208A	n	7	3	8	6	10	0
	Mean (SD)	83.2 (20.6)	52.0 (64.9)	10.6 (19.2)	2.8 (0.8)	2.1 (0.9)	
	Median	82.7	26.1	4.1	2.9	1.9	
	Min. – max.	55.4 – 118.3	4.1 – 125.9	2.7 – 58.2	1.7 – 3.9	1.0 – 3.9	
19.4.208B	n	8	9	10	7	9	0
	Mean (SD)	79.0 (26.0)	35.5 (42.1)	5.1 (2.4)	3.4 (1.9)	3.0 (2.2)	
	Median	70.6	13.3	4.5	2.5	2.5	
	Min. – max.	59.8 – 141.1	3.5 – 113.5	1.6 – 8.8	2.1 – 7.1	1.3 – 8.5	
Total	n	19	18	26	21	26	4
	Mean (SD)	74.2 (26.8)	29.0 (40.1)	6.0 (10.8)	2.8 (1.3)	2.3 (1.5)	1.4 (0.5)
	Median	72.8	9.1	3.6	2.7	1.9	1.4
	Min. – max.	27.1 – 141.1	3.5 – 125.9	1.4 – 58.2	1.3 – 7.1	1.0 – 8.5	0.8 – 2.0

***Routine reversaln (profound) – Reversal at 1–2 PTC and reversal at 15 minutes after rocuronium or vecuronium:***

Rocuronium:

Data from four clinical studies (doses of 0 to 8 mg/kg) were pooled for analysis to support the dose selection of Org 25969 for reversal of profound blockade induced by rocuronium. One of these studies evaluated recovery at 15 minutes following administration of an intubating dose of

0.6 mg/kg rocuronium (Study 202). The other three trials studied recovery from a blockade at 1–2 PTC (Studies 204, 209A and 209B). The Sponsor stated that the depth of blockade 15 minutes after 0.6 mg/kg of rocuronium corresponds well with a blockade at 1–2 PTC responses (the time to a first response to PTC was found to be 12 minutes). Therefore, the Sponsor considered it is justified to pool recovery data of reversal at 1–2 PTC and 15 minutes after rocuronium for the selection of the Org 25969 dose for Phase 3 investigation of reversal at profound blockade. Table 2.2.4.4 presents a summary of the primary variable of efficacy by dose group, within and across studies.

The mean recovery times decreased from approximately 36 min after placebo and 66 min after 0.5 mg/kg to 1.8 min after a dose of 4.0 mg/kg Org 25969. Doubling the dose from 4.0 to 8.0 mg./kg resulted in a small further reduction of 0.5 min in the overall mean recovery time from 1.8 to 1.3 min. A dose of 4 mg/kg was selected to be studied Phase 3 trials. The shortest recovery time observed in individual subjects at Org 25969 dose levels of 4 mg/kg and higher was 0.6 min and longest recovery time was 5.9 min.

**Table 2.2.4.4. Org 25969 administered at 1–2 PTC after rocuronium administration or 15 min after 0.6 mg/kg rocuronium: summary of the time to recovery of T<sub>4</sub>:T<sub>1</sub> to 0.9 (min) by dose, within and across studies.**

Trial		Dose of Org 25969 (mg/kg)						
		Placebo	0.5	1.0	2.0	4.0	6.0	8.0
202	n	3	0	6	6	6	6	6
	Mean (SD)	35.6 (9.0)		6.5 (1.7)	2.7 (0.7)	2.0 (1.2)	2.1 (2.0)	1.3 (0.2) 1.3
	Median	30.6		6.2	2.5	1.5	1.1	1.1 – 1.7
	Min.–max.	30.1 – 46.0		4.8 – 9.0	2.1 – 4.0	1.1 – 4.2	1.0 – 5.9	
204	n	0	4	5	8	4	0	8
	Mean (SD)		38.3(30.6)	14.5(13.6)	5.0(4.3)	2.6(1.3)		1.3(0.5)
	Median		24.2	5.1	4.1	2.3		1.0
	Min.–max.		20.6 –84.1	4.5 – 33.2	1.8 –15.2	1.5 – 4.5		0.8 – 2.1
209A	n	0	6	7	10	11	0	10
	Mean (SD)		66.9(34.6)	4.7 (1.7)	3.4 (2.5)	1.6 (0.9)		1.3 (0.6)
	Median		62.7	4.7	2.9	1.2		1.2
	Min.–max.		15.5–114.2	1.6 - 7.5	1.4 - 9.3	0.8 - 4.0		0.6 - 2.4
209B	n	0	8	9	10	10	0	10
	Mean (SD)		79.8 (33.0)	28.0(43.7)	3.2 (1.5)	1.6 (0.7)		1.1 (0.3)
	Median		87.5	7.4	3.2	1.5		1.1
	Min.–max.		24.4–131.7	3.6 –117.1	1.1 - 6.6	0.8 - 2.9		0.8 - 2.0
<b>Total</b>	<b>n</b>	<b>3</b>	<b>18</b>	<b>27</b>	<b>34</b>	<b>31</b>	<b>6</b>	<b>34</b>
	<b>Mean (SD)</b>	<b>35.6 (9.0)</b>	<b>66.3 (35.2)</b>	<b>14.7(26.9)</b>	<b>3.6 (2.6)</b>	<b>1.8 (1.0)</b>	<b>2.1 (2.0)</b>	<b>1.3 (0.4)</b>
	<b>Median</b>	<b>30.6</b>	<b>65.4</b>	<b>5.5</b>	<b>3.0</b>	<b>1.6</b>	<b>1.1</b>	<b>1.2</b>
	<b>Min.–max.</b>	<b>30.1 - 46.0</b>	<b>15.5–131.7</b>	<b>1.6 –117.1</b>	<b>1.1 - 15.2</b>	<b>0.8 - 4.5</b>	<b>1.0 - 5.9</b>	<b>0.6 - 2.4</b>

Vecuronium:

Data from Clinical Studies 209A and 209B were used to support the dose selection of Org 25969 for reversal of profound blockade induced by vecuronium (Table 2.2.4.5).

The mean recovery time decreased from 73 min at the lowest dose level to 2.3 min at the highest dose level studied (8 mg/kg). Based on mean and median recovery times, Org 25969 doses of 4.0 and 8.0 mg/kg can be considered effective doses for reversal of profound blockade induced by

vecuronium. A dose of 4.0 mg/kg was selected for Phase 3 studies, taking into account the advantage of eventually having a single dose recommendation in the indication of reversal of profound blockade after use of both rocuronium as well as vecuronium. The shortest recovery time observed in individual subjects at Org 25969 dose levels of 4 mg/kg and higher was 0.7 min and longest recovery time was 13.5 min.

**Table 2.2.4.5. Org 25969 administered at 1–2 PTC following vecuronium administration: summary of the time to recovery of T<sub>4</sub>:T<sub>1</sub> to 0.9 (min) by dose, within and across studies.**

Trial		Dose of Org 25969 (mg/kg)				
		0.5	1.0	2.0	4.0	8.0
19.4.209A	n	5	7	10	10	10
	Mean (SD)	79.5 (46.2)	39.8 (45.8)	16.0 (42.2)	3.0 (2.4)	2.9 (3.8)
	Median	76.5	8.9	2.8	1.9	1.4
	Min. – max.	17.7 – 143.9	3.9 – 116.2	1.5 – 136.1	0.9 – 8.4	1.2 – 13.5
19.4.209B	n	7	9	11	8	10
	Mean (SD)	68.4 (31.9)	25.1 (24.9)	9.1 (20.6)	3.3 (3.5)	1.7 (0.7)
	Median	59.1	15.7	2.8	2.3	1.6
	Min. – max.	29.4 – 124.9	2.7 – 66.9	1.6 – 71.0	1.0 – 11.7	0.7 – 2.9
Total	n	12	16	21	18	20
	Mean (SD)	73.0 (37.0)	31.6 (35.0)	12.4 (32.0)	3.2 (2.8)	2.3 (2.7)
	Median	69.3	12.3	2.8	2.1	1.5
	Min. – max.	17.7 – 143.9	2.7 – 116.2	1.5 – 136.1	0.9 – 11.7	0.7 – 13.5

***Immediate reversal – Reversal at 3 and 5 minutes after rocuronium:***

Recovery at early time-points of 3 and 5 minutes following administration of a dose of 1.2 mg/kg rocuronium was studied in two clinical studies: Study 205 (5 minutes) and Study 206 (3 minutes). Data from these studies were pooled for analysis to determine the appropriate dose of Org 25969 in immediate reversal situations. Table 2.2.4.6 presents a summary of the primary variable of efficacy, within and across studies.

Org 25969 doses of 12.0 and 16.0 mg/kg induced a fast reversal of NMB at three or five minutes after 1.2 mg/kg rocuronium, with mean recovery times of 1.8 and 1.6 min, respectively. Although the difference between these two dose levels is small, the situation of immediate reversal requires optimal efficacy. For this reason a dose of 16.0 mg/kg Org 25969 was selected for Phase 3 investigation of immediate reversal after rocuronium. Reversal at the time-point of 3 minutes was considered a more relevant time-point than 5 minutes, to reflect a clinical situation of immediate reversal. Therefore reversal at the time-point of 5 minutes after rocuronium has not been studied any further in Phase 3 studies. The shortest recovery time observed in individual subjects at Org 25969 dose levels of 16 mg/kg was 0.7 min and longest recovery time was 6.9 min. As of note, doses higher than 16 mg/kg have not been studied.

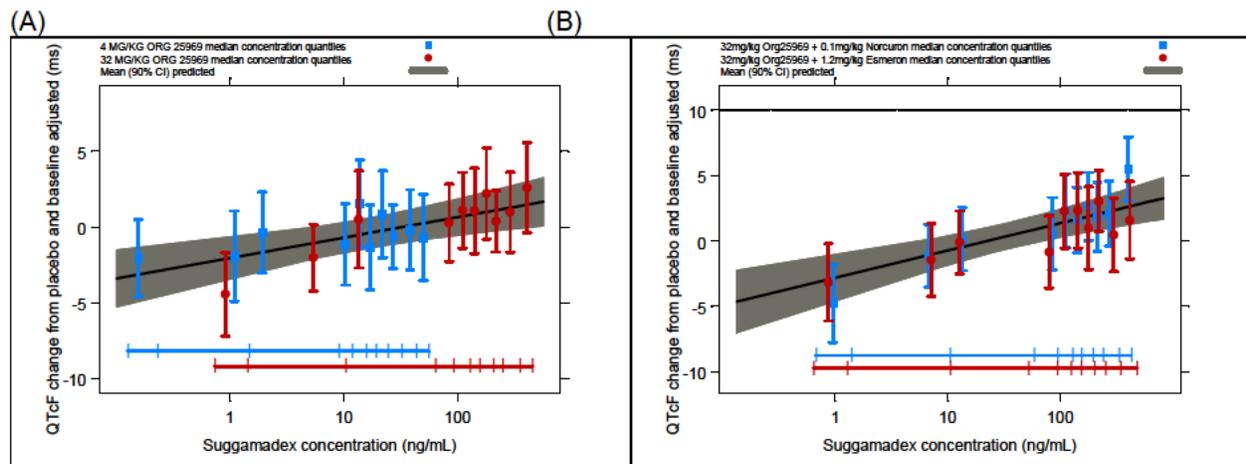
**Table 2.2.4.6. Org 25969 administered at 3 or 5 minutes after 1.2 mg/kg rocuronium: summary of the time to recovery of T<sub>4</sub>/T<sub>1</sub> to 0.9 (min) by dose, within and across studies.**

Trial		Dose of Org 25969 (mg/kg)					
		Placebo	2.0	4.0	8.0	12.0	16.0
205 (5 min)	n	4	5	5	12	7	7
	Mean (SD)	122.1(18.1)	56.5 (5.4)	15.8(17.7)	2.8 (0.5)	1.4 (0.3)	1.9 (2.2)
	Median	126.1	55.3	12.3	2.5	1.3	1.3
	Min.–max.	96.8 - 139.4	50.5 - 65.1	3.3 - 46.6	2.2 - 3.7	1.0 - 1.9	0.7 - 6.9
206 (3 min)	n	4	9	8	11	10	11
	Mean (SD)	123.0 (28.5)	65.7 (24.6)	13.8 (7.6)	3.2 (1.0)	2.1 (0.9)	1.3 (0.4)
	Median	124.3	63.3	11.3	3.6	1.9	1.3
	Min.–max.	87.3 - 156.1	36.3 -117.2	5.3 - 28.5	1.5 - 4.7	1.2 - 4.1	0.8 - 2.3
<b>Total</b>	<b>n</b>	<b>8</b>	<b>14</b>	<b>13</b>	<b>23</b>	<b>17</b>	<b>18</b>
	<b>Mean (SD)</b>	<b>122.5 (22.1)</b>	<b>62.4 (20.0)</b>	<b>14.6(11.8)</b>	<b>3.0 (0.8)</b>	<b>1.8 (0.8)</b>	<b>1.6 (1.4)</b>
	<b>Median</b>	<b>126.1</b>	<b>56.1</b>	<b>11.8</b>	<b>2.8</b>	<b>1.7</b>	<b>1.3</b>
	<b>Min.–max.</b>	<b>87.3 - 156.1</b>	<b>36.3 -117.2</b>	<b>3.3 - 46.6</b>	<b>1.5 - 4.7</b>	<b>1.0 - 4.1</b>	<b>0.7 - 6.9</b>

Vecuronium has not been studied for the immediate reversal scenario.

**2.2.5 Does sugammadex prolong QT or QTc interval?**

Yes, there is a concentration-dependent increase in QTcI (Figure 2.2.5.1). However, the mean increase in QTcI for the suprathereapeutic dose (32 mg/kg) is below 10 msec, the regulatory threshold for concern. This dose gives 2-fold higher peak concentrations than the dose recommended for immediate reversal, 16 mg/kg, and 8- and 16-fold higher peak concentrations of the doses recommended for routine reversal. See PM review (Appendix 4.3) and consult review from QT-IRT.



**Figure 2.2.5.1. (A) Median concentration quantile with corresponding observed mean (90% CI)  $\Delta\Delta$ QTcF following 4 and 32 mg/kg Org25969. (B) Median concentration quantile with corresponding observed mean (90% CI)  $\Delta\Delta$ QTcF following 32 mg/kg Org 25969+0.1 mg/kg and 32 mg/kg Org25969 + 1.2 mg/kg rocuronium bromide.**

## 2.2.6 What are the PK characteristics of sugammadex?

### 2.2.6.1 What are single dose PK parameters of sugammadex?

In five Phase 1 studies the PK profile of sugammadex was investigated when sugammadex was administered alone, in healthy volunteers who did not receive anesthesia (Studies 101, 102, 105, 106, and 107). Table 2.2.6.1.1 presents the main PK parameters determined in these studies. A summary of urinary excretion of sugammadex is presented in Table 2.2.6.1.2.

The mean CL of sugammadex ranges from 97 to 138 mL/min (Table 2.2.6.1.1), similar to those of glomerular filtration rate in healthy humans. On average, 65 to 97 percent of the administered dose was recovered in urine as sugammadex, as determined using an HPLC-MS assay (Table 2.2.6.1.2) indicating sugammadex is mainly eliminated via kidney.

Mean C<sub>max</sub> of sugammadex at the highest proposed dose of 16 mg/kg is ~ 200 mcg/mL (90 µM).

**Table 2.2.6.1.1. Summary of PK parameters of sugammadex in healthy subjects who were not anesthetized.**

Trial No. Trial particulars	Race N, Gender: M/F Age: mean [range] yr	Org 25969 dose	CL [mL/min]	wn-CL [mL/min/kg]	V <sub>ss</sub> [L] †	wn-V <sub>ss</sub> [mL/kg]	t <sub>1/2, β</sub> [min]
19.4.101 First-in-Man Part 1: Org 25969 only	Caucasian 17 M 29.3 [20 – 40]	0.1 mg/kg (n=4)	123 (9.33)	1.58 (8.89)	10.1 (21.8)	130 (21.1)	65.8 (32.6)
		0.2 mg/kg (n=4)	99.2 (8.33)	1.35 (3.46)	11.1 (10.2)	151 (14.7)	94.5 (12.0)
		0.5 mg/kg (n=4)	107 (12.7)	1.38 (8.49)	13.1 (15.5)	168 (7.87)	108 (16.9)
		1.0 mg/kg (n=6)	119 (7.47)	1.51 (14.8)	15.9 (10.7)	201 (13.8)	128 (12.2)
		2.0 mg/kg (n=6)	138 (14.9)	1.78 (14.5)	17.0 (15.3)	220 (12.3)	105 (7.05)
		4.0 mg/kg (n=4)	118 (24.0)	1.48 (25.9)	14.0 (19.8)	176 (20.4)	103 (9.46)
		8.0 mg/kg (n=2)	122 (2.64)	1.64 (0.981)	12.7 (16.4)	171 (12.8)	97.9 (4.69)
19.4.102 Comparison Japanese / Caucasian Org 25969 only	Japanese 7 M/7 F 25.2 [21 – 33]	1.0 mg/kg (n=14)	106 (16.7)	1.78 (14.2)	12.1 (13.5)	203 (9.92)	107 (13.9)
		8.0 mg/kg (n=14)	103 (9.02)	1.74 (10.0)	11.8 (15.5)	198 (14.1)	132 (17.5)
		16.0 mg/kg (n=14)	98.4 (15.5)	1.65 (13.5)	11.4 (15.0)	191 (11.8)	143 (22.5)
	Caucasian 7 M/7 F 23.1 [20 – 26]	1.0 mg/kg (n=14)	125 (17.7)	1.89 (17.2)	14.1 (19.1)	213 (16.0)	101 (16.7)
		8.0 mg/kg (n=14)	109 (13.5)	1.66 (12.6)	13.2 (21.0)	200 (17.3)	161 (39.9)
		16.0 mg/kg (n=14)	104 (10.9)	1.57 (14.0)	12.6 (11.2)	191 (12.4)	181 (30.5)
19.4.105 QT/QTc trial Org 25969 only	Caucasian 31 M/31 F 45 [22 – 65]	4.0 mg/kg (n=59)	112	1.51	16.1	217	n.a.
		32.0 mg/kg (n=61)	120	1.62	‡	‡	‡
19.4.106 High dose administration Org 25969 only	Caucasian 6 M/6 F 38.9 [20 – 58]	32.0 mg/kg (n=12)	111 (18.5)	1.38 (15.0)	15.0 (28.8)	187 (19.4)	232 (48.1)
		64.0 mg/kg (n=12)	107 (16.3)	1.33 (18.9)	14.7 (14.7)	182 (12.2)	260 (63.9)
		96.0 mg/kg (n=12)	104 (14.8)	1.29 (16.2)	13.0 (16.0)	161 (10.8)	187 (13.1)
19.4.107 Excretion balance [ <sup>14</sup> C]-Org 25969	Caucasian 6 M 52.8 [20 – 64]	4.0 mg/kg (n=6)	96.9 (23.7)	1.29 (22.8)	14.0 (18.8)	186 (13.6)	152 (30.8)
19.4.109 QT/QTc trial Org 25969 only and combined with rocuronium or vecuronium	79 Caucasian/ 2 Asian/ 2 Black 41 M/42 F 34.4 [19 – 45]	4.0 mg/kg (n=83)	114	1.61	13.8	194	n.a.
		32.0 mg/kg (n=82)	114	‡	‡	‡	‡
		32.0 mg/kg + 1.2 mg/kg rocuronium (n=81)	118	‡	‡	‡	‡
		32.0 mg/kg + 0.1 mg/kg vecuronium (n=81)	114	‡	‡	‡	‡

**Table 2.2.6.1.2. Summary of urinary excretion of Org 25969 in healthy subjects who were not anesthetized.**

Trial No. Trial particulars	Race N, Gender: M/F Age: mean [range] yr	Org 25969 dose	Amount excreted unchanged as % of dose		
			n	median	[minimum – maximum]
19.4.101 First-in-Man Part 1: Org 25969 only	Caucasian 17 M 29.3 [20 – 40]	1.0 mg/kg	5	70.1	[ 56.2 – 74.9 ]
		2.0 mg/kg	6	69.5	[ 20.5 – 79.8 ]
		4.0 mg/kg	5	83.8	[ 65.3 – 91.6 ]
		8.0 mg/kg	2	73.6	[ 71.2 – 75.9 ]
19.4.102 Comparison Japanese / Caucasian Org 25969 only	Japanese 7 M/7 F 25.2 [21 – 33]	1.0 mg/kg	14	64.8	[ 16.3 – 79.4 ]
		8.0 mg/kg	14	73.4	[ 42.0 – 102 ]
		16.0 mg/kg	13	78.1	[ 62.9 – 93.0 ]
	Caucasian 7 M/7 F 23.1 [20 – 26]	1.0 mg/kg	14	66.0	[ 52.5 – 95.2 ]
		8.0 mg/kg	14	72.1	[ 49.9 – 93.6 ]
		16.0 mg/kg	14	71.0	[ 67.1 – 91.9 ]
19.4.106 High dose administration Org 25969 only	Caucasian 6 M/6 F 38.9 [20 – 58]	32.0 mg/kg	12	96.8	[ 56.5 – 121 ]
		64.0 mg/kg	10	92.7	[ 62.3 – 102 ]
		96.0 mg/kg	12	96.4	[ 52.5 – 119 ]
19.4.107 Excretion balance [ <sup>14</sup> C]-Org 25969	Caucasian 6 M 52.8 [20 – 64]	4.0 mg/kg	6	91.8	[ 85.3 – 94.3 ]

**2.2.6.2 How does the PK of sugammadex in healthy subjects compare to that in patients under anesthesia and following rocuronium administration?**

Clearance of sugammadex appears to be slightly lower for subjects under anesthesia and following rocuronium administration (Table 2.2.6.2.1) compared to subjects not under anesthesia (Table 2.2.6.1.1).

**Table 2.2.6.2.1. Summary of PK parameters of Org 25969 in anesthetized subjects.**

Trial No. Trial particulars	Subjects N, Gender: M/F Age: mean [range] yr	Org 25969 dose	CL [mL/min]	wn-CL [mL/min/kg]	V <sub>ss</sub> [L]	wn-V <sub>ss</sub> [mL/kg]	t <sub>1/2,β</sub> [min]
Study 101 First-in-Man Part 2: Org 25969 at 3 min after 0.6 mg/kg rocuronium	Healthy volunteers 10 M (treated) 32.4 [21 – 38]	1.0 mg/kg (n=2)	74.7 (19.7)	0.976 (19.7)	10.7 (15.5)	139 (15.5)	118 (2.22)
		2.0 mg/kg (n=2)	94.5 (11.8)	1.19 (3.14)	13.1 (8.29)	166 (0.371)	111 (6.45)
		4.0 mg/kg (n=2)	84.8 (14.3)	1.14 (22.8)	11.7 (6.14)	156 (14.5)	119 (16.1)
		8.0 mg/kg (n=2) †	118 (2.16)	1.56 (0.850)	13.4 (2.11)	178 (0.799)	112 (7.04)
					‡		
19.4.304 Comparison impaired vs normal renal function Org 25969 at reapp. T2 after 0.6 mg/kg roc.	Control patients ASA Class 1-2 CLCR ≥80 mL/min 6 M/9 F (treated) 54 [32 – 70]	2.0 mg/kg (n=13)	95.2 (22.1)	1.16 (34.8)	13.8 (20.5)	168 (22.0)	139 (44.4)

Presented statistics for the PK parameters are geometric mean (geometric coefficient of variation). † data from 2 subjects who received 0.1 and 0.5 mg/kg are not presented. ‡ For clinical trial 19.4.101 V<sub>ss</sub> was calculated from the reported MRT and CL (V<sub>ss</sub> = MRT \* CL).

Table 2.2.6.3.1 showed that % of dose recovered in urine is similar to what obtained in subjects without rocuronium (Table 2.2.6.1.2)

**Table 2.2.6.3.1. Summary of urinary excretion of Org 25969 in patients of ASA Class 1–2.**

Trial No. Trial particulars	Subjects N, Gender: M/F Age: mean [range] yr	Org 25969 dose	Amount excreted unchanged as % of dose		
			n	median	[minimum – maximum]
19.4.201 Dose finding Org 25969 at reapp. T <sub>2</sub> after 0.6 mg/kg rocuronium	27 M (treated) 40 [20 – 64]	0.5 mg/kg	3	85.1	[ 63.2 – 102 ]
		1.0 mg/kg	2	68.7	[ 26.4 – 111 ]
		2.0 mg/kg	2	83.6	[ 70.7 – 96.5 ]
		3.0 mg/kg	3	84.6	[ 71.3 – 148 ]
		4.0 mg/kg	3	72.4	[ 40.2 – 85.9 ]
19.4.202 Dose finding Org 25969 at 3, 5 or 15 min after 0.6 mg/kg rocuronium	98 M (treated) 39 [19 – 63]	1.0 mg/kg	6	76.2	[ 39.6 – 117 ]
		2.0 mg/kg	5	47.7	[ 15.5 – 89.0 ]
		4.0 mg/kg	5	83.9	[ 78.5 – 95.1 ]
		6.0 mg/kg	6	86.2	[ 33.8 – 110 ]
		8.0 mg/kg	6	63.5	[ 18.7 – 84.8 ]
19.4.205 Dose finding Org 25969 at 5 min after 1.2 mg/kg rocuronium	22M/21F (treated) 42 [18 – 63]	2.0 mg/kg	5	97.1	[ 43.2 – 140 ]
		4.0 mg/kg	4	75.2	[ 33.9 – 85.0 ]
		8.0 mg/kg	12	103	[ 55.0 – 129 ]
		12.0 mg/kg	7	73.4	[ 1.85 – 232 ]
		16.0 mg/kg	6	106	[ 9.17 – 118 ]
19.4.304 Comparison impaired vs normal renal function Org 25969 at reapp. T <sub>2</sub> after 0.6 mg/kg roc.	Control group (CL <sub>CR</sub> ≥80 mL/min) 6 M/9 F (treated) 54 [32 – 70]	2.0 mg/kg	11	73.1	[ 55.7 – 101 ]

#### 2.2.6.4 What are the characteristics of drug absorption?

Not applicable. Sugammadex is intended for IV.

#### 2.2.6.5 What are the characteristics of drug distribution?

Across studies and across dose groups (1.0 to 96.0 mg/kg), V<sub>ss</sub> of sugammadex was approximately 12 to 15 L (Table 2.2.6.1.1), indicating that sugammadex distributes into the extra-cellular water of the body.

*In vitro* binding studies (equilibrium dialysis) showed that sugammadex (0.3 to 125 μM) does not bind to human plasma proteins or to erythrocytes. The concentration range studied is likely to cover the therapeutic range as the mean C<sub>max</sub> at 16 mg/kg is 90 μM.

In the same study, the binding of rocuronium in the presence and absence of sugammadex was studied. In the absence of sugammadex, approximately 37% of rocuronium binds to plasma proteins. The extent of protein binding declines when sugammadex was added, and none is bound to plasma proteins at equimolar concentrations of the two drugs (Table 2.2.6.5.1). Rocuronium does not bind to erythrocytes, alone or in combination with sugammadex.

**Table 2.2.6.5.1. *In vitro* binding of [<sup>3</sup>H]-Org 9426 (rocuronium) combined with Org 25969 (sugammadex) to male human plasma proteins.**

Ratio Org 25969/ Org 9426	[Org 9426] <sup>a/b</sup> (nmol·mL <sup>-1</sup> )	[Org 25969] (nmol·mL <sup>-1</sup> )	Binding			Recovery		
			1 (%)	2 (%)	Mean (%)	1 (%)	2 (%)	Mean (%)
0	0.24	0	35.5	39.3	37.4	79.6	81.3	80.4
0.4	0.35	0.125	27.0	21.9	24.4	85.4	87.7	86.5
0.7	0.7	0.5	1.6	3.3	2.4	93.6	96.8	95.2
0.9	1.4	1.25	-0.4	0.4	0.0	95.5	96.8	96.2
1.1	4.6	5	-15.0	-16.4	-15.7	96.1	101.9	99.0
1.1	11.1	12.5	-26.7	-17.5	-22.1	96.7	97.9	97.3
						Mean ± SD: 92.4 ± 7.2		

<sup>a</sup> All plasma and buffer samples contained 1.85 kBq·mL<sup>-1</sup> [<sup>3</sup>H]-Org 9426, which is equivalent to 0.0013 nmol·mL<sup>-1</sup>.

<sup>b</sup> 50% of the Org 9426/ [<sup>3</sup>H]-Org 9426 and Org 25969 was spiked in plasma and an equal concentration of Org 9426/ [<sup>3</sup>H]-Org 9426 and Org 25969 was spiked in buffer. The spiked concentrations are given in the table above.

**2.2.6.6 Dose the mass balance study suggest renal or hepatic as the major route of elimination?**

The mass balance study suggests that the elimination of sugammadex is mainly through renal excretion. The metabolism of sugammadex is minimal (~5%). The results from the consequent metabolic profiling (Study 050351) indicated higher percentage for metabolites (~30%) which may be confounded by the *ex vivo* conversion in plasma or urine (the samples were stored between 6 months to 1 year before analysis). The study did, however, confirm that the presence of Org 48302 is not a metabolite of Org 25969.

Results from a <sup>14</sup>C-ADME study (Study 107) in 6 healthy Caucasian male subjects receiving 4 mg/kg sugammadex demonstrated that on average 96% of the radioactive dose was recovered in urine and <0.02% in either feces or expired air. Org 48302 was present at ~6% of the dose and was monitored as well. The mean cumulative recovery of radioactivity in urine was >90% at 24 hours post-dose. The recovery of the administered dose in urine was very similar for <sup>14</sup>C, sugammadex (Org 25969) and Org 48302 (Table 2.2.6.6.1). Based on these data, 95 % of the radioactivity in urine can be attributed to Org 25969 and Org 48302 and at most 5% could be present as metabolites.

**Table 2.2.6.6.1. Summary of urinary excretion of radioactivity, Org 25969 and Org 48302.**

	Percentage of the dose recovered in urine (fe)		
	Total Radioactivity	Org 25969	Org 48302
<b>Subject 1</b>	85.0	90.1	101
<b>Subject 2</b>	101	85.3	81.8
<b>Subject 3</b>	84.8	89.8	101
<b>Subject 4</b>	96.5	93.4	90.7
<b>Subject 5</b>	106	94.3	110
<b>Subject 6</b>	103	93.9	101
<b>Mean ± SD</b>	96.1 ± 9.2	91.1 ± 3.5	97.6 ± 9.9

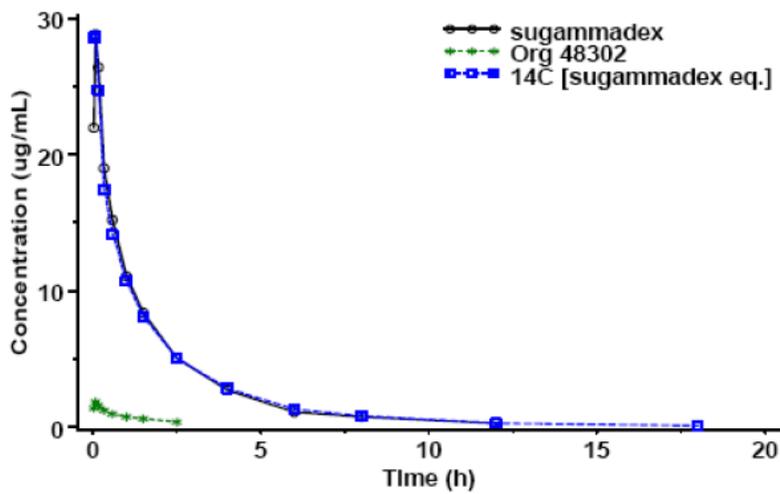
2.2.6.7 What are the characteristics of drug metabolism?

*In vitro* metabolism has not been conducted. *In vivo* <sup>14</sup>C-ADME studies indicated that sugammadex is minimally metabolized (<5%). The similarity of the plasma and urinary PK of <sup>14</sup>C and Org 25969 is reflected in the PK parameters of these compounds (Table 2.2.6.7.1). A comparison of the AUC<sub>0-∞</sub> of <sup>14</sup>C and Org 25969 shows that, on average 99.9 % of the radioactivity in plasma can be attributed to Org 25969 (Figure 2.2.6.7.1).

**Table 2.2.6.7.1. Summary of the PK parameters of radioactivity, Org 25969 and Org 48302.**

Parameter (unit)	<sup>14</sup> C		Org 25969		Org 48302	
	Mean*	CV* (%)	Mean*	CV* (%)	Mean*	CV* (%)
Cmax (µg/mL)	33.0	22	32.2	19	1.97	14
Tmax (min)	4	2 - 5	5	2 - 10	5	3 - 10
t <sub>1/2</sub> (min)	190	20	152	31	89	29
AUC <sub>0-tlast</sub> (µg*min/mL)	2618	25	2586	23	125	26
AUC <sub>0-∞</sub> (µg*min/mL)	2632	25	2629	23	159	26
CL (mL/min)	96.8	25	96.9	24	102	25
V <sub>ss</sub> (mL)	15360	19	14027	19	12189	12
t <sub>1/2, effective</sub> (min)	110	16	100	19	82.5	26
CLR (mL/min)	92.7	29	88.3	25	99.6	26

\* Mean = geometric mean (median for t<sub>max</sub>) and CV (%) = geometric CV (%) (min-max for t<sub>max</sub>)



**Figure 2.2.6.7.1. Geometric Mean Plasma Concentration vs. Time Plot of radioactivity, Org 25969 and Org 48302.**

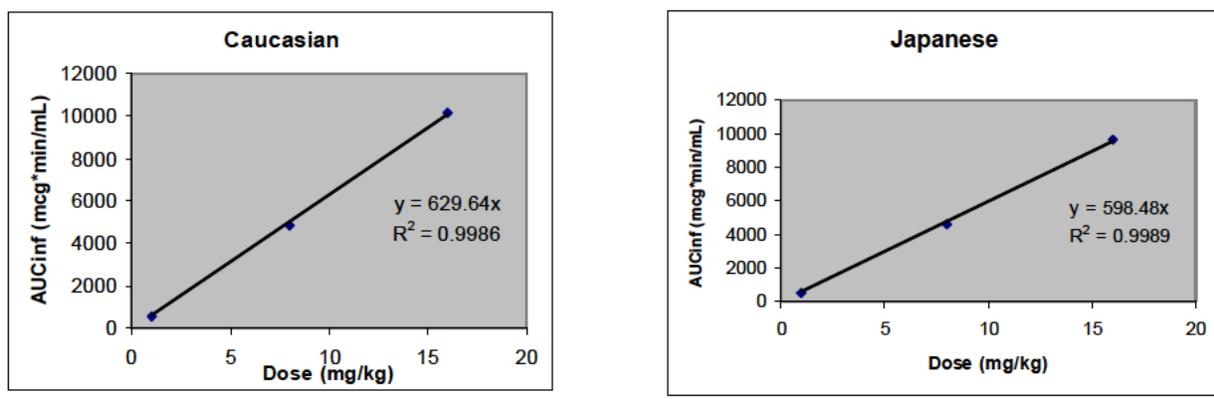
2.2.6.8 What are the characteristics of drug excretion?

See Section 2.2.6.6.

The mean steady-state plasma elimination half-lives of sugammadex were approximately 1.5 to 3 hours at clinical doses (Table 2.2.6.1.1).

2.2.6.9 Based on PK parameters, what is the degree of linearity in the dose-exposure relationship?

The exposure of sugammadex in plasma were approximately dose-proportional at the proposed clinical dose range (1 to 16 mg/kg) as evidenced by the linear relationship between  $AUC_{\infty}$  and dose. Data from Caucasian and Japanese subjects (Study 102) were plotted in Figure 2.2.6.9.1 as an example. PK parameters for both Japanese and Caucasian subjects from Study 102 are listed in Table 2.2.6.9.1.



**Figure 2.2.6.9.1. Relationship between sugammadex  $AUC_{\infty}$  and dose in Caucasians (left) and Japanese (right).**

**Table 2.2.6.9.1. PK parameters for Org 25969 in plasma (Study 102).**

Parameter (unit)		Japanese (n=14)			Caucasian (n=14)		
		1 mg/kg	8 mg/kg	16 mg/kg	1 mg/kg	8 mg/kg	16 mg/kg
C <sub>max</sub> (µg/mL)	Mean	9.22	93.7	206	9.30	88.0	202
	CV (%)	19.0	14.0	14.6	24.8	23.3	17.6
t <sub>max</sub> (min)	Median	2	2	2	2	2	2
	Range	2-10	2-4	2-4	2-6	2-10	2-4
dn-C <sub>max</sub> (µg/mL/mg)	Mean	0.155	0.197	0.217	0.141	0.166	0.191
	CV (%)	21.0	18.7	18.0	26.6	25.9	16.9
t <sub>1/2</sub> (min)	Mean	107	132	143	101	161	181
	CV (%)	13.9	17.5	22.5	16.7	39.9	30.5
AUC <sub>0-tlast</sub> (µg*min/mL)	Mean	541	4573	9638	507	4795	10143
	CV (%)	14.4	10.1	13.5	17.3	12.7	14.0
AUC <sub>0-∞</sub> (µg*min/mL)	Mean	561	4604	9670	530	4828	10185
	CV (%)	14.2	10.0	13.5	17.2	12.6	14.0
dn-AUC <sub>0-∞</sub> (µg*min/mL/mg)	Mean	9.44	9.68	10.2	8.02	9.13	9.63
	CV (%)	16.7	9.02	15.5	17.7	13.5	10.9
MRT (min)	Mean	114	114	116	113	121	122
	CV (%)	10.5	10.8	12.1	13.1	16.6	10.6
CL (mL/min)	Mean	106	103	98.4	125	109	104
	CV (%)	16.7	9.02	15.5	17.7	13.5	10.9
wn-CL (mL/min/kg)	Mean	1.78	1.74	1.65	1.89	1.66	1.57
	CV (%)	14.2	10.0	13.5	17.2	12.6	14.0
V <sub>ss</sub> (mL)	Mean	12071	11799	11370	14053	13246	12617
	CV (%)	13.5	15.5	15.0	19.1	21.0	11.2
wn-V <sub>ss</sub> (mL/kg)	Mean	203	198	191	213	200	191
	CV (%)	9.92	14.1	11.8	16.0	17.3	12.4

2.2.6.10 What is the inter- and intra-subject variability of PK parameters, and what are the major cause of variability?

The variability in sugammadex PK is low. In terms of AUC, within-subject variation was 7.6-11.5% and between-subject variation was 13.4-16.8%.

**2.2.7 What are the PD characteristics of sugammadex?**

The reversal of rocuronium- or vecuronium-induced NMB by sugammadex is based on its capability to form an inclusion complex with the NMB agents (NMBA). Upon complexation, the amount of NMBA available to bind to receptors in the neuromuscular junction is reduced, resulting in the reversal of the blockade. The PD effect of the reversal agent was monitored via a TOF-Watch SX® accelerometer, a train-of-four (TOF) twitch monitor device.

This mechanism of action of encapsulation could also be illustrated by PK data of rocuronium or vecuronium. Assuming 1:1 complex, the molar dose ration between sugammadex and rocuronium or vecuronium may indicate whether excess sugammadex may be present. Molecular weight for sugammadex is 2178 and for rocuronium is 609.7. Therefore a dose ratio of 2.6 (sugammadex to rocuronium) in mg is the equal molar dose. For example, 2.2 mg/kg of sugammadex is at equal molar dose of 0.6 mg/kg rocuronium.

PK data suggested that sugammadex affected PK of rocuronium or vecuronium as indicated by increased plasma concentrations, decreased elimination half-life, and decreased total clearance. In addition, with increased doses of sugammadex, increased amount of rocuronium was

recovered in urine. For detailed data, refer to Section 2.4.2 (drug-drug interactions). *In vitro* assay also suggest that sugammadex decreases plasma protein binding of rocuronium (Section 2.2.6.5).

**2.2.8 What are waiting times for re-administration of rocuronium or vecuronium in patients for intubation who were initially administered sugammadex and rocuronium or vecuronium?**

In clinical, there might be situation that neuromuscular blockade (NB) is required after dosing with sugammadex. A nonsteroidal NB agent is preferred for no waiting time.

Appropriate waiting would be needed for readministration of rocuronium or vecuronium. When Org 25969 is still present in the circulation, the effectiveness of the re-treatment with NMBA may be affected, to a degree depending on the dose of Org 25969 administered and on the time between reversal and re-treatment with NMBA. Based on the half-life of Org 25969, molar concentrations of Org 25969, rocuronium, vecuronium, the waiting times were derived (Table 2.2.8.1). They seemed acceptable (see PM review, Appendix 4.3).

**Table 2.2.8.1. Recommended waiting times for re-administration with rocuronium or vecuronium after reversal with sugammadex.**

In patients with normal renal function (creatinine clearance $\geq$ 80 mL/min)			
Administered dose of sugammadex	Time before readministration (hours)		
	Readministration dose of 0.6 mg/kg rocuronium bromide	Readministration dose of 1.2 mg/kg rocuronium bromide	Readministration dose of 0.1 mg/kg vecuronium bromide
2 (mg/kg)	6 hours	No waiting time	10 hours
4 (mg/kg)	8 hours	2 hours	12 hours
16 (mg/kg)	12 hours	6 hours	16 hours

The basis for proposed waiting times for rocuronium and vecuronium is discussed below:

Rocuronium

- For rocuronium, the re-administration will be effective when the surplus in moles of rocuronium versus Org 25969 is approximately equivalent to the standard intubating dose of 0.6 mg/kg rocuronium. In that case onset time can be expected to be essentially similar to that after a standard intubating dose of 0.6 mg/kg.
- The molecular weight of rocuronium is 609.70 while the molecular weight of Org 25969 is 2178. Hence, in terms of moles (Weight in Grams/Molecular Weight) a 1.2 mg/kg dose of rocuronium is equivalent to 4 mg/kg of Org 25969.

Vecuronium

- The molecular weight of vecuronium is 637.74 which is similar to that of rocuronium (609.70).
- The vecuronium dose used for intubation (0.1 mg/kg) is lower than rocuronium doses used for intubation (0.6 to 1.2 mg/kg).

Currently, there is no clinical experience on the waiting time for re-administration of rocuronium or vecuronium in patients for intubation who are initially administered Org 25969 and rocuronium or vecuronium. Individual variation in waiting time is anticipated.

### **2.2.9 Does sugammadex interfere with laboratory tests?**

*In vitro* studies were conducted to study possible effects of Org 25969 and Org 48302 on clinical chemistry analyses (19.4.004 and 19.4.007). Overall, sugammadex or Org 48302 does not interfere with laboratory tests with the possible exception of the serum progesterone assay and some coagulation parameters [APTT, PT and PT(inr)]. This interference was observed in plasma samples spiked with a concentration of sugammadex (100 µg/mL) in the same range as obtained for C<sub>max</sub> after a dose of 8 mg/kg.

## **2.3 Intrinsic Factors**

### **2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the safety or efficacy?**

The Sponsor evaluated the effect of the following intrinsic factors on exposure and PD response to sugammadex: age, gender, race, renal impairment, and hepatic impairment. As described below, renal impairment affected sugammadex exposure. In renal impairment patients, exposure increased 15-fold compared to healthy subjects.

### **2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

#### **2.3.2.1 Elderly (Study 305)**

In Study 305, (b) (4) (2 mg/kg) has been administered to a total of 102 geriatric patients (ASA 1-3): 62 patients (65-74 years) and 40 patients (>75 years). The time to recovery from neuromuscular blockade induced by rocuronium (0.6 mg/kg) following administration of 2.0 mg/kg (b) (4)<sup>TM</sup> given at the first signs of recovery (reappearance of T<sub>2</sub>) was compared with 48 adult patients (18-64 years).

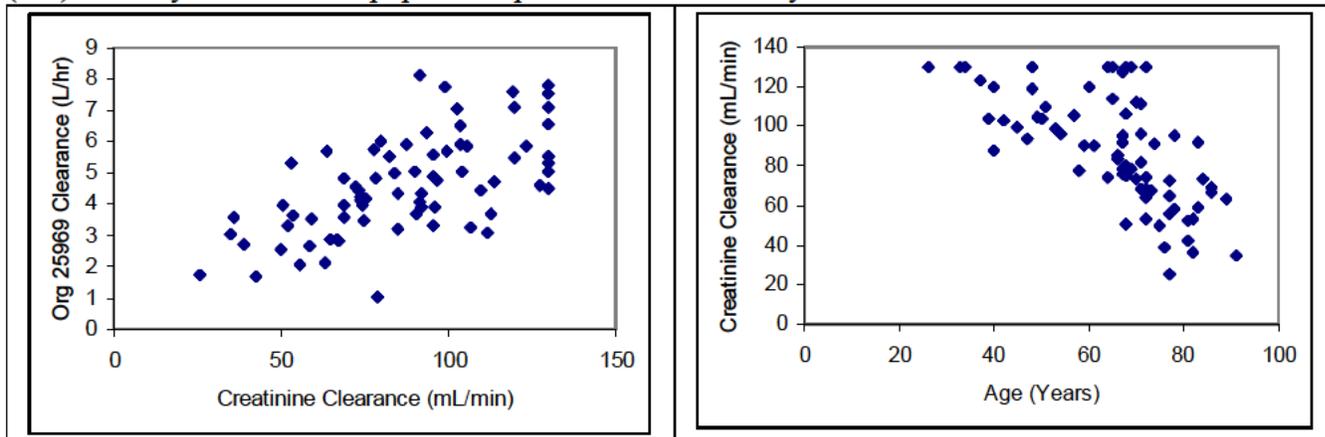
Increased exposure of sugammadex was observed with increased age which is attributed to decrease in renal function with age (Table 2.3.2.1.1).

**Table 2.3.2.1.1. Median values of demographic variables and pharmacokinetic parameters by age group (Study 305).**

Age group	Age [years]	Weight [kg]	CL <sub>CR</sub> [mL/min]	CL [L/min]	V <sub>c</sub> [L]	V <sub>ss</sub> [L]	t <sub>1/2,eff</sub> [min]
18 - 64 years	48.5	84	104	0.103	4.36	20.99	141.3
65 - 74 years	68	86.1	84.8	0.076	4.42	21.05	192.5
>= 75 years	81	71.5	58.6	0.052	3.98	20.61	273.1

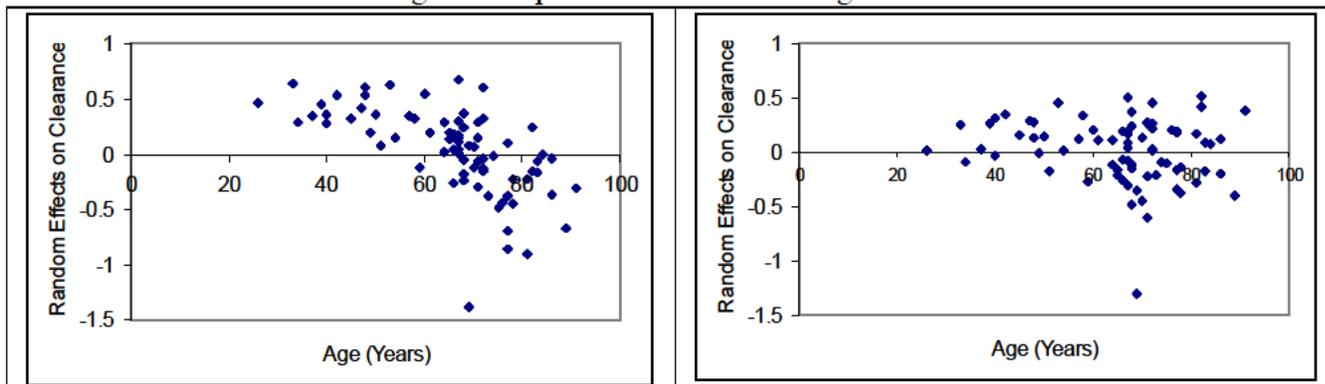
V<sub>ss</sub> was calculated as V<sub>ss</sub>=V<sub>c</sub>+V<sub>2</sub>+V<sub>3</sub>. t<sub>1/2,eff</sub> was calculated as t<sub>1/2,eff</sub>= ln(2)\*(V<sub>ss</sub>/CL).

Figure 2.3.2.1.1 shows the relationship between creatinine clearance and Org 25969 clearance (L/h) in Study 305 based on population pharmacokinetic analysis.



**Figure 2.3.2.1.1. (Left) Relationship between Org 25969 clearance (L/hr) and creatinine clearance (mL/min). (Right) Relationship between creatinine clearance and age (years).**

After inclusion of creatinine clearance as covariate in the population pharmacokinetic analysis, there is no additional effect of age on the pharmacokinetics of Org 25969 as shown in Figure 2.3.2.1.2. Note the trend between random effects of clearance versus age before accounting for renal function differences with age as shown in Figure 2.3.2.1.1 above. After inclusion of age in the analysis, there is no trend between random effects of clearance versus age, indicating that there is no additional effect of age on the pharmacokinetics of Org 25969.



**Figure 2.3.2.1.2. (Left) Relationship between random effects of clearance versus age prior to inclusion of age in the population pharmacokinetic analysis (Right) Relationship between random effects of clearance versus age after inclusion of age in the population pharmacokinetic analysis.**

For efficacy evaluation, with increased age, there is an increased time in recovery from NMB following sugammadex administration (Table 2.3.2.1.2) even though PK showed higher exposure of sugammadex. The sponsor did not propose dose adjustment for elderly.

**Table 2.3.2.1.2. Summary of the time (min:sec) from start of administration of IP to recovery of the T4/T1 ratio to 0.9 by age group (Intent-to-Treat group).**

		Age group			
		Adult	Geriatric		
		18-64 (N=48)	65-74 <sup>*</sup> (N=62)	75+ (N=40)	Subtotal <sup>*</sup> (N=102)
Including imputed data	n	48	62	40	102
	Geom. mean	2:16	2:34	3:36	2:56
	Mean (SD)	2:32 (1:21)	2:55 (1:38)	3:56 (1:40)	3:19 (1:43)
	Median	2:11	2:33	3:37	2:56
	Min.-max.	1:10 - 7:25	0:54 - 8:49	1:01 - 9:55	0:54 - 9:55
Complete cases	n	45	57	35	92
	Geom. mean	2:08	2:24	3:22	2:44
	Mean (SD)	2:19 (1:03)	2:39 (1:26)	3:41 (1:38)	3:03 (1:35)
	Median	2:06	2:27	3:29	2:47
	Min.-max.	1:10 - 6:11	0:54 - 8:49	1:01 - 9:55	0:54 - 9:55

### 2.3.2.2 Pediatric Patients (Study 306)

Although the Sponsor initiated a study in pediatric patients (Study 306) (b) (4) The Sponsor requested a deferral for pediatric assessment for this product.

### 2.3.2.3 Gender (Study 102)

The PK of sugammadex is similar in female and male subjects. No statistically significant gender effects were observed for AUC, CL, wn-CL, wn-Vss,  $t_{1/2\beta}$ , MRT and fe as demonstrated by data from Study 102.

**Table 2.3.2.3.1. PK results for gender comparison (Study 102).**

Parameter (unit)	Ethnic Group	Point Estimate of $\mu(\text{females})/\mu(\text{males})$	95% Confidence Interval
dn-AUC <sub>0-∞</sub> ( $\mu\text{g}\cdot\text{min}/\text{mL}/\text{mg}$ )	Overall (n=14 vs n=14)	1.08	1.00-1.16
	Japanese (n=7 vs n=7)	1.13	1.02-1.26
	Caucasian (n=7 vs n=7)	1.02	0.92-1.13
t <sub>1/2</sub> (min)	Overall (n=14 vs n=14)	0.92	0.80-1.06
	Japanese (n=7 vs n=7)	1.03	0.85-1.26
	Caucasian (n=7 vs n=7)	0.82	0.67-1.00
CL (mL/min)	Overall (n=14 vs n=14)	0.93	0.86-1.00
	Japanese (n=7 vs n=7)	0.88	0.80-0.98
	Caucasian (n=7 vs n=7)	0.98	0.88-1.09
wn-CL (mL/min/kg)	Overall (n=14 vs n=14)	1.05	0.98-1.13
	Japanese (n=7 vs n=7)	1.01	0.91-1.12
	Caucasian (n=7 vs n=7)	1.10	0.99-1.22
V <sub>ss</sub> (mL)	Overall (n=14 vs n=14)	0.89	0.81-0.97
	Japanese (n=7 vs n=7)	0.90	0.79-1.03
	Caucasian (n=7 vs n=7)	0.87	0.77-0.99
wn-V <sub>ss</sub> (mL/kg)	Overall (n=14 vs n=14)	1.01	0.93-1.09
	Japanese (n=7 vs n=7)	1.03	0.92-1.15
	Caucasian (n=7 vs n=7)	0.98	0.88-1.09

In the pooled population analysis of the PK of sugammadex as part of the PK/PD interaction model, gender was not identified as a significant covariate, confirming the absence of a gender effect on the PK of sugammadex.

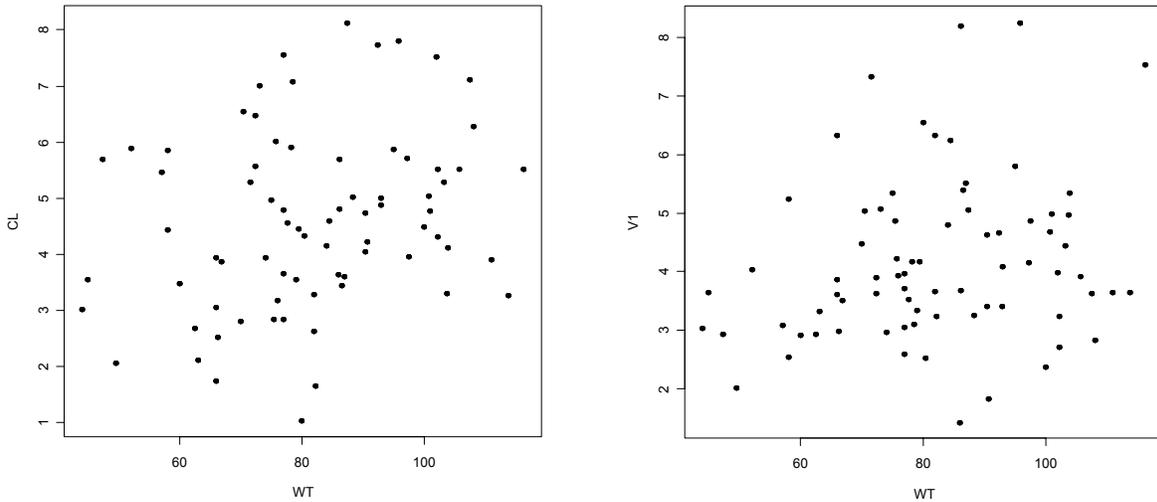
#### 2.3.2.4 Race (Study 102)

The race information is mainly for Caucasians and Japanese. Data from Study 102 suggested no major differences in PK of sugammadex between Japanese and Caucasian subjects (Tables 2.2.6.9.1 and 2.3.2.3.1). CL was 9% lower and V<sub>ss</sub> was 12% lower in the Japanese compared to the Caucasian subjects. The difference is not considered clinically relevant. After body weight normalization (wn-), CL and V<sub>ss</sub> were similar in both ethnic groups. As of note, the dose was body-weight based and there is no clear body weight effect on the PK of sugammadex based on population PK analysis (see Section 2.3.2.5).

The pooled data set used in the population PK/PD evaluation containing data from a total of 709 subjects included 13 Black subjects and 6 subjects of other race. These relatively low numbers did not allow for separate evaluation of these race effects on the PK of sugammadex.

#### 2.3.2.5. Body weight

Population PK analysis showed no relevant relationship of clearance and volume of distribution with body weight. Figure 2.3.2.5.1 shows the effect of bodyweight on the clearance and volume of distribution of central compartment in Study 19.4.305. No clear weight effect can be seen on the PK parameters of Org 25969. See PM review for details (Appendix 4.3).



**Figure 2.3.2.5.1. Relationship between clearance, volume of distribution and body weight in Study 19.4.305.**

2.3.2.6 Renal impairment (Study 304)

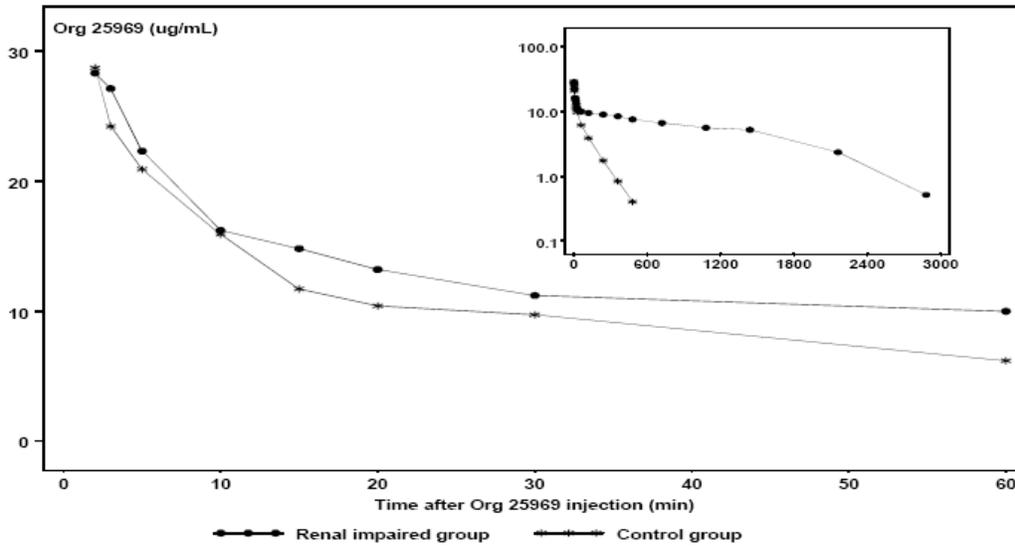
In Study 304, (b) (4) (2 mg/kg) has been administered to a total of 30 patients: 15 renally impaired subjects (Clcr < 30 mL/min, severe, ASA 1-3) and 15 control subjects (CLcr ≥ 80 mL/min, ASA 1-2). As expected, renal function affects sugammadex PK. In severely renal impaired patients (including 9 patients who were on hemodialysis) CL of sugammadex was reduced approximately 16-fold and  $t_{1/2\beta}$  increased 15-fold compared to normal patients. Vss of sugammadex was increased 25% compared to normal patients. This resulted in a 17-fold higher exposure to sugammadex in renal impaired patients (Table 2.3.2.6.1). As of note, 52% of AUC was based on extrapolation for patient with severe renal impairment and may lead to inaccurate estimatin of AUCinf. The effect on Cmax was little. During the first 60 minutes post administration of Org 25969 there was little difference in plasma levels between the two groups (Figure 2.3.2.6.1).

Sugammadex and rocuronium complex was not efficiently removed from plasma using low flux filter (5 subjects), consistent with the *in vitro* dialysis finding, High flux filter showed a variable effectiveness for removing sugammadex and rocuronium (4 subjects) while *in vitro* dialysis study suggested that high flux filter could efficiently remove sugammadex and rocuronium.

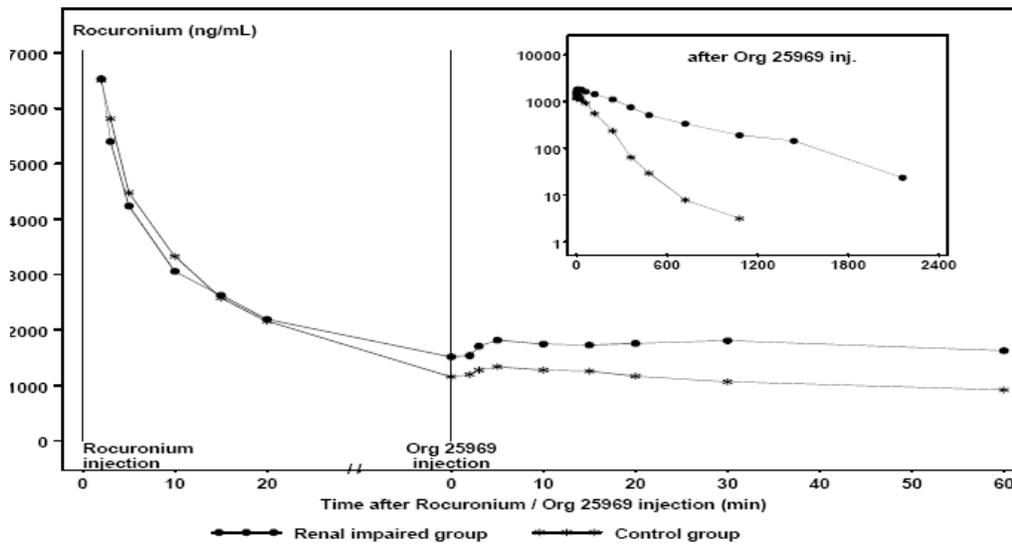
**Table 2.3.2.6.1. Summary of the plasma PK parameters of Org 25969 and rocuronium.**

		Org 25969		rocuronium	
		Control	Renally impaired	Control	Renally impaired
<b>t<sub>1/2, β</sub> (min)</b>	Mean	139	2139	179	450
	CV (%)	44.4	121	67.5	39.9
<b>t<sub>1/2, effective</sub> (min)</b>	Mean	100	2003	79.6	366
	CV (%)	25.5	132	29.2	52.7
<b>AUC<sub>0-inf</sub> (μg·min·mL<sup>-1</sup>)</b>	Mean	1728	27463	296	1084
	CV (%)	34.8	114	37.4	53.8
<b>AUC-extrapolated (%)</b>	Median	2.37	52.3	0.199	4.12
	Range	0.933–4.32	3.59-88.4	0.0590–0.627	0.0546 – 22.7
<b>CL (mL·min<sup>-1</sup>)</b>	Mean	95.2	5.53	167	41.8
	CV (%)	22.1	108	30.8	46.9
<b>V<sub>ss</sub> (mL)</b>	Mean	13800	15986	19125	22092
	CV (%)	20.5	35.5	28.3	29.9
<b>MRT (min)</b>	Mean	145	2890	115	528
	CV (%)	25.5	132	29.2	52.7

In the same study, it was found that renal impairment also affected PK of rocuronium (in the presence of sugammadex) but to a lesser extent. CL of rocuronium in the presence of Org 25969 was reduced approximately 3.7-fold and t<sub>1/2,β</sub> increased 2.5-fold in severely renal impaired patients compared to normal patients (Table 2.3.2.6.1). V<sub>ss</sub> of rocuronium was increased with 25% compared to normal patients. This resulted in a 4-fold higher exposure to rocuronium (bound and unbound) in renal impaired subjects. The much smaller effect of renal impairment on the t<sub>1/2,β</sub> of rocuronium than on that of Org 25969 suggests that a substantial portion of rocuronium was eliminated via the liver, despite the presence of excess binding agent. Urinary excretion of Org 25969 and rocuronium was much slower in the renal impaired subjects than in the control subjects (Table 2.3.2.6.1 and Figure 2.3.2.6.2). The data indicate that rocuronium, even in the presence of excess sugammadex, can still be cleared hepatically to a substantial degree.

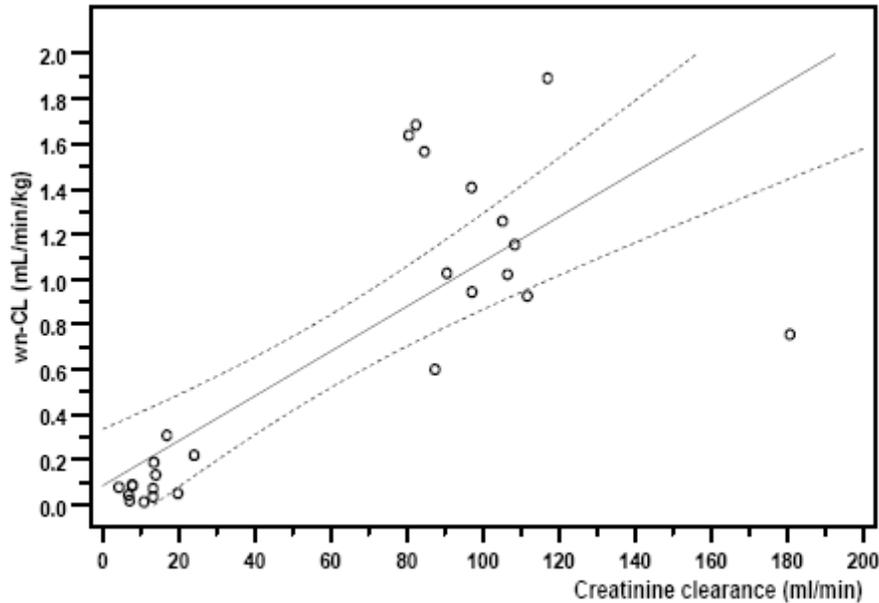


**Figure 2.3.2.6.1. Median Org 25969 concentration versus time plots.**



**Figure 2.3.2.6.2. Median Rocuronium concentration versus time plot.**

PK and safety of sugammadex was not studied in young adult patients with mild or moderate renal impairment patients. Based on the fact that sugammadex is mainly eliminated unchanged in urine, a proportional relationship of PK with CL<sub>cr</sub> may be expected. Correlation plots were made of individual weight-normalized (wn) CL against the creatinine clearance (Figure 2.3.2.6.3). Regression analysis showed that the correlation of wn-CL and CL<sub>cr</sub> is highly significant. Increase in AUC and half-life in mild or moderate renal impairment patients is expected as compared to patients with normal renal function.



**Figure 2.3.2.6.3. Regression plots of the Org 25969 wn-CL vs. CLcr.**

Effect of mild and moderate renal impairment on sugammadex PK and PD was obtained from a study in elderly patients (Study 305). The study suggested that renal impairment is the main covariate that affected sugammadex PK and there was no additional effect from age (see Section 2.3.2.1).

The sponsor evaluated the effect of renal function on the pharmacokinetics of Org 25969 using data from all the studies in the development of PK model for rocuronium-Org 25969 interaction. The relationship between clearance of Org 25969 and creatinine clearance was described using a linear model which is described below:

$$CL_{\text{Org25969}} = 87 \text{ mL / min} + 0.6 \bullet (\text{Creatinine Clearance} - 105.44)$$

Based on this equation, sponsor proposes the following table in the label.

(b) (4)

The model seems to project higher clearance in severely renally impaired patients (based on CLcr) than clearance observed in Study 304.

An equation of  $CL=4.46(CL_{cr}/88)^{0.941}$  was found to best describe the data (see PM review) and data for severe renal impairment patients were found to fit into the same relationship.

Efficacy evaluation based on a mean time from start of administration of sugammadex to recovery of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9 suggested that efficacy is comparable between the two groups: 2 minutes for the renally impaired subjects, and 1 min:39 sec for the control subjects (Table 2.3.2.6.2).

**Table 2.3.2.6.2. Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T<sub>4</sub>:T<sub>1</sub> ratio to 0.9 by subject group.**

	Subject group	
	CR <sub>CL</sub> <30 ml/min (N=15)	CR <sub>CL</sub> ≥80 ml/min (N=14)
n	15	14
Mean (SD)	2:00 (0:43)	1:39 (0:38)
Median	1:38	1:25
Min. - max.	1:09 - 3:41	0:58 - 3:05

The Sponsor concluded that there were no appreciable differences in terms of safety between the two groups. Per discussion of this reviewer with Dr. Simone (Medical Officer for safety review), this will be addressed in his review.

The Sponsor proposes no dose adjustment for mild or moderate renal impairment patients and they strongly discourage usage of sugammadex in severe renal impairment patients. We recommend contraindication in patients with severe renal impairment for the immediate reversal indication if the dose of 16 mg/kg is approved because of lack of safety database to support 16-fold increase in AUC (equivalent to a dose of 256 mg/kg in normal patients).

PK of sugammadex has not been evaluated in patients with renal impairment whose NMB are induced by vecuronium. Because vecuronium or rocuronium shows little effect on sugammadex PK, the studies conducted with rocuronium-induced NMB (Study 304) may be extrapolable to vecuronium-induced NMB.

#### 2.3.2.7 Hepatic Impairment (simulation)

No study has been conducted in patients with hepatic impairment because sugammadex is mainly eliminated in the kidney. However, hepatic impairment would affect PK of rocuronium. The Sponsor applied the population PK/PD interaction model with rocuronium to simulate the reversal of rocuronium-induced neuromuscular blockade (NMB) by sugammadex in hepatic impairment patients.

The pharmacokinetics of rocuronium was evaluated in 10 normal subjects and 9 patients with alcoholic liver cirrhosis (Organon Study P021-009). The study showed that the pharmacokinetic parameters of rocuronium were altered in the presence of severe liver impairment as shown in Table 2.3.2.7.1. Using the PK/PD model with the assumptions of PK changes for rocuronium

and/or Org 25969, the sponsor simulated the recovery time of  $T_4/T_1$  to 0.9 for the following scenarios:

**Scenario 1: Org 25969 administration 3 minutes after rocuronium**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 12, 16 or 20 mg/kg Org 25969 was administered iv 3 minutes after rocuronium administration.

**Scenario 2: Org 25969 administration 15 minutes after rocuronium**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 2, 4 or 8 mg/kg Org 25969 was administered iv 15 minutes after rocuronium administration.

**Scenario 3: Org 25969 administration at reoccurrence of  $T_2$**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 2 or 4 mg/kg Org 25969 was administered iv at reoccurrence of  $T_2$ .

**Table 2.3.2.7.1. Summary of observed PK changes for rocuronium in patients with severe hepatic impairment relative to normal. Shown are assumptions of PK changes for Org 25969 in subjects with hepatic impairment.**

	CL	Vc	Vp1	Vp2
Rocuronium PK changes in hepatic impairment relative to normal	↓ 21%	↑ 52%	↑ 74%	↑ 141%
Org 25969 PK changes in hepatic impairment relative to normal	↔	↔	↔	↔
Org 25969 PK changes in hepatic impairment relative to normal	↔	↑ 52%	↑ 74%	↑ 141%

The PK/PD model for rocuronium links the first peripheral compartment concentrations to the TOF ratio. Due to increase in volume of distribution of rocuronium and Org 25969 into central and second peripheral compartment, one would expect that the concentrations in the first peripheral compartment would be lower in patients with hepatic impairment. The onset will be slightly delayed. With lower concentrations of Org 25969 to bind to rocuronium due to greater distribution volume, the recovery will be slower which is dependent on (A) Dose of Org 25969 (B) Time between the administration of rocuronium and Org 25969. The information on recovery times in patients with hepatic impairment was calculated and is shown in Table 2.3.2.7.2 below.

**Table 2.3.2.7.2. Time to recovery of T<sub>4</sub>/T<sub>1</sub> ratio of 0.9 in patients with and without severe hepatic impairment.**

(b) (4) dose/ time point of administration	Normal patient (minutes)	Severe hepatic impairment (minutes)
2 mg/kg at reappearance of T <sub>2</sub> after 0.6 mg/kg rocuronium bromide.	1.86	4.38
4 mg/kg, 15 minutes after 0.6 mg/kg rocuronium bromide.	1.76	3.43
16 mg/kg , 3 minutes after 1.2 mg/kg rocuronium bromide.	1.32	1.90

A prolongation of recovery time in hepatic impaired patients was predicted. Refer to PM review (Appendix 4.3) for details. For better clinical guidance, a study in hepatic impairment patients should be conducted to confirm the above projection.

## 2.4 Extrinsic Factors

### 2.4.1 *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?*

Because sugammadex is an IV drug, the most significant extrinsic factors that could affect PK or PD are from comedications that patients may receive during surgery or commonly-prescribed drugs. The Sponsor evaluated the effects of drug-drug interactions based on evaluation for potenatil complexation of sugammadex with drugs other than rocuronium or vecuronium.

### 2.4.2 *Drug-drug interaction*

#### 2.4.2.1 Is there an in vitro basis to suspect drug-drug interaction?

*In vitro* metabolism or transport study for sugammadex has not been conducted. Drug interactions via CYP inhibition or induction are not anticipated. Sugammadex is not likely to be metabolized by CYP enzymes and susceptible to drug interaction with CYP inhibitors or inducers because of large molecular size and 3-dimentional structure of sugammadex, limited metabolism observed *in vivo*, and limited liver distribution as suggested by the animal studies. Sugammadex also is not likely to affect other drugs' metabolism as an inhibitor or inducer because of limited liver distribution and single-use nature.

However, transport-based drug-drug interaction cannot be ruled out. Sugammadex may affect other drugs' transport in the kidney. Transport-based drug-drug interactions were not studied.

#### 2.4.2.2 What co-medications are likely to be administered to the target patient population?

Three major kinds of drugs were likely to be administered to the target patient population: drugs commonly used in anesthesia; drugs that are most frequently prescribed; and steroidal molecules.

#### 2.4.2.7 What are the in vivo drug-drug interaction studies for sugammadex?

Drug interaction of sugammadex and rocuronium/vecuronium was evaluated based on PK assessments from various studies. With regard to drugs other than rocuronium or vecuronium, potential drug-drug interactions based on complexation with sugammadex have been evaluated using in-vitro assessments, preclinical assessment, and PK/PD modeling.

#### ***Effects of Other Drugs on Sugammadex***

***Rocuronium and Vecuronium:*** The presence of rocuronium or vecuronium showed little effect on PK of sugammadex.

***Other Drugs:*** The displacement interaction potential caused by the presence of a third drug either before or after sugammadex administration was evaluated using a PK/PD model. Three major kinds of drugs were evaluated by the model: drugs commonly used in anesthesia; drugs that are most frequently prescribed; and steroidal molecules. The brief description of the model is described in the modeling section. Toremifene, flucloxacillin and fusidic acid were identified to carry a risk of displacement interaction with sugammadex. Only toremifene is currently marketed in the U.S.. Tamoxifen, a structurally-similar molecule to toremifene was used in the clinical studies. The data suggested recurarization in some patients who were on tamoxifen. As of note, tamoxifen showed lower affinity to sugammadex than toremifene and fell below the critical line based on the modeling. The clinical database also suggested corticosteroid coadministration may contribute to recurarization in some patients. The label will need to include cautionary languages for drugs with steroidal structures. Refer to PM review (Appendix 4.3) for detailed evaluation of the PK/PD model in drug interaction prediction.

#### ***Effects of Sugammadex on Other Drugs***

***Rocuronium and Vecuronium:*** Sugammadex affects PK of rocuronium and vecuronium as indicated by increased plasma concentrations, decreased elimination half-life, and decreased total clearance. With increased doses of sugammadex, increased amount of rocuronium was recovered in urine. In vitro assay also suggest that sugammadex decreases plasma protein binding of rocuronium or vecuronium.

The following tables list the PK parameters for rocuronium from Study 101.

**Table 2.4.2.7.1. Summary of the pharmacokinetic parameters of rocuronium in plasma.**

Rocuronium Parameter	Org 25969 Dose						
	0.1 mg/kg (n=1) *	0.5 mg/kg (n=1) *	1 mg/kg (n=2) #	2 mg/kg (n=2) #	4 mg/kg (n=2) #	8 mg/kg (n=2) #	Placebo (n=10) #
AUC <sub>0-∞</sub> (mcg*min/mL)	200	158	182 (9.46)	302 (12.1)	364 (25.4)	331 (6.75)	139 (20.9)
dn-AUC <sub>0-∞</sub> (mcg*min/mL/mg)	4.27	3.67	4.02 (9.54)	6.46 (2.13)	8.27 (16.7)	7.43 (4.26)	3.06 (19.4)
CL (mL/min)	234	272	249 (9.54)	155 (2.13)	121 (16.7)	135 (4.26)	327 (19.4)
V <sub>z</sub> (mL)	38085	34390	22354 (17.3)	15124 (6.43)	12487 (3.23)	15434 (12.3)	49310 (24.7)
t <sub>1/2,β</sub> (min)	113	87.5	62.3 (7.66)	67.7 (4.29)	71.6 (13.4)	79.5 (16.6)	104 (21.0)

\* individual parameter presented; # geometric mean (geometric coefficient of variation) presented;

**Table 2.4.2.7.2. Summary of urinary excretion of rocuronium.**

Rocuronium Parameter	Org 25969 Dose						
	0.1 mg/kg (n=1) *	0.5 mg/kg (n=1) *	1 mg/kg (n=2) *	2 mg/kg (n=2) *	4 mg/kg (n=2) *	8 mg/kg (n=2) *	Placebo (n=10) #
Total Amount Excreted (% dose)	18.9	21.5	24.7	32.1	44.0	39.2 <sup>c</sup>	14.3 (34.0)
t <sub>1/2,u</sub> (h)	14.7	4.48	23.7 8.08	12.9 5.53	6.42 1.53	1.68 1.63	11.7 (52.5)

\* individual parameter presented; # geometric mean (geometric coefficient of variation) presented; n.c.: not calculable; <sup>c</sup> underestimated value due to missing urine concentrations;

**Other Drugs:** The capturing interaction potential caused by complexation between a third drug and sugammadex and thus reduces the clinical effect of the third drug was evaluated using the PK/PD model. A clinically relevant interaction cannot be ruled out for hormonal contraceptives. Refer to PM review (Appendix 4.3) for detailed evaluation of the PK/PD model.

## 2.5 General Biopharmaceutics

### 2.5.1 What is formulation (quantitative composition) of sugammadex injection solution?

Org 25969 Solution for Injection 100 mg/mL is a clear, colorless to slightly yellow aqueous solution for injection filled in 2 R DIN (2 mL solution per vial) or 6 R DIN (5 mL solution per

vial) glass vials. Its composition is given in Table 2.5.1.1. Org 25969 drug product contains both Org 25969 and the related  $\gamma$ -cyclodextrin compound Org 48302 that is present at concentrations up to 7% in the drug substance.

**Table 2.5.1.1. Complete composition Org 25969 solution for injection 100 mg/mL (2 mL per vial).**

Component	Reference to quality standard	Function(s)	Quantity per vial (2.0 mL <sup>1</sup> )	Quantity per mL
Org 25969 + Org 48302 <sup>2</sup>	In-house standard	Drug substance	200 mg	100 mg
Sodium hydroxide <sup>3</sup>	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5
Hydrochloric acid <sup>3</sup>	Ph. Eur., NF, JP	pH adjuster	q.s. to pH 7.5	q.s. to pH 7.5

(b) (4)

1 Extractable volume

2 Declared amount of 100 mg/mL drug substance corresponds with 108.8 mg/mL Org 25969 (sodium salt)

(b) (4)

**2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?**

Not applicable because sugammadex is intended for IV injection.

**2.5.3 What is the formulation development process for (b) (4) Was the to-be-marketed formulation used in the pivotal clinical trials?**

The to-be-marketed formulation was used in the pivotal clinical studies.

During development, two different formulation strengths have been used: a 25 mg/mL solution and a 100 mg/mL solution (to-be-marketed). For the 25 mg/mL solution (b) (4)

The drug product specification of pH 7.5 was applied from clinical batch CW157 onwards,

The concentration of 25 mg/mL was used in the early development (clinical phases 1 and 2): studies 101, 1202, 201 and 207. The later clinical studies including pivotal Phase 3 studies used the to-be-marketed formulation.

Because (b) (4) is a solution intended for intravenous administration, the changes in formulations (b) (4) are not likely to affect the bioavailability. No relative BA study is needed to link the old and new formulations.

**2.5.4 Has the Sponsor developed an appropriate dissolution method and specifications that will ensure in vivo performance and quality of the product?**

Not applicable because the drug product is intended for IV injection.

**2.6 Analytical**

**2.6.1 What active moieties were measured in the plasma and other biological fluids in the clinical pharmacology and biopharmaceutics studies?**

Sugammadex, Org 48032, rocuronium and vecuronium were identified and measured in the plasma and urine.

**2.6.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The analytical methods measured total concentrations of sugammadex and Org 48032 in human plasma and urine. Assay interference from rocuronium was checked during assay validation. It should be noted that the assay methods used to determine sugammadex and rocuronium do not discriminate between complexed (sugammadex-rocuronium complex) and non-complexed sugammadex and rocuronium. Thus, concentrations in plasma pertain to total concentrations of sugammadex and rocuronium in plasma.

**2.6.3 What bioanalytical methods are used to assess concentrations?**

Individual method information, including linear range, sensitivity, quality control concentrations, precision and accuracy, is presented in the following tables. Overall, the analytical methods adequately determined the concentrations of the compounds of interest.

**Table 2.6.3.1. Summary of Analytical Methods.**

Analytes	Matrix	Internal Standard	LOQ	Linear Range	Intra-Assay Precision (CV)	Intra-Assay Precision (CV)	Long-Term Stability at -20°C
Sugammadex	Urine	(b) (4)	100 µg/mL	100-1000 µg/mL	2.5%-4.1%	3.6%-6.9%	6 mo and 24 d
			5 µg/mL	5-200 µg/mL	1.6%-5.1%	3.0%-5.6%	8 mo and 18 d
Plasma	0.1 µg/mL		0.1-40 µg/mL	3.4%-5.6%	4.9%-7.3%	1 yr 11 mo and 16 d	
Org 48032	Urine		0.5 µg/mL	0.5-50 µg/mL	4.3%-6.3%	4.8%-6.2%	12 mo and 8 d
	Plasma		0.2 µg/mL	0.2-20 µg/mL	3.2%-7.6%	4.7%-13%	12 mo and 11 d
Rocuronium	Urine		0.05 µg/mL	0.05-10 µg/mL	2.5%-7.6%	2.4%-9.2%	1 yr and 4 mo
	Plasma		0.1 ng/mL	0.1-100 ng/mL	2.3%-17.8%	3.0%-14.4%	6 mo and 19 d
			2 ng/mL	2-1000 ng/mL	3.2%-11.2%	5.9%-14.5%	31 mo
Vecuronium	Plasma	5 mg/mL	5-1000 ng/mL	3.5%-5.9%	5.8%-7.0%	11 mo	

**Sugammadex**

Assay	Method name	Method description	Validation reports	Validation report code
1	LC-MS assay for the determination of Org 25969 in human urine	Org 25969 and its internal standard (b) (4) are isolated from human urine (after addition of blank human plasma for stabilization) using solid-phase extraction. Liquid chromatography coupled to mass spectrometry (LC-MS) using electron spray ionization in multi reaction monitoring (MRM) mode is performed in order to quantify the concentration of Org 25969 in human urine samples.	Validation of the LC-MS assay for the determination of Org 25969 in human urine by liquid chromatography with mass spectrometric detection <i>Amendment I</i> Long-term stability of Org 25969 in human urine <i>Amendment II</i> Revalidation of the LC-MS assay for the assessment of 5-200 µg Org 25969 per mL human urine <i>Amendment III</i> Long-term stability for concentrations of 5-200 µg Org 25969 per mL human urine <i>Amendment IV</i> Selectivity of Org 9426 on Org 25969 for concentrations of 5-200 µg Org 25969 per mL human urine <i>Amendment V</i> 250-fold dilution for concentrations of 5-200 µg Org 25969 per mL human urine	NL0035843  NL0040076  NL0045323  NL0051399  NL0060104  NL0067326
2	LC-MS assay for the determination of Org 25969 in human plasma	Org 25969 and its internal standard (b) (4) are isolated from human plasma by solid-phase extraction. LC-MS using electron spray ionization in MRM mode is performed in order to quantify the concentration of Org 25969 in human plasma samples.	Validation of the LC-MS assay for the determination of Org 25969 in human plasma <i>Amendment I</i> Long-term stability of Org 25969 in human plasma <i>Amendment II</i> <i>Amendment III</i>  Additional validation of the LC-MS assay for the determination of Org 25969 in human plasma. Assessment of the accuracy in incurred samples, long-term stability and interference of Org 9426	NL0033768  NL0039962  NL0052776 NL0054620  NL0052757

**Org 48032**

Assay	Method name	Method description	Validation reports	Validation report code
3	LC-MS assay for the determination of Org 48302 in human urine	Org 48302 and its internal standard (b) (4) are isolated from human urine (after addition of human heparin plasma for stabilization) by solid phase extraction. LC-MS using electron spray ionization in MRM mode is performed in order to quantify the concentration of Org 48302 in human urine samples.	Validation of the LC-MS assay for the determination of Org 48302 in human urine <i>Amendment I</i> long-term stability  Re-validation of the LC-MS for the determination of Org 48302 (in the presence of Org 25969) in human urine <i>Amendment I</i> long-term stability	NL0063322  NL0064905  INT00006784  INT00036821
4	LC-MS assay for the determination of Org 48302 in human plasma	Org 48302 and its internal standard (b) (4) are isolated from human heparin plasma by solid phase extraction. LC-MS using electron spray ionization in MRM mode is performed in order to quantify the concentration of Org 48302 in human heparin plasma samples.	Validation of the LC-MS assay for the determination of Org 48302 in human heparin plasma <i>Amendment I</i> long-term stability  Re-validation of the LC-MS for the determination of Org 48302 (in the presence of Org 25969) in human plasma <i>Amendment I</i> <i>Amendment II</i> long-term stability	NL0063381  NL0066903  INT00006478  INT00033079 INT00036818

**Rocuronium**

Assay	Method name	Method description	Validation reports	Validation report code
5	LC-MS assay for the determination of Org 9426 in human urine	Org 9426 and its internal standard (b) (4) are determined in human urine using dilution as sample preparation. Liquid chromatography coupled to mass spectrometry (LC-MS) using electron spray ionization in multi reaction monitoring (MRM) mode is performed in order to quantify the concentration of Org 9426 in human urine samples.	Validation of the LC-MS assay for the determination of Org 9426 in human urine <i>Amendment I</i> <i>Amendment II</i> <i>Amendment III</i> (selectivity with respect to Org 25969) Bioanalytical report on clinical trial 194101 (see section 2.2.4)	NL0034539  NL0042020 NL0050494 NL0060079  NL0041698
6	LC-MS assay for the determination of Org 9426 in human plasma	Org 9426 and its internal standard (b) (4) are isolated from human plasma by solid phase extraction. LC-MS using electron spray ionization in MRM mode is performed in order to quantify the concentration of Org 9426 in human plasma samples.	Validation of the LC-MS assay for the determination of Org 9426 in human plasma by liquid chromatography with mass spectrometric detection <i>Amendment I</i> (assessment influence Org 25969) <i>Amendment II</i> <i>Amendment III</i>  Revalidation of the LC-MS assay for the determination of Org 9426 in human plasma and a cross validation of it with a GC-NPD method <i>Amendment I</i> (selectivity with respect to Org 25969) <i>Amendment II</i> <i>Amendment III</i>	NL0031240  NL0035161 NL0037368 NL0041906  NL0046784  NL0055970 INT00024249 INT00032278

### ***Vecuronium***

Assay	Method name	Method description	Validation reports	Validation report code
8	LC-MS assay for the determination of Org NC 45 in human plasma	Org NC 45 and its internal standard (b)(4) are isolated from human plasma by solid phase extraction. LC-MS using electron spray ionization in MRM mode is performed in order to quantify the concentration of Org NC 45 in human plasma samples.	Validation of the LC-MS assay for the determination of Org NC 45 in human plasma <i>Amendment I</i> (assessment influence Org 25969) <i>Amendment II</i> (assessment influence Org 25969)	NL0050966  NL0052464  NL0059979

### **3 LABELING RECOMMENDATIONS**

Line-by-line recommendations for labeling will be included in a separate review at a later time.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4.2 Individual Study Reviews

### 4.2.1 *In Vitro* Studies

#### 4.2.1.1 *In Vitro* Plasam Protein Binding

**Study NL0046285:** An *In Vitro* Binding Study of Org 25969 and/or Org 9426 to Male Rat, Rabbit, Cat, Dog and Human Plasma Proteins

**Objectives:** To determine the extent of binding of [<sup>14</sup>C]-Org 25969 to male rat, rabbit, cat, dog and human plasma proteins *in vitro*; to determine the extent of binding of [<sup>3</sup>H]-Org 9426 to male rabbit plasma proteins *in vitro*; to determine the extent of binding of [<sup>3</sup>H]-Org 9426 (rocuronium) in combination with Org 25969 to male rat, rabbit, cat, dog and human plasma proteins *in vitro*.

**Method:** The extent of binding of [<sup>14</sup>C]-Org 25969 or [<sup>3</sup>H]-Org 9426 to plasma proteins was determined by equilibrium dialysis in plasma.

The extent of *in vitro* protein binding was calculated as:

$$B(\%) = \frac{C_p - C_b}{C_p} \cdot 100\%$$

Where: B = fraction of radioactivity bound to plasma proteins  
C<sub>p</sub> = concentration of radioactivity in plasma (Bq·mL<sup>-1</sup>)  
C<sub>b</sub> = concentration of radioactivity in buffer (Bq·mL<sup>-1</sup>)

The amount of radioactivity recovered after equilibrium dialysis was calculated as:

$$R(\%) = \frac{C_p + C_b}{C_0} \cdot 100\%$$

where: R = recovery of radioactivity  
C<sub>0</sub> = added concentration of radioactivity (Bq·mL<sup>-1</sup>)

### Results:

After approximately 3 h equilibrium was reached in the plasma and buffer samples spiked with [<sup>14</sup>C]-Org 25969.

[<sup>14</sup>C]-Org 25969 did not bind to plasma proteins. This was indicated by negative binding values, which are interpreted as zero (no binding) (Table 1).

[<sup>3</sup>H]-Org 9426 in combination with Org 25969 binds to male rat, rabbit, cat, dog and human plasma proteins. Increasing the relative Org 25969 concentration decreases the [<sup>3</sup>H]-Org 9426 plasma protein binding in all species tested. At approximately equimolar concentrations of Org 9426 and Org 25969 the extent of [<sup>3</sup>H]-Org 9426 binding is zero (Table 2 and Figure 1). In all

species tested the plasma protein binding of Org 9426 declines to 0% when the concentration ratio of Org 25969/ Org 9426 approximated 1.

**Table 1. *In vitro* binding of [<sup>14</sup>C]-Org 25969 to male human plasma proteins.**

[Org 25969] <sup>a,b</sup> (nmol·mL <sup>-1</sup> )	Binding			Recovery			
	1 (%)	2 (%)	Mean (%)	1 (%)	2 (%)	Mean (%)	
0.3	-9.4	-11.7	-10.6	99.0	98.9	99.0	
0.4	-8.1	-8.9	-8.5	100.5	99.5	100.0	
0.8	-13.7	-8.5	-11.1	98.7	97.8	98.3	
1.5	-11.2	-8.4	-9.8	99.1	100.3	99.7	
5.3	-9.6	-8.0	-8.8	101.8	100.1	101.0	
12.8	-10.0	-8.3	-9.1	98.9	99.2	99.1	
50	-8.2	-9.3	-8.7	100.9	100.3	100.6	
125	-4.9	-10.2	-7.6	99.0	101.0	100.0	
Mean binding ± SD:			-9.3 ± 1.9	Mean recovery ± SD:			99.7 ± 1.1

<sup>a</sup> All plasma and buffer samples contained 1.85 kBq·mL<sup>-1</sup> [<sup>14</sup>C]-Org 25969, which is equivalent to 0.3 nmol·mL<sup>-1</sup>.

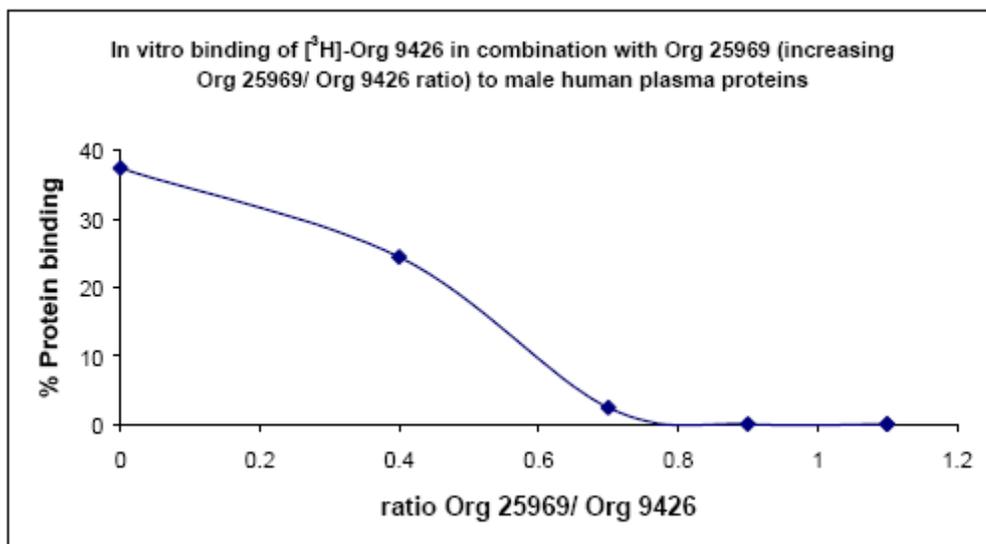
<sup>b</sup> 50% of the Org 25969/ [<sup>14</sup>C]-Org 25969 was spiked in plasma and an equal concentration of Org 25969/ [<sup>14</sup>C]-Org 25969 was spiked in buffer. The concentrations spiked are given in the table above.

**Table 2. *In vitro* binding of [<sup>3</sup>H]-Org 9426 (rocuronium) combined with Org 25969 (sugammadex) to male human plasma proteins.**

Ratio Org 25969/ Org 9426	[Org 9426] <sup>a,b</sup> (nmol·mL <sup>-1</sup> )	[Org 25969] (nmol·mL <sup>-1</sup> )	Binding			Recovery		
			1 (%)	2 (%)	Mean (%)	1 (%)	2 (%)	Mean (%)
0	0.24	0	35.5	39.3	37.4	79.6	81.3	80.4
0.4	0.35	0.125	27.0	21.9	24.4	85.4	87.7	86.5
0.7	0.7	0.5	1.6	3.3	2.4	93.6	96.8	95.2
0.9	1.4	1.25	-0.4	0.4	0.0	95.5	96.8	96.2
1.1	4.6	5	-15.0	-16.4	-15.7	96.1	101.9	99.0
1.1	11.1	12.5	-26.7	-17.5	-22.1	96.7	97.9	97.3
						Mean ± SD: 92.4 ± 7.2		

<sup>a</sup> All plasma and buffer samples contained 1.85 kBq·mL<sup>-1</sup> [<sup>3</sup>H]-Org 9426, which is equivalent to 0.0013 nmol·mL<sup>-1</sup>.

<sup>b</sup> 50% of the Org 9426/ [<sup>3</sup>H]-Org 9426 and Org 25969 was spiked in plasma and an equal concentration of Org 9426/ [<sup>3</sup>H]-Org 9426 and Org 25969 was spiked in buffer. The spiked concentrations are given in the table above.



**Figure 1.** *In vitro* binding of [<sup>3</sup>H]-Org 9426 in combination with Org 25969 (increasing Org 25969/Org 9426 ratio) to male human plasma proteins.

**Conclusions:**

- *In vitro* binding studies (equilibrium dialysis) showed that sugammadex (0.3 to 125 μM) does not bind to human plasma proteins. The concentration range studied is likely to cover the therapeutic range as the mean C<sub>max</sub> at 16 mg/kg is 90 μM.
- In the absence of sugammadex, approximately 37% of rocuronium binds to plasma proteins. The extent of protein binding declines when sugammadex was added, and none is bound to plasma proteins at equimolar concentrations of the two drugs.

4.2.1.2 In Vitro Erythrocyte Binding

**Study NL0047787:** An *In Vitro* Binding Study of Org 25969 to Male Rat, Rabbit, Cat, Dog and Human Erythrocytes and Org 9426 with or without Org 25969 to Male Human Erythrocytes

**Objectives:** To determine the extent of binding of [<sup>14</sup>C]-Org 25969 to male rat, rabbit, cat, dog and human erythrocytes *in vitro*; to determine the extent of binding of [<sup>3</sup>H]-Org 9426 to male human erythrocytes *in vitro*; to determine the extent of binding of [<sup>3</sup>H]-Org 9426 in combination with Org 25969 to male human erythrocytes *in vitro*.

**Methods:** The extent of binding of Org 25969 of Org 9426 or combination to erythrocytes was determined by incubation of blood in the presence of various concentrations of test compound. Samples were taken after 5 and 60 min of incubation for the determination of the radioactivity in whole blood. Radioactivity was determined in plasma samples collected at the same time points, as well. Hematocrit values were determined before (for untreated blood) and after incubation.

The extent of in vitro erythrocyte binding was calculated as:

$$E = \frac{H+R-1}{R} * 100\%$$

where:

E = fraction of radioactivity bound to erythrocytes (%)

H = hematocrit value\*

$$R = \frac{\text{radioactivity in whole blood}^{**} (\text{Bq} \cdot \text{mL}^{-1})}{\text{radioactivity in plasma} (\text{Bq} \cdot \text{mL}^{-1})}$$

\* For "hematocrit value" the mean value of the measurements performed after the 60 min incubations was used here as fraction

\*\* For "radioactivity in whole blood" the mean value of radioactivity measured in blood samples taken after 5 and 60 min of incubation was used.

### Results:

For male rat, male rabbit, male cat, male dog, and male human blood, the mean hematocrit values, determined after finishing the incubation (60 minutes), were 0.437, 0.414, 0.320, 0.358 and 0.413; no hemolysis had occurred during the incubation for all species. No binding of Org 25969 to erythrocytes was observed at the concentrations and incubation times tested (Table 1). Binding of Org 9426 to erythrocytes did not occur at both incubation times (Table 2). The combination of the two drugs did not show binding to erythrocytes when increasing the ratio of Org 25969: Org 9426 concentration (Table 3). The blood of all the species tested did not bind Org 25969 or Org 9426 or the combination (data not shown).

**Table 1. *In vitro* binding of [<sup>14</sup>C]-Org 25969 to male human erythrocytes.**

[ <sup>14</sup> C]-Org 25969 <sup>1</sup> (nmol·mL <sup>-1</sup> )	Time (min)	H	Radioactivity Whole blood (Bq·mL <sup>-1</sup> )	Radioactivity Plasma (Bq·mL <sup>-1</sup> )	R	E <sup>4</sup> (%)
	0 <sup>2</sup>	0.415				
250	5		2960	5216	0.56	-4
25			2885	5140	0.55	-7
2.5			2844	5085	0.55	-6
1			2842	5096	0.56	-5
0.25			2779	4939	0.57	-3
0			2891	4981	0.58	-1
Mean ± SD					0.56 ± 0.01	-4 ± 2
250	60	0.405	2921	5357	0.55	-7
25		0.410	2757	5210	0.54	-8
2.5		0.420	2772	5172	0.54	-8
1		0.420	2846	5132	0.55	-6
0.25		0.405	2849	5094	0.55	-6
0		0.420	2891	4750	0.61	4
Mean ± SD		0.413 <sup>3</sup>			0.56 ± 0.03	-5 ± 5

Key:

- <sup>1</sup> Blood samples were spiked with 0, 0.25, 1, 2.5, 25, 250 nmol·mL<sup>-1</sup> unlabeled Org 25969 and 2.9 kBq·mL<sup>-1</sup> [<sup>14</sup>C]-Org 25969 (equivalent 0.4280 nmol/mL)
- <sup>2</sup> Time = 0 means before the start of the incubations
- <sup>3</sup> Mean value after 60 minutes of incubation
- <sup>4</sup> Mean values ≤ 2 were interpreted as no binding

**Table 2. *In vitro* binding of [<sup>3</sup>H]-Org 9426 to male human erythrocytes.**

Org 9426 <sup>1</sup> (nmol·mL <sup>-1</sup> )	Time (min)	H	Radioactivity Whole blood (Bq·mL <sup>-1</sup> )	Radioactivity Plasma (Bq·mL <sup>-1</sup> )	R	E <sup>3</sup> (%)
	0 <sup>2</sup>	0.448				
3.1	5		3851	7152	0.54	-2
3.1	60	0.445	3941	7209	0.54	-3

- <sup>1</sup> Blood samples were spiked with 3.1 nmol·mL<sup>-1</sup> unlabeled Org 9426 and 3.9 kBq·mL<sup>-1</sup> [<sup>3</sup>H]-Org 9426 (equivalent 0.0026 nmol·mL<sup>-1</sup>)
- <sup>2</sup> Time = 0 means before the start of the incubations
- <sup>3</sup> Values ≤ 2 were interpreted as no binding

**Table 3. *In vitro* Combi binding of [<sup>3</sup>H]-Org 9426, Org 9426 and Org 25969 to male Human erythrocytes.**

Org 9426 <sup>1</sup> +Org 25969	Org 25969: Org 9426	Time (min)	H	Radioactivity whole blood (Bq·mL <sup>-1</sup> )	Radioactivity Plasma (Bq·mL <sup>-1</sup> )	R	E <sup>4</sup> (%)
nmol·mL <sup>-1</sup>	Ratio	0 <sup>2</sup>	0.448				
12.4	4	5		4203	7943	0.52	-6
6.2	2			4059	7830	0.52	-7
3.1	1			4123	8029	0.52	-6
1.6	0.5			4231	7949	0.53	-5
0.8	0.3			4355	7921	0.53	-5
Mean ± SD						0.52 ± 0.01	-6 ± 1
12.4	4	60	0.445	4119	7662	0.54	-2
6.2	2		0.450	4083	7389	0.55	-1
3.1	1		0.445	4232	7694	0.54	-2
1.6	0.5		0.445	4147	7578	0.55	0
0.8	0.3		0.445	4031	7452	0.56	2
Mean ± SD			0.446 <sup>3</sup>			0.55 ± 0.01	-1 ± 2

Key:

- <sup>1</sup> Blood samples were spiked with 0.8, 1.6, 3.1, 6.2, 12.4 nmol·mL<sup>-1</sup> unlabeled Org 25969 and 3.1 nmol·mL<sup>-1</sup> unlabeled Org 9426 with 4.1 kBq·mL<sup>-1</sup> [<sup>3</sup>H]-Org 9426 (equivalent 0.0028 nmol·mL<sup>-1</sup>)
- <sup>2</sup> Time = 0 means before the start of the incubations
- <sup>3</sup> Mean value after 60 minutes of incubation
- <sup>4</sup> Mean values ≤ 2 were interpreted as no binding

### Conclusions:

- Org 25969 does not bind *in vitro* to erythrocytes of male human blood independent of the concentration and independent of the incubation time.

NDA 22-225

(b) (4) (Sugammadex Sodium)  
Solution for Injection (100 mg/mL)  
Original NDA Review

- Org 9426 (Rocuronium) does not bind to male human erythrocytes independent of the incubation time.
- Org 25969, Org 9426 and Org 25969 + Org 9426 did not induce hemolysis up to concentrations of 250  $\mu$ M, 3.1  $\mu$ M and 12.1  $\mu$ M:3.1  $\mu$ M, respectively.
- No binding was observed of Org 9426 to male human erythrocytes in combination with increasing concentrations of Org 25969.

#### 4.2.1.3 In Vitro Study on the Dialysability of Org 25969

**Study No. 19.4.006 (Report NL0061451):** *In vitro* study on the dialysability of Org 25969

**Objective:** To explore the dialysability of Org 25969 in the presence and absence of rocuronium *in vitro*, and, if applicable, to explore the dialysis characteristics of these compounds.

#### **Methods:**

An overview of the experiments performed in this study is presented in the table below:

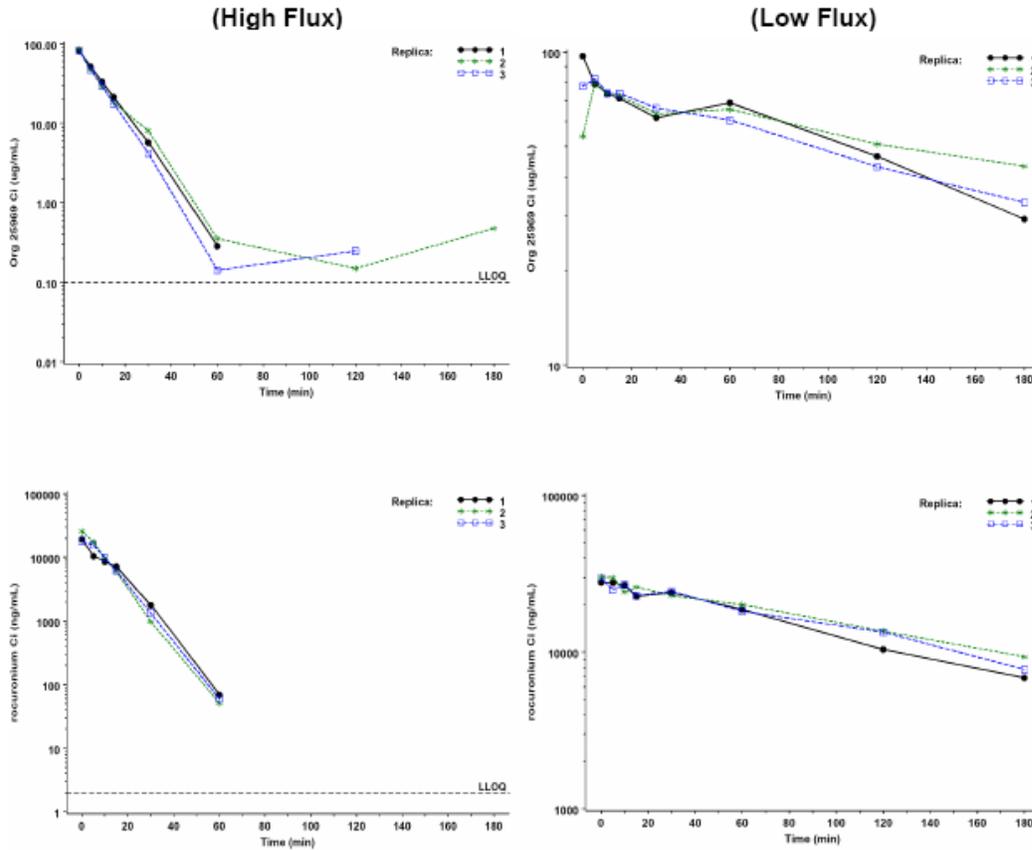
<b>Exp. No.</b>	<b>Plasma composition</b>	<b>Filter</b>	<b># of replicas</b>	<b>Dialysate flow</b>
<b>1</b>	<b>Org 25969 + rocuronium</b>	<b>High Flux (FX 60)</b>	3	Yes
<b>2</b>	<b>Org 25969 + rocuronium</b>	<b>Low Flux (F6 HPS)</b>	3	Yes
<b>3</b>	<b>Org 25969</b>	<b>Low Flux (F6 HPS)</b>	3	Yes
<b>4</b>	<b>Org 25969 + rocuronium</b>	<b>High Flux (FX 60)</b>	1	No (control)

An *in-vitro* dialysis set-up was used with a 900 mL pool of human plasma and a phosphate bicarbonate buffer as dialysate. Plasma flow was 200 mL/min and was recirculated. The dialysate flow was 500 mL/min and was not recirculated. The temperature was kept at 37°C. Two filters, a high- and a low-flux filter were used. The combination of Org 25969 and rocuronium was tested with both filters. Org 25969-only was tested with the low-flux filter only. The experiments were done in triplicate except the control experiment. Org 25969 was added to the plasma pool to a concentration of 100  $\mu$ g/mL, rocuronium up to a concentration of 30  $\mu$ g/mL, in order to have a molar stoichiometry of 1:1. Samples from the plasma pool were taken before entrance of the filter and just after leaving the filter (=  $C_i$  and  $C_o$ ). Samples for Org 25969 (1.0 mL) and rocuronium (0.5 mL) measurements were taken at 0, 5, 10, 15, 30, 60, 120 and 180 min. At the same time points, a sample of the dialysate was taken for exploratory investigations. A control experiment without dialysate was performed to test sticking of the drugs to the filter material (polysulfone).

**Results:****Table 1. *In vitro* clearance (CL) values of Org 25969 and rocuronium as determined from the decline in plasma concentrations (C<sub>i</sub>).**

Experiment	Filter	Analyte	N	CL (mL/min)	Range (mL/min)
1: Org 25969 + Roc.	High Flux	Org 25969 rocuronium	3	86.3	79.3 – 94.8
				89.0	83.5 – 95.0
2: Org 25969 + Roc.	Low Flux	Org 25969 rocuronium	3	3.9	2.4 – 4.9
				6.3	5.6 – 7.2
3: Org 25969 only.	Low Flux	Org 25969	3	6.0	5.4 – 6.7
4: Org 25969 + Roc.	High Flux (Control)	Org 25969 rocuronium	1	0.2	
				0.2	

**Figure 1** Plasma concentration ( $C_i$ ) versus time curves of Org 25969 (upper panels) and rocuronium (lower panels) using high flux (left) and low flux (right) filters.



**Conclusions:**

Org 25969 and rocuronium can be efficiently removed from plasma by dialysis when using a high flux membrane. Under these conditions the clearance of Org 25969 and rocuronium was 86 and 89 mL/min, respectively. The use of a low flux membrane results in a much lower clearance of 4 to 6 mL/min for the two compounds. The clearance of Org 25969 in the absence of rocuronium under low flux conditions was comparable at 6 mL/min. The results of the control experiment show that the amount of Org 25969 and rocuronium removed from plasma in the absence of dialysate flow was negligible.

4.2.1.4 Possible Effects of Org 25969 on Clinical Chemical Analysis

**Study No. 19.4.004 (Report (b) (4) -035803):** Study on the Possible Effects of Org 25969 on Clinical Chemical Analysis

**Objectives:** To assess possible interferences of ORG25969 in various Clinical Chemistry tests and to prepare ORG25969 stability samples for testing at the Sponsors site.

**Methods:** Fresh matrix from 6 healthy subjects (3 male and 3 female) was used to prepare study samples of serum, plasma or whole blood. Samples (3 samples per subject) were spiked with Org 25969 (100 µg/mL), or unspiked. For each prepared sample, three aliquots were analyzed in 72 analytical tests (see list of assays below). Additionally, to investigate the effect of Org 25969 on abnormal (positive) assay results, spiked (500 µg/mL) and un-spiked urine samples from 2 patients (1 male and 1 female) were tested in 13 assays.

Six individual heparin whole blood samples were obtained for stability experiments of ORG25969 in heparin plasma.

Although the Sponsor intended to target the Org 25969 concentrations in the spiked samples to approximate maximal concentrations in men after administration of 16.0 mg/kg Org 25969 (~200 µg/mL), the concentration studied was about half of C<sub>max</sub> achieved at 16 mg/kg. The data were evaluated with respect to statistical significance and clinical relevance.

**Table 1. List of Assays.**

The following assays were performed for the current study.

<b>Analyte</b>	<b>Analyser</b>	<b>Category</b>	<b>Matrix</b>
ALAT	Vitros	Clinical Chemistry	Serum
Albumin	Vitros	Clinical Chemistry	Serum
Alkaline Phosphatase	Vitros	Clinical Chemistry	Serum
Amylase	Vitros	Clinical Chemistry	Serum
Anorganic Phosphate	Vitros	Clinical Chemistry	Serum
ASAT	Vitros	Clinical Chemistry	Serum
Bicarbonate	Vitros	Clinical Chemistry	Serum
Calcium	Vitros	Clinical Chemistry	Serum
Chloride	Vitros	Clinical Chemistry	Serum
Cholinesterase	Vitros	Clinical Chemistry	Serum
Creatinine	Vitros	Clinical Chemistry	Serum
Creatine Kinase	Vitros	Clinical Chemistry	Serum
Direct Billirubin	Vitros	Clinical Chemistry	Serum
Fe (iron)	Vitros	Clinical Chemistry	Serum
Gamma-GT	Vitros	Clinical Chemistry	Serum
Glucose	Vitros	Clinical Chemistry	Serum
LDH	Vitros	Clinical Chemistry	Serum
Lipase	Vitros	Clinical Chemistry	Serum
Lithium	Vitros	Clinical Chemistry	Serum
Magnesium	Vitros	Clinical Chemistry	Serum
Potassium	Vitros	Clinical Chemistry	Serum
Sodium	Vitros	Clinical Chemistry	Serum
Total Bilirubin	Vitros	Clinical Chemistry	Serum
Total Protein	Vitros	Clinical Chemistry	Serum
Triglycerides	Vitros	Clinical Chemistry	Serum
Urea (Blood Urea Nitrogen)	Vitros	Clinical Chemistry	Serum
Uric Acid	Vitros	Clinical Chemistry	Serum
Cholesterol	Beckman CX5	Clinical Chemistry	Serum
HDL-Cholesterol	Beckman CX5	Clinical Chemistry	Serum
LDL-Cholesterol	Beckman CX5	Clinical Chemistry	Serum
CBC and Five Partial Dif.	CelDyn	Haematology	EDTA Whole Blood (Complete blood cell count and five partial differential count including Haematocrit, Haemoglobin, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin and Mean Corpuscular Haemoglobin Concentration)
APTT	ACL-9000	Coagulation	Citrate Plasma
Fibrinogen	ACL-9000	Coagulation	Citrate Plasma
PT (INR)	ACL-9000	Coagulation	Citrate Plasma
PT	ACL-9000	Coagulation	Citrate Plasma
TT	ACL-9000	Coagulation	Citrate Plasma

Analyte	Analyser	Category	Matrix
β-hCG	AxSYM	Hormones	Serum
Estradiol	AxSYM	Hormones	Serum
Ferritin	AxSYM	Hormones	Serum
FSH	AxSYM	Hormones	Serum
Insulin	AxSYM	Hormones	Serum
LH	AxSYM	Hormones	Serum
Progesterone	AxSYM	Hormones	Serum
Prolactin	AxSYM	Hormones	Serum
T3	AxSYM	Hormones	Serum
T4	AxSYM	Hormones	Serum
TSH	AxSYM	Hormones	Serum
Anti-HAV-Ig	AxSYM	Immunology	Serum
Anti-HAV-IgM	AxSYM	Immunology	Serum
Anti-HBc-Ig	AxSYM	Immunology	Serum
Anti-HBc-IgM	AxSYM	Immunology	Serum
Anti-HCV	AxSYM	Immunology	Serum
Anti-HIV 1/2	AxSYM	Immunology	Serum
HbsAg	AxSYM	Immunology	Serum
ACTH	Immulite	Hormones	EDTA Plasma (kept on ice)
Cortisol	Immulite	Hormones	Serum
hGH	Immulite	Hormones	Serum
SHBG	Immulite	Hormones	Serum
Testosterone (total)	Immulite	Hormones	Serum
Haptoglobin	Array 360	Specialty test	Serum
Microalbumin	Array 360	Urine test	Urine
β2-Microglobulin	AxSYM	Urine test	Urine
Alcohol	AxSYM	Drugscreen	Urine
Amphetamines	AxSYM	Drugscreen	Urine
Barbiturates	AxSYM	Drugscreen	Urine
Benzodiazepines	AxSYM	Drugscreen	Urine
Cannabinoids	AxSYM	Drugscreen	Urine
Cocaine	AxSYM	Drugscreen	Urine
Opiates (including Morphine)	AxSYM	Drugscreen	Urine
βN-Acetyl Glucosaminidase	Beckman CX5	Urine test	Urine
Pregnancy Test	Manual	Urine test	Urine
Dipstick (Meditron)	Meditron	Urine test	Urine
		(Qualitative measurement of Leukocytes, Nitrite, Protein, Glucose, Ketones, Urobilinogen, Bilirubin, Haemoglobin, Specific Gravity, pH)	

**Results:** See Table 2 for results.

The following tests showed both different results for each gender and statistically significant differences between spiked ('treatment') and unspiked ('blank') samples for the indicated gender.

Males:

- Direct bilirubin
- Uric acid
- PT(inr)
- PT
- TT
- Core-M (index)

Females:

- CK
- PT(inr)
- PT
- TT
- Progesterone

The following 17 tests showed statistically significant differences between spiked ('treatment') and unspiked ('blank') samples:

- Albumin
- ASAT
- Direct bilirubin
- Inorganic phosphate
- Total protein
- Triglycerides
- Uric acid
- MCV
- APTT
- PT(inr)
- PT
- TT
- Estradiol
- Progesterone
- Testosterone
- $\beta$ 2-Microglobulin (urine)
- Ethanol (urine)

In addition to and independently from the statistical evaluation, the clinical relevance of a possible (maximal) effect caused by addition of ORG 25969 was evaluated for each test method. For clinical chemistry tests of activated partial thromboplastin time (APTT), prothrombin time (PT) and PT (international normalized ratio) (PT(inr)), the mean values were statistically significant higher for samples spiked with Org 25969 compared to un-spiked samples. However, these mean values were within the normal ranges as applied by the Clinical Chemistry lab (b) (4). Even when the absolute differences found between spiked and un-spiked samples of APTT, PT and PT(inr) were superimposed on the upper limit of the normal range for these parameters, none of these parameters would reach a value that would result in notification of a physician according to the criteria of (b) (4). For APTT, PT(inr) and PT, the absolute differences found between the mean concentrations of treated and untreated samples, superimposed on the upper reference range limits, were 48.9 sec, 1.322 sec and 17.11 sec, respectively. However, the threshold values for physician notification for these compounds were >100 sec, >6 sec and >75 sec, respectively. The threshold values used are documented and archived at the Clinical Chemistry lab (b) (4).

For the Ethanol in urine assay, a general interference of the test was observed after spiking. It was concluded that the reliability of the test was compromised after spiking with ORG25969.

For the progesterone assay, a clinically relevant effect of Org 25969 was found in samples from female subjects. Although the observed deviations after spiking would not lead to a pathological classification, conclusions from this assay may be compromised when used in the presence of Org 25969 for the purpose of identifying reproductive phases in female subjects.

**Table 2. Statistical analysis - including gender term in ANOVA.**

Test Label	means				treatment P values				spike - blank			reference range		unit
	Female		Male		overall	by*	diff.	diff.	differences		female (or both)	male (or both)		
	Spiked Blank	Spiked Blank	Spiked Blank	Spiked Blank					both	female male				
ALAT (SGPT)	32	33	32	32	0.9285	0.3276	.	.	0.1	.	.	<69	both	U/L
Albumin	42	42	46	45	0.0132*	0.0692	.	.	0.4	.	.	37 - 52	both	g/L
Alkaline phosphatase	60	60	73	72	0.2563	0.1235	.	.	0.3	.	.	<130	both	U/L
Total amylase	56	56	58	60	0.2843	0.4199	.	.	-1.3	.	.	<110	both	U/L
ASAT (SGOT)	22	22	22	22	0.0320*	0.2688	.	.	-0.2	.	.	<52	both	U/L
Bicarbonate	27	27	28	28	0.7736	0.3910	.	.	-0.1	.	.	25 - 32	both	mmol/L
Calcium	2.27	2.28	2.38	2.37	1.0000	0.1182	.	.	0.000	.	.	2.21 - 2.61	both	mmol/L
Cholinesterase	5853	5835	8237	8230	0.7378	0.8735	.	.	12	.	.		both	
Chloride	106	106	106	106	0.3103	0.7331	.	.	0.2	.	.	98 - 109	both	mmol/L
CHOL CX-5	4.7	4.7	4.5	4.5	0.1792	1.0000	.	.	0.02	.	.	<6.8	both	mmol/L
CK	80	79	99	99	0.2170	0.0114	0.0090	0.3161	0.4	1.2	-0.4	<200	both	U/L
Creatinine	67	67	86	86	0.6499	0.6499	.	.	0.1	.	.	<96	both	µmol/L
Direct bilirubin	0	0	1	0	0.0066*	0.0066	1.0000	0.0003	0.2	0.0	0.4	<7	both	µmol/L
Ferritin	32	34	51	51	0.3070	0.3070	.	.	-0.8	.	.	7 - 282	both	ng/mL
Gamma GT	41	41	21	21	0.7433	0.7433	.	.	0.1	.	.	<70	both	U/L
Glucose	5.7	5.8	4.5	4.6	0.0772	0.7165	.	.	-0.03	.	.	<6.2	both	mmol/L
Haptoglobin	0.8	0.8	1.0	1.0	0.3259	0.3259	.	.	0.01	.	.	0.5 - 2.5	both	g/L
HDL-DIRECT	1.6	1.6	1.1	1.1	0.3342	1.0000	.	.	0.01	.	.	>1.0	both	mmol/L
Iron	22.5	22.6	17.7	17.7	0.9216	0.9738	.	.	-0.02	.	.	6.6 - 30.4	both	µmol/L
Potassium	3.9	3.9	4.3	4.3	0.6994	0.6994	.	.	-0.01	.	.	3.6 - 5.2	both	mmol/L
LDH	355	358	384	388	0.1585	0.8425	.	.	-3.6	.	.	<650	both	U/L
LDL-DIRECT	3.0	3.0	3.2	3.2	0.5036	0.1862	.	.	0.01	.	.	<5.7	both	mmol/L
Lipase	149	150	81	85	0.0640	0.1473	.	.	-2.4	.	.	23 - 300	both	U/L
Magnesium	0.79	0.79	0.78	0.78	0.4929	0.4929	.	.	0.002	.	.	0.63 - 0.94	both	mmol/L
Sodium	141	141	144	144	0.0589	0.2000	.	.	0.3	.	.	135 - 147	both	mmol/L
Inorganic phosphate	1.1	1.1	1.1	1.1	0.0018*	0.0584	.	.	-0.01	.	.	0.8 - 1.5	both	mmol/L
SHBG	61	61	26	26	0.7853	0.9638	.	.	0.4	.	.	18 - 114	both	nmol/L
Total bilirubin	8	8	8	8	0.6009	0.6009	.	.	0.1	.	.	<30	both	µmol/L
Total protein	68	67	73	71	0.0036*	0.0763	.	.	1.1	.	.	63 - 84	both	g/L
Triglycerides	0.79	0.78	0.96	0.95	0.0533	0.8558	.	.	0.006	.	.	<2.70	both	mmol/L
Uric acid	0.22	0.22	0.33	0.34	0.0072*	0.0072	1.0000	0.0003	-0.003	0.000	-0.007	<0.48	both	mmol/L
Urea	4.4	4.4	5.0	5.0	0.1328	0.7591	.	.	-0.03	.	.	<6.7	both	mmol/L

NOTE: - differences and P-values by gender shown only when treatment\*gender term P<0.05  
 - \* when overall treatment P<0.05

Haematology

Test Label	means				treatment P values				spike - blank			reference range		unit
	Female		Male		overall	by*	diff.	diff.	differences		female (or both)	male (or both)		
	Spiked Blank	Spiked Blank	Spiked Blank	Spiked Blank					both	female male				
Basophils	0.0	0.0	0.0	-0.0	0.6410	0.6410	.	.	0.01	.	.	<0.2	both	10 <sup>9</sup> /L
Eosinophils	0.1	0.1	0.1	0.1	0.2688	0.2688	.	.	0.01	.	.	<0.6	both	10 <sup>9</sup> /L
Haemoglobin	8.6	8.6	9.6	9.6	0.6694	0.6694	.	.	-0.03	.	.	7.3 - 9.5	both	mmol/L
Haematocrit	0.39	0.37	0.44	0.43	0.1136	0.5904	.	.	0.013	.	.	0.34 - 0.45	both	L/L
Lymphocytes	2.0	2.0	1.8	1.8	0.7869	0.7869	.	.	0.01	.	.	1.1 - 3.2	both	10 <sup>9</sup> /L
MCH	1971	2100	1970	1983	0.2243	0.3213	.	.	-71.1	.	.	1600 - 2100	both	amol
MCHC	22.0	23.6	21.8	22.1	0.1397	0.3098	.	.	-0.94	.	.	19.5 - 22.1	both	mmol/L
MCV	90	89	91	90	0.0003*	0.0692	.	.	0.6	.	.	80 - 97	both	fL
Monocytes	0.3	0.3	0.5	0.5	0.3787	1.0000	.	.	-0.01	.	.	0.3 - 0.9	both	10 <sup>9</sup> /L
Neutrophils	2.9	2.9	2.4	2.4	0.4783	0.2411	.	.	-0.02	.	.	1.9 - 7.9	both	10 <sup>9</sup> /L
Thrombocytes	256	244	270	266	0.0790	0.3442	.	.	8.0	.	.	150 - 370	both	10 <sup>9</sup> /L
Erythrocytes	4.4	4.2	4.9	4.8	0.2063	0.5152	.	.	0.12	.	.	3.8 - 5.2	both	4.2 - 5.7
Leukocytes	5.3	5.3	4.8	4.8	0.6994	0.6994	.	.	-0.01	.	.	3.8 - 11	both	10 <sup>9</sup> /L

Coagulation

Test Label	means				treatment P values				spike - blank			reference range		unit
	Female		Male		overall	by*	diff.	diff.	differences		female (or both)	male (or both)		
	Spiked Blank	Spiked Blank	Spiked Blank	Spiked Blank					both	female male				
APTT	42	36	40	34	<.0001*	0.8117	.	.	5.9	.	.	26 - 43	both	sec
Fibrinogen	3.8	3.8	3.5	3.5	0.7440	0.3309	.	.	0.02	.	.	2 - 5.6	both	g/L
PT (inr)	1.01	0.89	1.13	0.99	<.0001*	0.0021	<.0001	<.0001	0.132	0.120	0.143	0.82 - 1.19	both	
PT	13.3	11.8	14.8	13.1	<.0001*	0.0026	<.0001	<.0001	1.61	1.48	1.73	11 - 15.5	both	sec
TT	15.6	16.2	16.4	16.6	<.0001*	0.0079	<.0001	0.0336	-0.44	-0.66	-0.23	12.4 - 17.6	both	sec

Immunology

Test Label	means				treatment P values			spike - blank			reference range		unit
	Female		Male		overall	by* gender	diff. female	diff. male	differences		female	male	
	Spiked Blank	Spiked Blank	both	female					male	(or both)	(or both)		
Havab-M (index)	0.14	0.14	0.11	0.11	0.6224	0.8693	.	.	-0.002	.	.	POS: >1.20	both
Havab (S/CO)	1.19	1.18	1.54	1.51	0.4471	0.8265	.	.	0.021	.	.	POS: <1.00	both
HBsAg (S/N)	0.76	0.73	0.72	0.74	0.8100	0.1738	.	.	0.004	.	.	POS: >2.00	both
Core-M (index)	0.05	0.06	0.05	0.04	0.1716	0.0028	0.1966	0.0026	0.002	-0.002	0.006	POS: >1.2	both
Core (S/CO)	2.00	2.00	1.97	1.94	0.7208	0.5301	.	.	0.011	.	.	POS: <1.00	both
HCV (S/CO)	0.34	0.32	0.36	0.35	0.3397	0.9752	.	.	0.017	.	.	POS: >1.00	both
HIV1/2 (S/CO)	0.32	0.33	0.32	0.32	0.6060	0.3920	.	.	-0.003	.	.	POS: >1.00	both

Hormone screen

Test Label	means				treatment P values			spike - blank			reference range		unit		
	Female		Male		overall	by* gender	diff. female	diff. male	differences		female	male			
	Spiked Blank	Spiked Blank	both	female					male	(or both)	(or both)				
ACTE	24	24	27	26	0.2915	0.7227	.	.	0.3	.	.	<46	both	pg/mL	
Cortisol	14	14	11	11	0.2526	0.6807	.	.	0.3	.	.	5 - 25	both	µg/dL	
Estradiol (axsym)	76	67	23	22	0.0414*	0.1500	.	.	4.9	.	.	<77	both	pg/mL	
FSH (axsym)	29	31	7	7	0.1676	0.1676	.	.	-1.1	.	.	1 - 8	both	U/L	
Growth hormone	7	7	0	0	0.4501	0.4720	.	.	-0	.	.		both		
Insulin (axsym)	12	12	10	10	0.6469	0.8784	.	.	-0.1	.	.	2 - 25	both	µU/mL	
LH (axsym)	14	14	4	4	0.5466	0.7533	.	.	0.1	.	.	2 - 12	both	U/L	
Progesterone	5.65	6.48	0.43	0.43	0.0265*	0.0261	0.0025	0.9965	-0.419	-0.839	0.001	<3.37	both	ng/mL	
Prolactin	15.05	15.23	5.91	5.83	0.7188	0.4073	.	.	-0.055	.	.	1.39 - 24.2	1.61 - 18.77	both	ng/mL
T3	1.18	1.17	0.96	0.97	0.9690	0.6421	.	.	0.001	.	.	0.64 - 1.64	both	ng/mL	
Thyroxine	7.9	7.9	7.2	7.0	0.2348	0.2348	.	.	0.09	.	.	4.5 - 11.3	both	µg/dL	
Testosterone	33	36	435	470	0.0384*	0.0668	.	.	-18.3	.	.	<110	270 - 800	both	ng/dL
TSH	1.45	1.41	1.34	1.33	0.2012	0.4451	.	.	0.027	.	.	0.38 - 4.1	both	mU/L	

Urine screen quantitative

Test Label	means				treatment P values			spike - blank			reference range		unit	
	Female		Male		overall	by* gender	diff. female	diff. male	differences		female	male		
	Spiked Blank	Spiked Blank	both	female					male	(or both)	(or both)			
B2-microglobulin (axsym)	50	57	54	60	<.0001*	0.4292	.	.	-6.4	.	.	5 - 154	both	µg/L
B-NAG	1.8	1.9	2.5	2.5	0.5974	0.2491	.	.	-0.02	.	.	<9.3	both	U/L
Microalbumin	0.6	0.6	0.5	0.5	0.4369	0.4369	.	.	-0.01	.	.	<1.9	both	mg/dL

Drug screen

Test Label	means				treatment P values			spike - blank			reference range		unit
	Female		Male		overall	by* gender	diff. female	diff. male	differences		female	male	
	Spiked Blank	Spiked Blank	both	female					male	(or both)	(or both)		
Ethanol (mg/dL)	2.3	0.9	3.5	1.5	<.0001*	0.3482	.	.	1.68	.	.	POS: >100	both
Amphetamine (ng/mL)	177.0	61.8	83.8	86.1	0.2133	0.1956	.	.	56.43	.	.	POS: >1000	both
Barbituraten (ng/mL)	3.2	0.7	8.4	10.7	0.9761	0.2888	.	.	0.07	.	.	POS: >200	both
Benzodiazepines (ng/mL)	14.7	11.8	19.8	18.5	0.4814	0.7949	.	.	2.17	.	.	POS: >200	both
Cannabis (ng/mL)	6.1	5.0	7.2	6.0	0.0625	0.9137	.	.	1.15	.	.	POS: >50	both
Cocaine (ng/mL)	3.3	3.3	5.8	5.6	0.7600	0.7981	.	.	0.16	.	.	POS: >300	both
Opiaten (ng/mL)	9.9	11.3	17.3	16.4	0.8911	0.4190	.	.	-0.19	.	.	POS: >300	both

Stability of ORG25969 was demonstrated at 37°C in heparin plasma for up to 264 hours.

4.2.1.5 Possible Effects of Org 48302 on Clinical Chemical Analysis

**Study No. 19.4.007 (Report (b) (4) -062103):** Study on the Possible Effects of Org 48302 on Clinical Chemical Analysis

**Objective:** The objective of this study is to assess possible interferences of ORG 48302 in various Clinical Chemistry tests in comparison with ORG 25969.

**Methods:** Fresh matrix from 6 healthy subjects (3 male and 3 female) was used to prepare study samples of serum, plasma, whole blood and urine. Samples were spiked with Org 25969 (90

µg/mL in serum, plasma or whole blood; 450 µg/mL in urine) or Org 48302 (10 µg/mL in serum, plasma or whole blood; 50 µg/mL in urine), or un-spiked. For each prepared sample, three aliquots were analyzed in 23 analytical tests. Although the Sponsor intended to target the Org 25969 and Org 48302 concentrations in the spiked samples to approximate maximal concentrations in men after administration of 16.0 mg/kg Org 25969 (~200 µg/mL for Org 25969), the concentration studied was about half of C<sub>max</sub> achieved at 16 mg/kg. The data were evaluated with respect to statistical significance and clinical relevance.

**Results:** The following tests showed statistically significant differences between non-spiked and spiked samples for the indicated compound.

All subjects	ORG 48302		All subjects	ORG 25969	
	Female	Male		Female	Male
Thrombocytes	Thrombocytes	Thrombocytes	Thrombocytes	Thrombocytes	Thrombocytes
APTT	APTT	APTT	APTT	APTT	APTT
PT (inr)					
PT	PT	PT	PT	PT	PT
			TT	TT	TT
Glucose	Glucose	Glucose		Glucose	
MCV	MCV		MCV		
Albumin					
Thyroxine					
	Lipase				
	Uric Acid				
			Progesterone		Progesterone
			Testosterone		Testosterone

In addition to and independently from the statistical evaluation, the clinical relevance of a possible (maximal) effect caused by addition of ORG 48302 or ORG 25969 was evaluated for each test method.

For APTT, PT (inr) and PT, clinically relevant differences were found between spiked samples with ORG 25969 and non-spiked samples. For ORG 48302, no clinical relevant differences were observed between spiked and non-spiked samples.

For ORG 25969, it was concluded that in combination with other pathologic findings, these differences would lead to pathological classifications of spiked samples. However, if evaluated as stand alone results, neither of these deviations would result in notification of a physician according to the criteria of the Clinical Chemistry lab (b) (4).

For APTT, PT (inr) and PT, the absolute differences found between the mean concentrations of ORG 25969-treated and untreated samples of all subjects (4.6, 0.109 and 1.37 sec, respectively), superimposed on the upper reference range limits (39, 1.19, and 15.5 sec, respectively), were 43.6 sec, 1.299 sec and 16.87 sec, respectively. However, the threshold values for physician notification for these compounds were >100 sec, >6 sec and >75 sec, respectively. The threshold

values used are documented and archived at the Clinical Chemistry lab [REDACTED]

(b) (4)

For all other tests that showed statistically significant differences between non-spiked and ORG 48302 or ORG 25969 spiked samples, no clinically relevant effect was observed.

#### 4.2.2 Single Ascending Dose Study

*Study 19.4.101: A phase I, randomized, double-blind, placebo-controlled, single rising dose study in healthy male volunteers to assess the tolerance, safety and pharmacokinetic properties of Org 25969 followed by a double-blind, placebo-controlled, crossover part to preliminary assess the efficacy of Org 25969*

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**Study Period:** July 18, 2001 to December 7, 2001  
**Sample Analysis Periods:** January 22, 2002 to May 1, 2002  
**Analytical Site:** N.V. Organon, Molenstraat 110, 5342 CC Oss, The Netherlands

#### Investigator

Steven De Bruyn, SGS Biopharma S.A.

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#### Clinical trial center

SGS Biopharma Research Unit, A.Z. Stuivenberg, Lange Beeldekenstraat 267, B-2060 Antwerp, Belgium.

#### Objectives

##### Primary objective

- To investigate the safety and tolerability of single iv doses of Org 25969 given alone (Part 1) and of single iv doses of Org 25969 given 3 minutes after administration of rocuronium (Part 2).

##### Secondary objectives

- To investigate the pharmacokinetic profile of Org 25969 and rocuronium after separate administration, and after administration of Org 25969 given 3 minutes after administration of rocuronium.
- To assess renal excretion of Org 25969 and rocuronium after separate administration, and after administration of Org 25969 given 3 minutes after administration of rocuronium.
- To explore the dose-response relation of Org 25969 as a reversal agent for rocuronium.

## Methodology

The study consisted of two parts: a single rising dose safety and tolerability part and a pilot efficacy part.

**Part 1** This part had a randomized, double-blind, placebo-controlled, single rising dose design.

Each subject received a single intravenous bolus of Org 25969 on two occasions and a single intravenous bolus of placebo on another occasion.

**Part 2** This part had a randomized, double-blind, placebo-controlled, crossover design. Subjects received a saline infusion of 2L.24h<sup>-1</sup> starting at least 6 h before anesthesia.

**Anesthesia.** Subjects were to receive anesthesia using an opioid and propofol. A urinary catheter and an intra-arterial line were to be inserted and pre-dose urinary and arterial samples were taken before the administration of rocuronium. Neuromuscular monitoring was to be performed using the TOF-Watch-SX<sup>®</sup>. Subjects received a bolus dose of 0.6 mg.kg<sup>-1</sup> rocuronium bromide (Esmeron<sup>®</sup>).

**Reversal.** At 3 minutes after the start of the administration of rocuronium subjects received a single intravenous infusion of Org 25969 on one occasion and placebo on another occasion, in a randomized order. Considering the possibility of re-curarization tracheal intubation and maintenance of anesthesia was to continue until a minimum of 90 minutes after the administration of Org 25969 or placebo and at least until complete neuromuscular recovery.

### Assessments part 1 and 2

**Blood sampling part 1:** Venous blood samples up to 480 minutes post Org 25969 dose for assessment of Org 25969 plasma concentrations.

**Blood sampling part 2:** Arterial blood samples up to 40 minutes and venous blood samples from 25 up to 480 minutes post Org 25969 dose for assessment of Org 25969 and rocuronium plasma concentrations.

**Urine collection part 1:** Urine collection up to 24 hours post Org 25969 dose for assessment of Org 25969 urine concentrations.

**Urine collection part 2:** Urine collection up to 24 hours post Org 25969 dose for assessment of Org 25969 and rocuronium urine concentrations.

**Safety assessments:** Blood pressure, heart rate, oxygen saturation, 12 lead ECG, clinical laboratory, urinalysis, physical examination, local intolerance, pre-treatment signs and symptoms, and (serious) adverse events. Interim safety reports were to be made to decide for continuation to a higher dose level in both parts and between part 1 and part 2.

**Follow-up** Follow-up visit was to be performed between day 7 and day 10 post final-dose.

**Assessments:** clinical laboratory, urinalysis, physical examination, 12 lead ECG, (serious) adverse events. Unless indicated otherwise, post-dose meant post Org 25969 dose.

In part 1 of the study treatment was to be given during 6 consecutive treatment periods.

Group I	treatment period		
	A	B	C
n=2	0.1 mg.kg <sup>-1</sup>	0.2 mg.kg <sup>-1</sup>	placebo
n=2	0.1 mg.kg <sup>-1</sup>	placebo	0.5 mg.kg <sup>-1</sup>
n=2	placebo	0.2 mg.kg <sup>-1</sup>	0.5 mg.kg <sup>-1</sup>

Groups II & IIa	treatment period			Q(*)
	D	E	F	
n=3	1.0 mg.kg <sup>-1</sup>	2.0 mg.kg <sup>-1</sup>	placebo	
n=3	1.0 mg.kg <sup>-1</sup>	placebo	4.0 mg.kg <sup>-1</sup>	
n=3	placebo	2.0 mg.kg <sup>-1</sup>	4.0 mg.kg <sup>-1</sup>	
n=2				8.0 mg.kg <sup>-1</sup>
n=2				placebo

In part 2 of the study treatment was to be given during 10 consecutive treatment periods (G to S).

Each subject was to receive general anesthesia using a dose of 0.6 mg.kg<sup>-1</sup> rocuronium bromide twice, in one treatment period followed by a single intravenous bolus of Org 25969 and in another treatment period followed by placebo, according to a randomized order. Group III consisted of 8 subjects. Based on the results of group III and according to Amendment 4, group IIIa consisted of 2 subjects.

Group III & IIIa	treatment period					
	G and H	I and J	K and L	M and N	O and P	R and S (**)
n= 1	0.1 mg.kg <sup>-1*</sup>					
n= 1		0.5 mg.kg <sup>-1*</sup>				
n= 2			1.0 mg.kg <sup>-1*</sup>			
n= 2				2.0 mg.kg <sup>-1*</sup>		
n= 2					4.0 mg.kg <sup>-1*</sup>	
n= 2						8.0 mg.kg <sup>-1*</sup>

\* in one treatment period active and placebo in another treatment period;

(\*\*) according to Amendment 4: group IIIa

#### Diagnosis and criteria for inclusion

1. Healthy male subjects;
2. Aged 18 u/i 40 years;
3. Body mass index 20-29 kg.m<sup>-2</sup> inclusive;
4. Weight between 60 and 90 kg inclusive;
5. No abnormal cardiovascular findings at examination (12 lead ECG), as assessed by a cardiologist as for normal pre-surgical screening;
6. Results of laboratory tests within the normal range of the laboratory or, if outside these ranges, be of no clinical importance in the opinion of the Investigator. In case of values outside the normal range the decision of including the subject into the trial is left to the sole responsibility of the clinical investigator, and will be justified;
7. Subjects given written informed consent.

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#### Test product, dose and mode of administration, batch No.

The test product was Org 25969 in part 1 and Org 25969 in combination with rocuronium bromide (Esmeron®) in part 2. Org 25969 was supplied by NV Organon in vials each containing 125 mg in 5 ml of a 25 mg.ml<sup>-1</sup> solution of active entity, batch number CV001. Rocuronium bromide was supplied by NV Organon as a solution of 100 mg in a 10 ml colorless vial (10 mg.ml<sup>-1</sup>), batch number CU229. Org 25969 and rocuronium were to be dosed on actual body weight and were to be administered as a 5 second bolus dose into a fast running infusion the forearm.

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#### Duration of treatment

Org 25969 was to be given as a single bolus dose.

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#### Reference therapy, dose and mode of administration, batch No.

Reference therapy consisted of placebo for Org 25969 (consisting of a commercially physiological salt solution, 0.9% NaCl) which was supplied by SGS Biopharma in minibags, batch number APB1307 Belgian Reg number 395IS9F12, lot 01F14G51. Placebo was to be administered as a 5 second bolus dose into a fast running infusion in the forearm.

## Criteria for evaluation

### Safety and tolerance

- Pre-treatment signs and symptoms;
- Clinically relevant cardiovascular changes;
- Clinically relevant changes in blood and urine laboratory results;
- Adverse events (including symptoms of local intolerance at the site of injection) and serious adverse events.

### Pharmacokinetics

- $V_z$ , clearance, AUC, MRT and  $t_{1/2}$
- Renal excretion parameters: amount excreted and excretion rate.

### Efficacy (part 2 only)

- Primary efficacy parameter: recovery time until TOF 0.8;
- Secondary efficacy parameters: recovery time until reappearance of third twitch, recovery times until TOF 0.7 and 0.9;
- Other parameters: maximum block and onset time.

## Statistical methods

As this is a Phase 1 trial, the sample size was not based on statistical power calculations. Demographic information, safety data, pharmacokinetic data, recovery times, maximum block and onset time (part 2 only) were to be listed by dose of Org 25969. Safety, pharmacokinetic, and efficacy data were to be summarized by descriptive statistics, as applicable. For data from part 2, the relations between the dose of Org 25969 and each of the recovery times were to be investigated in an explorative way. The data were to be presented in figures as plots of the doses of Org 25969 against the data of the different recovery times. Parameters of different models, as suggested by the data plots, were to be fitted to the obtained data in order to find a model which best explained the dose-effect relationship.

**Sample Analysis:** Bioanalysis of Org 25969 and rocuronium in plasma and urine was performed under experiment number 020005 at the Department of Drug Metabolism & Kinetics, Section Chromatography, Organon, Oss, according to standard operating procedures and methods.

**Subjects:** A total of 29 subjects were enrolled in this trial. All were Caucasian males. 19 subjects participated in part 1 (groups I-IIa) and 10 subjects participated in part 2 (III & IIIa). Their mean (SD) age was 30.5 (5.9) years and their mean (SD) weight and height were 76.8 (6.2) kg and 179.2 (5.7) cm, respectively. Subject no. 13 dropped out because of cardiac problems and he was not replaced.

**Table 1. Number (%) of subjects exposed to anesthetics by dose group, All-Subject-Treated group, Part 2 (N = 10).**

Drug name	Dose group (mg.kg <sup>-1</sup> Org 25969)						
	Placebo (N = 10)	0.1 (N = 1)	0.5 (N = 1)	1.0 (N = 2)	2.0 (N = 2)	4.0 (N = 2)	8.0 (N = 2)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
atropine	10 (100)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	2 (100)
NaCl 0.9%	10 (100)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	2 (100)
O <sub>2</sub>	9 (90)	0 (0)	1 (100)	2 (100)	2 (100)	1 (50)	2 (100)
O <sub>2</sub> 100%	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)
O <sub>2</sub> 40%	1 (10)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)	0 (0)
propofol	3 (30)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)
propofol tci	7 (70)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	1 (50)
remifentanil	10 (100)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	2 (100)
rocuronium	10 (100)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	2 (100)
Temesta							
expedit	10 (100)	1 (100)	1 (100)	2 (100)	2 (100)	2 (100)	2 (100)

**Results:**

**Efficacy:**

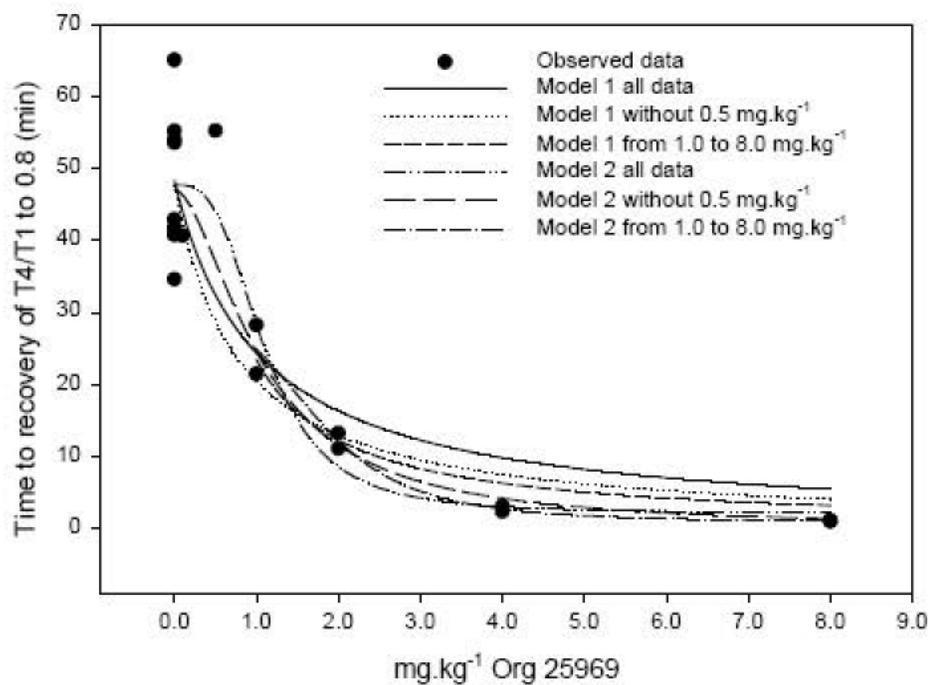
The primary efficacy parameter of this study was the recovery time of TOF, T<sub>4</sub>/T<sub>1</sub> to 0.8. Later studies used the recovery time of TOF, T<sub>4</sub>/T<sub>1</sub> to 0.9 as the primary efficacy parameter. Both data were shown in Table 2. The data suggests a plateau effect at doses above 4.0 mg/kg Org 25969 (Table 2 and Figure 1).

**Table 2. Summary of the time to recovery of T<sub>4</sub>/T<sub>1</sub> to 0.8 and 0.9 (min) by dose group, Per-Protocol group, Part 2 (N = 10).**

Parameter	Subject	Dose group (mg.kg <sup>-1</sup> Org 25969)						
		placebo (N = 9)	0.1 (N = 1)	0.5 (N = 1)	1.0 (N = 2)	2.0 (N = 2)	4.0 (N = 2)	8.0 (N = 2)
Time to recovery of	16	Excluded	40.67					
T <sub>4</sub> /T <sub>1</sub> to 0.8 (min)	17	53.97	55.25					
	18	40.75		28.25				
	19	53.58			11.08			
	20	42.92				2.32		
	25	55.20						1.02
	218	40.85		21.43				
	219	41.73			13.22			
	220	65.05				3.03		
	225	34.60						1.02

Parameter	Subject	Dose group (mg.kg <sup>-1</sup> Org 25969)						
		Placebo (N = 10)	0.1 (N = 1)	0.5 (N = 1)	1.0 (N = 2)	2.0 (N = 2)	4.0 (N = 2)	8.0 (N = 2)
Time to recovery of T4/T1 to 0.9 (min)	16	Excl.	43.17					
	17	63.72		71.00				
	18	45.50			31.00			
	19	60.33				12.58		
	20	46.67					2.57	
	25	57.70						1.02
	218	43.35			23.18			
	219	56.23				17.47		
	220	69.30					3.28	
	225	35.35						1.27

**Figure 1** Graphical presentation of the time to recovery of T<sub>4</sub>/T<sub>1</sub> to 0.8 by dose group, Per-Protocol group, Part 2 (N = 10)



1. Model 1: an inhibitory effect model with a baseline effect parameter,

$$\text{recovery time (dose)} = E_{\max} - (E_{\max} - E_0) * \frac{\text{dose}}{\text{dose} + ED_{50}},$$

where -  $E_{\max}$  is the maximum recovery time,  
 -  $E_0$  is the minimum recovery time, and  
 -  $ED_{50}$  is the median effective dose, the dose at which effect is 50% of maximum effect.

2. Model 2: a sigmoid inhibitory effect model with a baseline effect parameter,

$$\text{recovery time (dose)} = E_{\max} - (E_{\max} - E_0) * \frac{\text{dose}^\gamma}{\text{dose}^\gamma + ED_{50}^\gamma},$$

where -  $E_{\max}$  is the maximum recovery time,  
 -  $E_0$  is the minimum recovery time,  
 -  $ED_{50}$  is the median effective dose, the dose at which effect is 50% of maximum effect, and  
 -  $\gamma$  is a shape parameter of the curve.

The best model fitting the relationship between the time to recovery of  $T_4/T_1$  to 0.8 and the dose was a sigmoid inhibitory effect model with a baseline effect parameter:

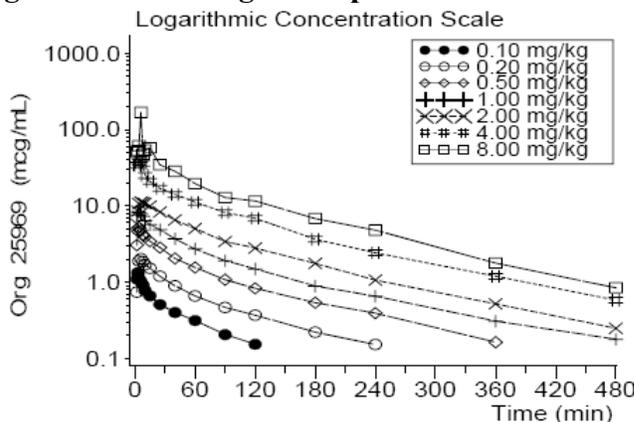
$$\text{recovery time (dose)} = E_{\max} - (E_{\max} - E_0) * \frac{\text{dose}^\gamma}{\text{dose}^\gamma + ED_{50}^\gamma}$$

The main parameter of interest from a clinical point of view was  $E_0$ , the minimum recovery time according to the model. The best fit was obtained when the model fitted the doses above or equal to 1.0 mg/kg Org 25969 ( $r = 0.98$ ).  $E_0$  estimate was 0.8 minutes.

**Pharmacokinetics:**

In Part 1, following administration of increasing single doses of Org 25969, exposure to Org 25969 as expressed by AUC increased proportionally to the dose over the dose range of 0.1 to 8.0 mg/kg (Table 3 and Figure 2). CL,  $V_z$  and  $t_{1/2,\beta}$  appeared to be independent of the dose administered.

**Figure 2. Mean Org 25969 plasma concentration-versus-time curve; Part 1.**



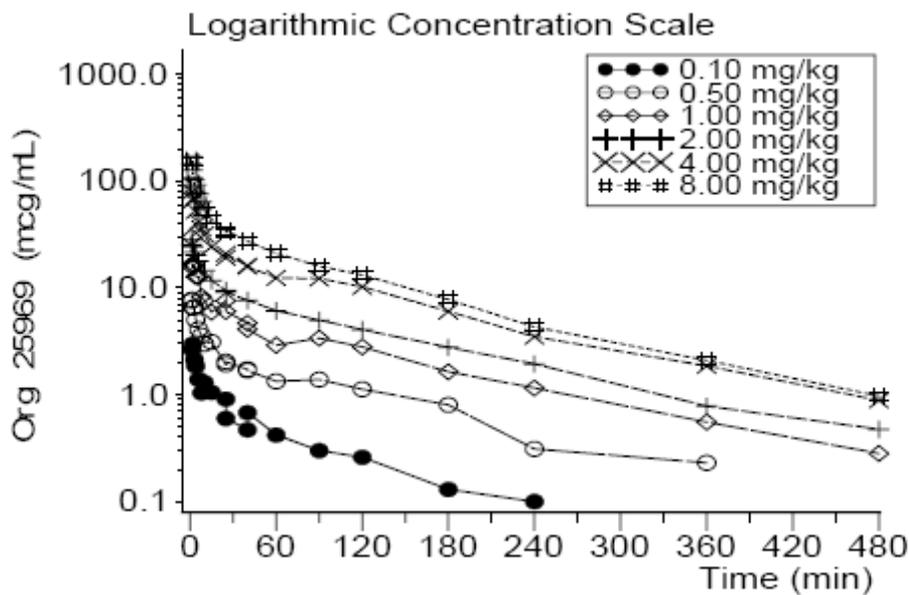
**Table 3. Summary of the pharmacokinetic parameters of Org 25969 in plasma; Part 1.**

Org 25969 Parameter #	0.1 mg/kg (n=4)	0.2 mg/kg (n=4)	0.5 mg/kg (n=4)	1 mg/kg (n=6)	2 mg/kg (n=6)	4 mg/kg (n=5)	8 mg/kg (n=2)
AUC <sub>0-∞</sub> (mcg*min/mL)	62.3 (17.0)	149 (3.09)	365 (4.44)	647 (13.7)	1100 (14.8)	2627 (26.8)	4837 (0.178)
dn-AUC <sub>0-∞</sub> (mcg*min/mL/mg)	8.10 (9.33)	10.1 (8.33)	9.32 (12.7)	8.41 (7.47)	7.27 (14.9)	8.45 (24.0)	8.20 (2.64)
CL (mL/min)	123 (9.33)	99.2 (8.33)	107 (12.7)	119 (7.47)	138 (14.9)	118 (24.0)	122 (2.64)
V <sub>z</sub> (mL)	11715 (26.2)	13526 (7.95)	16673 (27.1)	21860 (10.7)	20857 (16.3)	17674 (30.8)	17227 (7.34)
t <sub>1/2,β</sub> (min)	65.8 (32.6)	94.5 (12.0)	108 (16.9)	128 (12.2)	105 (7.05)	103 (9.46)	97.9 (4.69)

# Geometric mean (geometric coefficient of variation)

In Part 2, where Org 25969 was administered 3 minutes following a single dose of 0.6 mg/kg rocuronium, the plasma AUC of total Org 25969 (free and in complex) appeared to be slightly higher compared to the same dose levels of Org 25969 administered without rocuronium in Part 1 (Table 4 and Figure 3). It should be noted, however, that the small number of subjects does not allow for a sound comparison between Part 1 and Part 2.

**Figure 3. Mean Org 25969 plasma concentration-versus-time curve; Part 2.**



**Table 4. Summary of the pharmacokinetic parameters of Org 25969 in plasma; Part 2.**

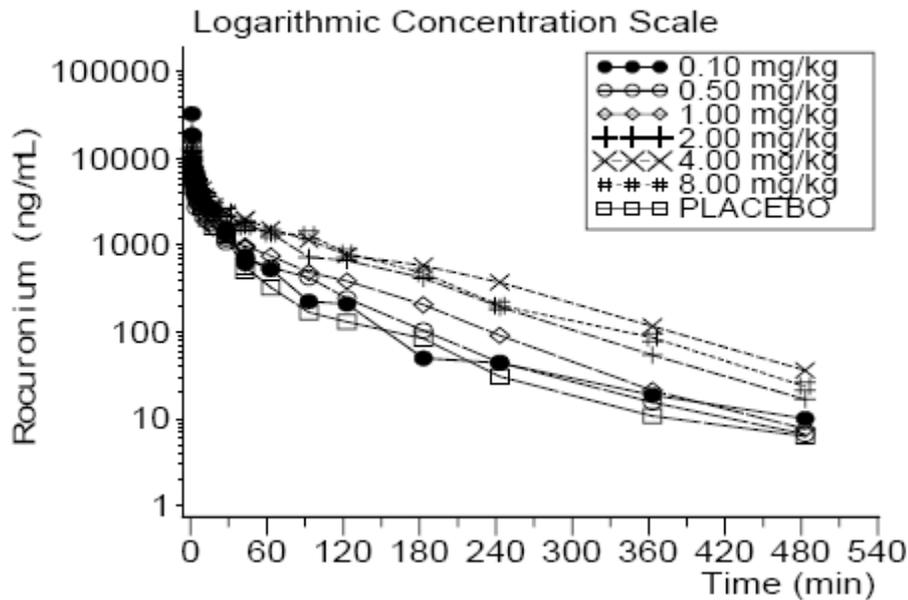
Org 25969 Parameter	0.1 mg/kg (n=1) *	0.5 mg/kg (n=1) *	1 mg/kg (n=2) #	2 mg/kg (n=2) #	4 mg/kg (n=2) <sup>3</sup>	8 mg/kg (n=2) #
AUC <sub>0-∞</sub> (mcg*min/mL)	99.2	377	985 (18.3)	1573 (3.33)	3494 (22.2)	5102 (2.39)
dn-AUC <sub>0-∞</sub> (mcg*min/mL/mg)	12.7	10.4	13.4 (19.7)	10.6 (11.8)	11.8 (14.3)	8.48 (2.16)
CL (mL/min)	78.6	95.7	74.7 (19.7)	94.5 (11.8)	84.8 (14.3)	118 (2.16)
V <sub>z</sub> (mL)	9643	14187	12728 (22.0)	15076 (5.35)	14560 (1.74)	19062 (9.21)
t <sub>1/2,β</sub> (min)	85.1	103	118 (2.22)	111 (6.45)	119 (16.1)	112 (7.04)

\* individual parameter presented; # geometric mean (geometric coefficient of variation) presented;

The rocuronium plasma concentrations increased with increasing dose of Org 25969 administered 3 minutes after 0.6 mg/kg rocuronium (Table 5 and Figure 4). The AUC of total rocuronium (in complex and not in complex with Org 25969) after treatment of 0.6 mg/kg rocuronium followed by 0.1 to 8.0 mg/kg of Org 25969 was higher compared to the AUC following administration of rocuronium only. Its value increased with more than a factor 2 when administration of rocuronium was followed by an Org 25969 dose of 2.0 mg/kg or higher. The volume of distribution V<sub>z</sub> of rocuronium decreased from about 50 L in the absence of Org 25969 to about 15 L when 2.0 to 8.0 mg/kg Org 25969 was given 3 minutes post-rocuronium. The terminal half-life of rocuronium in plasma decreased up to 40% if rocuronium was followed by Org 25969 administration.

On average 14% of the dose was recovered in urine up to 24h after administration of 0.6 mg/kg rocuronium (Table 6). When rocuronium dosing was followed by administration of Org 25969, the percentage of the dose excreted in urine as unchanged rocuronium increased with increasing Org 25969 up to at least 68% at the highest dose level of 8.0 mg/kg Org 25969 (Table 6). The rocuronium half-life calculated from urine data, which was estimated to be about 12h on average in the absence of Org 25969, was shortened with increasing Org 25969 dose to about 1.6 h at the highest dose level of 8 mg/kg.

**Figure 4. Mean rocuronium plasma concentration-versus-time curve; Part 2.**



**Table 5. Summary of the pharmacokinetic parameters of rocuronium in plasma; Part 2.**

Rocuronium Parameter	Org 25969 Dose						
	0.1 mg/kg (n=1) *	0.5 mg/kg (n=1) *	1 mg/kg (n=2) #	2 mg/kg (n=2) #	4 mg/kg (n=2) #	8 mg/kg (n=2) #	Placebo (n=10) #
AUC <sub>0-∞</sub> (mg*min/mL)	200	158	182 (9.46)	302 (12.1)	364 (25.4)	331 (6.75)	139 (20.9)
dn-AUC <sub>0-∞</sub> (mg*min/mL/mg)	4.27	3.67	4.02 (9.54)	6.46 (2.13)	8.27 (16.7)	7.43 (4.26)	3.06 (19.4)
CL (mL/min)	234	272	249 (9.54)	155 (2.13)	121 (16.7)	135 (4.26)	327 (19.4)
V <sub>z</sub> (mL)	38085	34390	22354 (17.3)	15124 (6.43)	12487 (3.23)	15434 (12.3)	49310 (24.7)
t <sub>1/2,β</sub> (min)	113	87.5	62.3 (7.66)	67.7 (4.29)	71.6 (13.4)	79.5 (16.6)	104 (21.0)

\* individual parameter presented; # geometric mean (geometric coefficient of variation) presented;

**Table 6. Summary of urinary excretion of rocuronium; Part 2.**

Rocuronium Parameter	Org 25969 Dose						
	0.1 mg/kg (n=1) *	0.5 mg/kg (n=1) *	1 mg/kg (n=2) *	2 mg/kg (n=2) *	4 mg/kg (n=2) *	8 mg/kg (n=2) *	Placebo (n=10) #
Total Amount	18.9	21.5	24.7	32.1	44.0	39.2 <sup>c</sup>	14.3
Excreted (% dose)			33.7	34.1	24.0 <sup>c</sup>	68.4 <sup>c</sup>	(34.0)
t <sub>1/2,u</sub> (h)	14.7	4.48	23.7 8.08	12.9 5.53	6.42 1.53	1.68 1.63	11.7 (52.5)

\* individual parameter presented; # geometric mean (geometric coefficient of variation) presented; n.c.: not calculable; <sup>c</sup> underestimated value due to missing urine concentrations;

**Discussion and Conclusions:**

Part 1: Org 25969 showed dose proportional pharmacokinetics over the dose range of 0.1 to 8.0 mg/kg with a total plasma clearance of about 100-120 mL/min, a volume of distribution of about 18 L and an elimination half-life of about 100 minutes.

Part 2: The clearance of Org 25969 seemed lower under anesthetic conditions and following administration of rocuronium, ranged from 75-120 mL/min. Rocuronium plasma concentrations and urinary excretion increased with increasing dose level of Org 25969, compared to administration of rocuronium alone.

The results showed that neuromuscular relaxation as a result of 0.6 mg/kg rocuronium bromide administration can be reversed by Org 25969 in man. The dose-effect relationship was described by a sigmoid inhibitory effect model with a plateau effect at doses above 4.0 mg/kg.

**4.2.3 Race and Gender**

*Study 19.4.102: A double-blind, randomized, placebo controlled trial to assess and compare safety, tolerability and pharmacokinetics of three ascending iv bolus doses with Org 25969 in Japanese and Caucasian healthy male and female volunteers*

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**Study Period:** March 4, 2003 to May 6, 2003  
**Sample Analysis Periods:** April 10, 2003 to May 26, 2003  
**Analytical Site:** The Department of Drug Metabolism and Kinetics, NV Organon, The Netherlands

**Investigator**  
U Lorch, MD MFPM FRCA

**Trial Center**  
Richmond Pharmacology Ltd, Atkinson Morley's Hospital, Copse Hill, Wimbledon, London, SW20 0NE, UK.

**Objectives:**

- To assess and compare safety parameters after single iv dose administration of three dose levels (1, 8 and 16 mg/kg Org 25969) of Org 25969 in Japanese and Caucasian healthy male and female volunteers.
- To assess and compare pharmacokinetics of Org 25969 in Japanese and Caucasian healthy male and female volunteers after single iv dose administration of three different dose levels of Org 25969 and in addition compare by gender per ethnic group.
- To investigate the dose-proportionality following single iv dose administration of Org 25969 at three different dose levels in Japanese and Caucasian healthy male and female volunteers.

**Methodology**

This was a single center, double blind, placebo controlled, single ascending iv dose study. Each subject was to receive three (1, 8, 16 mg/kg) single iv bolus dose administrations of Org 25969 in ascending order plus a placebo dose interspersed (placebo treatment was randomized either to be in period 1, 2, 3 or 4.). Administrations per subjects were separated by at least a one-week wash out.

**Diagnosis and Criteria for Inclusion**

**Japanese subjects:** Japanese citizens with 100% Japanese parentage and 1<sup>st</sup> generation non-immigrants (the subject was to be born in Japan and was to have left Japan less than 10 years ago).

**Caucasian subjects:** Both parents had to be Caucasian. Subjects had to have a home address in the UK.

**General criteria:**

1. Subjects were male or female and at least 20 years of age and not older than 45 years of age at the day of the first dosing (both inclusive).
2. Subjects were Caucasian or Japanese.
3. Subjects had a body weight (females 45-70 kg; males 55-85 kg, extremes included) resulting in a body mass index (BMI) of  $18 \leq \text{BMI} \leq 25 \text{ kg/m}^2$ .
4. Subjects were able and willing to sign the Informed Consent Form prior to screening evaluations.
5. Subjects with a (history of) good physical and mental health as determined by history taking, physical and laboratory examinations, 12-lead ECG and vital signs recordings.
6. Subjects who smoked less than 10 cigarettes or equivalent per day
7. Female subjects were non-pregnant (urinary hCG test), sterile or practicing an acceptable method of birth control: condom and diaphragm with spermicide, vasectomized partner [ $\geq 6$  months], IUD, abstinence, tubal ligation, hysterectomy or postmenopausal [ $\geq 2$  years]).

**Test Product, Dose and Mode of Administration, Batch No**

Each 10mL vial contained 100 mg/mL of Org 25969 (Batch Number CW157, Expiry Date: November 2003). Subjects received three (1, 8 and 16 mg/kg) single iv bolus administrations in ascending order plus a placebo dose (speed of infusion was 1 mL/second) into a fast running infusion in the forearm via a 3-way stop-cock, followed by flushing the stop-cock. All doses were given in an identical volume to the 16mg/kg dose, with dilutions made up using saline which was approximately iso-osmotic to the 100 mg/mL Org 25969 solution.

**Reference Therapy, Dose and Mode of Administration, Batch No.**

Placebo – saline approximately iso-osmotic to the 100mg/mL Org 25969 solution (Batch Numbers: 00SC02 and 00SC002; Expiry Date: May 2003, and Batch Number: 01SC02; Expiry Date: October 2004).

**Criteria for Evaluation**

Safety

Safety and tolerability parameters comprised blood chemistry, hematology (including haptoglobin, bilirubin total and conjugated bilirubin) and urinalysis, 12 lead-ECG, vital signs, physical examination, adverse events, local tolerance (injection site examination) and concomitant medication.

### Pharmacokinetics

Venous blood samples were drawn predose (up to -5 minutes) and at 2, 4, 6, 8, 10, 15, 25, 40, 60, 90 minutes and 2, 3, 4, 6, 8, 12, 16, 20 and 24 hours post dose (20 samples). Urinary samples were collected during the following intervals (predose, 0-2, 2-4, 4-8, 8-12, 12-16 and 16-24 hrs).

Single-dose plasma and urine concentrations of Org 25969 were determined by means of LC-MS (Liquid Chromatographic Mass Spectrometric) assays. The following plasma pharmacokinetic parameters were calculated: peak concentration ( $C_{max}$ ) and the time of  $C_{max}$  occurrence ( $t_{max}$ ); dose-normalized peak concentration (dn- $C_{max}$ ); terminal elimination half-life ( $t_{1/2}$ ); area under the plasma-concentration-versus-time curve until the last time point with a measurable concentration  $t_{last}$  ( $AUC_{0-t_{last}}$ ) and until infinity ( $AUC_{0-\infty}$ ); dose-normalized AUC until  $t_{last}$  (dn- $AUC_{0-t_{last}}$ ) and until infinity (dn- $AUC_{0-\infty}$ ); mean residence time (MRT); (weight-normalized) clearance ((wn-)CL) and (weight-normalized) volume of distribution assuming steady-state conditions ((wn-)V<sub>ss</sub>). The following urine pharmacokinetic parameters were calculated: fraction of the amount entering the circulation that is excreted unchanged (fe) and renal clearance CL<sub>R</sub>.

### Statistical Methods

#### Safety

Descriptive summary statistics (number of observations, mean, standard deviation, median and minimum-maximum values). Adverse events are categorized by body system and coded using MedDRA.

### Pharmacokinetics

Descriptive statistics for the Org 25969 concentrations in plasma and the pharmacokinetic parameters for Org 25969 in plasma and urine. Regression plots of the main pharmacokinetic parameters versus dose by ethnic group. Analysis of Variance (ANOVA) on log<sub>e</sub>-transformed pharmacokinetic parameters with factors ethnic group, gender and dose level and interaction terms; all tests at the 5% level of significance.

**Sample Analysis:** Determination of Org 25969 in plasma and urine was performed by the Department of Drug Metabolism and Kinetics, NV Organon, The Netherlands, using validated liquid chromatographic mass spectrometric methods.

**Subjects:** A total of 28 subjects were enrolled into the study: 14 Japanese and 14 Caucasian. As planned in the protocol within each ethnic group 7 males and 7 females were enrolled. All 28 subjects were randomized and received all three doses (1, 8 and 16 mg/kg) of Org 25969 plus a placebo dose. The Caucasian group was slightly taller and heavier than the Japanese group (Table 1). The mean blood pressure and heart rate readings from the Caucasian group were also slightly higher compared to the Japanese group at the screening assessment.

**Table 1. Subject Characteristics at the Screening.**

Characteristic	Caucasian mean (SD) (n=14)	Japanese mean (SD) (n=14)
Gender		
Male n (%)	7 (50.0%)	7 (50.0%)
Female n (%)	7 (50.0%)	7 (50.0%)
Age (years)	23.1 (1.59)	25.2 (3.19)
Height (cm)	172.9 (9.34)	166.7 (7.53)
Weight (kg)	66.49 (5.365)	59.45 (5.054)
Systolic BP (mmHg)	113.6 (7.29)	104.8 (16.78)
Diastolic BP (mmHg)	65.5 (9.12)	58.6 (8.07)
Heart rate (bpm)	62.2 (5.45)	58.3 (11.48)
Respiratory rate (resp/min)	15.4 (1.99)	14.6 (3.15)
Auricular temperature (°C)	36.59 (0.389)	36.66 (0.533)

## Results:

### Pharmacokinetics:

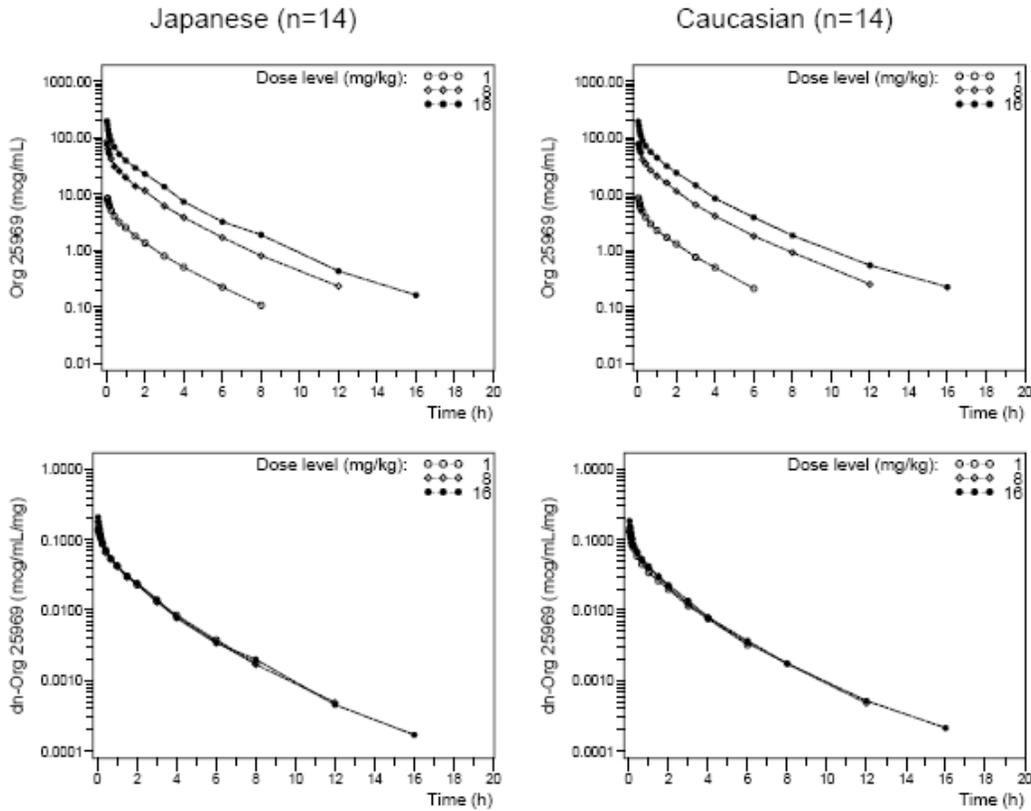
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(b) (4) (Sugammadex Sodium)

Solution for Injection (100 mg/mL)

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**Figure 1 Mean Org 25969 plasma concentration-versus-time curves**



Upper panels: geometric mean Org 25969 concentrations in logarithmical scale.  
 Lower panels: geometric mean dose-normalized Org 25969 concentrations in logarithmical scale.

**Table 2. Overall summary of the PK parameters for Org 25969 in plasma.**

Parameter (unit)		Japanese (n=14)			Caucasian (n=14)		
		1 mg/kg	8 mg/kg	16 mg/kg	1 mg/kg	8 mg/kg	16 mg/kg
$C_{max}$ ( $\mu\text{g/mL}$ )	Mean	9.22	93.7	206	9.30	88.0	202
	CV (%)	19.0	14.0	14.6	24.8	23.3	17.6
$t_{max}$ (min)	Median	2	2	2	2	2	2
	Range	2-10	2-4	2-4	2-6	2-10	2-4
$dn-C_{max}$ ( $\mu\text{g/mL/mg}$ )	Mean	0.155	0.197	0.217	0.141	0.166	0.191
	CV (%)	21.0	18.7	18.0	26.6	25.9	16.9
$t_{1/2}$ (min)	Mean	107	132	143	101	161	181
	CV (%)	13.9	17.5	22.5	16.7	39.9	30.5
$AUC_{0-t_{last}}$ ( $\mu\text{g}\cdot\text{min/mL}$ )	Mean	541	4573	9638	507	4795	10143
	CV (%)	14.4	10.1	13.5	17.3	12.7	14.0
$AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{min/mL}$ )	Mean	561	4604	9670	530	4828	10185
	CV (%)	14.2	10.0	13.5	17.2	12.6	14.0
$dn-AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{min/mL/mg}$ )	Mean	9.44	9.68	10.2	8.02	9.13	9.63
	CV (%)	16.7	9.02	15.5	17.7	13.5	10.9
MRT (min)	Mean	114	114	116	113	121	122
	CV (%)	10.5	10.8	12.1	13.1	16.6	10.6
CL (mL/min)	Mean	106	103	98.4	125	109	104
	CV (%)	16.7	9.02	15.5	17.7	13.5	10.9
$wn-CL$ (mL/min/kg)	Mean	1.78	1.74	1.65	1.89	1.66	1.57
	CV (%)	14.2	10.0	13.5	17.2	12.6	14.0
$V_{ss}$ (mL)	Mean	12071	11799	11370	14053	13246	12617
	CV (%)	13.5	15.5	15.0	19.1	21.0	11.2
$wn-V_{ss}$ (mL/kg)	Mean	203	198	191	213	200	191
	CV (%)	9.92	14.1	11.8	16.0	17.3	12.4

Presented statistics are geometric mean and geometric coefficient of variation (for  $t_{max}$  median and range (min max)).

**Table 3. Summary of the PK parameters for Japanese subjects only (Male vs. Female).**

Parameter (unit)		Male (n=7)			Female (n=7)		
		1 mg/kg	8 mg/kg	16 mg/kg	1 mg/kg	8 mg/kg	16 mg/kg
C <sub>max</sub> (µg/mL)	Mean	9.35	91.8	207	9.10	95.6	205
	CV (%)	22.3	13.0	15.1	16.8	15.7	15.4
t <sub>max</sub> (min)	Median	4	2	2	2	2	2
	Range	2-6	2-4	2-4	2-10	2-4	2-2
dn-C <sub>max</sub> (µg/mL/mg)	Mean	0.147	0.181	0.203	0.163	0.215	0.231
	CV (%)	23.4	11.1	16.6	18.5	21.5	18.2
t <sub>1/2</sub> (min)	Mean	102	133	141	113	130	145
	CV (%)	15.4	16.5	25.5	11.3	19.8	21.1
AUC <sub>0-tlast</sub> (µg*min/mL)	Mean	530	4831	9446	552	4329	9833
	CV (%)	13.3	5.72	18.3	16.3	10.8	7.40
AUC <sub>0-∞</sub> (µg*min/mL)	Mean	549	4862	9475	574	4361	9870
	CV (%)	12.9	5.74	18.2	16.1	10.7	7.44
dn-AUC <sub>0-∞</sub> (µg*min/mL/mg)	Mean	8.64	9.57	9.32	10.3	9.79	11.1
	CV (%)	14.7	6.09	17.0	14.0	11.7	7.37
MRT (min)	Mean	111	113	116	117	116	115
	CV (%)	8.67	9.14	15.6	12.1	12.8	8.62
CL (mL/min)	Mean	116	105	107	96.9	102	90.2
	CV (%)	14.7	6.09	17.0	14.0	11.7	7.37
wn-CL (mL/min/kg)	Mean	1.82	1.65	1.69	1.74	1.83	1.62
	CV (%)	12.9	5.74	18.2	16.1	10.7	7.44
V <sub>ss</sub> (mL)	Mean	12866	11799	12433	11325	11799	10398
	CV (%)	12.7	9.80	11.9	11.7	20.7	12.5
wn-V <sub>ss</sub> (mL/kg)	Mean	203	186	196	203	212	187
	CV (%)	10.6	9.33	14.6	10.1	15.5	8.83

Presented statistics are geometric mean and geometric coefficient of variation (for t<sub>max</sub> median and range (min-max)).

**Table 4. Summary of the PK parameters for Caucasian subjects only (Male vs. Female).**

Parameter (unit)		Male (n=7)			Female (n=7)		
		1 mg/kg	8 mg/kg	16 mg/kg	1 mg/kg	8 mg/kg	16 mg/kg
C <sub>max</sub> (µg/mL)	Mean	9.40	89.7	218	9.20	86.3	187
	CV (%)	27.8	15.2	15.3	23.7	30.9	17.1
t <sub>max</sub> (min)	Median	2	2	2	2	2	2
	Range	2-6	2-4	2-4	2-6	2-10	2-2
dn-C <sub>max</sub> (µg/mL/mg)	Mean	0.134	0.160	0.195	0.147	0.173	0.187
	CV (%)	27.1	17.5	17.6	27.3	33.6	17.3
t <sub>1/2</sub> (min)	Mean	110	168	215	92.7	154	153
	CV (%)	16.4	44.2	32.8	12.9	38.3	16.2
AUC <sub>0-tlast</sub> (µg*min/mL)	Mean	516	4891	11223	499	4701	9167
	CV (%)	22.0	9.44	9.62	12.6	15.8	9.42
AUC <sub>0-∞</sub> (µg*min/mL)	Mean	540	4924	11275	520	4735	9200
	CV (%)	21.5	9.48	9.57	13.2	15.7	9.41
dn-AUC <sub>0-∞</sub> (µg*min/mL/mg)	Mean	7.72	8.80	10.1	8.33	9.48	9.21
	CV (%)	23.3	13.4	11.5	10.2	13.6	8.92
MRT (min)	Mean	120	128	128	106	114	115
	CV (%)	10.6	12.4	9.06	13.4	19.1	9.79
CL (mL/min)	Mean	130	114	99.3	120	105	109
	CV (%)	23.3	13.4	11.5	10.2	13.6	8.92
wn-CL (mL/min/kg)	Mean	1.85	1.62	1.42	1.92	1.69	1.74
	CV (%)	21.5	9.48	9.57	13.2	15.7	9.41
V <sub>ss</sub> (mL)	Mean	15481	14599	12712	12757	12018	12522
	CV (%)	18.9	18.1	11.9	14.6	19.9	11.3
wn-V <sub>ss</sub> (mL/kg)	Mean	221	209	182	204	193	201
	CV (%)	18.0	17.5	12.9	13.8	17.4	10.4

Presented statistics are geometric mean and geometric coefficient of variation (for t<sub>max</sub> median and range (min-max)).

**Table 5. Summary of Urinary Excretion of Org 25969 (Japanese vs. Caucasian).**

Urine parameter (unit)		Japanese			Caucasian		
		1 mg/kg (n=14)	8 mg/kg (n=14)	16 mg/kg (n=13)	1 mg/kg (n=14)	8 mg/kg (n=14)	16 mg/kg (n=14)
fe (Total Amount Excreted in % dose)	Mean	59.1	71.3	77.0	67.6	72.1	74.2
	CV (%)	40.1	21.4	12.4	17.1	15.5	10.7
CL <sub>R</sub> (mL/min)	Mean	62.7	73.7	76.2	84.3	78.9	77.0
	CV (%)	36.8	26.0	19.1	24.5	22.0	6.7

Presented statistics are geometric mean and geometric coefficient of variation.

Ethnic Group Comparison (Japanese vs. Caucasian)

Exposure to Org 25969 for the Japanese subjects was found to be on an average 10% higher compared to Caucasian subjects (Table 6).

**Table 6. PK results of Ethnic Group Comparison.**

Parameter (unit)	Gender	Point Estimate of $\mu(\text{Japanese})/\mu(\text{Caucasian})$	95% Confidence Interval
dn-AUC <sub>0-∞</sub> (μg*min/mL/mg)	Overall (n=14 vs n=14)	1.10	1.02-1.18
	Female (n=7 vs n=7)	1.15	1.04-1.28
	Male (n=7 vs n=7)	1.04	0.94-1.16
t <sub>1/2</sub> (min)	Overall (n=14 vs n=14)	0.88	0.77-1.02
	Female (n=7 vs n=7)	0.99	0.81-1.21
	Male (n=7 vs n=7)	0.79	0.65-0.96
CL (mL/min)	Overall (n=14 vs n=14)	0.91	0.85-0.98
	Female (n=7 vs n=7)	0.87	0.78-0.96
	Male (n=7 vs n=7)	0.96	0.87-1.07
wn-CL (mL/min/kg)	Overall (n=14 vs n=14)	1.01	0.94-1.09
	Female (n=7 vs n=7)	0.97	0.88-1.08
	Male (n=7 vs n=7)	1.06	0.96-1.17
V <sub>ss</sub> (mL)	Overall (n=14 vs n=14)	0.88	0.81-0.97
	Female (n=7 vs n=7)	0.90	0.79-1.02
	Male (n=7 vs n=7)	0.87	0.76-0.99
wn-V <sub>ss</sub> (mL/kg)	Overall (n=14 vs n=14)	0.98	0.91-1.06
	Female (n=7 vs n=7)	1.01	0.90-1.12
	Male (n=7 vs n=7)	0.96	0.86-1.07

Based on ANOVA using all 28 subjects.

Dose Proportionality

**Table 7. Dose Proportionality for Japanese subjects.**

Parameter (unit)	Gender	Dose level (mg/kg)		Point Estimate of $\mu(\text{High})/\mu(\text{Low})$	95% Confidence Interval
		Highest dose	Lowest dose		
dn-AUC <sub>0-∞</sub> (μg-min/mL/mg)	Overall (n=14 vs n=14)	16	1	1.08	0.99-1.18
	Female (n=7 vs n=7)	16	1	1.07	0.95-1.22
	Male (n=7 vs n=7)	16	1	1.08	0.95-1.22
t <sub>1/2</sub> (min)	Overall (n=14 vs n=14)	16	1	1.33	1.15-1.55
	Female (n=7 vs n=7)	16	1	1.29	1.04-1.59
	Male (n=7 vs n=7)	16	1	1.38	1.12-1.71
dn-AUC <sub>0-last</sub> (μg-min/mL/mg)	Overall (n=14 vs n=14)	16	1	1.11	1.02-1.22
	Female (n=7 vs n=7)	16	1	1.11	0.98-1.26
	Male (n=7 vs n=7)	16	1	1.12	0.98-1.26

Based on ANOVA using all 28 subjects.

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(b) (4) (Sugammadex Sodium)

Solution for Injection (100 mg/mL)

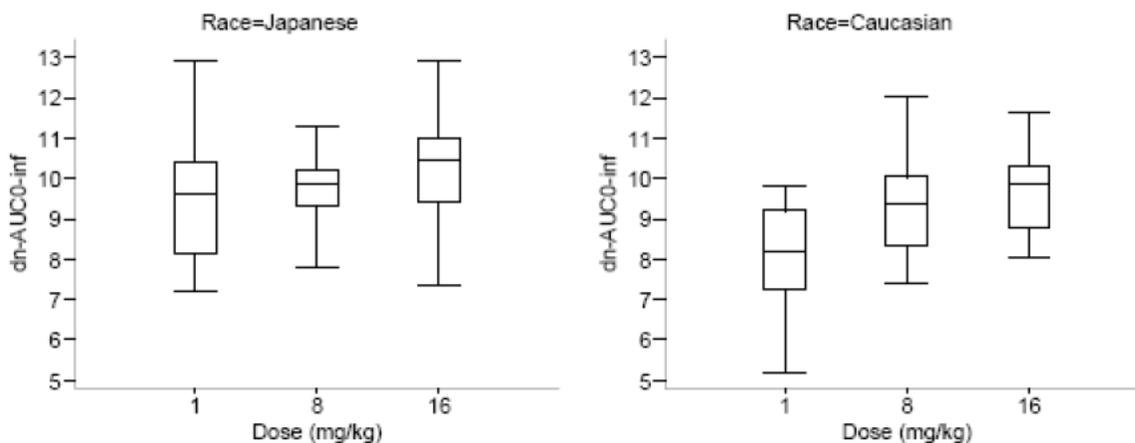
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**Table 8. Dose Proportionality for Caucasian subjects.**

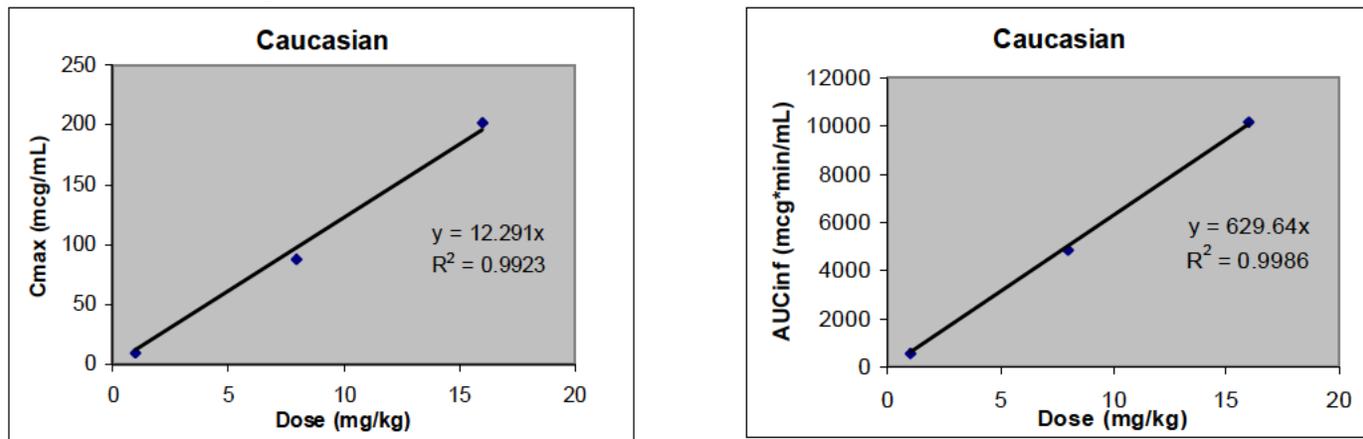
Parameter (unit)	Gender	Dose level (mg/kg)		Point Estimate of $\mu(\text{High})/\mu(\text{Low})$	95% Confidence Interval
		Highest dose	Lowest dose		
dn-AUC <sub>0-∞</sub> ( $\mu\text{g}\cdot\text{min}/\text{mL}/\text{mg}$ )	Overall (n=14 vs n=14)	16	1	1.20	1.10-1.31
	Female (n=7 vs n=7)	16	1	1.11	0.98-1.25
	Male (n=7 vs n=7)	16	1	1.31	1.15-1.48
t <sub>1/2</sub> (min)	Overall (n=14 vs n=14)	16	1	1.80	1.55-2.09
	Female (n=7 vs n=7)	16	1	1.66	1.34-2.04
	Male (n=7 vs n=7)	16	1	1.96	1.59-2.41
dn-AUC <sub>0-tlast</sub> ( $\mu\text{g}\cdot\text{min}/\text{mL}/\text{mg}$ )	Overall (n=14 vs n=14)	16	1	1.25	1.14-1.36
	Female (n=7 vs n=7)	16	1	1.15	1.02-1.30
	Male (n=7 vs n=7)	16	1	1.36	1.20-1.54

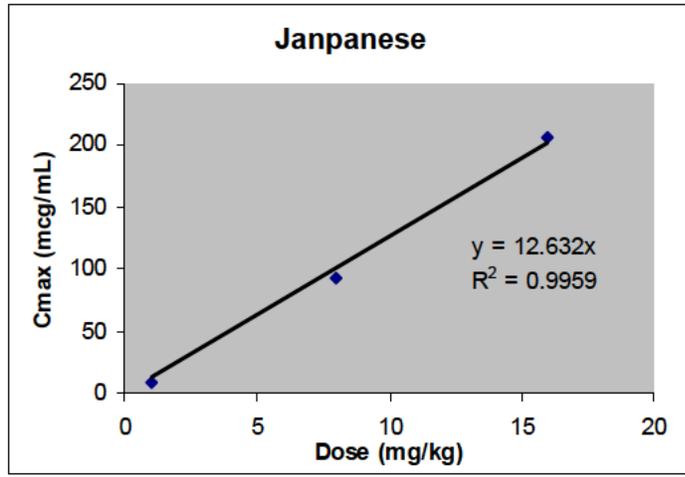
Based on ANOVA using all 28 subjects.

**Figure 2** Box-and-whisker plots of dn-AUC<sub>0-∞</sub>

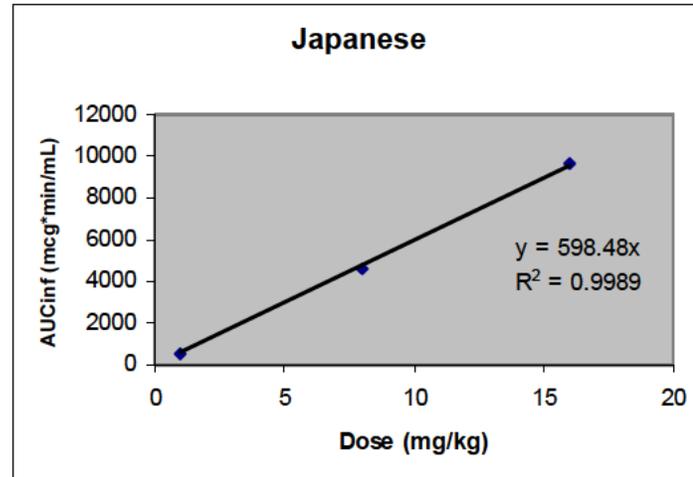


**Figure 3. Relationship between Cmax and Dose, and AUC and Dose.**





**Cmax**



**AUC**

As sugammadex is dosed intravenously, Cmax would be dependent on the infusion rate and sampling time.

Gender Comparison

**Table 9. PK results of Gender Comparison.**

Parameter (unit)	Ethnic Group	Point Estimate of $\mu(\text{females})/\mu(\text{males})$	95% Confidence Interval
dn-AUC <sub>0-∞</sub> ( $\mu\text{g}\cdot\text{min}/\text{mL}/\text{mg}$ )	Overall (n=14 vs n=14)	1.08	1.00-1.16
	Japanese (n=7 vs n=7)	1.13	1.02-1.26
	Caucasian (n=7 vs n=7)	1.02	0.92-1.13
t <sub>1/2</sub> (min)	Overall (n=14 vs n=14)	0.92	0.80-1.06
	Japanese (n=7 vs n=7)	1.03	0.85-1.26
	Caucasian (n=7 vs n=7)	0.82	0.67-1.00
CL (mL/min)	Overall (n=14 vs n=14)	0.93	0.86-1.00
	Japanese (n=7 vs n=7)	0.88	0.80-0.98
	Caucasian (n=7 vs n=7)	0.98	0.88-1.09
wn-CL (mL/min/kg)	Overall (n=14 vs n=14)	1.05	0.98-1.13
	Japanese (n=7 vs n=7)	1.01	0.91-1.12
	Caucasian (n=7 vs n=7)	1.10	0.99-1.22
V <sub>ss</sub> (mL)	Overall (n=14 vs n=14)	0.89	0.81-0.97
	Japanese (n=7 vs n=7)	0.90	0.79-1.03
	Caucasian (n=7 vs n=7)	0.87	0.77-0.99
wn-V <sub>ss</sub> (mL/kg)	Overall (n=14 vs n=14)	1.01	0.93-1.09
	Japanese (n=7 vs n=7)	1.03	0.92-1.15
	Caucasian (n=7 vs n=7)	0.98	0.88-1.09

Based on ANOVA using all 28 subjects.

**Discussion and Conclusions:**

Following single-dose iv bolus infusions of 1, 8 and 16 mg/kg Org 25969, no major differences in pharmacokinetics of Org 25969 were observed between Japanese and Caucasian subjects. CL was 9% lower and V<sub>ss</sub> was 12% lower in the Japanese compared to the Caucasian subjects. The difference is not considered clinically relevant. After body weight normalization (wn-), CL and V<sub>ss</sub> were similar in both ethnic groups. As of note, the dose was body-weight based and there is no clear body weight effect on the PK of sugammadex based on population PK analysis.

The PK of sugammadex is similar in female and male subjects.

Across the dose range of 1 to 16 mg/kg, the data indicated dose proportionality with respect to systemic Org 25969 exposure for the Japanese population. For the Caucasian population a slightly more than proportional increase in systemic exposure to Org 25969 with increasing dose was observed (~20% increase compare 16 mg/kg with 1 mg/kg). Overall, exposure is approximately dose-proportional between 1 and 16 mg/kg.

#### 4.2.4 High Dose Study

*Study 19.4.106: Randomized, double-blind, placebo-controlled 4 periods ascending single iv dose study to assess the safety and tolerability of high doses of Org 25969 in healthy male and female volunteers*

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**Study Period:** April 2005 to May 2006  
**Sample Analysis Periods:** May 25, 2005 to August 4, 2005  
Reanalysis: March 31, 2006 to April 19, 2006  
**Analytical Site:** The Department of Clinical Pharmacology & Kinetics, section Chromatography, Organon Oss, The Netherlands  
Reanalysis: The Department of Bioanalytics, Research & Development, N.V. Organon, Oss, The Netherlands

<b>Investigator</b>
M.P. van Iersel
<b>Clinical trial center</b>
Xendo Drug Development Services BV Hanzeplein 1, Entrance 53 9713 GZ, Groningen, The Netherlands
<b>Objectives</b>
Primary objectives: To assess safety and tolerability after high single iv doses of Org 25969 in healthy male and female subjects To explore the pharmacokinetics (including dose proportionality) after high doses of Org 25969 To explore the pharmacokinetics of Org 48302.
<b>Methodology</b>
This single-center study followed a randomized, double-blind, placebo-controlled, four periods single iv ascending dose design. All subjects but one (subject 008) received all four treatments (three ascending doses of Org 25969 with placebo randomly interspersed). Male and female subjects were divided as equally as possible over the four treatment sequences.

**Diagnosis and main criteria for inclusion****Subjects:**

- were male or female and at least 18 and not older than 65 years of age at the day of the first dosing.
- had a body weight resulting in a body mass index (BMI) between 18 and 30 kg/m<sup>2</sup>
- were able and willing to sign the Informed Consent Form prior to screening evaluations.
- were in a good age-appropriate healthy condition as established by medical history, physical examination, vital signs, and electrocardiogram, results of biochemistry, hematology and urinalysis testing within 3 weeks prior to the first dose

**Test product, dose and mode of administration, batch No.**

Org 25969 was supplied as 100 mg/mL Org 25969; 5 mL/vial, AE-batch. Approximately (b) (4)% of the active entity consists of Org 48302 which has the same pharmacological properties compared with Org 25969.

Placebo was supplied (0.9% NaCl-solution for iv, 100 mL/vial). Placebo was also used to adjust the volume of the low and middle dose of Org 25969 to the volume of the highest dose of Org 25969.

Generic name: modified gamma-cyclodextrin, sugammadex, Org 25969

Dosage form: fluid for injection, vial 5 ml, 100mg/ml

Mode of administration: single iv dose

Dose: 32, 64 and 96 mg/kg

Batch number: (PZ002)C4039

Expiry date: Oct 2006

Manufacturer: NV Organon, Oss, The Netherlands

**Duration of treatment:** Four periods of single iv dosing with a wash out of 7 days between successive dosing periods.

**Criteria for evaluation****Safety:**

12-lead ECG recordings (HR, PR, QRS, QT QTc), blood pressure and pulse rate were recorded at screening, follow up, at baseline of each period (for ECGs three baseline recordings) and at t=2 and 35 minutes and 1, 2, 3, 4, 6, 12, 24 hours post dose administration of each period.

Safety laboratory parameters: blood chemistry (sodium, potassium, chloride, ionized calcium, ionized magnesium, creatinine, blood urea nitrogen, ALAT, ASAT, gamma-GT, alkaline phosphatase, creatinine kinase, lactate dehydrogenase, bilirubin total, protein total, albumin, glucose fasting, cholesterol total, triglycerides fasting and haptoglobin); hematology (hematocrit, hemoglobin, erythrocyte count, leucocyte count, differential count and platelet count) and urinalysis (leukocytes, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin and glucose, N-acetyl glucosaminidase,  $\beta$ 2-microglobulin and microglobulin) were assessed at screening, follow up and at baseline and t=24 hours post dosing of each period.

Occurrence of adverse events were assessed by asking non-leading questions at baseline and at t=1, 2, 4, 6 hours of each period. Also, subjects were instructed to report adverse events spontaneously.

**Pharmacokinetics:**

Plasma and urine concentrations of Org 25969 and Org 48302 were measured at several time points. The following plasma pharmacokinetic parameters were calculated: (dose-normalized) peak concentration ((dn-)C<sub>max</sub>) and its time of occurrence (t<sub>max</sub>), terminal half-life (t<sub>1/2</sub>), effective half-life (t<sub>1/2, effective</sub>), (dose-normalized) area-under-the-curve ((dn-)AUC<sub>0-tlast</sub> and (dn-)AUC<sub>0-∞</sub>), mean residence time (MRT), (weight-normalized) clearance ((wn-)CL), (weight-normalized) volume of distribution during terminal phase ((wn-)V<sub>z</sub>) and (weight-normalized) volume of distribution at steady-state ((wn-)V<sub>ss</sub>). The following urine pharmacokinetic parameters were calculated: fraction of the amount entering the circulation that is excreted unchanged (f<sub>e</sub>) and renal clearance (CLR).

**Pharmacodynamics:** Not applicable.

### Statistical methods

Demographics (ethnic group, gender, age, body weight, height and BMI) of all treated subjects is presented individually. Descriptive statistics for the demographics in the ASPE group is presented by gender and overall and were to comprise number of observations (n), arithmetic mean, standard deviation, minimum, median and maximum.

**Safety:** (Serious) adverse events (AEs) reported either spontaneously throughout the whole trial period. Clinical safety, including a comprehensive medical (physical) examination, vital signs (blood pressure and pulse rate) and ECG. Laboratory safety, including routine hematology, biochemistry, and urinalysis.

**PK:** Descriptive statistics for the Org 25969 and Org 48302 concentrations in plasma and the pharmacokinetic parameters for Org 25969 and Org 48302 in plasma and urine. Box-and-whisker plots of the main pharmacokinetic parameters versus dose. Analysis of Variance (ANOVA) on loge-transformed pharmacokinetic parameters with factors gender and dose level and interaction term; all tests at the 5% level of significance.

**PD:** Not applicable

For PK analysis in plasma, blood samples (6 mL) were to be drawn at the predefined time points (pre dose, t=0 (end of infusion), 2, 5, 10, 20 and 35 minutes post dose and 1, 1:30, 2, 2:30, 4, 6, 8, 12, 18, 24 and 48 hours post dose).

For PK analysis in urine, aliquots were to be taken from the urine collected during the predefined intervals (predose -12:00 – 00:00; 00:00 – 06:00; 06:00 – 12:00; 12:00 – 24:00 and 24:00 – 48:00).

**Sample Analysis:** Initial PK analysis suggested that Org 25969 in plasma and urine samples had a negative influence on the analysis results for Org 48302 in human heparin plasma samples and human urine samples. Therefore all plasma and urine samples of this study were reanalysed with the re-validated LC-MS assays for the determination of Org 48302 (in the presence of Org 25969) in human heparin plasma or in human urine (Validation Report: Organon R&D RR INT00006478). The assay was re-validated in the presence of Org 25969 (Org 48302/Org 25969 in the same ratio as the medication which was dosed in Studies 106 and 107). As in the revalidated assays calibration and QC samples contain a similar ratio of Org 48302/Org 25969 as the unknown samples, the negative influence of Org 25969 on the Org 48302 results is expected to be compensated for.

**Subjects:** A total of 21 subjects were screened (Figure 1). Five subjects were not eligible due to smoking, low heart rate, difficult venous accessibility or declined. Three subjects acted as reserve. In total, 13 subjects (6 female and 7 male) were randomized and 12 (6 male and 6 female) of them completed the study. All subjects were Caucasians.

Subject 008 (male) was withdrawn from the study because of an adverse event (skin paraesthesia and vision disturbances) observed during the administration of the medication in Period 1. The infusion of subject 008 (male) was stopped prematurely in period 1. Subject 008 received approximately 8.4 mg/kg Org 25969 as an intravenous dose of about 1 minute duration. Subject 008 did not participate in the remaining periods of the study and, in agreement with the sponsor; the subject was replaced by subject 108. Subject 008 participated in a later study (19.4.110) in which hypersensitivity issue was addressed specifically. Refer to Dr. Simone's review on the assessment of potential hypersensitivity reaction caused by sugammadex.

**Table 1. Subject baseline characteristics. All-Subjects-Treated group (N = 13).**

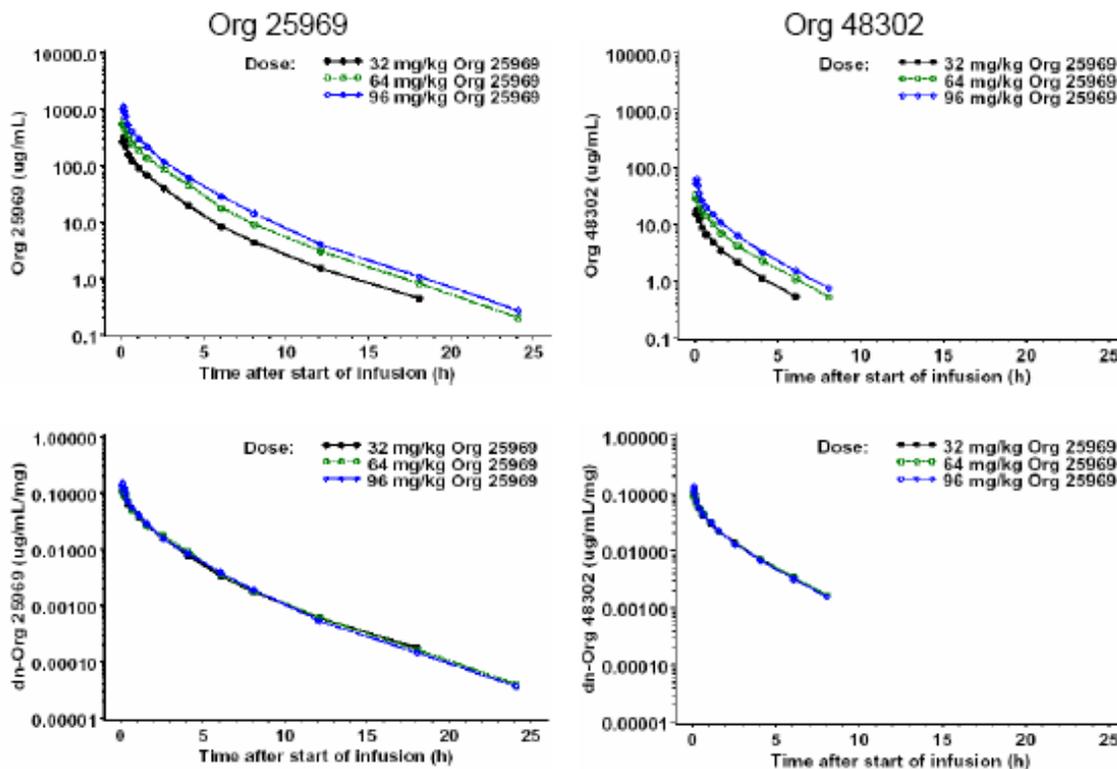
Age (years)	Mean ± SD	38.0	± 12.7
	Median (min – max)	36	(20 - 58)
Weight (kg)	Mean ± SD	80.68	± 10.41
	Median (min – max)	82.1	(59.5 – 95.1)
Height (m)	Mean ± SD	177.6	± 6.3
	Median (min – max)	177	(168 – 189)
Body mass index (kg/m <sup>2</sup> )	Mean ± SD	25.54	± 2.99
	Median (min – max)	24.2	(21.1 – 30.0)

**Results:**

*Pharmacokinetics:*

Figure 1 shows that the dose-normalized concentration-time curves overlap to a great extent, both for Org 25969 and Org 48302. This indicates dose proportionality of the concentrations within the dose range studied. Overall exposure of Org 48302 was approximately 5% of that of Org 25969, which may reflect the % of Org 48320 in the product used in this study.

**Figure 1. (dose-normalized) Geometric mean Org 25969 (left panels) and Org 48302 (right panels) plasma concentration-versus-time curves**



Curves based on n=12 subjects.

**Table 2. Overall summary of the PK parameters for Org 25969 and Org 48302 in Plasma.**

Parameter (unit)		Org 25969 (n=12)			Org 48302 (n=12)		
		32 mg/kg	64 mg/kg	96 mg/kg	32 mg/kg	64 mg/kg	96 mg/kg
C <sub>max</sub> (µg/mL)	Mean	343	648	1168	18.0	34.7	64.4
	CV(%)	35.2	27.4	21.1	24.2	32.7	24.9
t <sub>max</sub> (min)	Median	7.00	7.00	7.00	6.50	7.00	7.00
	Minimum	5.00	5.00	5.00	5.00	5.00	5.00
	Maximum	10.0	10.0	10.0	10.0	15.0	10.0
dn-C <sub>max</sub> (µg/mL/mg)	Mean	0.139	0.131	0.157	0.113	0.108	0.134
	CV(%)	37.5	20.1	15.1	30.9	25.3	17.9
t <sub>1/2</sub> (min)	Mean	232	260	187	109	116	123
	CV(%)	48.1	63.9	13.1	18.8	12.3	17.1
AUC <sub>0-last</sub> (µg*min/mL)	Mean	22235	46168	71184	1138	2303	3540
	CV(%)	15.0	18.9	16.1	17.2	20.1	17.4
dn-AUC <sub>0-last</sub> (µg*min/mL/mg)	Mean	8.99	9.33	9.59	7.11	7.20	7.38
	CV(%)	18.5	16.3	14.8	20.2	18.1	14.4
AUC <sub>0-∞</sub> (µg*min/mL)	Mean	22301	46245	71273	1199	2371	3611
	CV(%)	15.0	18.9	16.2	17.3	19.8	17.1
dn-AUC <sub>0-∞</sub> (µg*min/mL/mg)	Mean	9.02	9.35	9.61	7.50	7.42	7.53
	CV(%)	18.5	16.3	14.8	19.6	18.2	14.0
CL (mL/min)	Mean	111	107	104	133	135	133
	CV(%)	18.5	16.3	14.8	19.6	18.2	14.0
wn-CL (mL/min/kg)	Mean	1.38	1.33	1.29	1.66	1.67	1.65
	CV(%)	15.0	18.9	16.2	17.3	19.8	17.1
V <sub>ss</sub> (mL)	Mean	15048	14710	13006	15944	16726	16017
	CV(%)	28.8	14.7	16.0	24.4	13.6	12.5
wn-V <sub>ss</sub> (mL/kg)	Mean	187	182	161	198	208	199
	CV(%)	19.4	12.2	10.8	13.9	12.5	9.40
t <sub>1/2, effective</sub> (min)	Mean	94.0	95.3	86.6	82.8	86.0	83.6
	CV(%)	23.8	20.3	14.9	20.1	15.0	14.4

dn = dose-normalized; wn = weight-normalized; Mean = geometric mean and CV(%) = geometric CV(%)

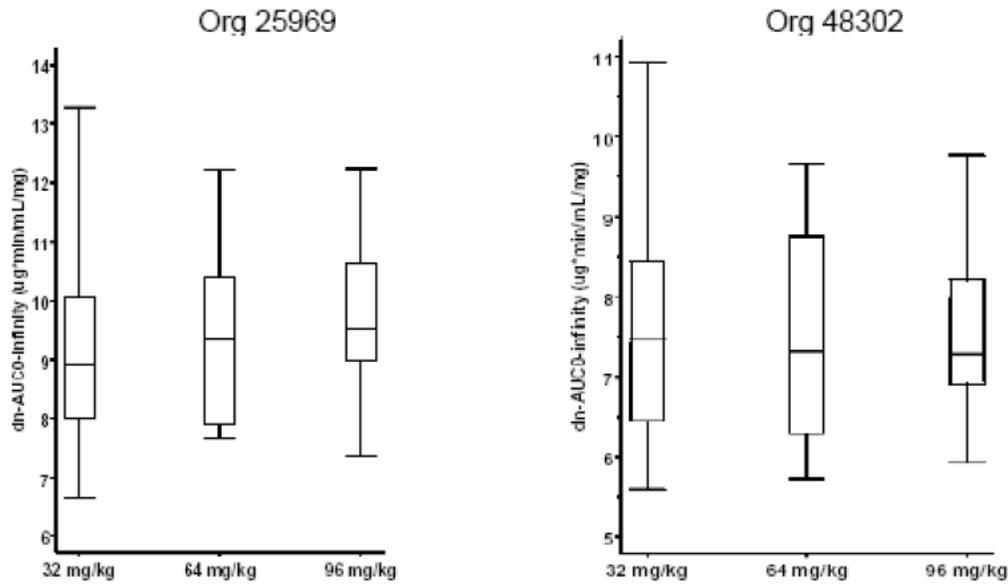
**Table 3. Summary of Urinary Excretion of Org 25969 and Org 48302.**

Parameter (unit)		Org 25969			Org 48302		
		32 mg/kg (n=12)	64 mg/kg (n=10)	96 mg/kg (n=12)	32 mg/kg (n=12)	64 mg/kg (n=10)	96 mg/kg (n=12)
CL <sub>R</sub> (mL/min)	Mean	103	94.8	94.1	116	116	107
	CV(%)	30.1	18.0	24.5	28.7	20.7	29.4
fe (Amount Excreted unchanged in % dose)	Mean	92.8	89.9	90.4	86.7	87.1	80.2
	CV(%)	18.9	14.2	24.0	13.0	11.4	25.2

Presented statistics are geometric mean and geometric coefficient of variation.

Dose-Proportionality

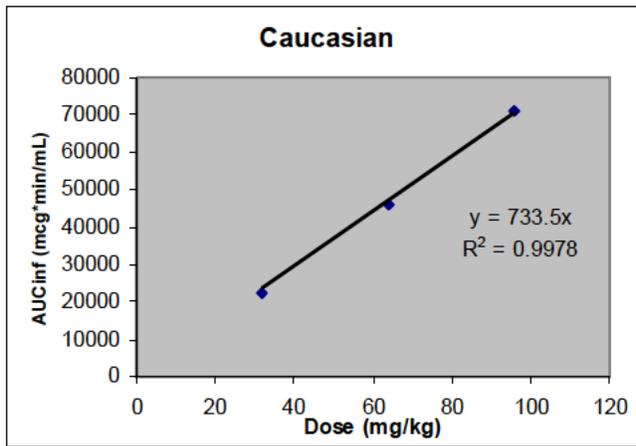
Figure 2. Box-and-whisker plots of  $dn-AUC_{0-\infty}$  for Org 25969 (left panel) and Org 48302 (right panel)



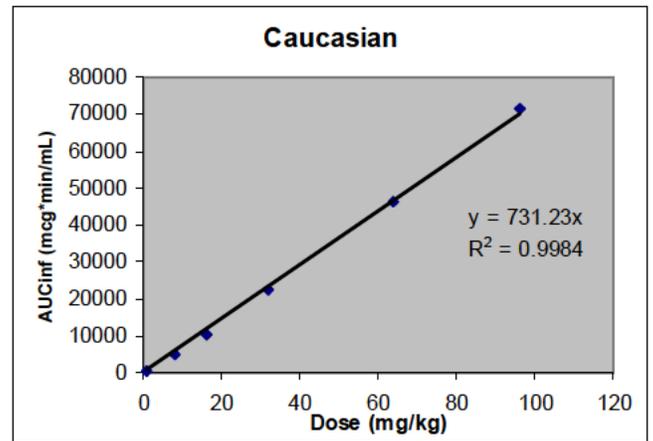
Data were taken from figures 5.2-1 and 5.4-1 in Appendix B1.

Presented are at the whiskers the high/low extremes and in the box the 25<sup>th</sup> and 75<sup>th</sup> percentiles and the median; each box n=12.

Figure 3. Relationship between AUC and Dose.



32-96 mg (This study)



1-96 mg (Combined with Caucasian data from Study 102)

**Conclusions:**

- Across the dose range of 32 to 96 mg/kg the data indicated dose proportionality with respect to exposure to both Org 25969 and Org 48302. When combined data from Study 102, the dose-proportionality maintained.
- The pharmacokinetics of Org 25969 and Org 48302 in plasma and urine were similar.

- The mean amount excreted unchanged in urine up to 48 hours varied between 90 and 93% of the administered dose for Org 25969 and between 80 and 87 % for Org 48302.
- The clinical response of subject 008 to infusion of Org 25969 is suggestive of an anaphylactic or an anaphylactoid reaction. This subject participated in study 19.4.110 to address the hypersensitivity issue.

#### 4.2.5 <sup>14</sup>C-ADME Study

*Study 19.4.107: Open, non-randomized, single center trial to determine the excretion balance, metabolite profile and pharmacokinetics of sugammadex after an intravenous dose of [<sup>14</sup>C]-labeled sugammadex.*

**Clinical Investigator:** SP van Marle, MD

**Study Center:** Pharma Bio-Research Group BV, Stationsweg 163, 9471 GP Zuidlaren, The Netherlands

**Study Period:** September to November 2005

**Objectives:**

- To determine the excretion balance (mass balance) of the total radioactivity in urine, feces and exhaled air after single iv dosing of [<sup>14</sup>C]-labeled Org 25969
- To determine the extent of metabolism and to identify metabolites in selected samples if applicable
- To determine the pharmacokinetics of total radioactivity and of Org 25969 and Org 48302 in plasma and urine

Secondary

- To collect and store DNA extracted from blood samples obtained from healthy male subjects treated with Org 25969 for future association studies of genotype with the pharmacokinetics and safety characteristics obtained in this trial

**Study Design:** This was an open label, non-randomized, single center trial involving the administration of a single intravenous (iv) dose of [<sup>14</sup>C]-labeled Org 25969 to six healthy male subjects.

**Test product, dose and mode of administration, batch No.**

Product	: Sugammadex (Org 25969)
Dosage form	: iv injection
Strength	: 100 mg active entity / mL (approximately (b) (4) % of the contents is Org 48302)
Dose	: 4 mg/kg Org 25969 containing 0.025 MBq/kg <sup>14</sup> C-radioactivity
Batch number	: CY039
Manufacturer	: NV Organon, Oss, The Netherlands

### **Sample Collection and Analysis:**

- Blood samples for **PK (bold)**, *radioactivity (RA) (italic)* and metabolic profiling (MP) (underlined) at **predose** and at t = **2, 5, 10, 20, 35, 60, 90**, minutes and at t = **2.5, 4, 6, 8, 12, 18, 24** and **48** h post dose.
- Collection intervals for urine samples for PK, RA and MP at predose (-12 to 0 h) and at 0-6, 6-12, 12-24 and 24-48 h post dose.
- Exhaled air samples for RA at predose and at t = 1, 2, 6 and 12 h post dose.
- Collection intervals for feces for RA and MP at predose (Day -3 until admission) and at 0-12, 12-24, and 24-48 h post dose.

Blood and urine samples were to be analyzed for Org 25969 and Org 48302 by the chromatography section of the Clinical Pharmacology & Kinetics (CPK) Department of Organon N.V. under Study No. 050333. Blood and urine samples were to be analyzed for RA by the bioanalytical laboratory of (b) (4). MP of blood and urine samples was to be performed by the Toxicology and Drug Disposition Department of Organon N.V.

### **Results:**

Study Population: A total of 6 healthy male subjects entered and completed the study as per protocol. All subjects were Caucasians.

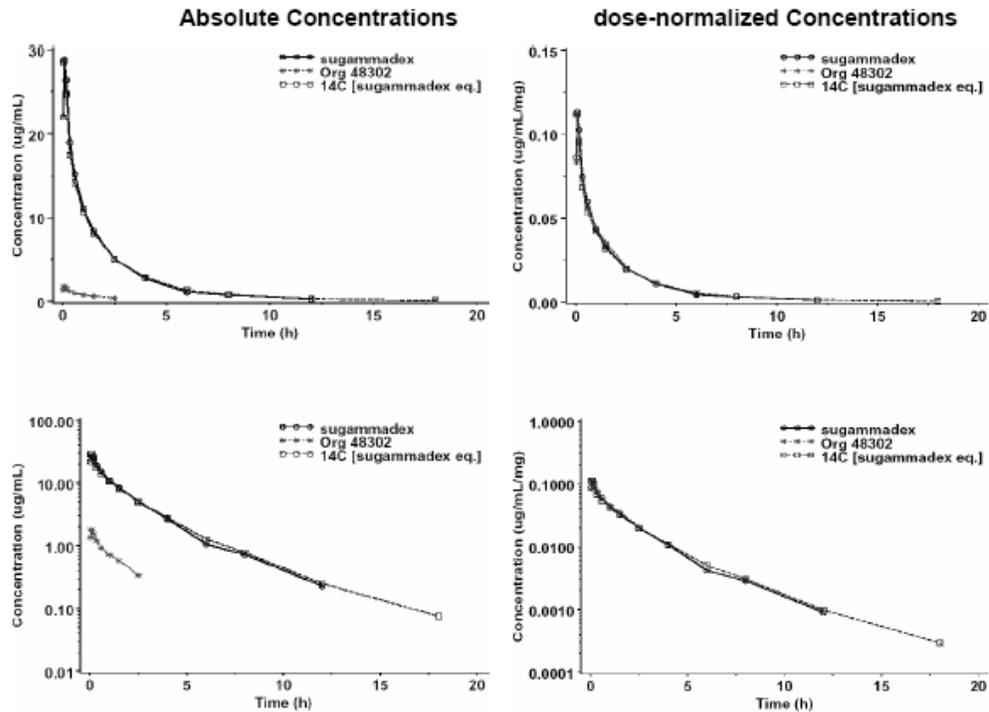
	n	Age (yr)	Height (cm)	Weight (kg)	BMI (kg/m <sup>2</sup> )
Mean (SD)	6	52.8 (16.3)	178.2 (9.7)	75.83 (9.93)	23.83 (1.90)
Min – Max		20 - 64	165 - 190	64.1 - 91.7	21.8 - 26.6

### Plasma Pharmacokinetics:

Figure 1 shows that the curves of radioactivity and Org 25969 overlap almost perfectly. This indicates that the radioactivity in plasma can be attributed almost exclusively to <sup>14</sup>C-Org 25969 and with limited radiolabelled metabolites of Org 25969 can be present in plasma. In the dose-normalized concentration-time curves, Org 48302 also overlaps almost perfectly with Org 25969, showing that these two compounds have identical PK profiles.

A comparison of the AUC<sub>0-∞</sub> of <sup>14</sup>C and Org 25969 shows that, on average 99.9 % of the radioactivity in plasma can be attributed to Org 25969 (Table 1).

**Figure 1. Geometric mean plasma concentration-versus-time curves of radioactivity, Org 25969 and Org 48302, absolute concentrations (left panels) or dose-normalized concentrations (right panels).**



Curves based on n=6 subjects.

**Table 1. Summary of the PK parameters of radioactivity, Org 25969 and Org 48302.**

Parameter (unit)	<sup>14</sup> C		Org 25969		Org 48302	
	Mean*	CV* (%)	Mean*	CV* (%)	Mean*	CV* (%)
C <sub>max</sub> (µg/mL)	33.0	22	32.2	19	1.97	14
t <sub>max</sub> (min)	4	2 - 5	5	2 - 10	5	3 - 10
t <sub>1/2</sub> (min)	190	20	152	31	89	29
AUC <sub>0-last</sub> (µg*min/mL)	2618	25	2586	23	125	26
AUC <sub>0-∞</sub> (µg*min/mL)	2632	25	2629	23	159	26
CL (mL/min)	96.8	25	96.9	24	102	25
V <sub>ss</sub> (mL)	15360	19	14027	19	12189	12
t <sub>1/2, effective</sub> (min)	110	16	100	19	82.5	26
CL <sub>R</sub> (mL/min)	92.7	29	88.3	25	99.6	26

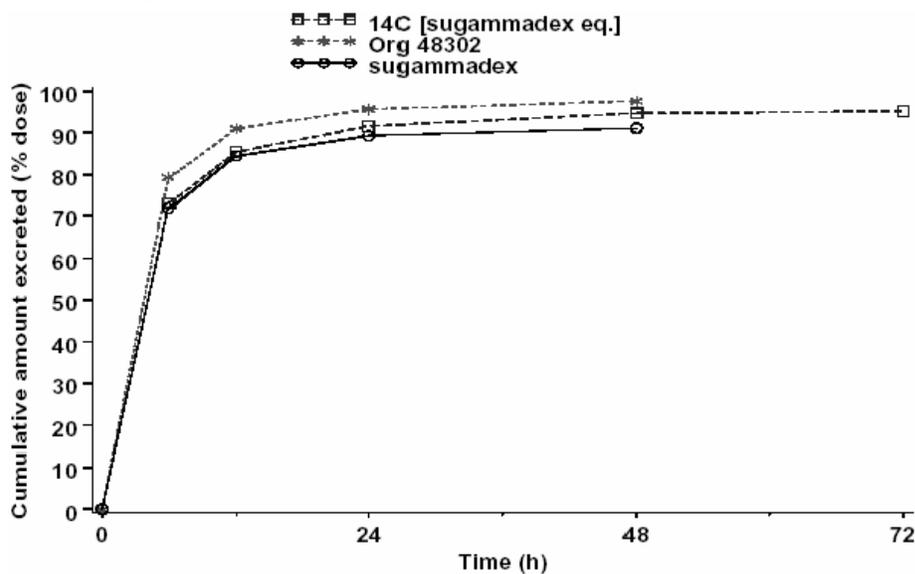
\*: Mean = geometric mean (median for t<sub>max</sub>) and CV (%) = geometric CV (%) (min-max for t<sub>max</sub>).

Urine/Feces/Expired Air

Radiolabelled Org 25969 was excreted mainly via the kidneys. On average 96% of the radioactive dose was recovered in urine and less than 0.02% in either feces or expired air (Table 2). The accumulation curves of radioactivity and of Org 25969 in urine overlap to a large extent indicating that the excreted radioactivity in urine was mainly unchanged Org 25969 (Figure 2). The cumulative amount of Org 25969 recovered was 91.1% of the dose (Table 2). Based on these data, 95% of the radioactivity in urine can be attributed to Org 25969 and at most 5% can be present as metabolites. This shows that metabolism of Org 25969 is limited and that the compound is almost exclusively excreted via renal excretion as the unchanged product.

On average >70 % of the radioactive dose was excreted within 6 hours and >90% within 24 hours (Figure 2).

Figure 2. Mean cumulative excretion in urine versus time for radioactivity, Org 25969 and Org 48302<sup>a)</sup>.



Curves based on n=6 subjects. Arithmetic means are presented.

The figure shows the data as percentage of the amount of the respective constituents.

Table 2. Summary of urinary excretion of radioactivity, Org 25969 and Org 48302.

	Percentage of the dose recovered in urine (fe)		
	Total Radioactivity	Org 25969	Org 48302
Subject 1	(b) (4)		
Subject 2			
Subject 3			
Subject 4			
Subject 5			
Subject 6			
<b>Mean ± SD</b>	96.1 ± 9.2	91.1 ± 3.5	97.6 ± 9.9

### Metabolic Profiling:

The results from the consequent metabolic profiling (Study No. 050351) indicated higher percentage for metabolites (~30%) which may be confounded by the *ex vivo* conversion in plasma or urine (the samples were stored between 6 months to 1 year before analysis). The study did, however, confirm that the presence of Org 48302 is not a metabolite of Org 25969.

**Conclusion:** The mass balance study suggests that the elimination of sugammadex is mainly through renal excretion (fe~96%). Excretion of radioactivity in feces and exhaled air was negligible as the cumulative amount excreted via these routes was less than 0.02% in all subjects. The metabolism of sugammadex is limited (~5%). The plasma and urine profiles of <sup>14</sup>C, Org 25969 and Org 48302 were overlapping to a large degree.

### *4.2.6 Renal Impairment Study*

*Study 19.4.304: A multi-center, parallel group, comparative trial evaluating the efficacy, pharmacokinetics and safety of Org 25969 in subjects with normal or impaired renal function*

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**Study Period:** June 2005 to April 2006  
**Sample Analysis Periods:** January 12, 2006 to June 13, 2006  
**Analytical Site:** N.V. Organon, Molenstraat 110, 5342 CC Oss, The Netherlands

<b>Investigator(s)</b> Prof. Dr. J.M. Hunter [GB 253]; Dr. J.J. Driessen [NL 001] and Dr. M.M.J. Snoeck [NL 115].
<b>Clinical trial center(s)</b> [GB 253] University Department of Anaesthesia, The Duncan Building Daulby Street, L69 3GA Liverpool, United Kingdom. [NL 001], Universitair Medisch Centrum St Radboud, Geert Grooteplein 10, 6525 GA Nijmegen, the Netherlands. [NL 115], Nijmeegs Interkonnefessioneel Ziekenhuis Canisius- Willehelmina, Weg door Jonkerbos 100, 6532 SZ Nijmegen, the Netherlands.

**Objectives**

The clinical trial objectives were:

- To show equivalence with respect to the efficacy of Org 25969 in subjects with normal or impaired renal function
- To compare the pharmacokinetics of Org 25969 in subjects with normal or impaired renal function
- To evaluate the safety of Org 25969 in subjects with impaired renal function

**Methodology**

This was a multi-center, parallel-group, comparative trial in two stages.

**Number of subjects (total and for each treatment)**

In total 30 subjects were enrolled into the trial; 15 renally impaired subjects and 15 control subjects. None of the subjects discontinued from the trial before administration of Org 25969. All 30 subjects, 16 females and 14 males, received a dose of Org 25969 and their age ranged from 29 to 81 years (inclusive). Except for two Asian subjects in the renally impaired group, all subjects were Caucasian. The ethnicity for all subjects was not Hispanic or Latino.

**Diagnosis and criteria for inclusion**

ASA class 1 – 3 for renally impaired patients, ASA class 1-2 for control group; Age at least 18 years; Scheduled for general anesthesia without further need for muscle relaxation other than one single dose of 0.6 mg.kg<sup>-1</sup> rocuronium; Scheduled for surgical procedures in the supine position; Written informed consent; Creatinine clearance (CL<sub>CR</sub>) < 30 mL/min for renally impaired group and CL<sub>CR</sub> ≥ 80 mL/min for control group.

One single dose of 0.6 mg/kg rocuronium was to be administered. At reappearance of T<sub>2</sub>, one single bolus dose of 2.0 mg/kg Org 25969 was to be administered. Blood and urine samples for PK were to be taken at multiple time points.

Plasma samples:

Sample no.	Sampling time	Rocuronium	Org 25969	Total mL blood
1	Pre-rocuronium	Yes	no	1.0 mL
2	2 min after rocuronium	Yes	no	1.0 mL
3	3 min after rocuronium	Yes	no	1.0 mL
4	5 min after rocuronium	Yes	no	1.0 mL
5	10 min after rocuronium	Yes	no	1.0 mL
6 *	15 min after rocuronium	Yes	no	1.0 mL
7 *	20 min after rocuronium	Yes	no	1.0 mL
8	Pre-Org 25969 25969 (reappearance T <sub>2</sub> )	Yes	yes	3.0 mL
9	2 min after Org 25969	Yes	yes	3.0 mL
10	3 min after Org 25969	Yes	yes	3.0 mL
11	5 min after Org 25969	Yes	yes	3.0 mL
12	10 min after Org 25969	Yes	yes	3.0 mL
13	15 min after Org 25969	Yes	yes	3.0 mL
14	20 min after Org 25969	Yes	yes	3.0 mL
15	30 min after Org 25969	Yes	yes	3.0 mL
16	60 min after Org 25969	Yes	yes	3.0 mL
17	2 hour after Org 25969	Yes	yes	3.0 mL
18	4 hour after Org 25969	Yes	yes	3.0 mL
19	6 hour after Org 25969	Yes	yes	3.0 mL
20	8 hour after Org 25969	Yes	yes	3.0 mL
21	12 hour after Org 25969	Yes	yes	3.0 mL
22	18 hour after Org 25969	Yes	yes	3.0 mL
23	24 hour after Org 25969	Yes	yes	3.0 mL
24 **	36 hour after Org 25969	Yes	yes	3.0 mL
25 **	48 hour after Org 25969	Yes	yes	3.0 mL
26 ***	Pre-dialysis	Yes	yes	3.0 mL
27 ***	Post-dialysis	Yes	yes	3.0 mL
<b>Total blood volume for PK purposes</b>				<b>67.0 mL</b>

\* do not take these samples if reappearance T<sub>2</sub> has already occurred

\*\* for renal patients only

\*\*\* only if the subject is dialysed between 0 – 72 h after administration of Org 25969

## Urine samples:

- From administration of rocuronium to 6 h after administration of Org 25969
- 6 – 12 h after administration of Org 25969
- 12 – 18 h after administration of Org 25969
- 18 – 24 h after administration of Org 25969
- 24 – 36 h after administration of Org 25969 (renal patients only)
- 36 – 48 h after administration of Org 25969 (renal patients only)
- 48 – 72 h after administration of Org 25969 (renal patients only)

If the subject was undergoing dialysis between 0 and 72 h after administration of Org 25969, a pre- and post-dialysis blood sample for PK was to be taken.

### Test product, dose and mode of administration, batch No.

- Org 25969 (investigational product, IP) supplied in 5-mL vials containing 500 mg active entity (i.e. 100 mg.mL<sup>-1</sup>) of Org 25969 (Batch numbers: CZ180 and CX203)
- Esmeron® (rocuronium bromide) supplied in colorless 10-mL vials containing 100 mg (i.e. 10 mg.mL<sup>-1</sup>) of rocuronium bromide (further referred to as rocuronium -> check waar dit voor het eerst al genoemd wordt) (Batch numbers: CZ191 and CX204)

### Duration of treatment

Org 25969 was to be given as a single bolus dose. Full recovery from neuromuscular blockade was to be expected at the end of anesthesia.

### Criteria for evaluation

#### *Neuromuscular variables*

##### Primary efficacy variable:

Time from start administration of Org 25969 to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.9.

##### Secondary efficacy variables:

Time from start administration of Org 25969 to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.7; Time from start administration of Org 25969 to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.8.

##### Other efficacy variables:

Time from start administration of Org 25969 to reappearance of T<sub>3</sub>; T<sub>1</sub> at reappearance of T<sub>3</sub>; Time from start administration of rocuronium to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.7; Time from start administration of rocuronium to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.8; Time from start administration of rocuronium to recovery T<sub>4</sub>/T<sub>1</sub> ratio to 0.9; Occurrence of recurarization; Time from start administration of Org 25969 to value of the lowest T<sub>4</sub>/T<sub>1</sub> ratio in case of recurarization; Value of the lowest T<sub>4</sub>/T<sub>1</sub> ratio in case of recurarization; Time from start administration of Org 25969 to return of T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 in case of recurarization.

##### Other neuromuscular variables:

Time from start administration of rocuronium to reappearance of T<sub>2</sub>; T<sub>1</sub> at reappearance of T<sub>2</sub>.

#### *Pharmacokinetic assessments*

Plasma pharmacokinetic parameters: terminal half-life (t<sub>1/2</sub>), effective half-life (t<sub>1/2</sub>.effective), (dose-normalized) area-under-the-curve ((dn-)AUC<sub>0-tlast</sub> and (dn-)AUC<sub>0-∞</sub>), mean residence time (MRT), (weight-normalized) clearance ((wn-)CL), (weight-normalized) volume of distribution during terminal phase ((wn-)V<sub>z</sub>) and (weight-normalized) volume of distribution at steady-state ((wn-)V<sub>ss</sub>).

Urine pharmacokinetic parameters: (cumulative) amount excreted in urine (Ae(cum,t)) and urinary excretion rate (Ru). In subjects receiving hemodialysis the rates and half-lives of dialysis were calculated.

#### *Safety assessments*

Vital signs, i.e. blood pressure (BP) and heart rate (HR); Physical examination; (Serious) adverse events; Laboratory assessments: hematology, biochemistry and urinalysis.

##### *Additional measures of safety*

Clinical evidence of recurarization or residual curarization, e.g. respiratory problems; Clinical assessments of recovery, i.e. consciousness, 5 seconds head lift test, presence of diplopia, check of general muscle weakness, tongue depressor test; Signs of possible interaction of Org 25969 with endogenous compounds or with exogenous compounds other than rocuronium.

### Statistical methods

For all variables appropriate descriptive statistics were calculated. To investigate equivalence, the primary efficacy variable was analyzed using a confidence interval (CI) approach for the subject group difference. Data of the secondary efficacy variables were analyzed in the same way as was done for the primary efficacy variable. For safety descriptive statistics are presented. Descriptive statistics for the Org 25969 and rocuronium concentrations in plasma and the pharmacokinetic parameters were calculated. Analysis of Variance (ANOVA) was used on log-transformed pharmacokinetic parameters with factor group at the 5% level of significance.

**Study Rationale:** Because Org 25969 is mainly cleared via the kidneys, reduction in renal function will heavily affect the exposure to Org 25969. However, efficacy of Org 25969 is not based on its mere presence in the body, but on the formation of a stable complex with its target drug, rocuronium. Because no effect of renal function on this complex formation and hence on efficacy is anticipated, the sponsor took a reduced or staged study design with severe renal impairment patients and normal renal function patients in this study and investigated whether subjects with an impaired renal function need an adjusted dose of Org 25969 after administration of rocuronium.

**Sample Analysis:** Rocuronium and Org 25969 in plasma and urine were to be determined using validated liquid chromatographic assay methods with mass spectrometric detection under the responsibility of the Department of Clinical Pharmacology and Kinetics, NV Organon, the Netherlands.

**Subjects:** The study was conducted at two trial sites in the Netherlands and one in the United Kingdom. The trial sites were located in Nijmegen and Liverpool. In total 30 subjects were enrolled; 15 renally impaired subjects and 15 control subjects. Each of the Nijmegen sites enrolled 13 subjects, and the Liverpool site enrolled four (4) subjects. The number of renally impaired versus control subjects was evenly distributed within the sites. All subjects received 2.0 mg/kg of Org 25969 and completed the study. The weight of the subjects ranged from 54 to 110 kg. The height of the subjects ranged from 152 to 193 cm. Except for two Asian subjects in the renally impaired group, all subjects were Caucasian. Five (5) (17%) subjects were classified as ASA class 1, 11 (37%) as ASA class 2 and 14 (47%) as ASA class 3 (Table 1). One (1) subject (Subject 102012, control group) was considered a major protocol violator due to poor recording. Consequently, all data for this subject were excluded from the PP (per-protocol) analysis.

**Table 1. Summary of demographics and other baseline characteristics by subject group and overall (AST group).**

		Subject group		Total
		CR <sub>CL</sub> <30 ml/min	CR <sub>CL</sub> ≥80 ml/min	
Age (yrs)	n	15	15	30
	Mean (SD)	61 (14)	54 (12)	57 (13)
	Median	62	54	60
	Min. - max.	29 - 81	32 - 70	29 - 81
Weight (kg)	n	15	15	30
	Mean (SD)	76 (13)	84 (15)	80 (15)
	Median	75	84	80
	Min. - max.	54 - 105	57 - 110	54 - 110
Height (cm)	n	15	15	30
	Mean (SD)	170 (9)	170 (11)	170 (10)
	Median	170	170	170
	Min. - max.	152 - 184	154 - 193	152 - 193
Gender (n (%))	Female	7 (47)	9 (60)	16 (53)
	Male	8 (53)	6 (40)	14 (47)
Race (n (%))	Asian	2 (13)	0 (0)	2 (7)
	Black, of African Heritage	0 (0)	0 (0)	0 (0)
	White/Caucasian	13 (87)	15 (100)	28 (93)
	American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
	Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
	Other	0 (0)	0 (0)	0 (0)
Ethnicity (n (%))	Hispanic or Latino	0 (0)	0 (0)	0 (0)
	Not Hispanic or Latino	15 (100)	15 (100)	30 (100)
ASA Class (n (%))	Class 1	0 (0)	5 (33)	5 (17)
	Class 2	1 (7)	10 (67)	11 (37)
	Class 3	14 (93)	0 (0)	14 (47)
Creatinine clearance (ml/min)	n	15	15	30
	Mean (SD)	12 (5)	103 (24)	57 (49)
	Median	11	99	52
	Min. - max.	4 - 24	81 - 181	4 - 181
Creatinine clearance (n (%))	<30 ml/min	15 (100)	0 (0)	15 (50)
	≥80 ml/min	0 (0)	15 (100)	15 (50)

**Table 2. Number and percentage of subjects exposed to anesthetics by subject group (AST group).**

Drug name preferred WHO name		Subject group		Total (N=30)
		CR <sub>CL</sub> <30 ml/min (N=15)	CR <sub>CL</sub> ≥80 ml/min (N=15)	
Propofol	n (%)	15 (100)	15 (100)	30 (100)
Fentanyl /00174601/	n (%)	7 (47)	6 (40)	13 (43)
Morphine /00036301/	n (%)	5 (33)	7 (47)	12 (40)
Remifentanyl hydrochloride	n (%)	5 (33)	6 (40)	11 (37)
Remifentanyl	n (%)	3 (20)	3 (20)	6 (20)
Alfentanil	n (%)	1 (7)	0 (0)	1 (3)
Piritramide	n (%)	1 (7)	0 (0)	1 (3)

## Results:

### *Efficacy:*

Administration of 2.0 mg/kg Org 25969 at reappearance of T<sub>2</sub> after an intubating dose of 0.6 mg/kg rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 of exactly 2 minutes for the renally impaired subjects, and 1 min:39 sec for the control subjects (PP-group) (Table 3).

**Table 3. Summary of the time (min:sec) from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 by subject group (PP group).**

	Subject group	
	CR <sub>CL</sub> <30 ml/min (N=15)	CR <sub>CL</sub> ≥80 ml/min (N=14)
n	15	14
Mean (SD)	2:00 (0:43)	1:39 (0:38)
Median	1:38	1:25
Min. - max.	1:09 - 3:41	0:58 - 3:05

For the PP analysis of the primary efficacy variable, the two-way full ANOVA model was applied, including subject group and center as factors. The estimated mean absolute difference in time from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 between renally impaired subjects and control subjects was +27.3 seconds. The corresponding 95% CI for this difference ranged from -10.9 to +65.5 seconds. The CI was not completely within the pre defined equivalence interval of -60 to +60 seconds and equivalence between the two subject groups according to the prespecified definition can therefore not be claimed. However, the additive model, excluding the subject group by center interaction, resulted in an estimated mean absolute difference in time from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 between renally impaired subjects and control subjects of +20.1 seconds. The corresponding 95% CI for this estimate ranged from -12.1 to +52.3 seconds. The observed 95% CI lied entirely within the pre-defined equivalence interval of -60 to +60 seconds.

According to protocol, a stage 2 of the trial should be performed in case no equivalence with respect to recovery from neuromuscular blockade between subjects with normal renal function and those with impaired renal function could be demonstrated. The objective of a stage 2 would be to investigate the optimal dose of Org 25969 in subjects with normal or impaired renal function. Given the results from Stage 1, a higher dose would not result in a clinically significant decrease in recovery time. Because a similar efficacy would be expected in Stage 2, it was not deemed necessary to continue the trial into Stage 2.

### *Pharmacokinetics:*

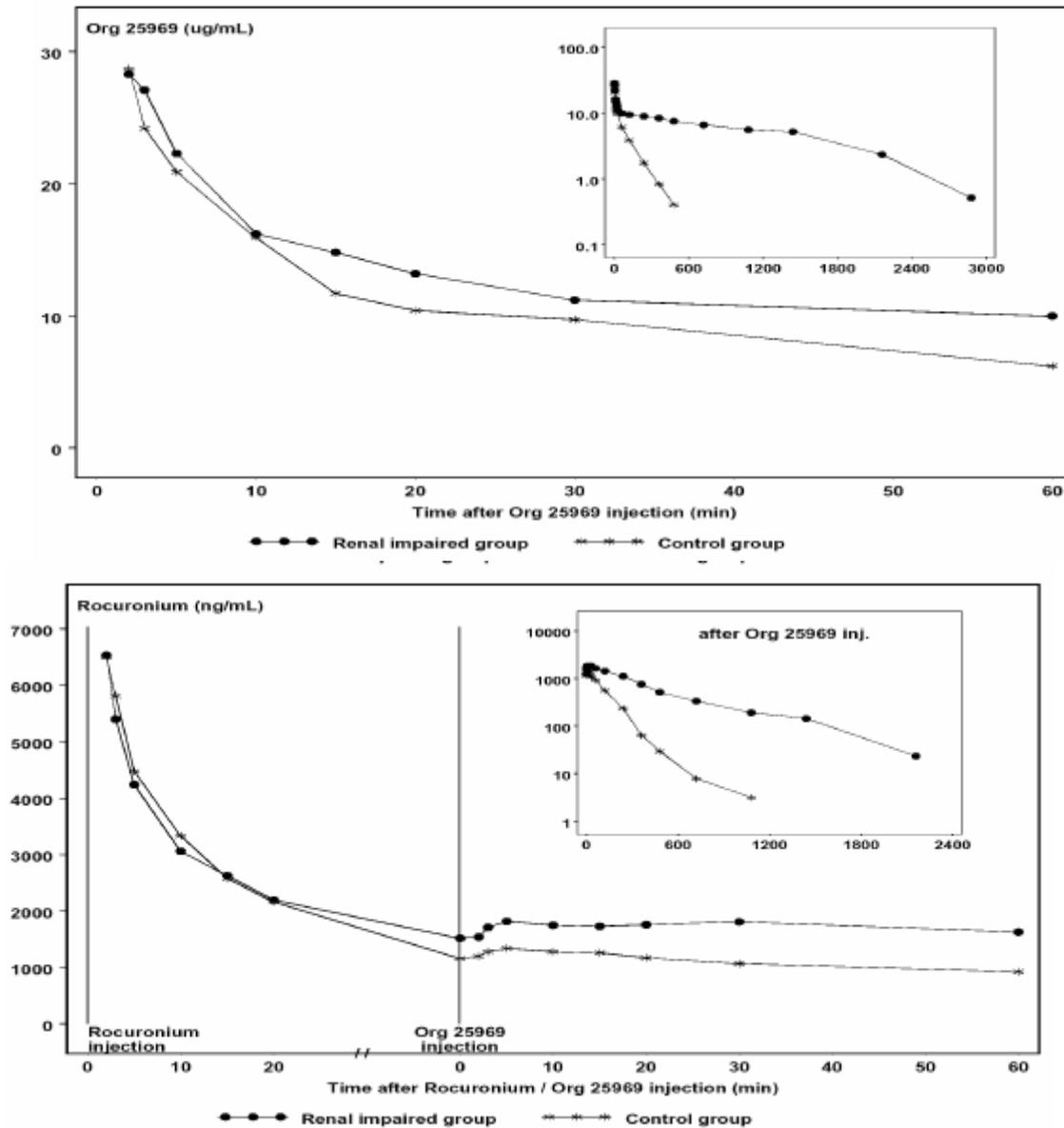
Due to potential sample switching, four (4) subjects (101003 (control), 101004 (renally impaired), 102009 (control), 102010 (renally impaired)) were excluded from the PK analysis which therefore consisted of 26 subjects. N=13 for each group.

Median concentrations for Org 25969 and rocuronium are graphically presented in-text in Figure 1. For those subjects in the renal impairment group with dialysis, the concentrations during and after dialysis were excluded from the descriptive statistics.

NDA 22-225

(b) (4) (Sugammadex Sodium)  
Solution for Injection (100 mg/mL)  
Original NDA Review

Figure 1 Median Org 25969 and rocuronium C-t plots



Curves based on n=13 subjects.

During the first 60 minutes after dosing median plasma concentrations of Org 25969 were very similar in the control and renally impaired groups. At later time points plasma concentrations of Org 25969 showed a smaller decrease in the renally impaired group compared to the control group. A similar effect can be seen for rocuronium.

The main pharmacokinetic parameters for Org 25969 and rocuronium summarized by group are presented in Table 4.

**Table 4. Summary of the plasma PK parameters of Org 25969 and rocuronium.**

		Org 25969		rocuronium	
		Control	Renally impaired	Control	Renally impaired
$t_{1/2, \beta}$ (min)	Mean	139	2139	179	450
	CV (%)	44.4	121	67.5	39.9
$t_{1/2\text{-effective}}$ (min)	Mean	100	2003	79.6	366
	CV (%)	25.5	132	29.2	52.7
$AUC_{0\text{-inf}}$ ( $\mu\text{g}\cdot\text{min}\cdot\text{mL}^{-1}$ )	Mean	1728	27463	296	1084
	CV (%)	34.8	114	37.4	53.8
$dn\text{-}AUC_{0\text{-inf}}$ ( $\mu\text{g}^*\text{min}/\text{mL}/\text{mg}$ )	Mean	10.5	181	6.00	23.9
	CV (%)	22.1	108	30.8	46.9
$AUC\text{-extrapolated}$ (%)	Median	2.37	52.3	0.199	4.12
	Range	0.933–4.32	3.59–88.4	0.0590–0.627	0.0546 – 22.7
CL ( $\text{mL}\cdot\text{min}^{-1}$ )	Mean	95.2	5.53	167	41.8
	CV (%)	22.1	108	30.8	46.9
$wn\text{-}CL$ ( $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ )	Mean	1.16	0.0731	2.03	0.553
	CV (%)	34.8	114	37.7	53.6
$V_{ss}$ (mL)	Mean	13800	15986	19125	22092
	CV (%)	20.5	35.5	28.3	29.9
$wn\text{-}V_{ss}$ ( $\text{mL}\cdot\text{kg}^{-1}$ )	Mean	168	211	233	292
	CV (%)	22.0	26.0	26.7	17.9
MRT (min)	Mean	145	2890	115	528
	CV (%)	25.5	132	29.2	52.7

dn = dose-normalized; wn = weight-normalized; Mean = geometric mean and CV(%) = geometric Coefficient of Variation (%).

It should be noted that the percentage extrapolated in the (dn-)AUC of Org 25969 was quite large (median 52%) and variable, ranging between 4 and 88 %. This is in part caused by the long and variable half-lives observed in the renally impaired group. The fact that 9 subjects received hemodialysis also influenced the AUCextrapolated because the C-t curve was extrapolated from the start of hemodialysis. This start of hemodialysis was subject specific and well before the scheduled last sampling time of 48 h. The percentage extrapolated of the AUC of rocuronium was always below 25% in the renally impaired group, as a result of the faster elimination of rocuronium compared to Org 25969.

The effect of renal impairment on PK parameters is smaller for rocuronium than for Org 25969.

Correlation plots were made of individual CL and wn-CL against the creatinine clearance (see Figure 2 below). Regression analysis showed that the correlation of (wn-)CL and CLcr is highly significant.

Figure 2 Regression plots of wn-CL versus CL<sub>CR</sub>

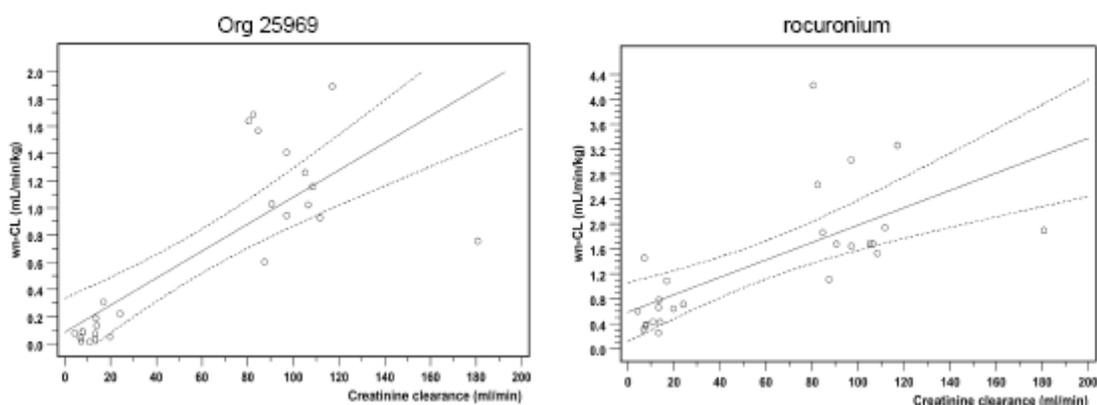


Table 5. Summary of statistics evaluating the differences between PK parameters obtained from renally impaired subjects and control subjects.

PK parameter	point estimate of ratio RI/control of geometric mean PK parameters	95% CI	Conclusion
<b>Org 25969</b>			
t <sub>1/2</sub>	15.4	8.49-28.0	significant
dn-AUC <sub>0-inf</sub>	17.2	10.3-28.9	significant
wn-CL	0.0629	0.0360-0.110	significant
wn-V <sub>ss</sub>	1.25	1.04-1.52	significant
MRT	19.9	11.0-36.1	significant
<b>rocuronium</b>			
t <sub>1/2</sub>	2.51	1.66-3.80	significant
dn-AUC <sub>0-inf</sub>	3.98	2.93-5.42	significant
wn-CL	0.272	0.191-0.388	significant
wn-V <sub>ss</sub>	1.25	1.04-1.50	significant
MRT	4.60	3.32-6.38	significant

*Dialysis Patients:*

Nine renally impaired subjects received hemodialysis within the first 72 h after surgery. Subject 101004 (not in ASPE group) was dialyzed peritoneally. The individual dialysis rates and half-lives of Org 25969 and rocuronium are listed in Tables 6 and 7.

**Table 6. Individual PK parameters for Org 25969 of subjects in the renal impairment group undergoing dialysis (All–Subjects–Pharmacokinetically–Evaluable group).**

Subject	Duration dialysis (min)	Filtertype	Total dialysis rate constant (1/min)	Total dialysis t1/2 (min)	Corrected dialysis rate constant (1/min)	Corrected dialysis t1/2 (min)
101005	225	1	0.000641	1082	0.000348	1994
101008	240	1	0.000421	1645	0.000190	3652
101011	240	2	*	*	*	*
101013	180	2	n.c.	n.c.	n.c.	n.c.
102001	150	2	0.000508	1365	0.00000299	231707
102002	225	1	0.00225	308	0.00186	372
102005	240	2	0.0000316	21959	0.0	0.0
102007	165	2	0.000610	1137	0.0000843	8227
102008	240	1	0.00236	294	0.00220	316

Filtertype 1: High flux Filtertype 2: Low flux

n.c.: Not calculable due to missing concentrations or PK outlier

**Table 7. Individual PK parameters for Rocuronium of subjects in the renal impairment group undergoing dialysis (All–Subjects–Pharmacokinetically–Evaluable group).**

Subject	Duration dialysis (min)	Filtertype	Total dialysis rate constant (1/min)	Total dialysis t1/2 (min)	Corrected dialysis rate constant (1/min)	Corrected dialysis t1/2 (min)
101005	225	1	0.00192	362	0.000541	1282
101008	240	1	0.00207	334	0.00118	588
101011	240	2	0.00127	547	0.0	0.0
101013	180	2	n.c.	n.c.	n.c.	n.c.
102001	150	2	0.00325	214	0.00182	381
102002	225	1	n.c.	n.c.	n.c.	n.c.
102005	240	2	0.000447	1550	0.0	0.0
102007	165	2	0.00337	205	0.00160	433
102008	240	1	0.00436	159	0.00308	225

Filtertype 1: High flux Filtertype 2: Low flux

n.c.: Not calculable due to missing concentrations or PK outlier

The small number of subjects per filter type (3 or 4) and the limited sampling means that results must be viewed as preliminary. Dialysis half-lives were consistently lower for rocuronium than for Org 25969 for both low and high flux filters. Low flux filters appeared to be almost ineffective for removing Org 25969 from circulation as plasma levels appeared to be unaffected by dialysis in these four cases. High flux filters showed a variable effectiveness with uncorrected dialysis half-lives ranging between 5 and 27 hours (in 4 subjects).

Urinary excretion of both rocuronium and Org 25969 was much slower in the renally impaired group than in the control group. This suggests that a collection interval of 0-72h is not long enough to determine complete urinary excretion of Org 25969 in renally impaired patients. In the case of rocuronium, a much smaller fraction of the dose was excreted renally in the renally impaired group than in the control group.

The mean time from start of administration of rocuronium to reappearance of T<sub>2</sub> was longer for the renally impaired subjects (53 min:49 sec) as compared to the control subjects (40 min:38 sec). Mean T<sub>1</sub> values at reappearance of T<sub>2</sub> were 18.0% and 15.7% in the renally impaired and control group, respectively.

### Discussion and Conclusions:

Administration of 2.0 mg/kg Org 25969 at reappearance of T<sub>2</sub> after an intubating dose of 0.6 mg/kg rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 of exactly 2 minutes for the renally impaired subjects, and 1 min:39 sec

for the control subjects (PP-group). The results were considered comparable efficacy between the groups.

In severely renally impaired patients the  $wn\text{-}CL$  of Org 25969 was reduced approximately 16-fold and terminal  $t_{1/2}$  increased 15-fold compared to normal patients. The  $wn\text{-}V_{ss}$  of Org 25969 was increased 25% compared to normal patients. This resulted in prolonged exposure and a 17-fold higher  $dn\text{-}AUC_{0\text{-}inf}$  of Org 25969 in renally impaired patients. However, during the first 60 minutes post administration of Org 25969 only a slight difference in plasma levels could be observed between the two groups.

In severely renally impaired patients  $wn\text{-}CL$  of rocuronium was reduced approximately 3.7-fold and terminal  $t_{1/2}$  increased 2.5-fold compared to normal patients. The  $wn\text{-}V_{ss}$  of rocuronium was increased with 25% compared to normal patients. This resulted in prolonged exposure and a 4-fold higher  $dn\text{-}AUC_{0\text{-}inf}$  of rocuronium (bound and unbound) in renally impaired subjects.

The clearance of Org 25969 and to a lesser extent rocuronium showed a highly significant correlation with creatinine clearance, confirming the importance of renal elimination for the clearance of Org 25969. The much smaller effect of renal impairment on the  $t_{1/2}$  of rocuronium than on that of Org 25969 indicates that a substantial portion of rocuronium was eliminated via the liver, despite the presence of excess binding agent.

*Reviewer's Note: The mild and moderate renal impairment patients ( $CL_{cr}$  between 30 and 80 mL/min) were not studied in this study. Mild and moderate renal impairment patients were studied in Study 305 where age was found to have not further effect on PK of Org 25969. The data were used to derive the relationship between  $CL$  and  $CL_{cr}$ . An equation of  $CL=4.46(CL_{cr}/88)^{0.941}$  was found to best describe the data (see PM review) and data for severe renal impairment patients were found to fit into the same relationship.*

Reference:

ASA Class      Classification of physical status established by the American Society of Anesthesiologists:

Class 1: A normal healthy patient;

Class 2: A patient with a mild systemic disease;

Class 3: A patient with a severe systemic disease that limits activity, but is not incapacitating;

Class 4: A patient with an incapacitating systemic disease that is a constant threat to life:

Class 5: A moribund patient not expected to survive 24 hours with or without operation.

The suffix E is added to the ASA Class in case of emergency surgery.

#### 4.2.7 Study in Elderly

*Study 19.4.305: A multicenter, parallel group, comparative, phase IIIa trial to compare the efficacy, safety, and pharmacokinetics of Org 25969 in elderly subjects with adult subjects*

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**Study Period:** October 2005 to September 2006  
**Sample Analysis Periods:** September 4, 2006 to January 12, 2007  
Reanalysis: March 31, 2006 to April 19, 2006  
**Analytical Site:** The Department of Bioanalytics-Oss, Research and Development, NV, Organon Oss, The Netherlands  
**Investigator(s):** T. Sloan (103), N. Gravenstein (104), A. Kovac (105), T. Monk (106), P. Benedict (108), S. Shenaq (109), L. Clark (110), N. Brister (111), D. Drover (112), M. Naguib (113), R. Jones (114), J. Wills (115), H. Minkowitz (117), M. Hudson (118)  
**Study Centers:** 14 sites in the U.S.

**Clinical trial center(s)**

(103) University of Colorado Health Sciences Center, Department of Anesthesiology, 4200 East Ninth Avenue, Campus Box B113, Denver, CO 80262  
(104) University of Florida, JHMHC College of Medicine, Department of Anesthesiology, 1600 SW Archer Road, PO Box 100254, Room M-509, Gainesville, FL, 32610  
(105) Department of Anesthesiology, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160  
(106) Department of Anesthesiology (112C), Durham VA Medical Center, 508 Fulton St., Durham, NC 27705  
(108) University of Michigan Health System, UH 1 H247, Box 0048, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-0048  
(109) Chief Anesthesiology, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Blvd, Houston, TX 77030 4298  
(110) Department of Anesthesiology and Perioperative Medicine, 530 South Jackson St., Louisville, KY 40202  
(111) Temple University Hospital, Room 341, Outpatient Building, Department of Anesthesiology, Broad and Ontario Street, Philadelphia, PA 19140  
(112) Stanford University Medical Center, 300 Pasteur Drive, Room S 007, Stanford, CA 94305-5117  
(113) The University of Texas, M.D. Anderson Cancer Center, 1400 Holcombe Blvd., Unit 409, Houston, Texas, 77030  
(114) Accurate Clinical Trials, Inc., 806 E. Avenue Pico, Suite I, PMB#333, San Clemente, CA 92672  
(115) University of New Mexico Health Sciences Center (UNMHSC), Department of Anesthesiology and Critical Care Medicine, 2701 Frontier Place, Suite 110/ MSC 11 6120, Albuquerque, NM 87131  
(117) Memorial Hermann Healthcare System, Memorial City Hospital, 921 Gessner, Anesthesia Department, Houston, TX 77024  
(118) UPMC-Shadyside Hospital, Dept of Anesthesiology, 5230 Centre Avenue, Pittsburgh, PA 15232

**Objective:** To compare the efficacy of Org 25969 in elderly subjects with adult subjects.

**Secondary objectives:** To compare the pharmacokinetics of Org 25969 in elderly subjects with adult subjects; to compare the safety of Org 25969 in elderly subjects with adult subjects.

**Methodology:** This was a multicenter, parallel group, comparative, open label trial. Subjects were to be selected from patients who were scheduled to undergo an elective surgical procedure under general anesthesia at the participating trial centers.

#### Diagnosis and criteria for inclusion

- Subjects who were 18 years old or older;
- Subjects of ASA Class 1 - 3;
- Subjects who were scheduled to undergo an elective surgical procedure under general anesthesia requiring neuromuscular relaxation with the use of rocuronium;
- Subjects who were scheduled to undergo surgical procedure in supine position;
- Subjects who had given written informed consent.

#### Test product, dose and mode of administration, batch No.

- Org 25969 was supplied in 5 mL vials containing 500 mg active entity (i.e., 100 mg.mL<sup>-1</sup>) of Org 25969 (Lot numbers CY039 and CZ180).
- Zemuron® Injection (rocuronium bromide) was supplied in colorless 10 mL vials containing 100 mg (i.e., 10 mg.mL<sup>-1</sup>) of rocuronium bromide (Lot numbers 1910804592, 133690115 and 1258902582).
- Each subject was to receive an intravenous single bolus dose of 0.6 mg.kg<sup>-1</sup> rocuronium. If further neuromuscular block was required after endotracheal intubation, maintenance dose(s) of 0.15 mg.kg<sup>-1</sup> rocuronium may have been administered.

Rocuronium and Org 25969 were to be administered intravenously in a 3-way stop cock. The bolus doses of rocuronium and Org 25969 were to be administered within 10 seconds into a fast running venous infusion. Rocuronium and Org 25969 were to be dosed on the actual body weight.

#### Duration of treatment

After the intubation dose or the previous maintenance dose of rocuronium, subjects were to be reversed at reappearance of T<sub>2</sub> with an intravenous single bolus dose of 2.0 mg.kg<sup>-1</sup> Org 25969.

The bolus doses of rocuronium and Org 25969 were to be administered within 10 seconds into a fast running venous infusion.

#### Criteria for evaluation

##### Efficacy

##### Primary efficacy variable:

- Time from start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9.

Several secondary variables.

#### Pharmacokinetics

Sparse blood samples (8 per subject) were collected in a subset of subjects (24 subjects for the 18 – 64 age group, 32 subjects for the 65 – 74 age group, and 19 subjects for the 75 and older age group). Rocuronium and Org 25969 plasma concentrations were listed individually and presented graphically. Descriptive statistics for the plasma concentrations were calculated by age group and time point. Compartmental pharmacokinetic modeling was used for analysis of the Org 25969 plasma concentrations.

Blood samples for PK analysis were to be obtained from a subset of subjects at the following time points (per Amendment 1, dated October, 2005):

- Prior to administration of intubation dose of rocuronium;
- Immediately prior to administration of Org 25969 (i.e., when T<sub>2</sub> was seen for the first time after the last dose of rocuronium);
- At 2 minutes after start of administration of Org 25969;
- At 5 minutes after start of administration of Org 25969;
- At 15 minutes after start of administration of Org 25969;
- At 60 minutes after start of administration of Org 25969;
- At 4 – 6 hours after start of administration of Org 25969;
- At the post-anesthetic visit: the following day after surgery, at least 10 hours after administration of Org 25969.

#### Statistical methods

Demographic, baseline, exposure and safety data were summarized by age group.

Times from start of administration of Org 25969 to recovery of the  $T_d/T_1$  ratio to 0.9, 0.8 and 0.7 were analyzed using a two-way ANOVA model.

The recovery time was taken as the response variable, and trial site and age group were the factors of the model.

For the ITT population two evaluations were performed: one for which missing recovery times were imputed and one that used only the available recovery times.

A 95% confidence interval for the differences between the two age groups was used to determine if the two age groups are equivalent.

Clinical signs of recovery were summarized by age group only.

**Study Rationale:** It is known that the pharmacokinetics and pharmacodynamics of neuromuscular blocking agents such as rocuronium may vary as a function of age, where the clinical duration is significantly prolonged in elderly subjects compared to younger subjects (42.4 min vs. 27.5 min). It is also well established that the elderly have a diminished body water content and smaller cellular mass. Aging is also associated with diminution of the plasma clearance. It is thus clear that the recovery time from a specific dose of rocuronium varies between the elderly and younger adult subjects. Previous studies have shown that Org 25969 can accelerate the time to full recovery in adult subjects. The current study was set up to explore whether the effect of Org 25969 was influenced by age. This trial allowed exploration of recovery times, pharmacokinetics, and safety following administration of Org 25969 in the different adult age groups.

**Sample Analysis:** Org 25969 concentrations in human heparin plasma were determined using a liquid chromatographic assay with mass spectrometric detection (LC-MS) after solid phase extraction.

Pharmacokinetic modeling was applied to the Org 25969 plasma concentrations to obtain estimates of the pharmacokinetic parameters clearance (CL) and volumes of distribution ( $V_c$  and  $V_{ss}$ ). The data was analyzed with the non-linear mixed effects modeling program NONMEM) using population analysis techniques.

**Subjects:** In total 162 subjects, 56 in the 18-64 age group, 64 in the 65-74 age group, and 42 in the 75+ age group, were enrolled. In total 150 subjects, 48 subjects in the 18-64 age group, 62 in the 65-74 age group, and 40 in the 75+ age group, were treated. In total, 149 subjects completed the trial: 48 in the 18-64 age group, 61 in the 65-74 age group, and 40 in the 75+ age group. It should be noted that 3 subjects in this trial were assigned incorrect subject i.d. numbers (Subject 104201, age 63, Subject 112103, age 77 and Subject 112104, age 67). This does not affect any analyses, as the subjects were analyzed in their appropriate age groups. For each individual, CL<sub>cr</sub> was calculated based on serum creatinine (s-Cr) determined before administration of rocuronium using the Cockcroft & Gault formula.

**Table 1. Summary of demographics and other baseline characteristics, by age group and overall (All-Subjects-Treated group).**

		Age group				Total (N=150)
		Adult	Geriatric			
		18-64 (N=48)	65-74 (N=62)	75+ (N=40)	Subtotal (N=102)	
Age (yrs)	n	48	62	40	102	150
	Mean (SD)	45.5 (11.32)	69.2 (2.53)	80.1 (4.08)	73.5 (6.23)	64.5 (15.41)
	Median	43.5	69.0	79.0	72.0	69.0
	Min. - max.	18.0 - 64.0	65.0 - 74.0	75.0 - 91.0	65.0 - 91.0	18.0 - 91.0
Weight (kg)	n	48	62	40	102	150
	Mean (SD)	84.2 (19.95)	84.1 (15.87)	73.9 (18.31)	80.1 (17.51)	81.4 (18.36)
	Median	81.6	83.0	72.8	78.0	78.8
	Min. - max.	47.3 - 123.0	53.0 - 137.3	44.0 - 111.1	44.0 - 137.3	44.0 - 137.3
Height (cm)	n	48	62	40	102	150
	Mean (SD)	171.0 (10.67)	171.8 (10.52)	167.6 (12.02)	170.1 (11.26)	170.4 (11.05)
	Median	168.9	170.2	167.6	170.1	170.1
	Min. - max.	152.4 - 191.8	147.3 - 193.0	132.0 - 195.6	132.0 - 195.6	132.0 - 195.6
Gender (n (%))	Female	29 (60.4)	27 (43.5)	24 (60)	51 (50)	80 (53.3)
	Male	19 (39.6)	35 (56.5)	16 (40)	51 (50)	70 (46.7)
Race (n (%))	Asian	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Black, of African Heritage	14 (29.2)	7 (11.3)	1 (2.5)	8 (7.8)	22 (14.7)
	White/Caucasian	33 (68.8)	53 (85.5)	38 (95)	91 (89.2)	124 (82.7)
	American Indian or Alaska Native	0 (0)	0 (0)	1 (2.5)	1 (1)	1 (0.7)
	Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Other	1 (2.1)	2 (3.2)	0 (0)	2 (2)	3 (2)
Ethnicity (n (%))	Hispanic or Latino	1 (2.1)	3 (4.8)	0 (0)	3 (2.9)	4 (2.7)
	Not Hispanic or Latino	47 (97.9)	59 (95.2)	40 (100)	99 (97.1)	146 (97.3)
ASA Class (n (%))	Class 1	8 (16.7)	0 (0)	0 (0)	0 (0)	8 (5.3)
	Class 2	32 (66.7)	34 (54.8)	16 (40)	50 (49)	82 (54.7)
	Class 3	8 (16.7)	28 (45.2)	24 (60)	52 (51)	60 (40)

**Table 2. Number (%) of subjects exposed to different anesthetics, for each age group (All-Subjects-Treated group).**

Drug name preferred WHO name	Age group				Total (N=150)
	Adult	Geriatric			
	18-64 (N=48)	65-74 (N=62)	75+ (N=40)	Subtotal (N=102)	
Desflurane	1 (2.1)	5 (8.1)	1 (2.5)	6 (5.9)	7 (4.7)
Dilaudid	3 (6.3)	4 (6.5)	2 (5)	6 (5.9)	9 (6)
Diprivan	0 (0)	0 (0)	2 (5)	2 (2)	2 (1.3)
Etomidate	0 (0)	2 (3.2)	0 (0)	2 (2)	2 (1.3)
Fentanyl	47 (97.9)	60 (96.8)	40 (100)	100 (98)	147 (98)
Hydromorphone	0 (0)	1 (1.6)	1 (2.5)	2 (2)	2 (1.3)
Isoflurane	13 (27.1)	15 (24.2)	12 (30)	27 (26.5)	40 (26.7)
Morphine	17 (35.4)	12 (19.4)	8 (20)	20 (19.6)	37 (24.7)
Nitrous oxide	26 (54.2)	31 (50)	20 (50)	51 (50)	77 (51.3)
Pentothal	1 (2.1)	0 (0)	1 (2.5)	1 (1)	2 (1.3)
Propofol	46 (95.8)	61 (98.4)	34 (85)	95 (93.1)	141 (94)
Propofol bolus	0 (0)	0 (0)	1 (2.5)	1 (1)	1 (0.7)
Propofol infusion	0 (0)	1 (1.6)	0 (0)	1 (1)	1 (0.7)
Remifentanyl	1 (2.1)	1 (1.6)	1 (2.5)	2 (2)	3 (2)
Sevoflurane	36 (75)	44 (71)	30 (75)	74 (72.5)	110 (73.3)
Sufentanyl	0 (0)	2 (3.2)	2 (5)	4 (3.9)	4 (2.7)
Thiopental	2 (4.2)	0 (0)	1 (2.5)	1 (1)	3 (2)

Data were taken from Appendix F, Table 3-1.

\* Drug name coded according to WHO Dictionary version 2004/4

## Results:

### *Efficacy:*

Table 3 presents a summary of the time from the start of the administration of Org 25969 to recovery of the  $T_4/T_1$  ratio to 0.9 by age group, for the ITT group. For this summary the observed recovery times were used as well as the imputed recovery times in case of missing times. It was noticed that for 75+ age group, the recovery times were slower compared to those observed in the adult group and 65-74 age group.

**Table 3. Summary of the time (min:sec) from start of administration of IP to recovery of the T4/T1 ratio to 0.9 by age group (Intent-to-Treat group).**

		Age group			
		Adult	Geriatric		
		18-64 (N=48)	65-74 <sup>*</sup> (N=62)	75+ (N=40)	Subtotal <sup>*</sup> (N=102)
Including imputed data	n	48	62	40	102
	Geom. mean	2:16	2:34	3:36	2:56
	Mean (SD)	2:32 (1:21)	2:55 (1:38)	3:56 (1:40)	3:19 (1:43)
	Median	2:11	2:33	3:37	2:56
	Min.-max.	1:10 - 7:25	0:54 - 8:49	1:01 - 9:55	0:54 - 9:55
Complete cases	n	45	57	35	92
	Geom. mean	2:08	2:24	3:22	2:44
	Mean (SD)	2:19 (1:03)	2:39 (1:26)	3:41 (1:38)	3:03 (1:35)
	Median	2:06	2:27	3:29	2:47
	Min.-max.	1:10 - 6:11	0:54 - 8:49	1:01 - 9:55	0:54 - 9:55

\*Subject 103203 (65-74 age group) received IP twice. The start of the first administration of IP is used as the start of administration of IP for this subject.

Table 4 presents the times from the start of administration of Org 25969 to recovery of the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9 for subjects who received only an intubating dose of rocuronium, and for subjects who received an intubating dose and at least one maintenance dose of rocuronium. The exploratory analysis indicated that reversal of neuromuscular block by Org 25969 did not differ between subjects who received only an intubating dose of rocuronium compared to subjects who received at least one maintenance dose as well.

**Table 4. Summary of time (min:sec) from start of administration of Org 25969 to the T<sub>4</sub>/T<sub>1</sub> ratio to 0.9, for subjects who received an intubating dose and those who received maintenance doses of rocuronium, (Intent-to-Treat group).**

			Age group			
			Adult	Geriatric		
			18-64 (N=48)	65-74 (N=62)	75+ (N=40)	Subtotal (N=102)
Intubating dose only	Including imputed data	n	16	25	21	46
		Geom. mean	2:18	2:28	3:21	2:50
		Mean (SD)	2:36 (1:37)	2:44 (1:18)	3:48 (2:01)	3:14 (1:44)
		Median	2:06	2:38	3:29	2:49
		Min.-max.	1:10 - 7:25	0:54 - 6:08	1:01 - 9:55	0:54 - 9:55
	Complete cases	n	14	23	19	42
		Geom. mean	1:59	2:17	3:10	2:39
		Mean (SD)	2:04 (0:37)	2:27 (0:54)	3:36 (2:00)	2:58 (1:35)
		Median	1:56	2:33	3:10	2:41
		Min.-max.	1:10 - 3:30	0:54 - 4:25	1:01 - 9:55	0:54 - 9:55
Intubating dose and maintenance dose	Including imputed data	n	32	37	19	56
		Geom. mean	2:16	2:39	3:53	3:01
		Mean (SD)	2:29 (1:13)	3:02 (1:50)	4:05 (1:14)	3:23 (1:43)
		Median	2:11	2:32	3:55	2:59
		Min.-max.	1:11 - 6:11	0:54 - 8:49	1:45 - 5:51	0:54 - 8:49
	Complete cases	n	31	34	16	50
		Geom. mean	2:13	2:28	3:38	2:48
		Mean (SD)	2:26 (1:11)	2:47 (1:42)	3:48 (1:08)	3:07 (1:36)
		Median	2:10	2:20	3:36	2:55
		Min.-max.	1:11 - 6:11	0:54 - 8:49	1:45 - 5:51	0:54 - 8:49

Note: Subject 103203, who was in 65-74 age group and received maintenance doses of rocuronium, received IP twice. The start of the first administration of IP is used as the start of administration of IP for this subject.

**Pharmacokinetics:**

The ASPE group consisted of a total of 75 subjects (24 subjects in the 18-64 age group, 32 subjects in the 65-74 age group and 19 subject in the 75 and older age group). Subject 117311 was removed from the ASPE group because of a protocol violation interfering with pharmacokinetics (dose of Org 25969: 20 mg/kg).

**Table 5. Summarized demographics by age group (ASPE).**

	Number of subjects	age (years)	weight (kg)	creatinine clearance (ml/min)
18 – 64 years	24	48.3 (26 - 64)	83.2 (47.3 – 108)	110 (73.8 – 162)
65 – 74 years	32	68.9 (65 – 74)	85.9 (58 – 116)	91.7 (50.6 – 144)
>= 75 years	19	81.2 (75 – 91)	73.1 (44 – 111)	58.1 (25.6 – 95.6)

Final model:

The Org 25969 plasma concentration-time data were best characterized by a three compartmental model with a zero order input and first order elimination from the central compartment, with (log-normally distributed) inter-individual variability on clearance CL, volume of central compartment V<sub>c</sub>, volume of first peripheral compartment V<sub>2</sub>, inter-compartmental clearance Q<sub>2</sub> and apparent infusion time D<sub>1</sub> and a combined proportional and additive residual error model.

Body weight, creatinine clearance and age were found to be significant covariates and were included in the final model as follows:

$$CL = CL_{\text{intercept}} + CL_{\text{slope1}} \times (\text{age} - 65.4) + CL_{\text{slope2}} \times (\text{CLCR} - 88.8)$$

$$V_c = V_{c \text{ intercept}} + V_{c \text{ slope}} \times (\text{Body weight} - 81.8)$$

The model parameters are presented in Table 6.

**Table 6. Summary of the final pharmacokinetic model parameter estimates.**

Parameter	Units	Population estimate	SE	CV%	IIV%
CL	L/min	0.081	0.0025	3.1 %	27.3 %
Effect of age		- 0.0010 x (age -65.4)	0.00023	21.8%	
Effect of creatinine clearance		+ 0.00038 x (Clcr -88.8)	0.00011	32.1%	
Vc	L	4.29	0.20	4.5 %	28.2 %
Effect of weight		+ 0.030 x (weight - 81.8)	0.0098	32.7%	
V <sub>2</sub>	L	9.07	0.38	4.2 %	21.0 %
Q <sub>2</sub>	L/min	0.27	0.017	6.3 %	31.3 %
V <sub>3</sub>	L	7.56	2.22	29.4 %	--
Q <sub>3</sub>	L/min	0.0088	0.00072	8.2 %	--
D <sub>1</sub>	min	3.47	0.83	23.8 %	64.3 %
<b>Residual error</b>				<b>CV (%)</b>	<b>SD</b>
σ <sub>1</sub> (proportional)		0.049	0.0088	22.1 %	---
σ <sub>2</sub> (additive)		0.00031	0.000077	---	0.018

\* SE is the standard error, CV% is coefficient of variation (100\*SE/pop.estimate), IIV (ω<sup>2</sup>) interindividual variability expressed as a variance, IIV% (100·√(IIV)). The CV of the proportional part of the residual error is 100·√σ<sub>1</sub> and the SD of the additional part of the residual error is √σ<sub>2</sub> μg/ml. Units of clearances were converted from L/h to L/min.

The median values of the demographic parameters age, body weight and creatinine clearance per age group were used to calculate pharmacokinetic parameters (CL, Vc, V<sub>ss</sub> and t<sub>1/2\_eff</sub>) for a typical subject in each age group with the final model (see Table 7).

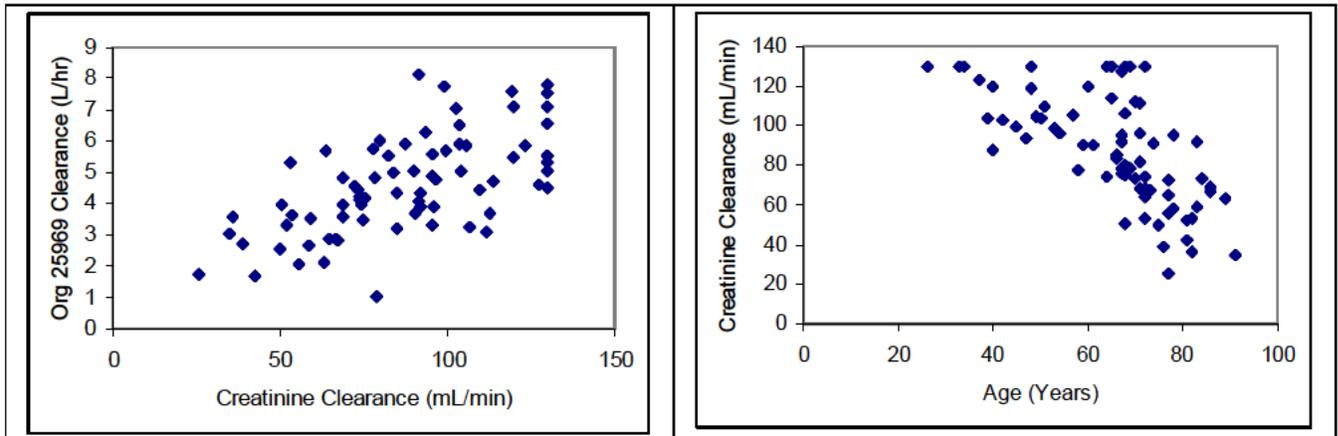
**Table 7. Derived pharmacokinetic parameters for a typical subject in each age group.**

Age group	Age	Weight	creatinine clearance	CL	Vc	V <sub>ss</sub>	t <sub>1/2_eff</sub>	t <sub>1/2_gamma</sub>
	years	kg	mL/min	[L/min]	[L]	[L]	[min]	[min]
18 - 64 years	48.5	84	104	0.103	4.36	20.99	141.3	654.7
65 - 74 years	68	86.1	84.8	0.076	4.42	21.05	192.5	680.1
>= 75 years	81	71.5	58.6	0.052	3.98	20.61	273.1	728.8

V<sub>ss</sub> is calculated as V<sub>ss</sub>=Vc+V<sub>2</sub>+V<sub>3</sub>. t<sub>1/2\_eff</sub> is calculated as t<sub>1/2\_eff</sub>= ln(2)\*(V<sub>ss</sub>/CL).

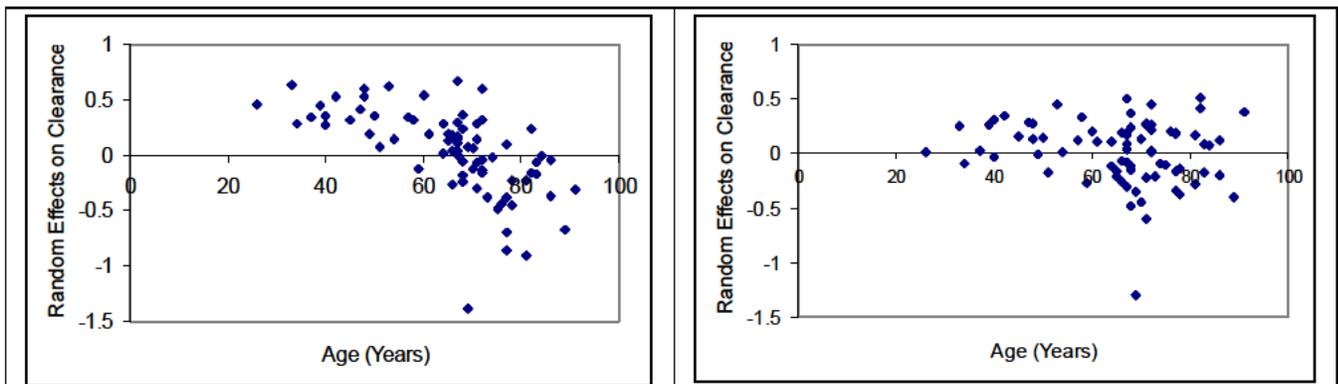
Data in Table 7 showed that increased exposure of sugammadex was observed with increased age. Further analysis showed that increased exposure or decreased clearance is attributed to decrease in renal function with age (see PM review).

Figure 1 shows the relationship between creatinine clearance and Org 25969 clearance (L/h) based on population pharmacokinetic analysis.



**Figure 1. (Left) Relationship between Org 25969 clearance (L/hr) and creatinine clearance (mL/min). (Right) Relationship between creatinine clearance and age (years).**

After inclusion of creatinine clearance as covariate in the population pharmacokinetic analysis, there is no additional effect of age on the pharmacokinetics of Org 25969 as shown in Figure 2. Note the trend between random effects of clearance versus age before accounting for renal function differences with age as shown in Figure 1 above. After inclusion of age in the analysis, there is no trend between random effects of clearance versus age, indicating that there is no additional effect of age on the pharmacokinetics of Org 25969.



**Figure 2. (Left) Relationship between random effects of clearance versus age prior to inclusion of age in the population pharmacokinetic analysis (Right) Relationship between random effects of clearance versus age after inclusion of age in the population pharmacokinetic analysis.**

**Conclusions:** The geometric mean time from administration of Org 25969 to recovery of the  $T_4/T_1$  ratio to 0.9 was 2 min:16 sec (adult group), 2 min:34 sec (65-74 years), and 3 min:36 sec ( $\geq 75$  years), respectively, when missing data were imputed. In the adult group 85% of subjects and in the geriatric group 75% of subjects achieved the  $T_4/T_1$  ratio recovery to 0.9 within 4 minutes. There was not enough evidence to support equivalence between the two age groups based on the fact that the two-sided 95% confidence interval for the difference between the two age groups of the time from the start of administration of Org 25969 to recovery of the  $T_4/T_1$  ratio to 0.9 did not lie entirely within the range from -1 minute to +1 minute.

An age-related decrease in clearance was observed. In the oldest age group (median age: 81 yr) clearance was decreased by 51% compared to the adult population (median age: 49 yr) and by 32% compared to the intermediate age group (median age: 68 yr). The decrease in clearance is attributed to decreased renal function with age. The lower clearance resulted in longer half-lives in the elderly groups.

### 4.3 Pharmacometric Review (Atul)

## Office of Clinical Pharmacology

NDA	22-225
Drug	Sugammadex (Org 25969)
Indication	<ul style="list-style-type: none"> <li>• Routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium.</li> <li>• Immediate reversal of neuromuscular blockade at 3 minutes after administration of rocuronium</li> </ul>
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram, Ph.D
Pharmacometrics Team Leader	Joga Gobburu, Ph.D
Clinical Pharmacology Reviewer	Lei Zhang, Ph.D
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## Introduction

Reversal agents are often given to accelerate the recovery of drug-induced neuromuscular blockade (NMB). Currently available reversal agents fall under the class of cholinesterase inhibitors like neostigmine, which prevent the normal hydrolysis of acetylcholine. An ideal NMB reversal agent should have a faster onset of action than neostigmine, a mechanism of action preventing recurarization, the capability of reversing profound blockade, and minimal side effects. Cyclodextrins (CDs) are well-known for their capability to form inclusion complexes with various drug molecules. Upon complexation with the neuromuscular blocking agent Esmeron® (rocuronium bromide), the cyclodextrin Org 25969 prevents the binding of rocuronium to nicotinic receptors in the neuromuscular junction, and hence results in reversal of neuromuscular blockade in vivo.

## Recommendations

The Pharmacometrics group in Office of Clinical Pharmacology has reviewed the submitted information and has the following recommendations

1. Sponsor should conduct a pharmacokinetic study of Org 25969 in patients with hepatic impairment.

## Comments to Medical Officer

The reviewer has addressed the labeling claims based on PK/PD analysis of rocuronium, vecuronium and Org 25969 regarding

- (1) Displacement potential of rocuronium or vecuronium by a third drug.
- (2) Effect of Org 25969 on pharmacokinetics of a third drug (Example: Oral contraceptives).
- (3) Waiting times before readministration of rocuronium, vecuronium in patients treated with Org 25969 and rocuronium or Org 25969 and vecuronium.
- (4) Recovery times of T4/T1 ratio to 0.9 in subjects with hepatic impairment.
- (5) Dose adjustment in patients with renal impairment.
- (6) Effect of bodyweight on pharmacokinetics of Org 25969.

Each issue is addressed individually followed by reviewer's comments. The proposed label has been edited to reflect the findings of the review.

## Regulatory Issues

The various dose finding studies for Org 25969 (Sugammadex) are discussed in Appendix-I. The PK/PD modeling as conducted by the sponsor is discussed in Appendix-II. The dose selection strategy is acceptable as robust drug effects are observed in registration trials as shown in Appendix-I. The PK/PD model developed by the sponsor is acceptable and is used for various labeling statements.

The review will focus on addressing the following issues:

- Issue 1 : Displacement potential of rocuronium or vecuronium from bound form to Org 25969 by other drugs and cause re-emergence of neuromuscular blockade
- Issue 2 : Capturing potential of other drugs by Org 25969 and lowering effectiveness of other drugs
- Issue 3 : Waiting times for re-administration of rocuronium or vecuronium in patients for intubation who were initially administered Org 25969 and rocuronium or Org 25969 and vecuronium.
- Issue 4 : Neuromuscular blockade reversal in patients with hepatic impairment
- Issue 5 : Need for dose adjustment in patients with renal impairment
- Issue 6 : Risk for QTc prolongation
- Issue 7 : Body Weight effects on pharmacokinetics.

**Issue 1 : Displacement potential of rocuronium or vecuronium from bound form to Org 25969 by other drugs and cause re-emergence of neuromuscular blockade**

The sponsor identified the potential for a third drug that can displace rocuronium or vecuronium in bound form to Org 25969 using information derived from the following three steps:

1. Determination of in vitro binding association constant for the third drug to Org 25969.
2. Non-clinical interaction studies using in vitro tissue preparations.
3. Clinical trial simulations using a PK/PD model.

The selection of the third drug was based on:

- Whether it is commonly used in anesthesia or in emergency procedures.
- Most commonly prescribed drugs.
- Presence of steroidal structure.

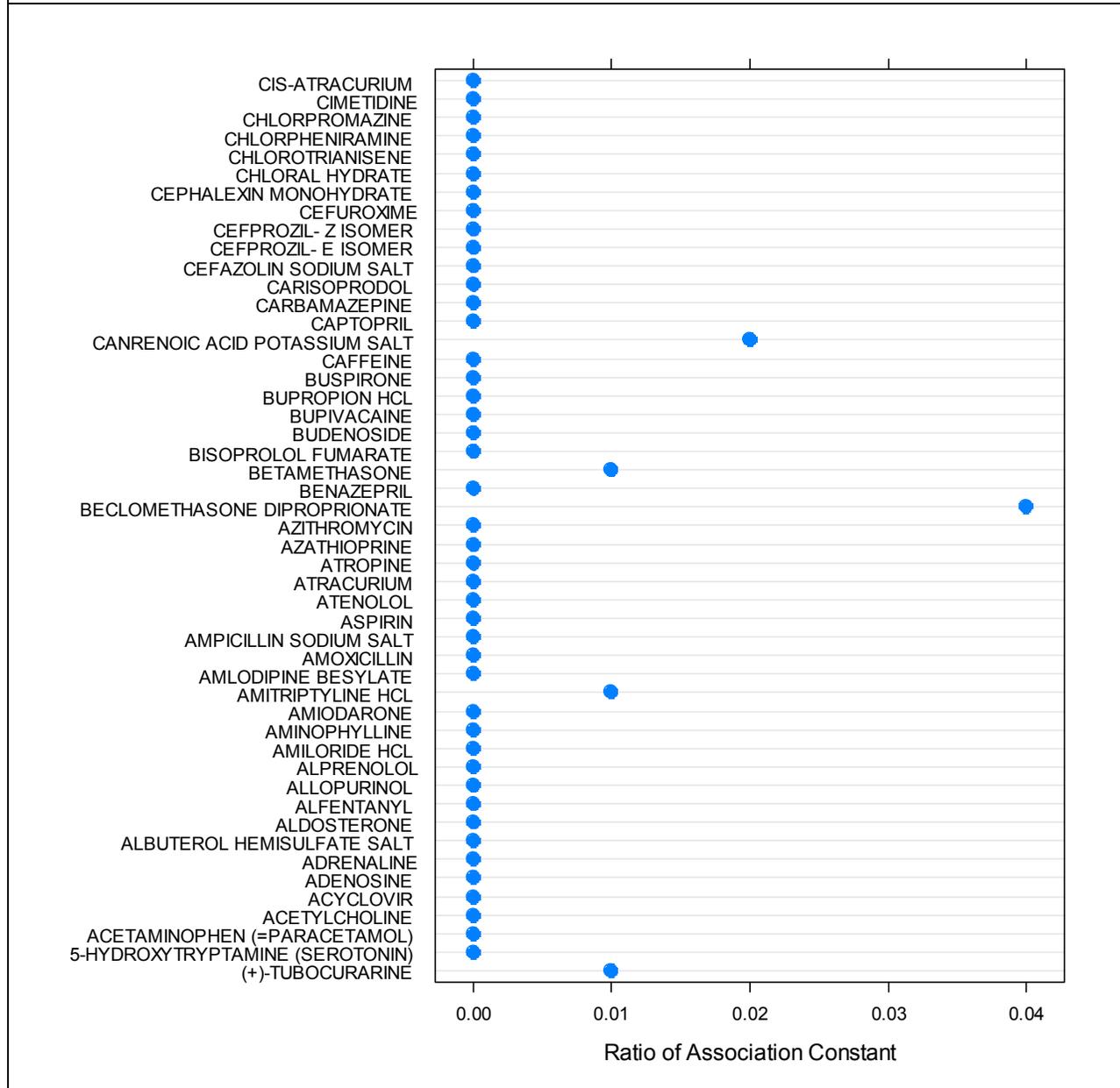
***In vitro association rate constant for the third drug to Org 25969***

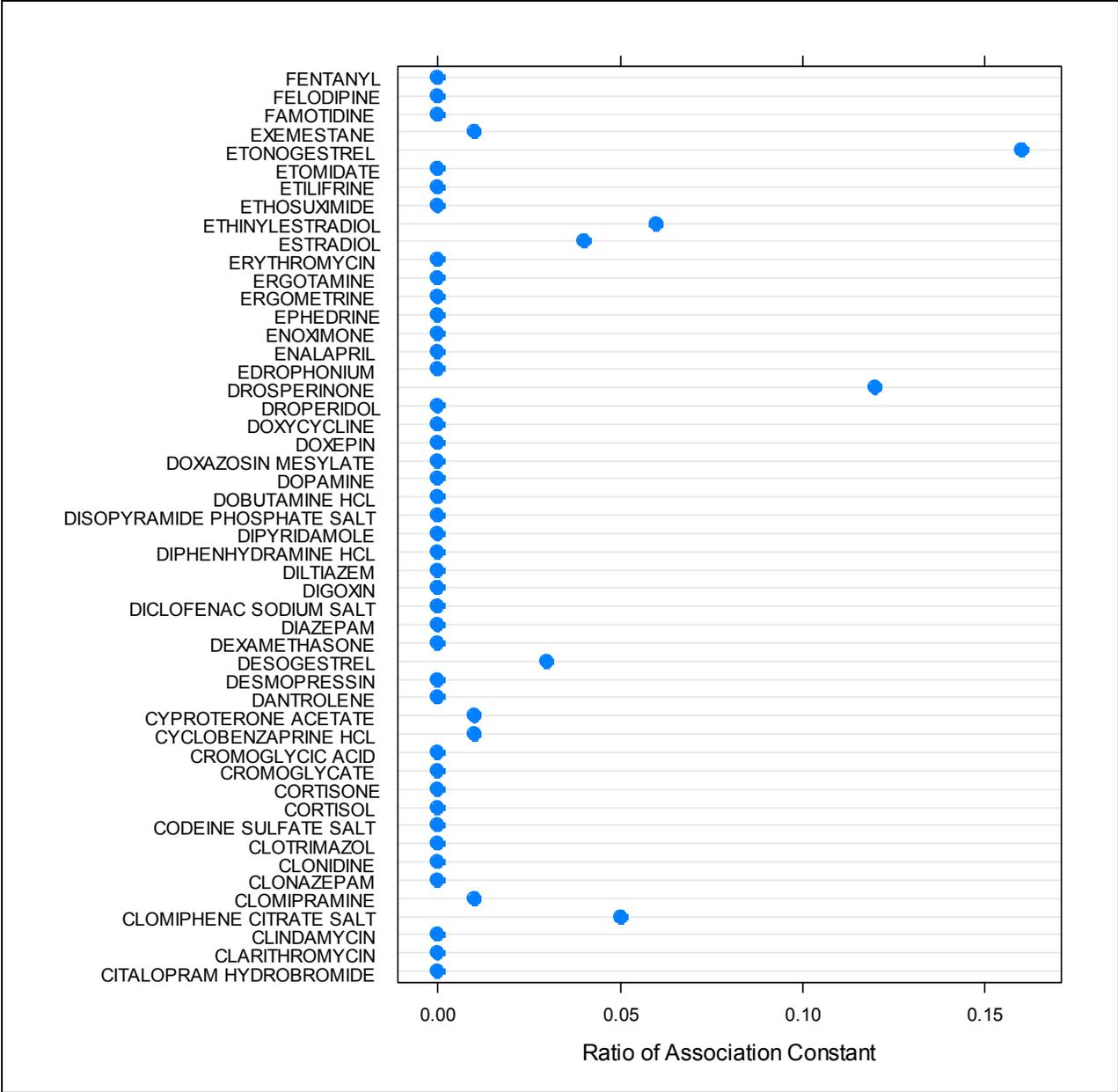
Figure 1 shows the ratio of association rate constant for other drugs (reference drug: Rocuronium) to Org 25969. A ratio of 1 implies that the other drug and rocuronium have similar association rate constant. Such drugs will displace rocuronium and vecuronium if sufficient free concentrations (after accounting for protein binding) are available. For purposes of illustration, ratios less than equal to 0.01 are rounded off to 0. Drugs that have steroidal structure have higher association constant in comparison to others.

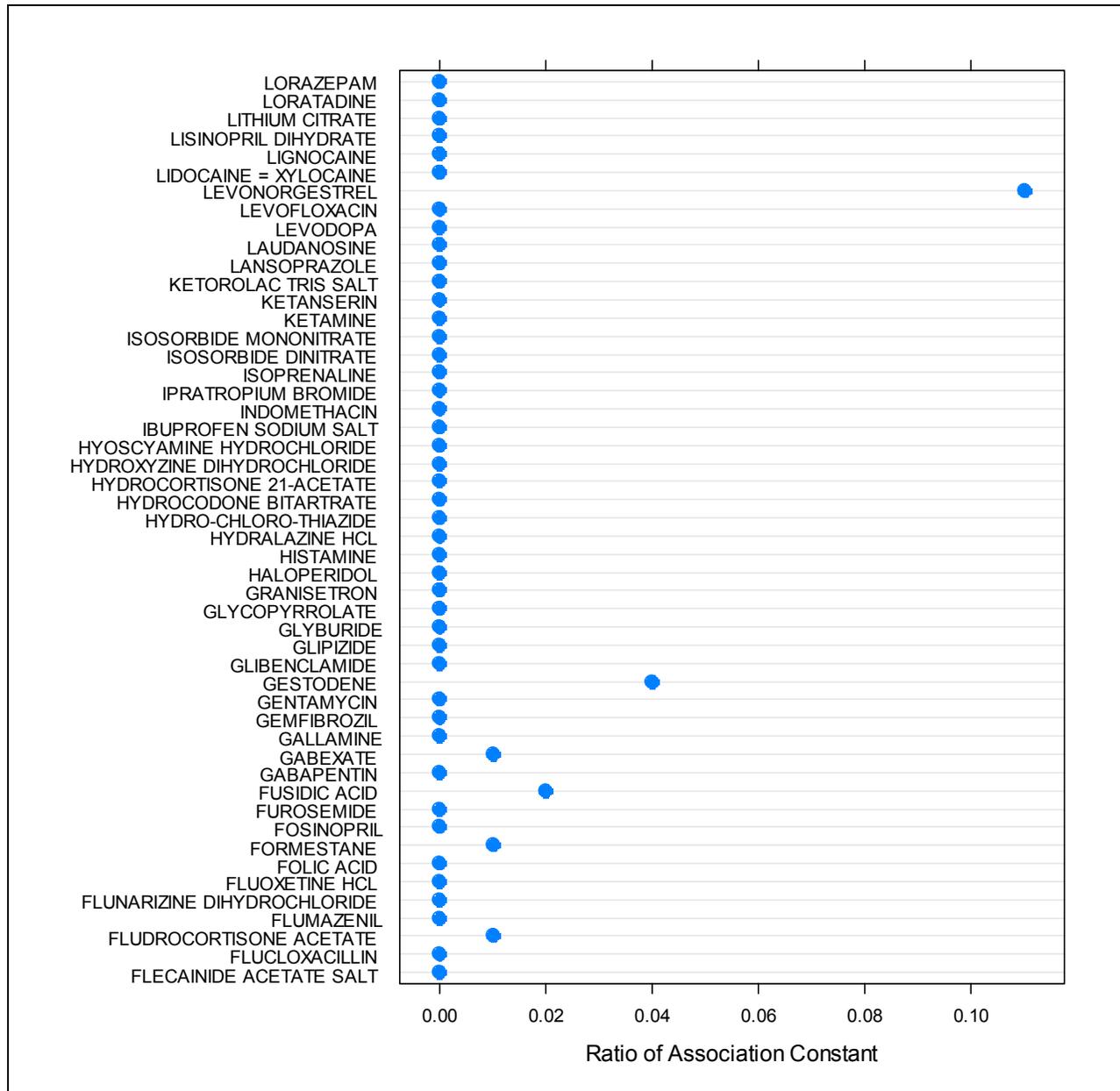
***Non-clinical interaction studies using in vitro tissue preparations***

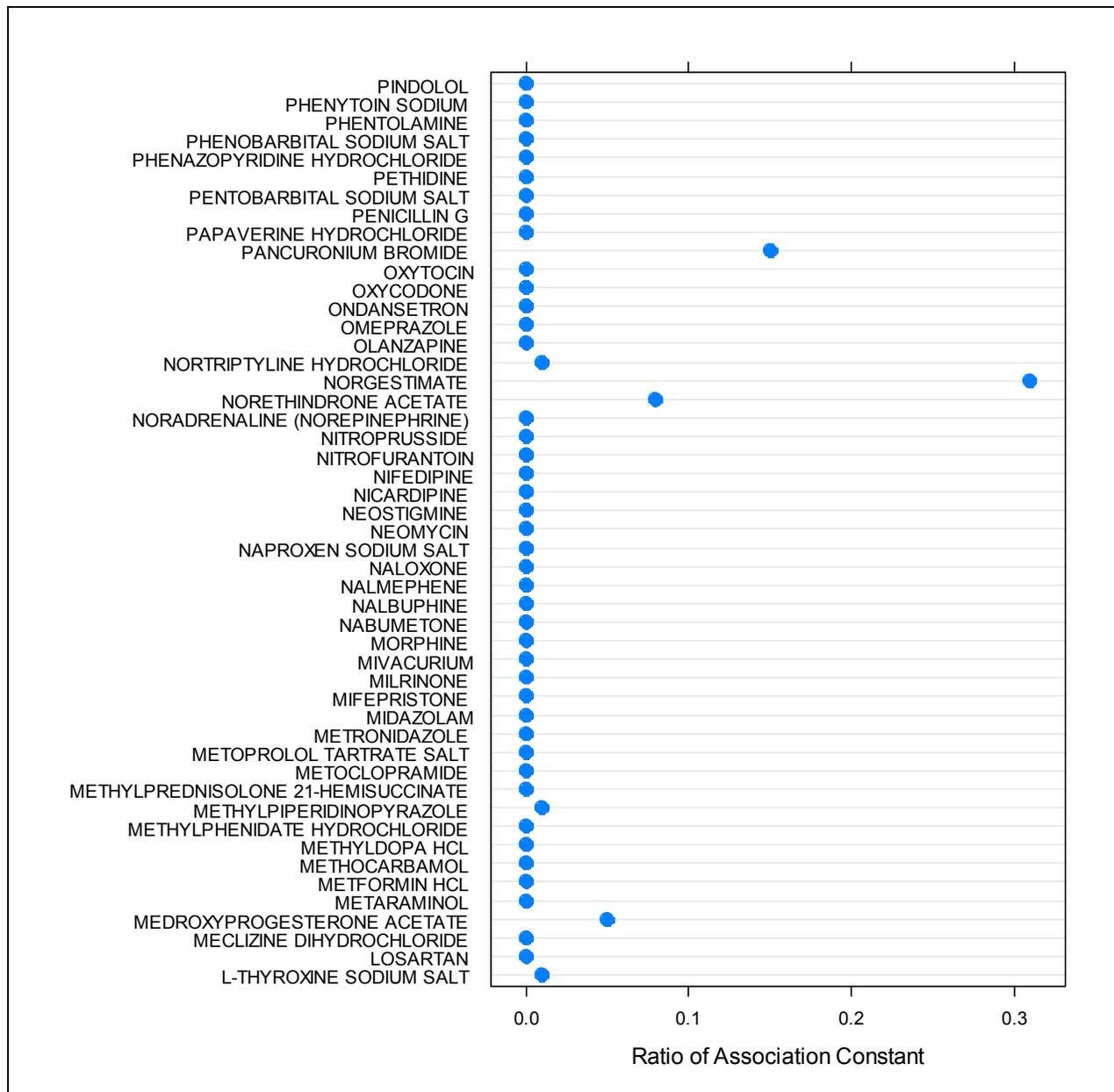
The mouse hemi-diaphragm in vitro system was also used to investigate displacement. Using 17-OH-rocuronium (Association rate constant= $27 \times 10^6$  L/mol in comparison to  $18 \times 10^6$  L/mol for rocuronium) it was shown that a compound with high affinity for Org 25969 can displace rocuronium or vecuronium from its complex, resulting in reoccurrence of neuromuscular blockade (NMB). Other drugs did not displace rocuronium as reflected in lack of reoccurrence of NMB in these studies.

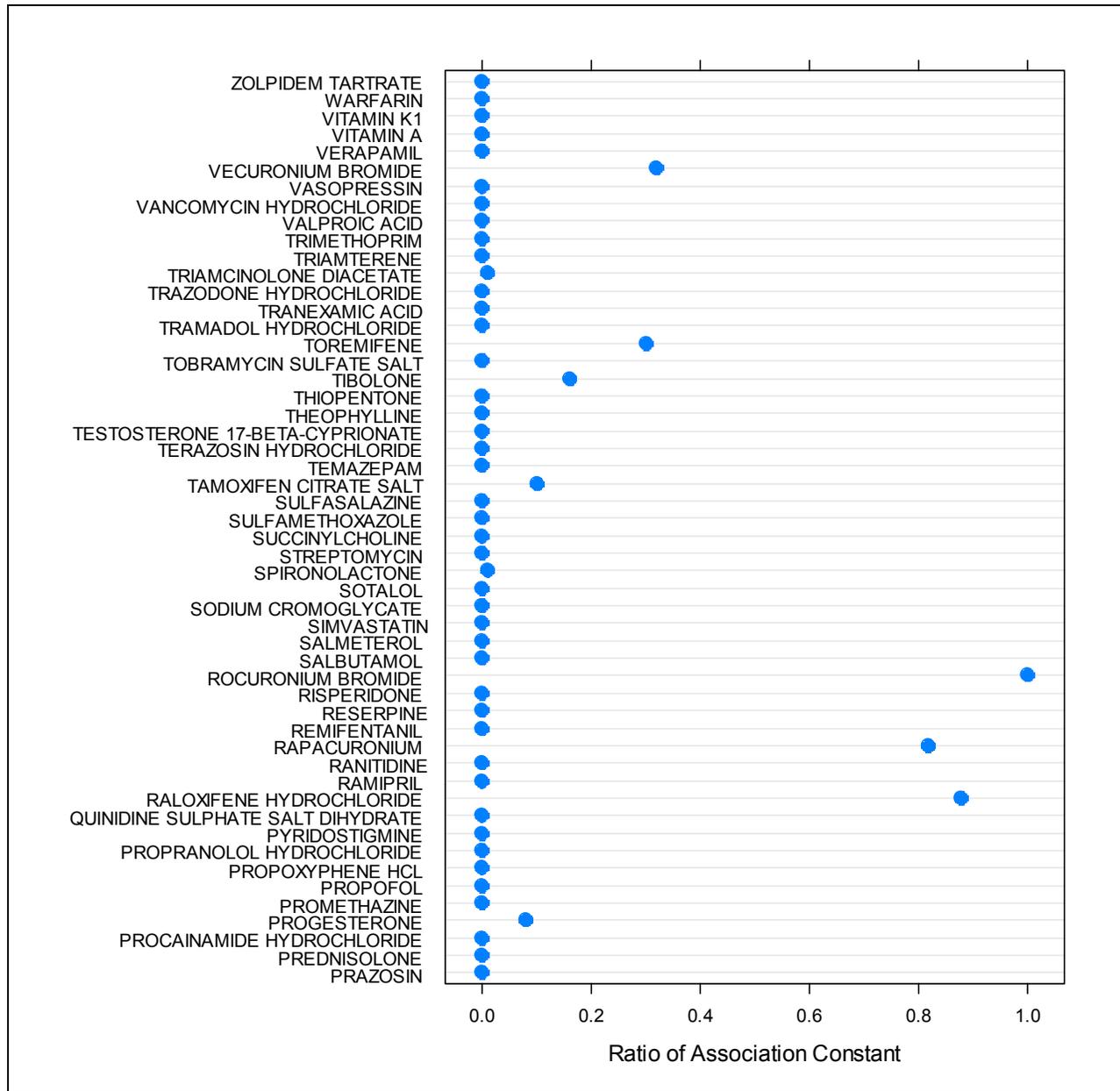
Figure 1. Ratio of in vitro association rate constants for various drugs (Reference: Rocuronium) to Org 25969. A ratio of 1 corresponds to association rate constant equal for rocuronium. Values less than 0.01 are rounded off to zero.











### ***Clinical Trial Simulations Using a PK/PD Model***

The sponsor conducted clinical trial simulations to quantify the risk of reoccurrence of neuromuscular blockade (NMB) using a PK/PD model which incorporated:

- Pharmacokinetics (PK) of Org 25969, rocuronium and vecuronium.
- Pharmacokinetic-pharmacodynamic (PK-PD) relationship of rocuronium and vecuronium with regard to NMB as measured with the TOF (Train of Four) ratio.
- The binding affinities of neuromuscular blocking agents (NMBAs) and other compounds for Org 25969 as determined by isothermal microcalorimetry.
- The theoretical relationship describing the unbound concentration of a NMBA in a situation with a complexing agent (Org 25969) in the presence of a third drug competing for the complex.

The risk of reoccurrence of NMB is determined by the following factors:

- The higher the binding affinity of the third drug for Org 25969, the higher the risk of displacement.
- The higher the plasma concentration of the third drug, the higher the risk of displacement.
- The higher the plasma concentration of NMBA the higher the risk of clinically relevant displacement.
- The lower the plasma concentration of Org 25969 the higher the risk of clinically relevant displacement.

The last two factors, the concentrations of NMBA (rocuronium, vecuronium) and Org 25969 were simulated using the PK model. The first two factors, concentration and association constant (KA) of compound X, are variable. The concentration of X that causes a clinically relevant displacement of NMBA from the complex was calculated. In this respect “clinically relevant” was defined as: causing a T4/T1 twitch ratio of the Train-of-Four (TOF) of less than 0.9 (TOF<0.9).

Plasma concentrations of rocuronium and vecuronium were simulated for the following scenarios:

1. Reversal at deep block of rocuronium: A dose of 1.2 mg/kg of rocuronium was followed after 15 minutes by a dose of 4.0 mg/kg of Org 25969.
2. Reversal at time to appearance of second twitch (T2) of rocuronium: A dose of 0.6 mg/kg of rocuronium was followed after 40 minutes by a dose of 2.0 mg/kg of Org 25969.
3. Reversal at deep block of vecuronium: A dose of 0.1 mg/kg of vecuronium was followed after 15 minutes by a dose of 4.0 mg/kg of Org 25969.
4. Reversal at T2 of vecuronium: A dose of 0.1 mg/kg of vecuronium was followed after 44 minutes by a dose of 2.0 mg/kg of Org 25969.

Table 1 lists the scenarios that were used for calculation of the critical combinations of KA and concentration for interacting drugs.

Table 1. Scenarios for which the critical combinations of KA and concentration were calculated.

Scenario		BW (kg)	Org 25969 conc.	NMBA conc.	Free NMBA needed for TOF=0.9
Nr	Name				
1	Deep block, median	75	median	median	mean
2	T2, mean	75	mean	mean	mean
3	Deep block, low Org 25969	75	5 <sup>th</sup> perc.	median	mean
4	Deep block, high rocuronium	75	median	95 <sup>th</sup> perc.	mean
5	Deep block, high sensitivity	75	median	median	5 <sup>th</sup> perc.
6	Deep block, low Org25969 / high sensit.	75	10 <sup>th</sup> perc.	median	10 <sup>th</sup> perc.
7	Deep block, high Roc. / high sensitivity	75	median	90 <sup>th</sup> perc.	10 <sup>th</sup> perc.
8	Deep block, low Org 25969 / low BW	50	10 <sup>th</sup> perc.	median	mean
9	Deep block, high rocuronium / high BW	100	median	90 <sup>th</sup> perc.	mean

\*: For the situation of reversal at the return of T2 only the population mean predictions were used

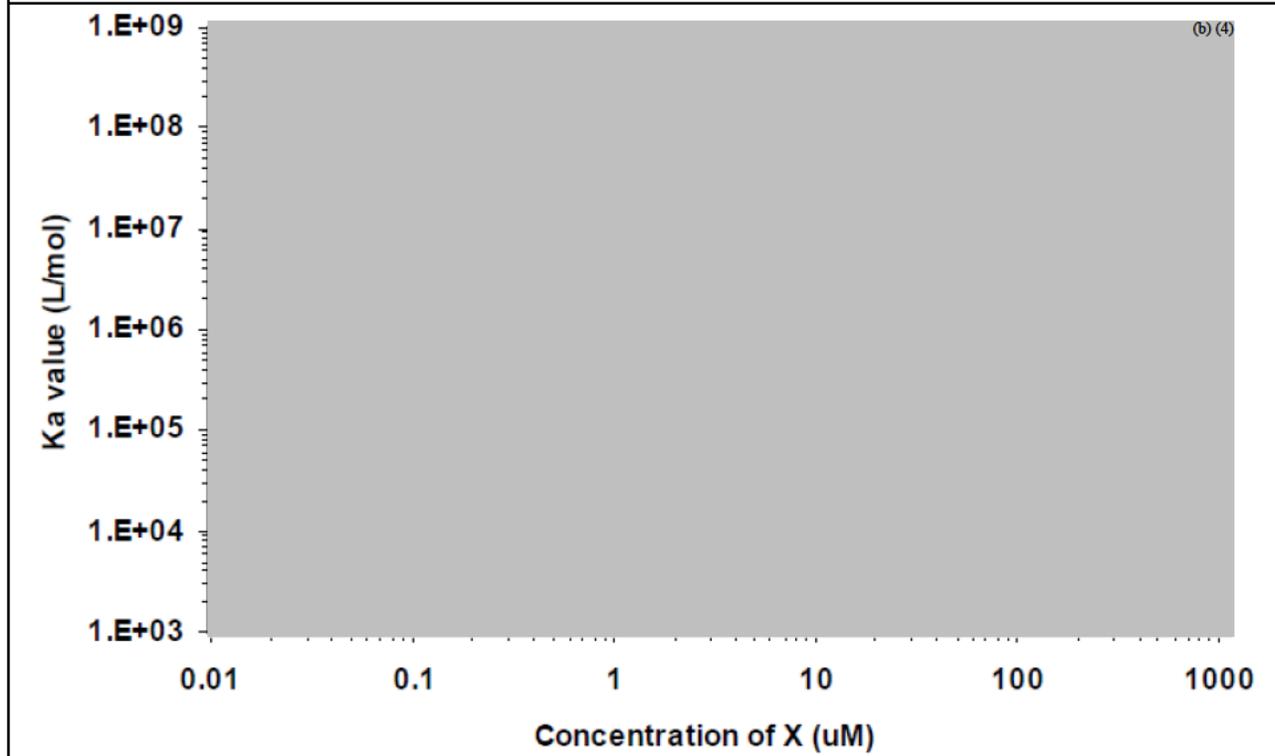
At every timepoint after dosing of Org 25969 a different combination of NMBA and Org 25969 exists. For every timepoint a line was calculated of critical combinations of KA and concentration of third drug. The minimum KA value for every concentration of X was determined and plotted.

Of the tested scenarios, the ones that are most sensitive to displacement are:

- Rocuronium: scenario 3, low concentrations of Org 25969.
- Vecuronium: scenario 6: the combination of low concentrations of Org 25969 and high sensitivity to the NMBA.

**Figure 2** shows the critical KA values for these two scenarios. **Figure 2** also shows individual markers, each of which represents a particular drug with its combination of KA and Cmax. Three compounds (toremifene, flucloxacillin and fusidic acid) are above the critical lines. The Cmax information was mainly obtained from databases (Drugdex and Martindale) and approved labels. In case more than one Cmax was found then the highest Cmax was used here.

Figure 2. Critical lines of rocuronium and vecuronium for the most sensitive scenarios. The figure also shows individual markers, each of which represents a particular drug with its combination of KA and Cmax. Three compounds (toremifene, flucloxacillin and fusidic acid) are above the critical lines indicating that there is a potential for causing reoccurrence of NMB under certain conditions.



### Reviewer's Analyses

Based on PK/PD simulations, the sponsor identified toremifene, flucoxacillin and fusidic acid as likely to cause displacement of rocuronium, vecuronium from bound form to Org 25969 and cause TOF ratio to be lower than (b) (4) (Figure 2). The reviewer analyzed the clinical trial database (File: medicati.xpt in ISS, 5.3.5.3.25.3.1) to identify patients who are taking these concomitant medications. There were no patients taking toremifene in the concomitant medications database. However, since toremifene is a chlorine derivative of tamoxifen, the reviewer made an assumption that if any effects are seen in patients taking tamoxifen then similar findings would be expected in patients taking toremifene. The effects on T4/T1 ratio on these patients were also obtained (File: neuromus.xpt in CSE, 5.3.5.25.3.1).

Patients taking Tamoxifen (Table 2, Table 3, Table 4):

- The time taken for return of T4/T1 ratio to 0.7, 0.8 is similar in patients taking tamoxifen and not taking tamoxifen.

- The time taken for return of T4/T1 ratio to 0.9 is longer in 2 out of 9 patients taking tamoxifen and not taking tamoxifen.

Patients taking Flucoxacillin (Table 5, Table 6, Table 7):

- The time taken for return of T4/T1 ratio to 0.7, 0.8, 0.9 is similar in patients taking flucoxacillin and not taking flucoxacillin.

Patients taking Fusidic Acid (Table 8, Table 9 and Table 10):

- The time taken for return of T4/T1 ratio to 0.7, 0.8, 0.9 is similar in patients taking fusidic acid and not taking fusidic acid.

Table 2. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.7 in patients taking tamoxifen (Yes) or not taking tamoxifen (No) in various studies

Study	Tamoxifen (Yes/No)	N	T4/T1	Mean	Standard Deviation
209	No	39	0.7	2:31	2:13
209	Yes	1	0.7	2:48	1:31
209	No	40	0.7	1:10	0:28
209	Yes	1	0.7	1:04	
301	No	80	0.7	8:49	7:50
301	Yes	1	0.7	6:42	
303	No	53	0.7	1:18	0:39
303	Yes	1	0.7	1:18	
304	No	29	0.7	1:19	0:26
304	Yes	1	0.7	0:42	
305	No	142	0.7	2:00	1:07
305	Yes	1	0.7	0:55	
309	No	37	0.7	1:08	0:22
309	Yes	1	0.7	1:22	
310	No	33	0.7	1:26	0:30
310	Yes	1	0.7	1:09	
312	No	50	0.7	1:02	0:16
312	Yes	1	0.7	1:05	

Table 3. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.8 in patients taking tamoxifen (Yes) or not taking tamoxifen (No) in various studies

Study	Tamoxifen (Yes/No)	N	T4/T1	Mean	Standard Deviation
209	No	39	0.8	3:35	6:07
209	Yes	1	0.8	3:18	1:52
209	No	40	0.8	1:15	0:29
209	Yes	1	0.8	1:04	
301	No	80	0.8	14:32	13:28
301	Yes	1	0.8	11:42	
303	No	53	0.8	1:29	1:05
303	Yes	1	0.8	1:48	
304	No	29	0.8	1:28	0:31
304	Yes	1	0.8	0:42	
305	No	142	0.8	2:18	1:17
305	Yes	1	0.8	1:10	
309	No	37	0.8	1:17	0:27
309	Yes	1	0.8	1:22	
310	No	33	0.8	1:40	0:39
310	Yes	1	0.8	1:24	
312	No	50	0.8	1:10	0:20
312	Yes	1	0.8	1:05	

Table 4. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.9 in patients taking tamoxifen (Yes) or not taking tamoxifen (No) in various studies

Study	Tamoxifen (Yes/No)	N	T4/T1	Mean	Standard Deviation
209	No	39	0.9	8:05	23:44
209	Yes	1	0.9	4:25	3:07
209	No	40	0.9	1:46	2:00
209	Yes	1	0.9	1:19	
301	No	80	0.9	25:56	22:38
301	Yes	1	0.9	15:42	
<b>303</b>	<b>No</b>	<b>53</b>	<b>0.9</b>	<b>2:01</b>	<b>1:26</b>
<b>303</b>	<b>Yes</b>	<b>1</b>	<b>0.9</b>	<b>14:18</b>	
304	No	29	0.9	2:04	1:22
304	Yes	1	0.9	1:27	
305	No	142	0.9	2:52	1:31
305	Yes	1	0.9	1:10	
309	No	37	0.9	1:30	0:38
309	Yes	1	0.9	1:37	
<b>310</b>	<b>No</b>	<b>33</b>	<b>0.9</b>	<b>1:58</b>	<b>0:52</b>
<b>310</b>	<b>Yes</b>	<b>1</b>	<b>0.9</b>	<b>6:24</b>	
312	No	50	0.9	1:23	0:26
312	Yes	1	0.9	1:20	

Table 5. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.7 in patients taking flucoxacillin (Yes) or not taking flucoxacillin (No) in various studies					
Study	Flucoxacillin (Yes/No)	N	T4/T1	Mean	Standard Deviation
301	No	95	0.7	1:26	0:37
301	Yes	1	0.7	0:57	
304	No	29	0.7	1:19	0:26
304	Yes	1	0.7	0:42	

Table 6. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.8 in patients taking flucoxacillin (Yes) or not taking flucoxacillin (No) in various studies					
Study	Flucoxacillin (Yes/No)	N	T4/T1	Mean	Standard Deviation
301	No	95	0.8	1:42	0:48
301	Yes	1	0.8	0:57	
304	No	29	0.8	1:28	0:48
304	Yes	1	0.8	0:42	

Table 7. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.9 in patients taking flucoxacillin (Yes) or not taking flucoxacillin (No) in various studies					
Study	Flucoxacillin (Yes/No)	N	T4/T1	Mean	Standard Deviation
301	No	95	0.9	2:58	6:43
301	Yes	1	0.9	1:12	
304	No	29	0.9	2:04	1:22
304	Yes	1	0.9	1:27	

Table 8. Summary of time (Minutes:Seconds) taken to reach T4/T1 ratio of 0.7 in patients taking fusidic acid (Yes) or not taking fusidic acid (No) in various studies					
Study	Fusidic Acid (Yes/No)	N	T4/T1	Mean	Standard Deviation
208	No	38	0.7	2:17	0:57
208	Yes	1	0.7	1:30	
309	No	37	0.7	1:23	0:30
309	Yes	1	0.7	1:09	

Study	Fusidic Acid (Yes/No)	N	T4/T1	Mean	Standard Deviation
208	No	38	0.8	2:49	1:24
208	Yes	1	0.8	3:30	
309	No	37	0.8	1:33	0:39
309	Yes	1	0.8	1:24	

Study	Fusidic Acid (Yes/No)	N	T4/T1	Mean	Standard Deviation
208	No	95	0.9	7:59	18:14
208	Yes	1	0.9	4:30	
309	No	29	0.9	1:58	1:12
309	Yes	1	0.9	1:39	

The reviewer's analysis also focused on patients who had longer time to reversal of T4/T1 ratio of 0.9 or who experienced recurarization in clinical trials. Other than study procedures that could have contributed to these observations it is possible that these findings are due to displacement of rocuronium or vecuronium from bound from to Org 25969 by other medications. The findings in this section are based on the clinical cases identified by Robert B. Shibuya (Medical Officer, Division of Anesthesiology, Analgesics and Rheumatology Drug Products, DAARP).

Dr Robert Shibuya states in his review "This reviewer notes that two of the outliers in Study 303 experienced recurarization. In addition Patient 310102003 received dexamethasone intraoperatively and was on tamoxifen and Patient 303106007 was also on tamoxifen. Patient 301109001 was exposed to mometasone and betamethasone. Patient 302102101 was on intranasal beclomethasone. Dexamethosone, mometasone, beclomethasone, and betamethasone are steroid hormones and tamoxifen is an estrogen receptor modulator. These concomitant medications could have interfered with the action of Org25969....." (For further details please refer to Dr Robert Shibuya's review).

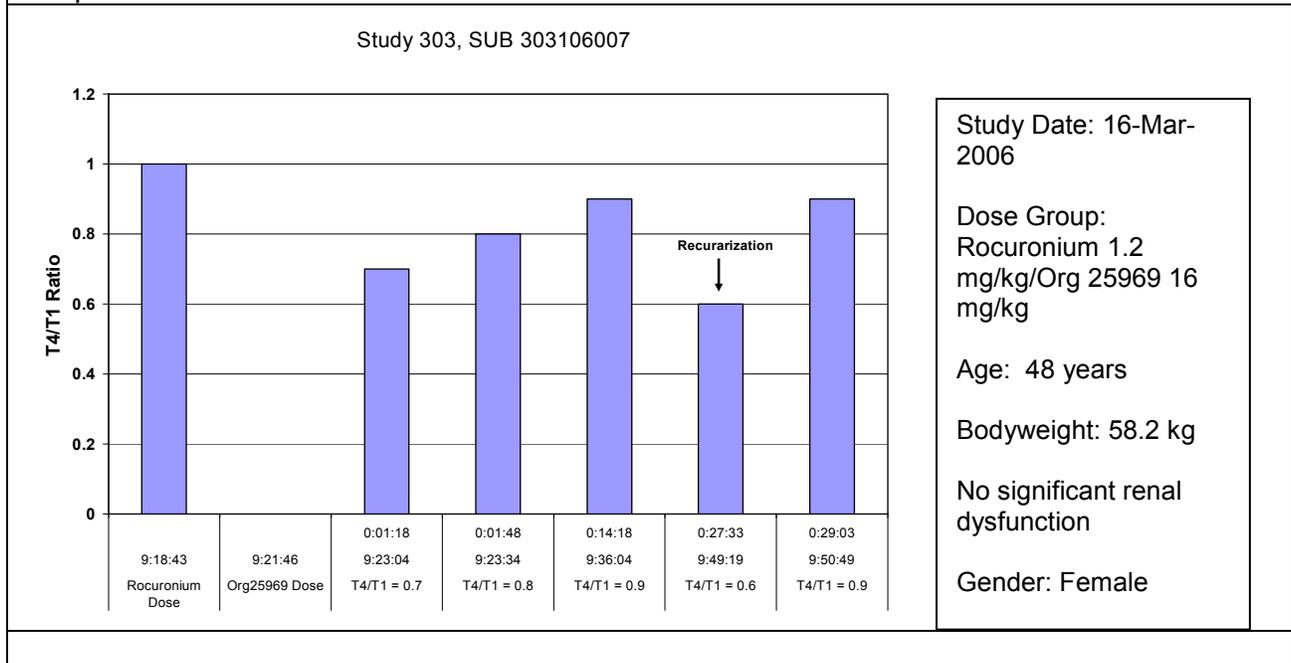
Based on Dr Robert Shibuya's comments, the reviewer conducted more analysis for the 4 subjects identified above. The issues of interest were

- List of concomitant medications being taken by the patients and their dose strength.
- Timing of the concomitant medications relative to the time of dosing of rocuronium or vecuronium. If the concomitant medications are given much later after Org 25969 administration i.e., when the unbound concentrations of Org 25969 are low, it is possible that the concomitant medications might displace bound rocuronium or vecuronium. Also if the patients are taking drugs that can bind to Org 25969 as a part of ongoing

therapy, then it is likely that these patients might have longer time to offset due to lack of unbound Org 25969 to bind to rocuronium or vecuronium.

Figure 3**Error! Reference source not found.**, Figure 4, Figure 5 and Figure 6 show the time to recovery of T4/T1 ratio along with list of concomitant medications (MEDC), route of administration (MEDROUF), date of start of concomitant medication (MEDBEGD), date of end of concomitant medication (MEDEND), if the concomitant medication is a part of ongoing treatment (MEDONGX), time of administration of concomitant medication (MEDBGT) and the dose of concomitant medication (MEDDOSE). Shown in these figures is also relevant demographic information on these patients, if they are older or if they have renal impairment.

Figure 3. Time course of T4/T1 ratio in Subject 303106007 in Study 19.4.303 who experienced reoccurarization indicating possible displacement of rocuronium from bound form to Org 25969 if study procedures are not the contributory factors. Also shown in the table below are the concomitant medications administered to the patient along with the timing of the medications. Shown also are the study date, dose and other information of the patient.



MEDC	MEDROUF	MEDBEGD	MEDEND	MEDONGX	MEDBGT	MEDDOSE
ZOLADEX	SC			X		3.6
TAMOXIFEN	PO	9-Aug-2004		X	22:00	10
MIDAZOLAM	IV	16-Mar-2006	16-Mar-2006		8:52	2
MIDAZOLAM	IV	16-Mar-2006	16-Mar-2006		8:56	2
MIDAZOLAM	IV	16-Mar-2006	16-Mar-2006		9:01	1
LIDOCAINE	IV	16-Mar-2006	16-Mar-2006		9:03	60
EPHEDRINE	IV	16-Mar-2006	16-Mar-2006		9:08	5
CEFAZOLIN	IV	16-Mar-2006	16-Mar-2006		9:11	1
EPHEDRINE	IV	16-Mar-2006	16-Mar-2006		9:19	5
ONDANSETRON	IV	16-Mar-2006	16-Mar-2006		10:10	4
MARCAINE	TO	16-Mar-2006	16-Mar-2006		10:28	0.5
EPINEPHRINE	TO	16-Mar-2006	16-Mar-2006		10:28	1/200.000
POLYMYXIN	TO	16-Mar-2006	16-Mar-2006		10:28	1
VANCOMYCIN						
IRRIGATION	TO	16-Mar-2006	16-Mar-2006		10:28	1
MORPHINE	IV	16-Mar-2006	16-Mar-2006		11:30	3
PERCOCET	PO	16-Mar-2006	16-Mar-2006		15:00	1
PERCOCET	PO	16-Mar-2006	16-Mar-2006		16:20	1
ANCEF	IV	16-Mar-2006	16-Mar-2006		17:00	1
PERCOCET	PO	16-Mar-2006	16-Mar-2006		17:30	1
CELEBREX	PO	16-Mar-2006	16-Mar-2006		18:30	1

Figure 4. Time course of T4/T1 ratio in Subject 310102003 in Study 19.4.310 who experienced a delay in recovery to T4/T1 ratio of 0.9 indicating possible displacement of rocuronium from bound form to Org 25969 if study procedures are not the contributory factors. Also shown in the table below are the concomitant medications administered to the patient along with the timing of the medications. Shown also are the study date, dose and other information of the patient.

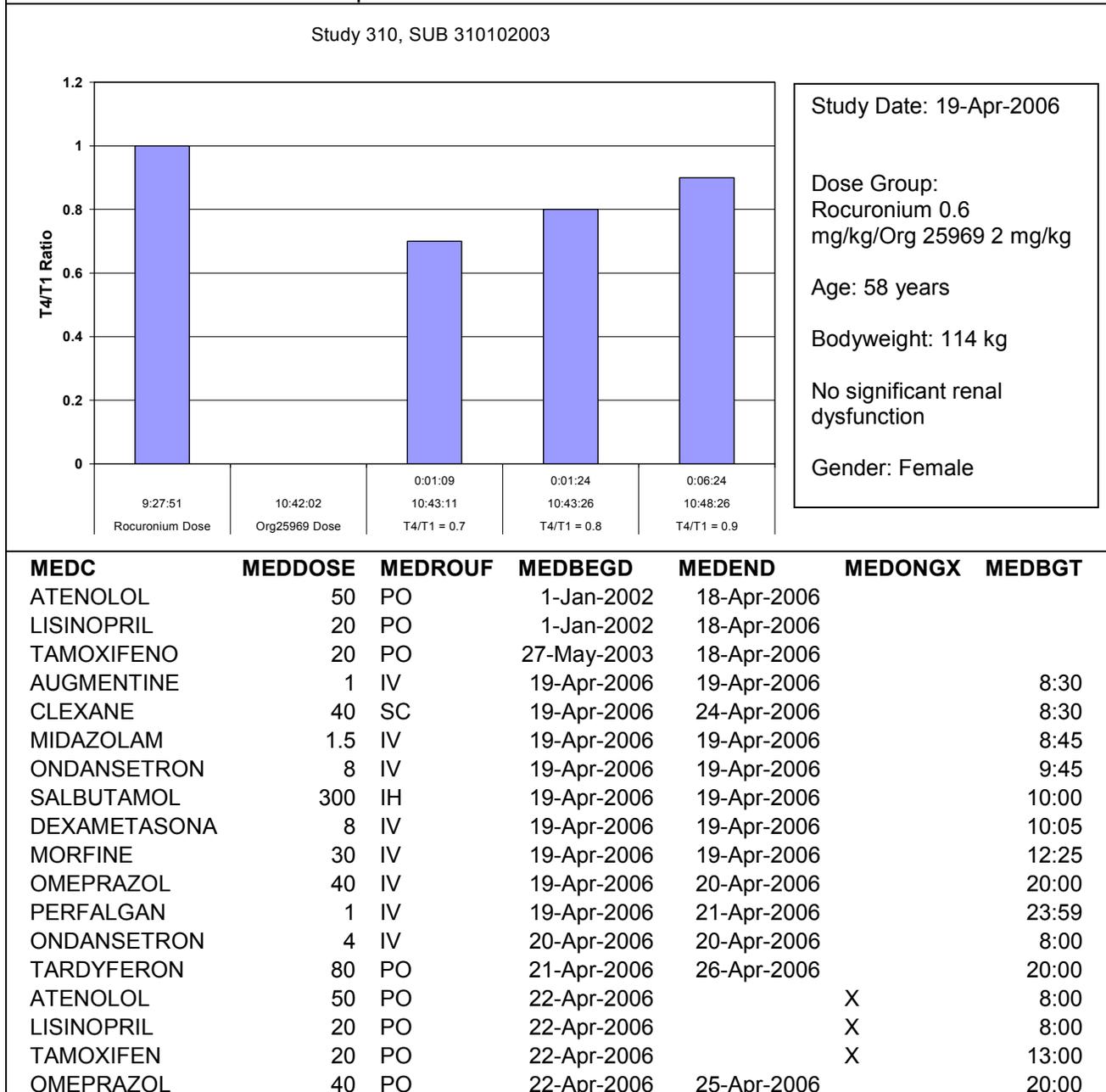


Figure 5. Time course of T4/T1 ratio in Subject 301109001 in Study 19.4.301 who experienced a delay in recovery to T4/T1 ratio of 0.9 indicating possible displacement of vecuronium from bound form to Org 25969 if study procedures are not the contributory factors. Also shown in the table below are the concomitant medications administered to the patient along with the timing of the medications. Shown also are the study date, dose and other information of the patient.

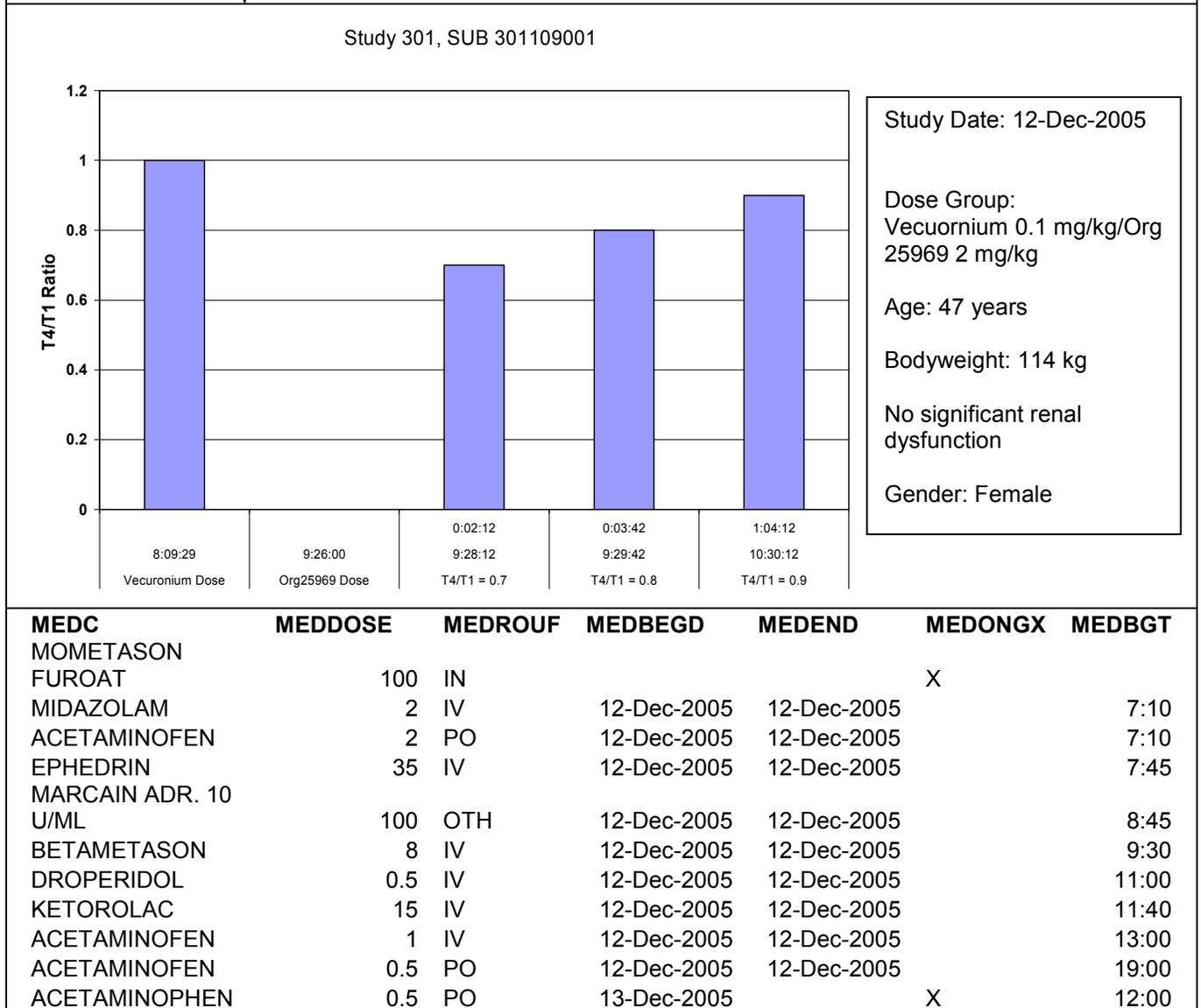
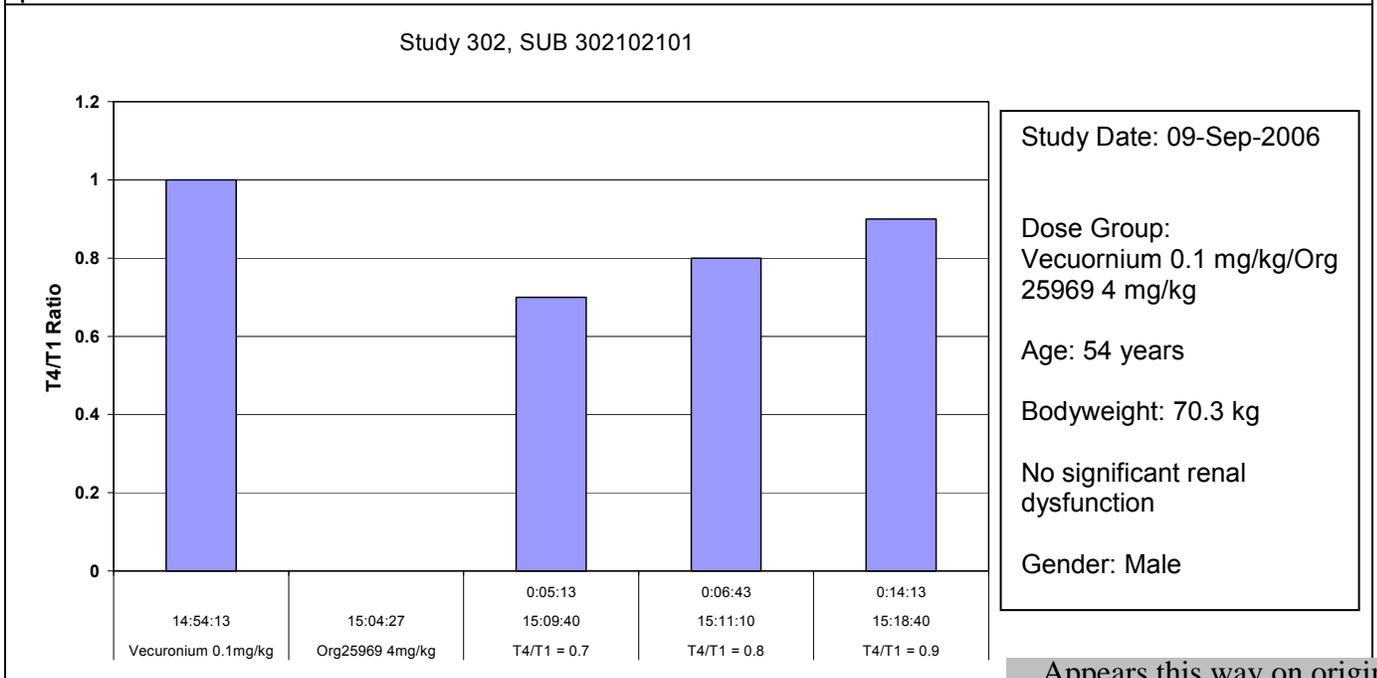


Figure 6. Time course of T4/T1 ratio in Subject 302102101 in Study 302 who experienced a delay in recovery to T4/T1 ratio of 0.9 indicating possible displacement of vecuronium from bound form to Org 25969 if study procedures are not the contributory factors. Also shown in the table below are the concomitant medications administered to the patient along with the timing of the medications. Shown also are the study date, dose and other information of the patient.



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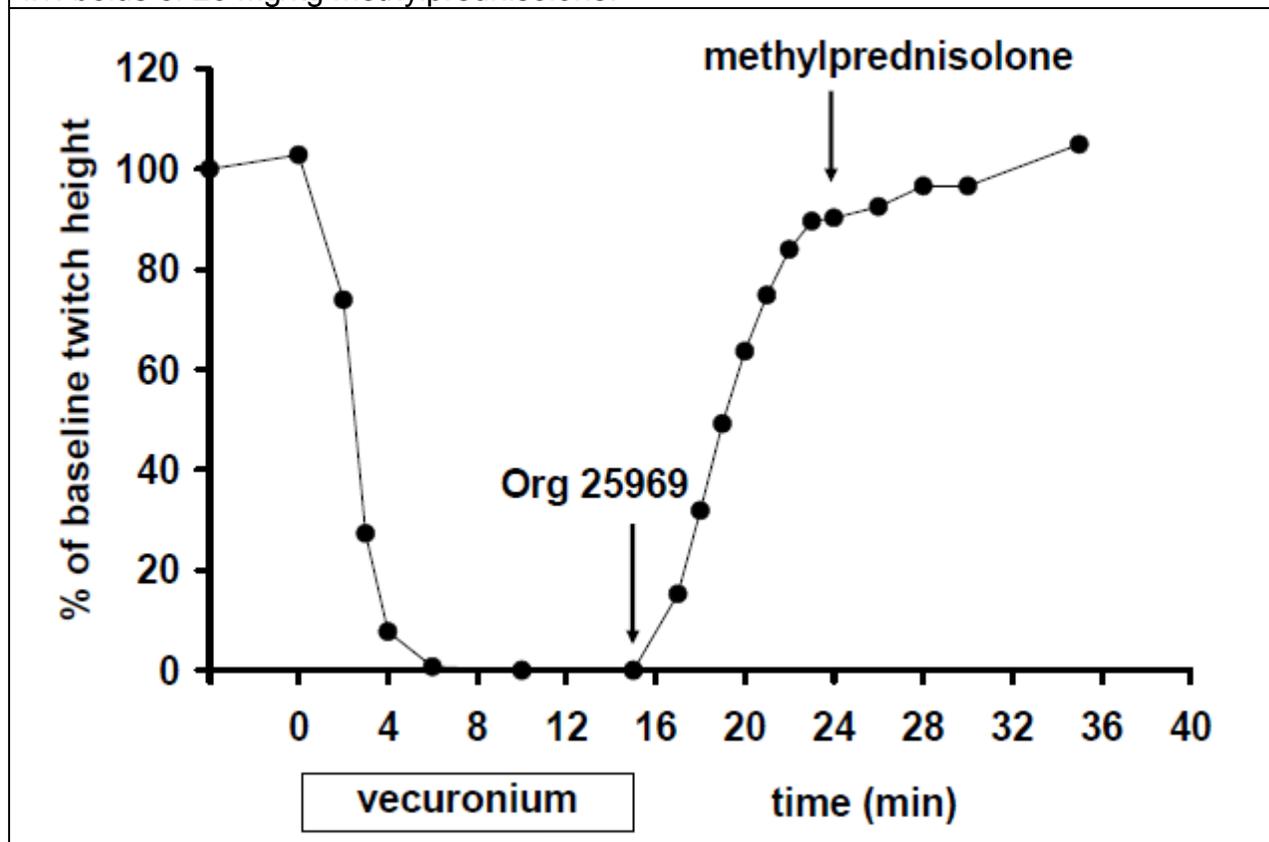
MEDC	MEDDOSE	MEDRO	UF	MEDBEGD	MEDEND	MEDONGX	MED
COD LIVER OIL			1 PO		12-Sep-2006		
IRON SUPPLEMENT	UNK		PO		12-Sep-2006		
BECONASE NASAL SPRAY	1 IN EACH NOSTRIL		IH		13-Sep-2006		
MIDAZOLAM		2	IV	13-Sep-2006	13-Sep-2006		1
KETZOL		1	IV	13-Sep-2006	13-Sep-2006		1
TORADOL		30	IV	13-Sep-2006	13-Sep-2006		1
ZOFRAN		4	IV	13-Sep-2006	13-Sep-2006		1
DEMEROL		12.5	IV	13-Sep-2006	13-Sep-2006		1
DEMEROL		12.5	IV	13-Sep-2006	13-Sep-2006		1
FENTANYL		50	IV	13-Sep-2006	13-Sep-2006		1
FENTANYL		50	IV	13-Sep-2006	13-Sep-2006		1
MORPHINE		19.49	IV	13-Sep-2006	14-Sep-2006		1
POTASSIUM CHLORIDE		20	IV	13-Sep-2006	13-Sep-2006		1
CALCIUM GLUCONATE		2	IV	13-Sep-2006	13-Sep-2006		2
FAMOTIDINE		20	IV	13-Sep-2006	15-Sep-2006		2
ONDANSETRON		4	IV	13-Sep-2006	13-Sep-2006		2
ONDANSETRON		4	IV	13-Sep-2006	13-Sep-2006		2
KETOROLAC		75	IV	14-Sep-2006	14-Sep-2006		
POTASSIUM CHLORIDE		20	IV	14-Sep-2006	14-Sep-2006		
CALCIUM		3.75	PO	14-Sep-2006	14-Sep-2006		1

As can be seen from Figure 4, Figure 5 and Figure 6, patients were being treated with corticosteroids. The number of patients in Studies 19.4.301 and 19.4.302 (From Integrated Summary of Safety, 5.3.5.3.28, ISS-appendix-a Tables) on concomitant medications such as Corticosteroids, Progestogens, Estrogens, Glucocorticoids are shown in **Error! Reference source not found.**Table 11. The sponsor used different ATC codes for drugs such as Budesonide (A) A07EA Corticosteroids for local use (B) D07AC Corticosteroids, potent (group iii) (C) H02AB Glucocorticoids (D) R01AD Corticosteroids (E) R03BA Glucocorticoids and hence these are reflected in more than one line in Table 11.

Table 11. Number of patients in Phase III controlled studies 19.4.301 and 19.4.302 whose ongoing concomitant medications such as corticosteroids, glucocorticoids, progestogens, estrogens..	
Drug Class	No.(%) of adult subjects in Phase III controlled studies 19.4.301 and 19.4.302 by ongoing concomitant medication..
Corticosteroids, weak	0/179
Corticosteroids, potent	2/179
Corticosteroids, very potent	1/179
Progestogens and estrogens, fixed combinations	2/179
Natural and semisynthetics estrogens, plain	7/179
Progestogens and estrogens, combinations	1/179
Progestogens and estrogens, sequential preparations	0/179
Glucocorticoids	6/179
Corticosteroids	4/179
Glucocorticoids	3/179
Corticosteroids, plain	2/179

Although the number of patients being treated with drugs such as corticosteroids is few, corticosteroids might contribute to the delay in recovery of T4/T1 ratio to 0.9 due to their binding potential to Org 25969. In animal studies where 3 mg/kg Org 25969 was administered 15 minutes after vecuronium administration followed by 20 mg/kg i.v methylprednisolone 9 min later, small re-occurrence of neuromuscular block in two of the four animals, resulting in an average decrease in twitch height of 17% after 0.4 ± 0.1 min (Figure 7).

Figure 7. Induction of block of *M. gastrocnemius* contractions with a vecuronium infusion and recovery with a sub-optimal dose of Org 25969 (3 mg/kg), followed by an i.v. bolus of 20 mg/kg methylprednisolone.



Based on the evidence of in vitro affinity bindings between Org 25969 (b) (4) and other drugs, preclinical experiments and simulations, the sponsor states the following in the label:

### Labeling Claims

#### **7.1 Interactions Potentially Affecting the Use of (b) (4) TM**

Toremifene

For toremifene, which has a relatively high affinity (b) (4) relatively high plasma concentrations, some displacement of vecuronium or rocuronium from the complex with (b) (4) could occur. The recovery to (b) (4) ratio of 0.9 could therefore be delayed in patients who have received toremifene on the same day of surgery.

### Reviewer's Comments

Typical language in drug labels for drug-drug interactions is based on evidence from In vivo studies which are designed to quantify the effect of an enzyme or from across clinical studies using population pharmacokinetic analysis methods. However, in the

current submission due to the nature of interaction between Org 25969 and other drugs being most likely due to complexation and rather than enzyme-mediated such as P450 enzymes, etc, sponsor evaluated most likely scenarios using in vitro data as well as simulations.. The current simulations do not consider protein binding of the third drug which can still lower the interaction potential.

Due to a lack of adequate number of patients taking these concomitant medications and also considering the fact that the patients are on multiple drugs, it is not possible to confirm the findings of PK/PD simulations using clinical trials database.

However, based on available data from patients in clinical trials being treated with tamoxifene and the observation that 2 patients had longer recovery times, it is probably reasonable to include language in the label describing probable interaction with toremifene which is a chlorinated derivative of tamoxifene. The label should also probably state about possible interaction with drugs that have steroidal structure which can also potentially bind to Org 25969. As of note, two other drugs that showed interaction potential by the model, flucloxacillin and fusidic acid, are not marketed in the U.S. so the proposed labeling does not include them.

**Issue 2 : Capturing potential of other drugs by Org 25969 and lowering effectiveness of other drugs**

Org 25969 shows affinity for steroids due to its molecular structure. For details of association constants refer to Figure 1. Among the steroids Org 25969 shows the highest affinity for etonogestrel (ENG), being the active metabolite of desogestrel (DSG), which is used as a progestogen in Marvelon®/Desogen®. Therefore, the effect of Org 25969 on the pharmacokinetics (PK) of ENG was evaluated using the PK characteristics for rocuronium, Org 25969 and ENG.

**Scenario 1**

After 14 days once daily administration of 150 µg DSG + 30 µg EE (Marvelon®/Desogen®), 0.6 mg/kg rocuronium was administered 0.9 hr after administration of Marvelon®/Desogen® on day 14. Twenty minutes thereafter 0, 1, 2, 4, 6, 8 or 16 mg/kg Org 25969 was administered to reverse rocuronium-induced NMB.

**Scenario 2**

After 14 days once daily administration of 150 µg DSG + 30 µg EE (Marvelon®/Desogen®), 0.6 mg/kg rocuronium was administered 6 hr after administration of Marvelon®/Desogen® on day 14. Twenty minutes thereafter 0, 1, 2, 4, 6, 8 or 16 mg/kg Org 25969 was administered to reverse rocuronium-induced NMB.

Figure 8 shows the effect of 0 - 16 mg/kg Org 25969 administered 20 minutes after 0.6 mg/kg rocuronium on the PK of unbound etonogestrel using dynamic equilibrium model. 150 µg etonogestrel was administered daily for 14 days. Rocuronium was administered (A) 0.9 h (B) 6 hr after administration of etonogestrel on day 14.

Figure 8. Effect of 0 - 16 mg/kg Org 25969 administered 20 minutes after 0.6 mg/kg rocuronium on the pharmacokinetics of unbound etonogestrel. 150 µg etonogestrel was administered daily for 14 days. Rocuronium was administered (A) 0.9 h (B) 6 hr after administration of etonogestrel on day 14.

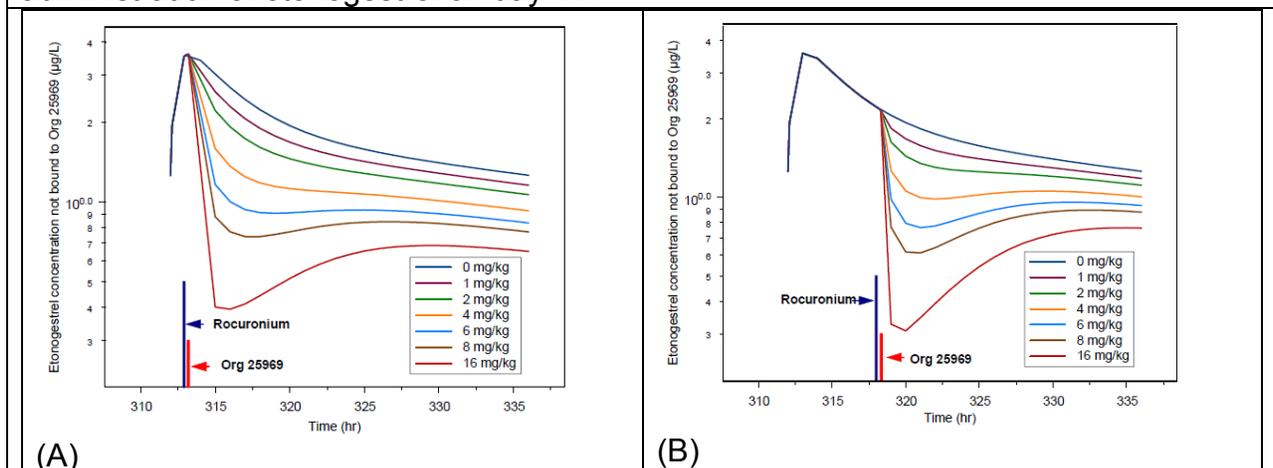


Table 12 and Table 13 show the effect of Org 25969 administration on the area under the curve (AUC) of etonogestrel plasma concentration that is not bound to Org 25969.

Table 12. Effect of 1 – 16 mg/kg Org 25969 administered 20 minutes after 0.6 mg/kg rocuronium on the AUC[0-24] of the unbound etonogestrel concentration. Rocuronium was administered 0.9 hr after administration of etonogestrel on day 14 (Scenario 1).

Dose Org 25969 (mg/kg)	AUC[0-24 h] (µg*min/L)	Rel. Difference from placebo (%)
0	2733.2	0
1	2448.4	-10.42
2	2195.3	-19.68
4	1808.0	-33.85
6	1550.0	-43.29
8	1376.1	-49.65
16	1045.9	-61.73

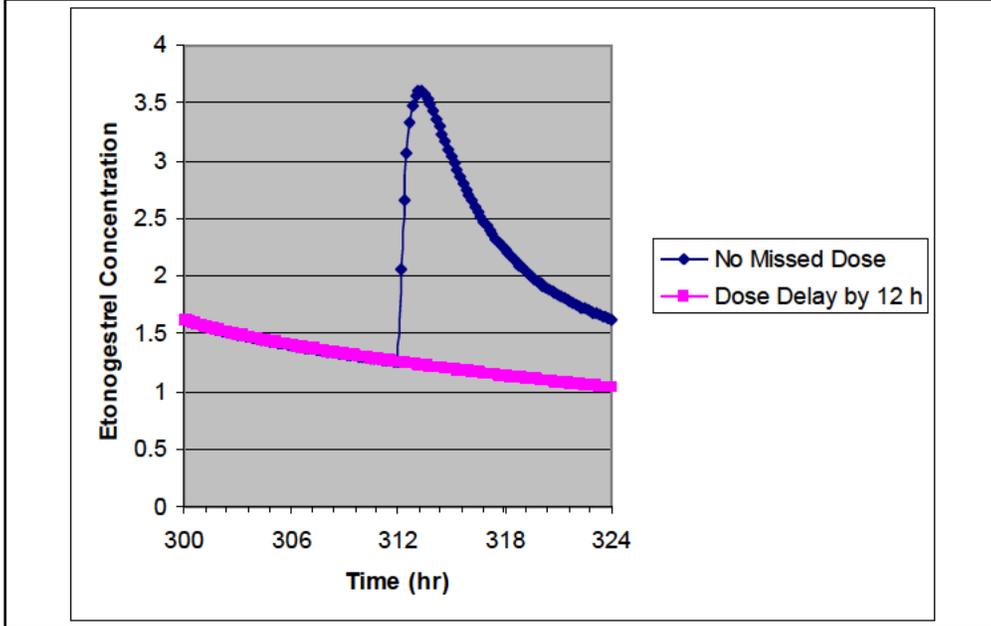
Table 13. Effect of 1 – 16 mg/kg Org 25969 administered 20 minutes after 0.6 mg/kg rocuronium on the AUC[0-24] of the unbound etonogestrel concentration. Rocuronium was administered 6 hr after administration of etonogestrel on day 14 (Scenario 2).

Dose Org 25969 (mg/kg)	AUC[0-24 h] (µg*min/L)	Rel. Difference from placebo (%)
0	2733.2	0
1	2573.0	-5.86
2	2429.0	-11.13
4	2204.3	-19.35
6	2049.8	-25
8	1941.9	-28.95
16	1720.6	-37.05

The sponsor states:

- Administration of 2 mg/kg Org 25969, 20 minutes (0.9 hr) after administration of 0.6 mg/kg rocuronium in Scenario 2, results in a decrease in AUC[0-24] by 11% relative to the AUC[0-24] of etonogestrel without Org 25969.
- When rocuronium and 2 mg/kg Org 25969 are administered around Tmax of etonogestrel (Scenario 1) the AUC[0-24] is decreased by 20%.
- The anti-conceptive action of Marvelon®/Desogen® is still guaranteed when a user is less than 12 hours late in taking a dose.
- It can be calculated that, for a typical subject of 70 kg, the AUC calculated from 12 hours before to 12 hours after a scheduled dose of Marvelon®/Desogen® the AUC drops with 32.7% when that dose is taken 12 hours too late as shown in Figure 9.

Figure 9. Mean time course of etonogestrel concentrations in two scenarios (No dose of Marvelon®/Desogen® is missed versus if the dose of Marvelon®/Desogen® is delayed by 12 hours)



This would imply that for Scenario 1 Org 25969 doses up to 2 mg/kg would not result in a reduction of the effectiveness of Marvelon®/Desogen®. In case of Scenario 2, the change in AUC of etonogestrel after 8 mg/kg Org25969 will still be smaller compared to the effect in AUC of taking a dose 12 hours too late.

**Labeling Claims**

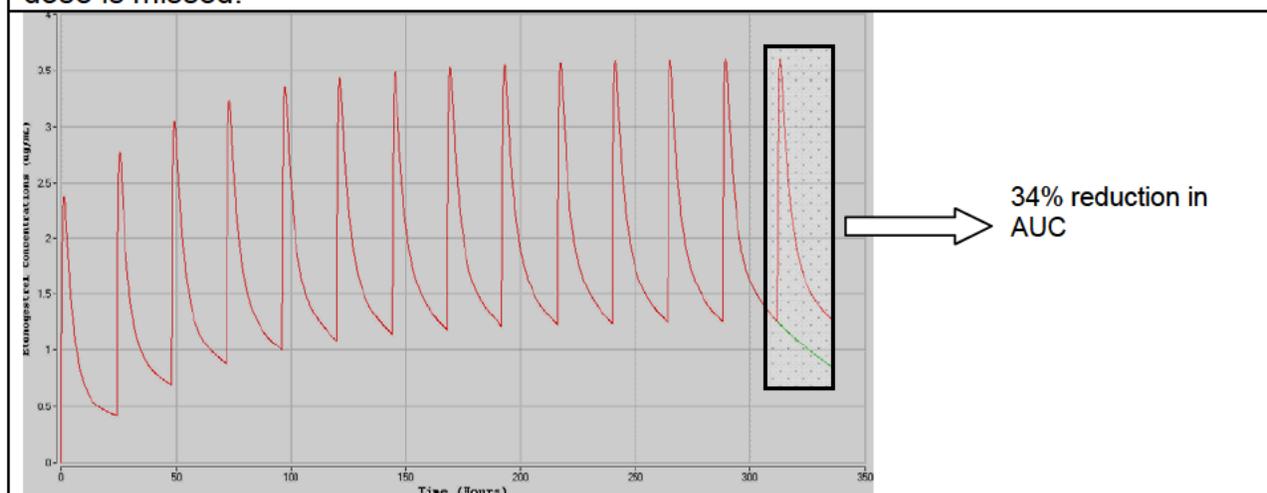
Hormonal contraceptives:

[Redacted content] (b) (4)

## Reviewer's Comments

- (1) The reviewer conducted simulations using Berkeley Madonna® to evaluate the impact of missed dose on the plasma concentrations of Etonogestrel. Figure 10 shows the mean time course of Etonogestrel concentrations after multiple doses of 150 µg etonogestrel. A 34% reduction in 24 hour AUC is seen if a patient were to miss the second dose of etonogestrel. If the second dose is taken 12 hours later, the peak concentrations of etonogestrel will be lower. The significance of these lower concentrations for a given dosing interval is not known.

Figure 10. Simulated mean time course of etonogestrel concentrations (Solid red line is for a scenario where dose is not missed, The solid green line is for a scenario when a dose is missed).



- (2) The sponsor states that the simulation study here is a worst-case scenario since the binding of etonogestrel (ETN) to sex hormone binding globulin (SHBG) was not taken into consideration. Lack of this assumption indicates that all ENG in plasma was available for complexation with Org 25969. However, due to the lack of empirical evidence, the 62% decrease in AUC[0-24] of unbound ETN concentrations when 16 mg/kg Org 25969 is administered around T<sub>max</sub> of Marvelon®/Desogen® can result in much lower effectiveness. This scenario is not described in the label adequately.
- (3) The sponsor states that "*The anti-conceptive action of Marvelon®/Desogen® is still guaranteed when a user is less than 12 hours late in taking a dose*". However, the approved label for Mircette® (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets which has for missed dose states the following.

### WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** "active" [white] pill:

- Take it as soon as you remember. Take the next pill at your regular time. This means you take 2 pills in 1 day.
- You do not need to use a back-up birth control method if you have sex.

Based on reasons that (A) Molar concentrations of rocuronium are higher than that of etonogestrel (B) Lower dissociation rate constant of etonogestrel in comparison to rocuronium (C) Caution to the patients that additional steps for ensuring adequate effectiveness of on-going contraceptive use, the proposed language is acceptable.

**Issue 3: Waiting times for re-administration of rocuronium in patients for intubation who were initially administered Org 25969 and rocuronium**

Currently, there is no clinical experience on the waiting time for re-administration of rocuronium in patients for intubation who are initially administered Org 25969 and rocuronium. When Org 25969 is still present in the circulation, the effectiveness of the re-treatment with NMBA may be affected, to a degree depending on the dose of Org 25969 administered and on the time between reversal and re-treatment with NMBA. Based on the half-life of Org 25969, molar concentrations of Org 25969, rocuronium, vecuronium, the waiting times were derived. The basis for proposed waiting times for rocuronium and vecuronium is discussed below:

**Rocuronium**

- For rocuronium, the re-administration will be effective when the surplus in moles of rocuronium versus Org 25969 is approximately equivalent to the standard intubating dose of 0.6 mg/kg rocuronium. In that case onset time can be expected to be essentially similar to that after a standard intubating dose of 0.6 mg/kg.
- The molecular weight of rocuronium is 609.70 while the molecular weight of Org 25969 is 2178. Hence, in terms of moles (Weight in Grams/Molecular Weight) a 1.2 mg/kg dose of rocuronium is equivalent to 4 mg/kg of Org 25969.

**Vecuronium**

- The molecular weight of vecuronium is 637.74 which is similar to that of rocuronium (609.70).
- The vecuronium dose used for intubation (0.1 mg/kg) is lower than rocuronium doses used for intubation (0.6 to 1.2 mg/kg).

Table 14 shows the calculations for the waiting times for dosing of 0.6 mg/kg rocuronium, 1.2 mg/kg rocuronium and 0.1 mg/kg vecuronium.



- The half-life of Org 25969 in normal patients is approximately 2 hours. In patients with severe renal impairment the half-life of Org 25969 is 27 hours. In elderly patients with normal, mild and moderate renal function the half-life of Org 25969 is approximately 3, 4 and 5 hours respectively. Hence, the waiting times for readministration of rocuronium in mild and moderate renal impairment need to be doubled and tripled respectively (Table 17).

- In situations where NMB after reversal with Org 25969 would be required before the recommended waiting time has passed, the sponsor recommends that a nonsteroidal NMBA should be used.

Table 17. Recommended waiting times for re-administration with rocuronium or vecuronium after reversal with Org 25969.



(b) (4)

**Reviewer's Comments:** There is no clinical data to support the recommendations. However, based on the pharmacokinetics of Org 25969 and binding characteristics between Org 25969 and rocuronium, sponsor's proposal is reasonable and would be useful to the clinician.

#### **Issue 4: NMB reversal in patients with hepatic impairment**

The sponsor did not evaluate pharmacokinetics of Org 25969 in patients with hepatic impairment. The pharmacokinetics of rocuronium was evaluated in 10 normal subjects and 9 patients with alcoholic liver cirrhosis (Organon study P021-009). The study showed that the pharmacokinetic parameters of rocuronium are altered in the presence of severe liver impairment as shown in Table 18. Using the PK/PD model with the assumptions of PK changes for rocuronium and/or Org 25969, the sponsor simulated the recovery time of T4/T1 to 0.9 for the following scenarios

#### **Scenario 1: Org 25969 administration 3 minutes after rocuronium**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 12, 16 or 20 mg/kg Org 25969 was administered iv 3 minutes after rocuronium administration.

#### **Scenario 2: Org 25969 administration 15 minutes after rocuronium**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 2, 4 or 8 mg/kg Org 25969 was administered iv 15 minutes after rocuronium administration.

#### **Scenario 3: Org 25969 administration at reoccurrence of T2**

Following an iv bolus dose of 0.6 or 1.2 mg/kg rocuronium, 2 or 4 mg/kg Org 25969 was administered iv at reoccurrence of T2.

Table 18. Summary of observed PK changes for rocuronium in patients with severe hepatic impairment relative to normal. Shown are assumptions of PK changes for Org 25969 in subjects with hepatic impairment.

	CL	Vc	Vp1	Vp2
Rocuronium PK changes in hepatic impairment relative to normal	↓ 21%	↑ 52%	↑ 74%	↑ 141%
Org 25969 PK changes in hepatic impairment relative to normal	↔	↔	↔	↔
Org 25969 PK changes in hepatic impairment relative to normal	↔	↑ 52%	↑ 74%	↑ 141%

The PK/PD model for rocuronium links the first peripheral compartment concentrations to the TOF ratio. Due to increase in volume of distribution of rocuronium and Org 25969 into central and second peripheral compartment, one would expect that the concentrations in the first peripheral compartment would be lower in patients with hepatic impairment. The onset will be slightly delayed. With lower concentrations of Org 25969 to bind to rocuronium due to greater distribution volume, the recovery will be slower which is dependent on (A) Dose of Org 25969 (B) Time between the

administration of rocuronium and Org 25969. The information on recovery times in patients with hepatic impairment was calculated and is shown in Table 19 below.



**Reviewer's Comments:** The main assumption in deriving the time to recovery of T4/T1 ratio to 0.9 as shown in Table 19 is that hepatic impairment affects both rocuronium and Org 25969 similarly in terms of extracellular space into which they are distributed. If the assumption of changes in extracellular space into which Org 25969 is distributed in hepatic impairment patients is not



**Issue 5: Need for dose adjustment in patients with renal impairment**

The sponsor evaluated the effects of renal function on the PK and PD of Org 25969 in two studies.

Study 19.4.304:

- A multi-center, parallel group, comparative trial evaluating the efficacy, pharmacokinetics and safety of Org 25969 in subjects (N=30) with normal ( $\geq 80$  mL/min, N=15) or severely impaired renal function ( $< 30$  mL/min, N=15).
- Dose: 0.6 mg/kg bolus dose of rocuronium. A 2 mg/kg dose of Org 25969 was administered at reappearance of T2.
- Administration of 2.0 mg/kg Org 25969 at reappearance of T2 after an intubating dose of 0.6 mg/kg rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T4/T1 ratio to 0.9 of 2 minutes for the severely renally impaired subjects, and 1 min:39 sec for the control subjects.

Study 19.4.305:

- A multicenter, parallel group, comparative, phase IIIa trial to compare the efficacy, safety, and pharmacokinetics of Org 25969 in elderly subjects (65 years old to 74 years old; N=60), and 75 years and older; N=40) with adult subjects (18 years old to 64 years old; N=40).
- Dose: 0.6 mg/kg bolus dose of rocuronium. A 2 mg/kg dose of Org 25969 was administered at reappearance of T2.
- The mean time from administration of Org 25969 to recovery of the T4/T1 ratio to 0.9 was 2 min:16 sec (adult group) and 2 min:56 sec (geriatric group), respectively. The results in various subgroups are shown in Table 20 below using imputed data and complete cases. The recovery time in patients who are 75 years and older is slightly longer than other age groups.

Table 20. Summary of time (min:sec) from start of administration of Org 25969 to the T4/T1 ratio to 0.9, for subjects who received an intubating dose and those who received maintenance doses of rocuronium, (Intent-to-Treat group)

			Age group			
			Adult	Geriatric		
			18-64 (N=48)	65-74 (N=62)	75+ (N=40)	Subtotal (N=102)
Intubating dose only	Including imputed data	n	16	25	21	46
		Geom. mean	2:18	2:28	3:21	2:50
		Mean (SD)	2:36 (1:37)	2:44 (1:18)	3:48 (2:01)	3:14 (1:44)
		Median	2:06	2:38	3:29	2:49
		Min.-max.	1:10 - 7:25	0:54 - 6:08	1:01 - 9:55	0:54 - 9:55
	Complete cases	n	14	23	19	42
		Geom. mean	1:59	2:17	3:10	2:39
		Mean (SD)	2:04 (0:37)	2:27 (0:54)	3:36 (2:00)	2:58 (1:35)
		Median	1:56	2:33	3:10	2:41
		Min.-max.	1:10 - 3:30	0:54 - 4:25	1:01 - 9:55	0:54 - 9:55
Intubating dose and maintenance dose	Including imputed data	n	32	37	19	56
		Geom. mean	2:16	2:39	3:53	3:01
		Mean (SD)	2:29 (1:13)	3:02 (1:50)	4:05 (1:14)	3:23 (1:43)
		Median	2:11	2:32	3:55	2:59
		Min.-max.	1:11 - 6:11	0:54 - 8:49	1:45 - 5:51	0:54 - 8:49
	Complete cases	n	31	34	16	50
		Geom. mean	2:13	2:28	3:38	2:48
		Mean (SD)	2:26 (1:11)	2:47 (1:42)	3:48 (1:08)	3:07 (1:36)
		Median	2:10	2:20	3:36	2:55
		Min.-max.	1:11 - 6:11	0:54 - 8:49	1:45 - 5:51	0:54 - 8:49

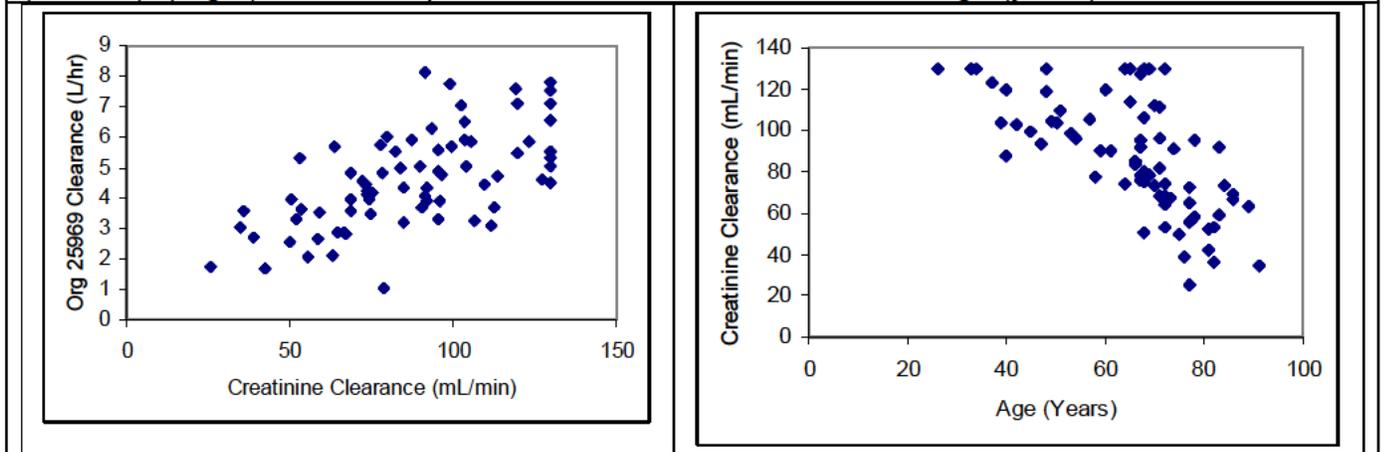
**Labeling Claim:**

(b) (4)

**Reviewer's Comments:**

Figure 11 shows the relationship between creatinine clearance and Org 25969 clearance (L/h) in Study 305 based on population pharmacokinetic analysis.

Figure 11. (Left) Relationship between Org 25969 clearance (L/hr) and creatinine clearance (mL/min). (Right) Relationship between creatinine clearance and age (years)

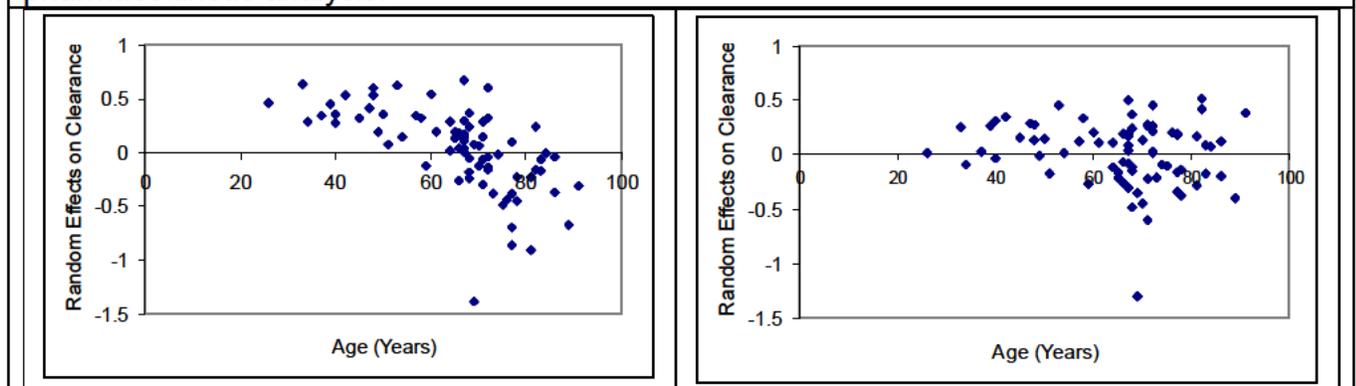


After inclusion of creatinine clearance as covariate in the population pharmacokinetic analysis, there is no additional effect of age on the pharmacokinetics of Org 25969 as shown in Figure 12. Note the trend between random effects of clearance versus age before accounting for renal function differences with age as shown in Figure 11 above. After inclusion of age in the analysis, there is no trend between random effects of clearance versus age, indicating that there is no additional effect of age on the pharmacokinetics of Org 25969.

The relationship between Org 25969 clearance and renal function can be described by:

$$CL = 4.46 \cdot \left( \frac{\text{Creatinine Clearance}}{88} \right)^{0.941}$$

Figure 12. (Left) Relationship between random effects of clearance versus age prior to inclusion of age in the population pharmacokinetic analysis (Right) Relationship between random effects of clearance versus age after inclusion of age in the population pharmacokinetic analysis.



In Study 19.4.305 the sponsor also obtained data on the recovery of T4/T1 ratio to 0.9 in these patients. There is a slight delay in the recovery of T4/T1 ratio in elderly patients.

In Study 19.4.304, patients with severe renal impairment administration of 2.0 mg/kg Org 25969 at reappearance of T2 after an intubating dose of 0.6 mg/kg rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T4/T1 ratio to 0.9 of 2 minutes for the severely renally impaired subjects, and 1 min:39 sec for the control subjects. Although the study did not include patients with mild and moderate renal impairment, one would expect that the T4/T1 ratio to be in between 1 min:39 sec and 2 minutes.

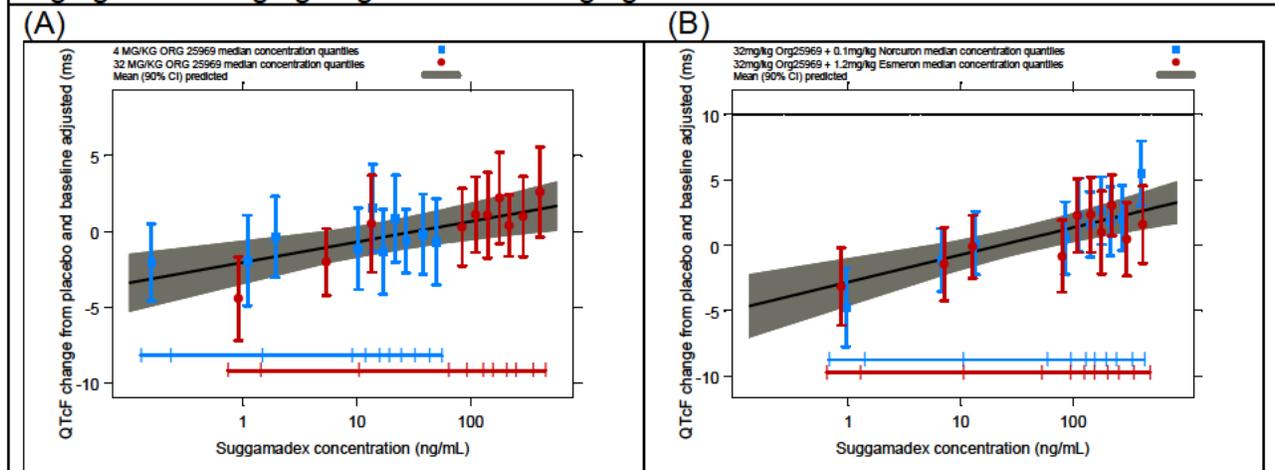
Due to these various pieces of evidence (PK, T4/T1 ratio) in patients (elderly/non-elderly) the reviewer is in agreement with the proposed language in the label.

**Issue 6: Risk for QTc prolongation**

The reviewer evaluated the risk for pro-arrhythmic potential using concentration- $\Delta\Delta$ QTcF (Baseline, Placebo Subtracted) data. The details of the analysis is reported as a part of the QT-Integrated Review Team (IRT) review. The relationship between concentration and  $\Delta\Delta$ QTcF could be described using a log-linear model as shown in Figure .

Overall, the largest upper limit of the two-sided 90% CI for the mean difference between (b) (4) (4 mg/kg and 32 mg/kg doses) alone and in combination of 32 mg/kg (b) (4) with rocuronium (1.2 mg/kg), vecuronium (0.1 mg/kg) and placebo was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

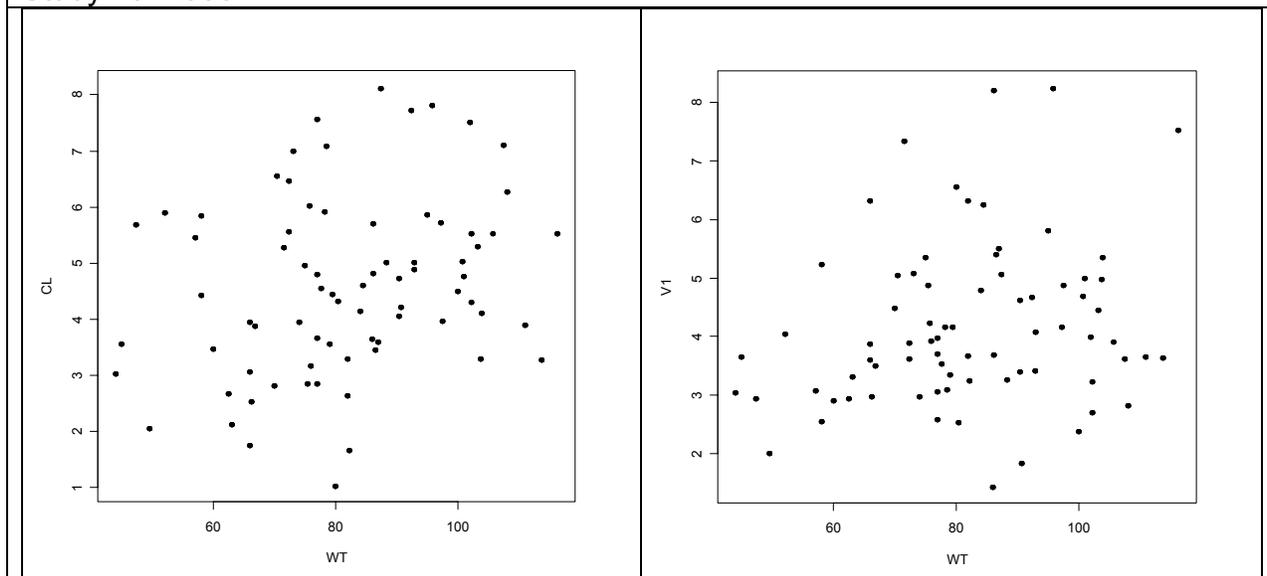
Figure 13. (A) Median concentration quantile with corresponding observed mean (90% CI)  $\Delta\Delta$ QTcF following 4 and 32 mg/kg Org25969. (B) Median concentration quantile with corresponding observed mean (90% CI)  $\Delta\Delta$ QTcF following 32 mg/kg Org 25969+0.1 mg/kg and 32 mg/kg Org25969 + 1.2 mg/kg Esmeron.



**Issue 7 : Body Weight Effects on PK in the label based on population pharmacokinetic analysis.**

Sponsor analyzed the influence of body weight on the pharmacokinetics of Org 25969 using population PK approach. Figure 14 shows the effect of bodyweight on the clearance and volume of distribution of central compartment in Study 19.4.305. No clear weight effect can be seen on the PK parameters of Org 25969.

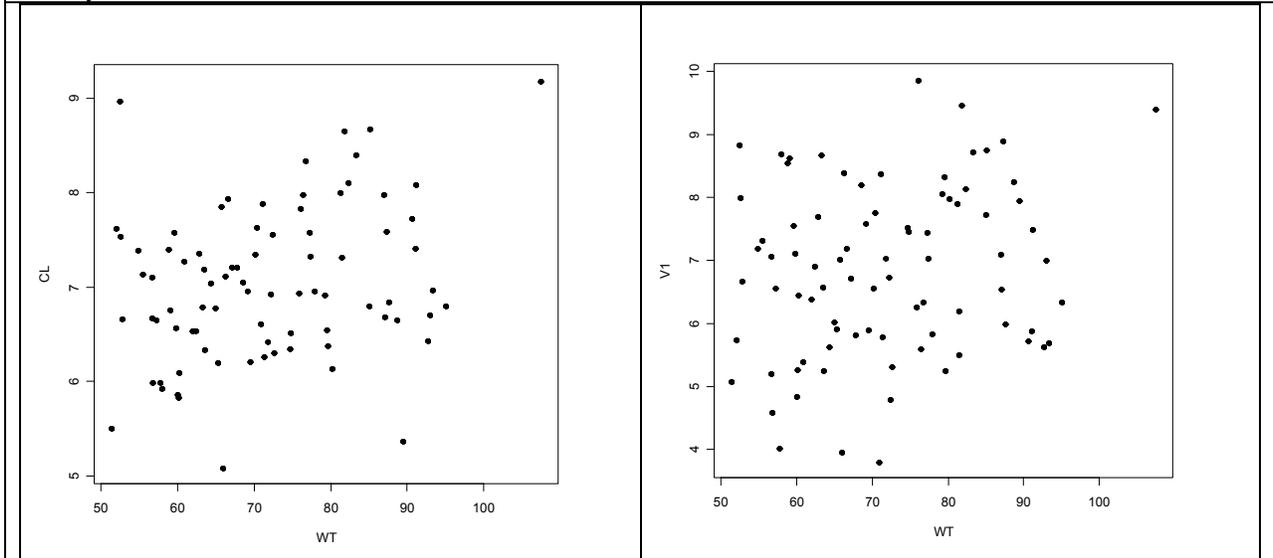
Figure 14. Relationship between clearance, volume of distribution and body weight in Study 19.4.305.



The inclusion of bodyweight as a covariate reduced the intersubject variability in clearance from 41% to 38%. The intersubject variability of volume of distribution of central compartment changed from 43% to 46% after inclusion of bodyweight as covariate.

Figure 15 shows the relationship between clearance, volume of distribution and bodyweight in Study 19.4.309. The inclusion of body weight as a covariate did not reduce the intersubject variability (14 vs 13%) of clearance.

Figure 15. Relationship between clearance, volume of distribution and body weight in Study 194305.



**Labeling Claim**

(b) (4)

**Reviewer Comments**

The reviewer is in agreement with the proposed language in the label.

## Appendix-I

### Dose Selection

Sponsor conducted several Phase-II studies to aid in selection of doses for the Phase-III trials as shown in Table 21. The primary endpoint in the studies was time to recovery of T4/T1 to 0.9.

Study	Patient Population (Years)	Rocuronium Dose	Comments
19.4.101	18-40	0.6 mg/kg	Org 25969 was administered 3 min after a single dose of rocuronium.
19.4.201	18-64	0.6 mg/kg	Org 25969 was administered at time of reappearance of T2.
19.4.202	18-64	0.6 mg/kg	Org 25969 was administered 3, 5 or 15 minutes after a single dose of rocuronium.
19.4.203	19-76	0.6 mg/kg followed by maintenance dose	Org 25969 was administered at time of reappearance of T2 following profound blockade.
19.4.204	>18	0.6 mg/kg or 1.2 mg/kg with maintenance dose	Org 25969 was administered at 1-2 PTC after rocuronium administration.
19.4.205	18-64	1.2 mg/kg	Org 25969 was administered 5 minutes after rocuronium administration.
19.4.206	>18	1 or 1.2mg/kg	Org 25969 was administered 3 or 15 minutes after rocuronium administration.
19.4.207	>18	0.6 mg/kg rocuronium, 0.1 mg/kg vecuronium, 0.1 mg/kg pancuronium	Org 25969 was administered at reappearance of T2.
19.4.208B	20-65	0.9 mg/kg rocuronium followed by maintenance doses	Org 25969 was administered at reappearance of T2.
19.4.209B	20-65	0.9 mg/kg rocuronium followed by	Org 25969 was administered at 1-2 PTC after rocuronium

		maintenance doses	administration.
19.4.306	Pediatric (Infants, Children, Adolescents), Adults	0.6 mg/kg rocuronium	Org 25969 administered at reappearance of T2.

Figure 16 and Figure 17 shows the dose-response (Time to recovery of T4/T1 ratio to 0.9) data from various studies

Figure 16. Relationship between Org 25969 dose (mg/kg) and response (Time to recovery of T4/T1 ratio to 0.9 (min)) in various studies.

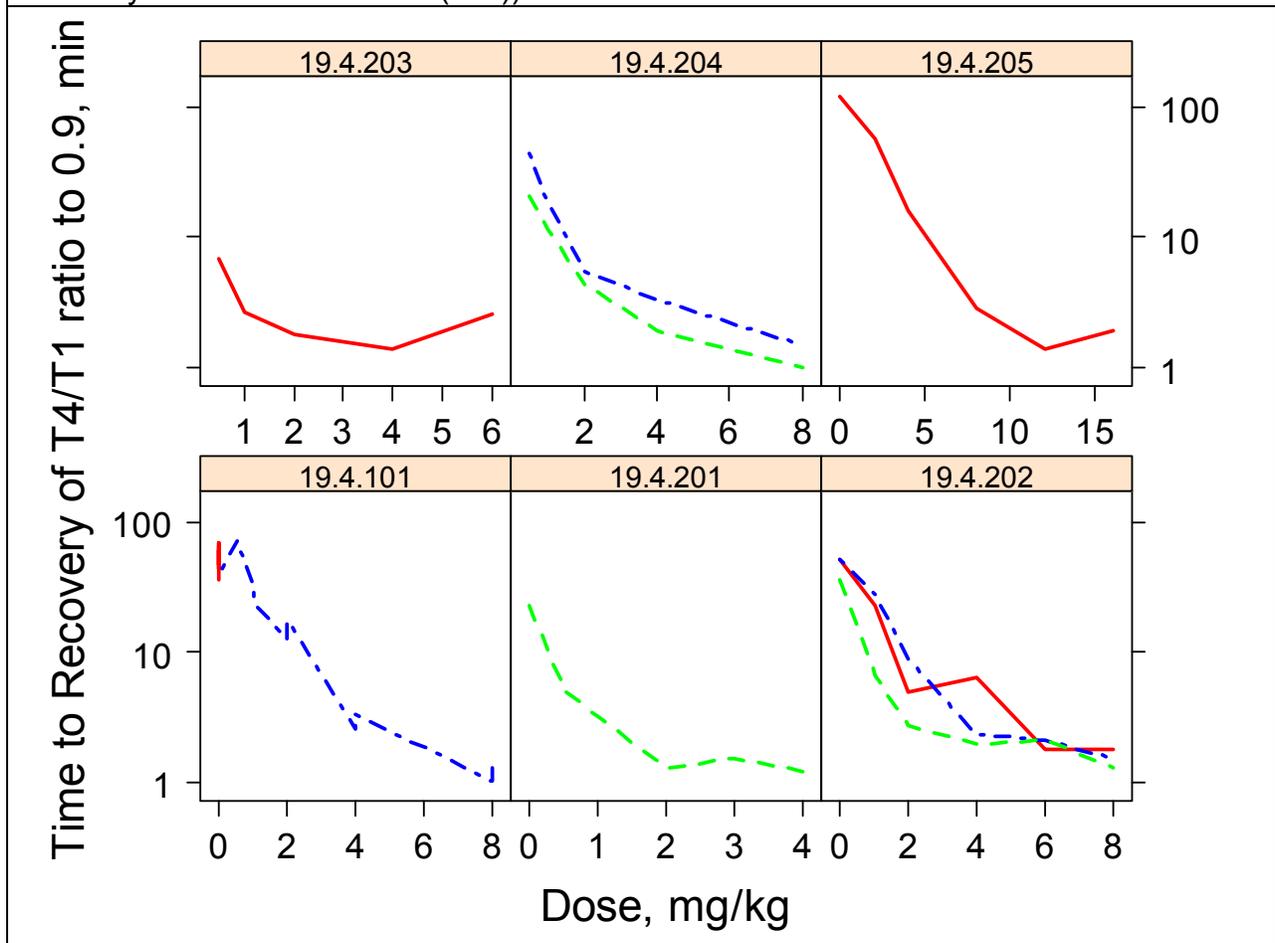
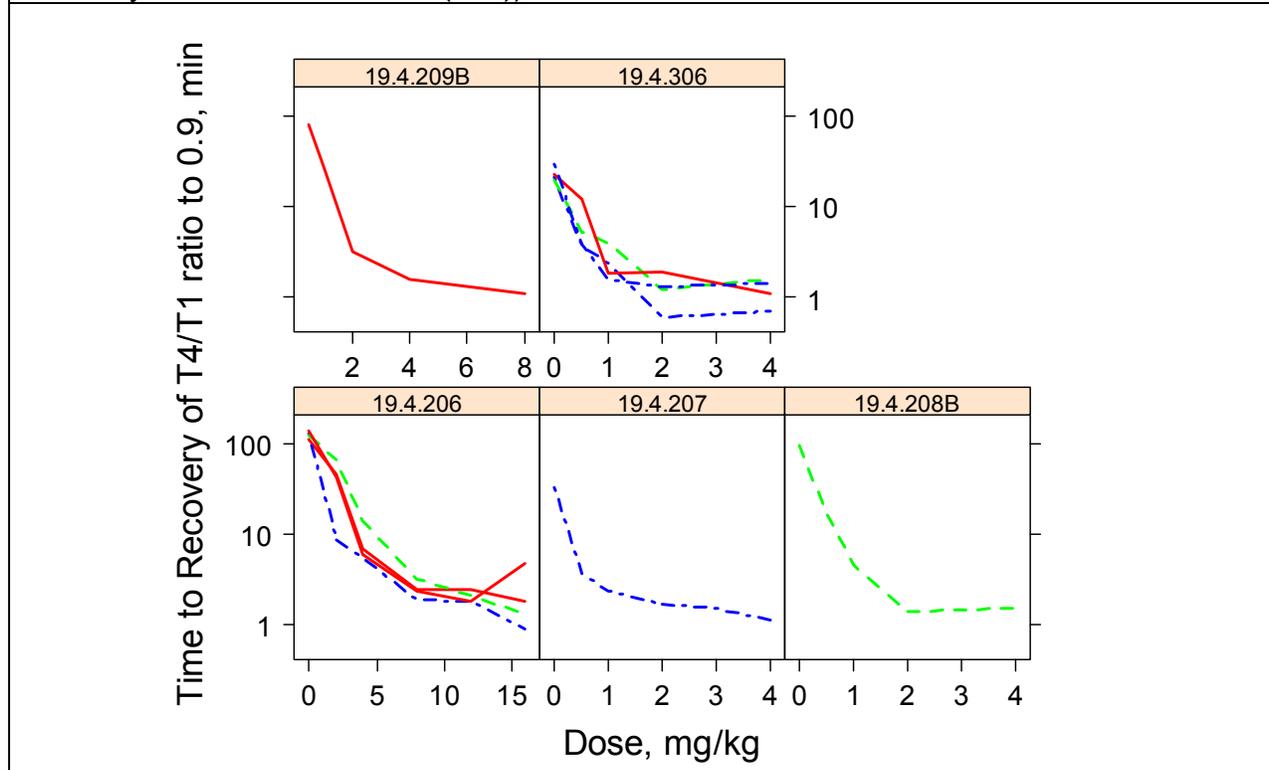


Figure 17. Relationship between Org 25969 dose (mg/kg) and response (Time to recovery of T4/T1 ratio to 0.9 (min)) in various studies.



Based on the dose-response information from dose finding studies, the sponsor studied the NMB (rocuronium or vecuronium) reversal effects of 2 mg/kg (shallow blockade), 4 mg/kg (profound blockade) and 16 mg/kg (immediate reversal) Org 25969 in pivotal trials and special populations (renal impairment, cardiac disease and pulmonary disease).

The results from the pivotal trials suggest that Org 25969 is effective in reversal of NMB as shown in Table 22 and Table 23 below.

Table 22. Summary of results from Study 301 and 302

Study	Scenario	Time to T4/T1 ratio = 0.9	
		Sugammadex	Neostigmine
301	Routine	01:29 (Rocuronium)	18:30
	Shallow	02:48 (Vecuronium)	16:48
302	Routine	02:52 (Rocuronium)	50:22
	Shallow	04:28 (Vecuronium)	66:12

Table 23. Summary of time (min:sec) from start of administration of rocuronium or succinylcholine to recovery of T1 to 10% by treatment group in Study 303			
Scenario		Treatment Group	
		Rocuronium+Org 25969	Succinylcholine
Immediate Reversal			
	Including imputed data	4:22	7:04
	Complete cases	4:21	7:09

**Routine Reversal:**

- A dose of 4.0 mg/kg Org 25969 if recovery has reached 1-2 post tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.
- A dose of 2.0 mg/kg Org 25969 if spontaneous recovery has reached the reappearance of T2 (shallow blockade) following rocuronium or vecuronium induced blockade.

**Immediate reversal:**

- If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg Org 25969 is recommended.

## Appendix II

### Pharmacokinetic-Pharmacodynamic (PK/PD) Modeling

#### Introduction

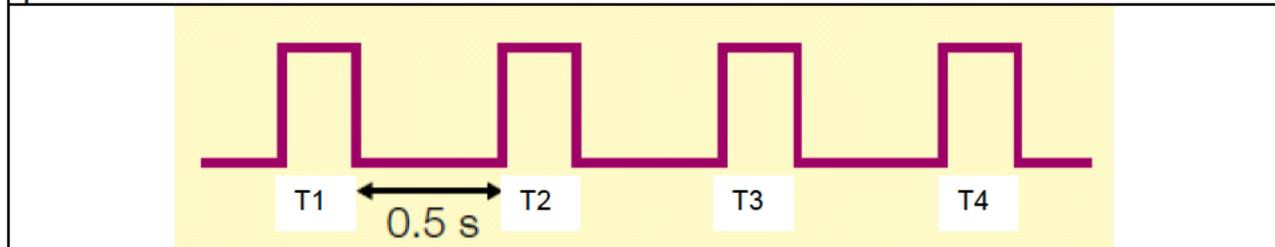
For adequate characterization of the relationship between rocuronium concentrations and influence of Org 25969 concentrations on the neuromuscular blockade (Changes in % TOF (Train of four ratio)), sponsor described the following using non-linear mixed effects technique in NONMEM:

- (A) PK of rocuronium in adult subjects and patients with renal, hepatic impairment.
- (B) PK of Org 25969 in adult subjects and patients with renal impairment.
- (C) Relationship between rocuronium concentrations and changes in %TOF (T4/T1 ratio) alone.
- (D) PK interaction between rocuronium and Org 25969.
- (E) Relationship between rocuronium concentrations in the presence of Org 25969 and changes in %TOF (T4/T1 ratio).

The pharmacodynamic endpoint used for the analysis was the primary endpoint (Train of four, TOF) utilized to demonstrate effectiveness of Org 25969.

**Train of four (TOF)** – Four stimuli are given at a frequency of 2 Hz, potentially eliciting 4 twitches (T1–T4) as shown in Figure 18. The ratio T4:T1 indicates the degree of neuromuscular block. Non-depolarizing NMBAs produce a decrease in magnitude of the first twitch compared with a pre-relaxant stimulus, and a progressive reduction in magnitude of T1–T4. The number of elicited twitches indicates the degree of receptor occupancy. Disappearance of T4, T3, T2, T1 corresponds to 75%, 80%, 90% and 100% occupancy. With recovery of neuromuscular function the twitches appear in the reverse order.

Figure 18. Pulse pattern in Train of four (TOF). Shown is the response in a subject prior to administration of neuromuscular blockade. The ratio of T4/T1 is 1.



## Data

Table 24 lists the dose groups, number of patients and observations in studies utilized for the PK and PK/PD modeling. The data collected was adequate to develop PK/PD models.

Table 24. List of dose groups, number of patients and observations in studies utilized for PK and PK/PD modeling.

Study protocol	Number of subjects	*Samples	Rocuronium dose (mg/kg)	Org25969 dose (mg/kg)
<b>PK model Rocuronium alone</b>				
CT 9903	59	19	0.3, 0.6, 0.9	0
CT 021-014	22	19	0.6	0
CT 021-009	20	20	0.6	0
CT 19.4.101	10	22	0.6	0
CT 19.4.201	25	1	0.6	0
CT 19.4.202	96	1	0.6	0
CT 19.4.205	6	5	1.2	0
CT 19.4.304	26	6	0.6	0
CT 19.4.305	27	1	0.6	0
CT 19.4.306	77	2	0.6	0
<b>PK-PD model Rocuronium alone</b>				
<i>TOF ratio- time profile</i>				
CT 19.4.101	10	395	0.6	0
CT 19.4.201	5	347	0.6	0
CT 19.4.202	7	360	0.6	0
CT 19.4.205	4	632	1.2	0
CT 19.4.206	14	612	1, 1.2	0
<i>Time of recovery of the TOF ratio to 0.9 relative to administration of rocuronium and Org 25969</i>				
CT 19.4.206	15	1	1	0
<i>T2 twitch height-time profile</i>				
CT 19.4.101	10	394	1	0
CT 19.4.201	5	347	1	0
CT 19.4.202	7	360	1	0
CT 19.4.205	4	632	2	0
CT 19.4.206	14	612	1	0
<i>Time to reappearance of T2 twitch height</i>				
CT 19.4.201	27	1	0.6	0
CT 19.4.207	34	1	0.6	0
CT 19.4.210	21	1	0.6	0
CT 19.4.304	29	1	0.6	0
<b>PK interaction model Rocuronium</b>				
CT 19.4.101	27	32	2, 1	0.5, 1, 2, 4, 8

Study protocol	Number of subjects	*Samples	Rocuronium dose (mg/kg)	Org25969 dose (mg/kg)
CT 19.4.201	25	9	0.6	0, 0.5, 1, 2, 3, 4
CT 19.4.202	96	9	2	0, 1, 2, 4, 6, 8
CT 19.4.205	41	8	1.2	0, 2, 4, 8, 12, 16
CT 19.4.304	24	31	2	2
CT 19.4.305	63	11	2	2
CT 19.4.306	77	10	2	0, 0.5, 1, 2, 4
<b>PK-PD interaction model Rocuronium</b>				
<i>Time of recovery of the TOF ratio to 0.9 relative to administration of rocuronium and Org 25969</i>				
CT 19.4.205	40	1	1.2	0, 2, 4, 8, 12, 16
CT 19.4.206	166	1	1	0, 2, 4, 8, 12, 16
CT 19.4.207	37	1	0.6	0, 0.5, 1, 2, 3, 4
CT 19.4.210	40	1	0.6	2
CT 19.4.305	59	8	0.6	2
CT 19.4.306	77	6	0.6	0, 0.5, 1, 2, 4

\*Median of the number of samples per subject

## Methodology

### PK of rocuronium

The time course of plasma concentrations of rocuronium after intravenous administration was best described using a 3 compartment model. The goodness of fit plots are shown in Figure 19 below. The analysis identified differences in the PK of rocuronium due to race (Japanese vs US+European). The clearance in the Japanese population was 30% lower than US+European population. The estimates of the PK parameters are shown in Table 25.

Figure 19. Diagnostic plots for model ROC.C.10 (Rocuronium PK Model) (A) Observed versus individual predicted plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations.

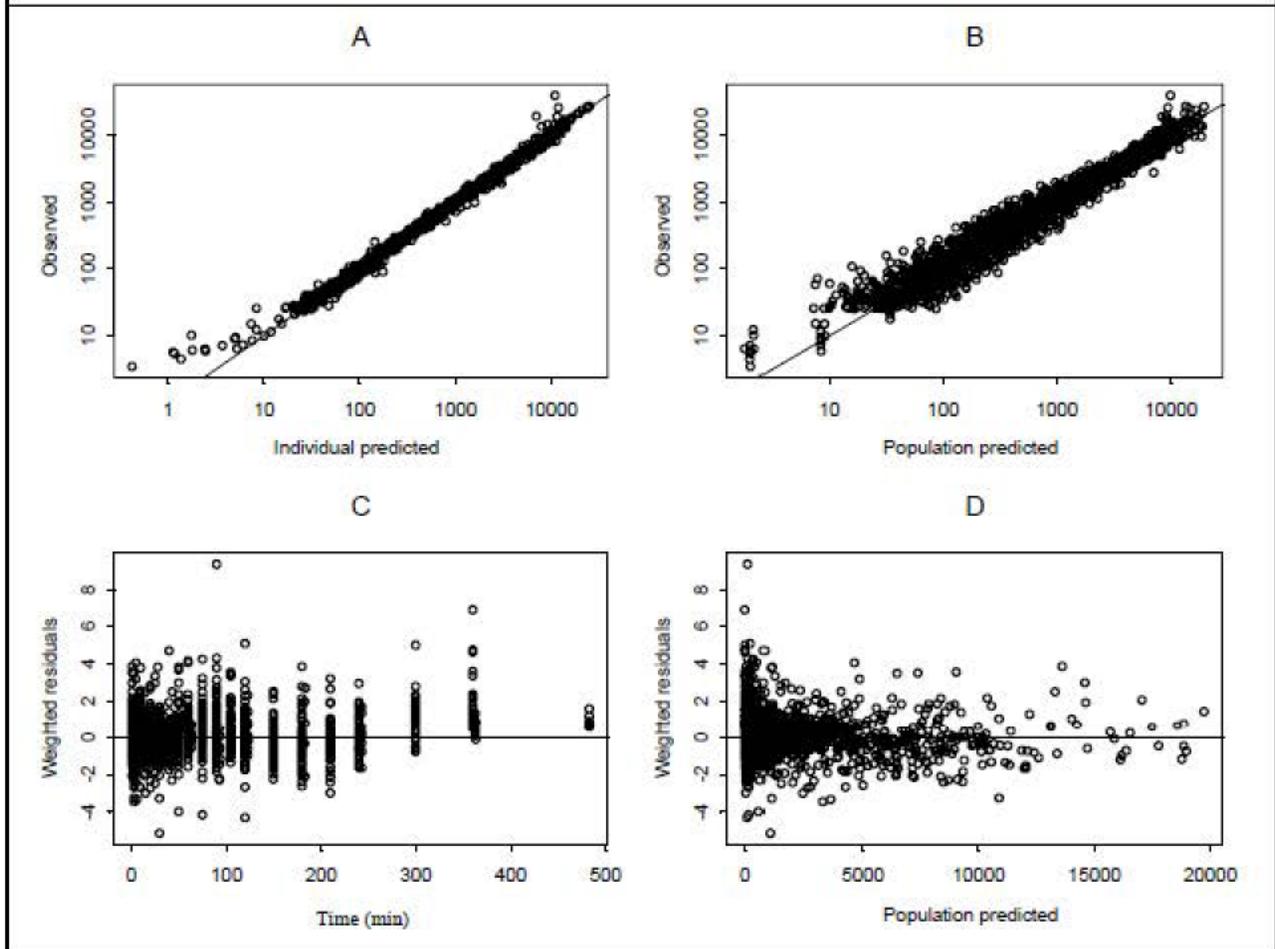


Table 25. Estimated structural and stochastic parameter values for Rocuronium

Parameter	Value	Se <sup>a</sup>	CV(%) <sup>b</sup>	LLCI <sup>c</sup>	ULCI <sup>d</sup>
Fixed effects					
C1 Jap. subpop. (L/min)	0.252	0.00768	3.0	0.237	0.267
V1 Jap subpop. (L)	2.56	0.14	5.5	2.29	2.83
Q2 Jap subpop. (L/min)	0.354	0.0172	4.9	0.320	0.388
V2	3.26	0.131	4.0	3.00	3.52
Q3 Jap. subpop. (L/min)	0.0584	0.00487	8.3	0.0489	0.0679
V3 Jap subpop. fraction of Q3 (min <sup>-1</sup> )	75.7	5.57	7.4	64.8	86.6
Q3 Us & Eur subpop. (L/min)	0.134	0.008	6.0	0.118	0.150
V1 3mg/kg (rel. difference from V1Jap subpop.)	-0.249	0.0979	-39.3	-0.441	-0.057
CL Us & European subpop. (rel. difference from CL Jap. subpop.)	0.4	0.0669	16.7	0.269	0.531
V1 US & European subpop. (rel. difference from V1 Jap. subpop.)	0.4	0.0669	16.7	0.269	0.531
Q2 US & European subpop. (rel. difference from Q2 Jap. subpop.)	0.597	0.114	19.1	0.374	0.820
V3 US & European subpop. (rel. difference from V3 Jap. subpop.)	-0.24	0.056	-23.3	-0.350	-0.130
Random effects (inter-individual (IIV); inter-occasion (IOV))					
$\omega^2_{CL(IIV)}$	0.054	0.00888	16.4	0.0366	0.0714
$\omega^2_{V1(IIV)}$	0.144	0.0258	17.9	0.0934	0.1946
$\omega^2_{V3(IIV)}$	0.048	0.0168	35.0	0.0151	0.0809
$\omega^2_{Q3(IIV)}$	0.1	0.027	27.0	0.0471	0.1529
$\omega^2_{V2(IIV)}$	0.0632	0.0146	23.1	0.0346	0.0918
$\omega^2_{Q2(IIV)}$	0.0339	0.014	41.3	0.0065	0.0613
$\omega^2_{CL\omega V1}$	0.0206	0.0107	51.9	-0.00037	0.04157
$\omega_{CL\omega V3}$	-0.0342	0.0102	-29.8	-0.0542	-0.0142
$\omega_{V1\omega V3}$	0.00454	0.0159	350.2	-0.0266	0.0357
$\omega_{CL\omega Q3}$	0.0379	0.0115	30.3	0.0154	0.0604
$\omega_{V1\omega Q3}$	0.032	0.0217	67.8	-0.0105	0.0745
$\omega_{V3\omega Q3}$	-0.0346	0.0163	-47.1	-0.0665	-0.0027
$\omega_{V2\omega Q2}$	0.0416	0.0132	31.7	0.0157	0.0675
Residual error					
$\sigma_1^2$ (proportional)	0.0103	0.00114	11.1	0.0081	0.0125
$\sigma_2^2$ (additive)	26.3	11.3	43.0	4.15	48.4

<sup>a</sup> Standard error of parameter estimate

<sup>b</sup> Coefficient of variation

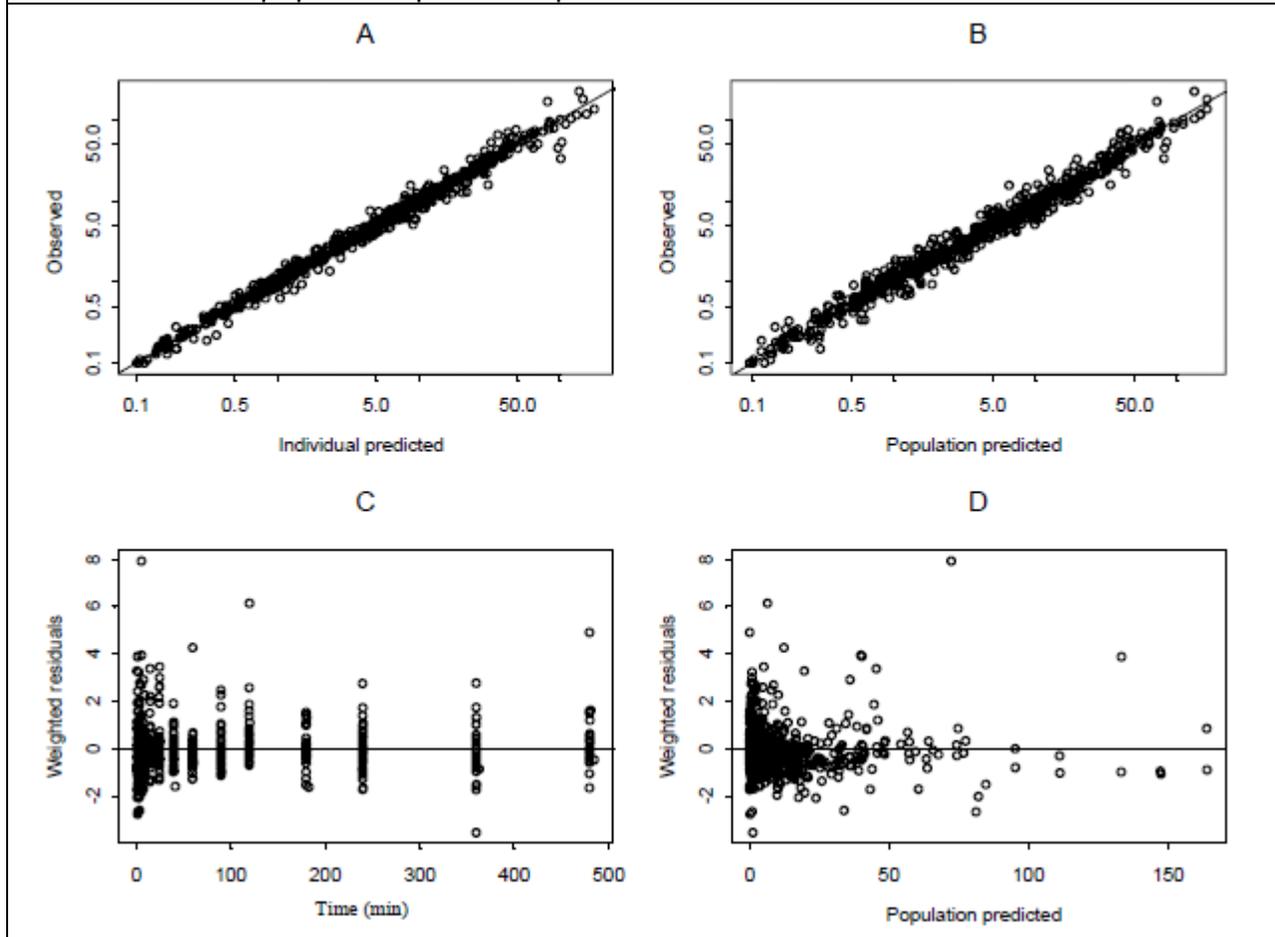
<sup>c</sup> Lower limit of 95% confidence interval

<sup>d</sup> Upper limit of 95% confidence interval

## PK of Org 25969

The time course of Org 25969 concentrations after intravenous administration of Org 25969 alone was best described using a 3 compartment model in healthy subjects. The goodness of fit plots are shown in Figure 20.

Figure 20. Diagnostic plots for model Org.F.1 (Org 25969 PK Model) (A) Observed versus individual predicted plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations.



The model was updated with data from Study 19.4.305 (elderly subjects). In Study 19.4.305, subjects were to be reversed at reappearance of T2 with an intravenous single bolus dose of 2.0 mg/kg Org 25969 After the intubation dose or the previous maintenance dose of rocuronium. Population pharmacokinetic analysis was conducted for the data collected from this study and are shown in Table 26. The pharmacokinetic parameters for a typical subject by age category is shown in Table 27 below.

Table 26. Estimated structural and stochastic parameter values for Org 25969 from Study 19.4.305

Parameter	Units	Population estimate	SE	CV%	IIV%
CL	L/min	0.081	0.0025	3.1 %	27.3 %
Effect of age		- 0.0010 x (age -65.4)	0.00023	21.8%	
Effect of creatinine clearance		+ 0.00038 x (Clcr -88.8)	0.00011	32.1%	
Vc	L	4.29	0.20	4.5 %	28.2 %
Effect of weight		+ 0.030 x (weight - 81.8)	0.0098	32.7%	
V <sub>2</sub>	L	9.07	0.38	4.2 %	21.0 %
Q <sub>2</sub>	L/min	0.27	0.017	6.3 %	31.3 %
V <sub>3</sub>	L	7.56	2.22	29.4 %	—
Q <sub>3</sub>	L/min	0.0088	0.00072	8.2 %	—
D <sub>1</sub>	min	3.47	0.83	23.8 %	64.3 %
<b>Residual error</b>				<b>CV (%)</b>	<b>SD</b>
σ <sub>1</sub> (proportional)		0.049	0.0088	22.1 %	—
σ <sub>2</sub> (additive)		0.00031	0.000077	—	0.018

\* SE is the standard error, CV% is coefficient of variation (100\*SE/pop.estimate), IIV ( $\omega^2$ ) interindividual variability expressed as a variance, IIV% (100- $\sqrt{\text{IIV}}$ ). The CV of the proportional part of the residual error is 100- $\sqrt{\sigma_1}$  and the SD of the additional part of the residual error is  $\sqrt{\sigma_2}$  µg/ml. Data was taken from Appendix BI-4, Table 4.1 and units of clearances were converted from L/h to L/min.

Table 27. Summary of PK parameters in a typical patient in various age groups.

Age group	Age	Weight	creatinine clearance	CL	Vc	Vss	t1/2_eff
	years	kg	mL/min	[L/min]	[L]	[L]	[min]
18 - 64 years	48.5	84	104	0.103	4.36	20.99	141.3
65 - 74 years	68	86.1	84.8	0.076	4.42	21.05	192.5
>= 75 years	81	71.5	58.6	0.052	3.98	20.61	273.1

The effect of renal function was also evaluated in Study 19.4.304 where 15 patients with severe renal impairment were compared to that of normal patients. The estimate of clearance of Org 25969 was 95.2 mL/min in control group and 5.53 mL/min in renally impaired group. The half-life of Org 25969 increased from 139 minutes to 2139 minutes.

The sponsor evaluated the effect of renal function on the pharmacokinetics of Org 25969 using data from all the studies in the development of PK model for rocuronium-Org 25969 interaction. The relationship between clearance of Org 25969 and creatinine clearance was described using a linear model which is described below:

$$CL_{\text{Org25969}} = 87 \text{ mL / min} + 0.6 \bullet (\text{Creatinine Clearance} - 105.44)$$

Based on this equation, sponsor proposes the following Table 28 in the label.

(b) (4)

### PK-PD of Rocuronium Alone

The relationship between plasma concentrations of rocuronium and changes in %TOF ratio were described using an effect compartment model. The effect compartment was used to account for the delay between plasma concentrations of rocuronium and effects on %TOF ratio. Figure 21 shows the time course of plasma concentrations of rocuronium and changes in % TOF ratio in Study 19.4.101.

Figure 21. Time course of plasma concentrations of rocuronium and changes in % TOF ratio

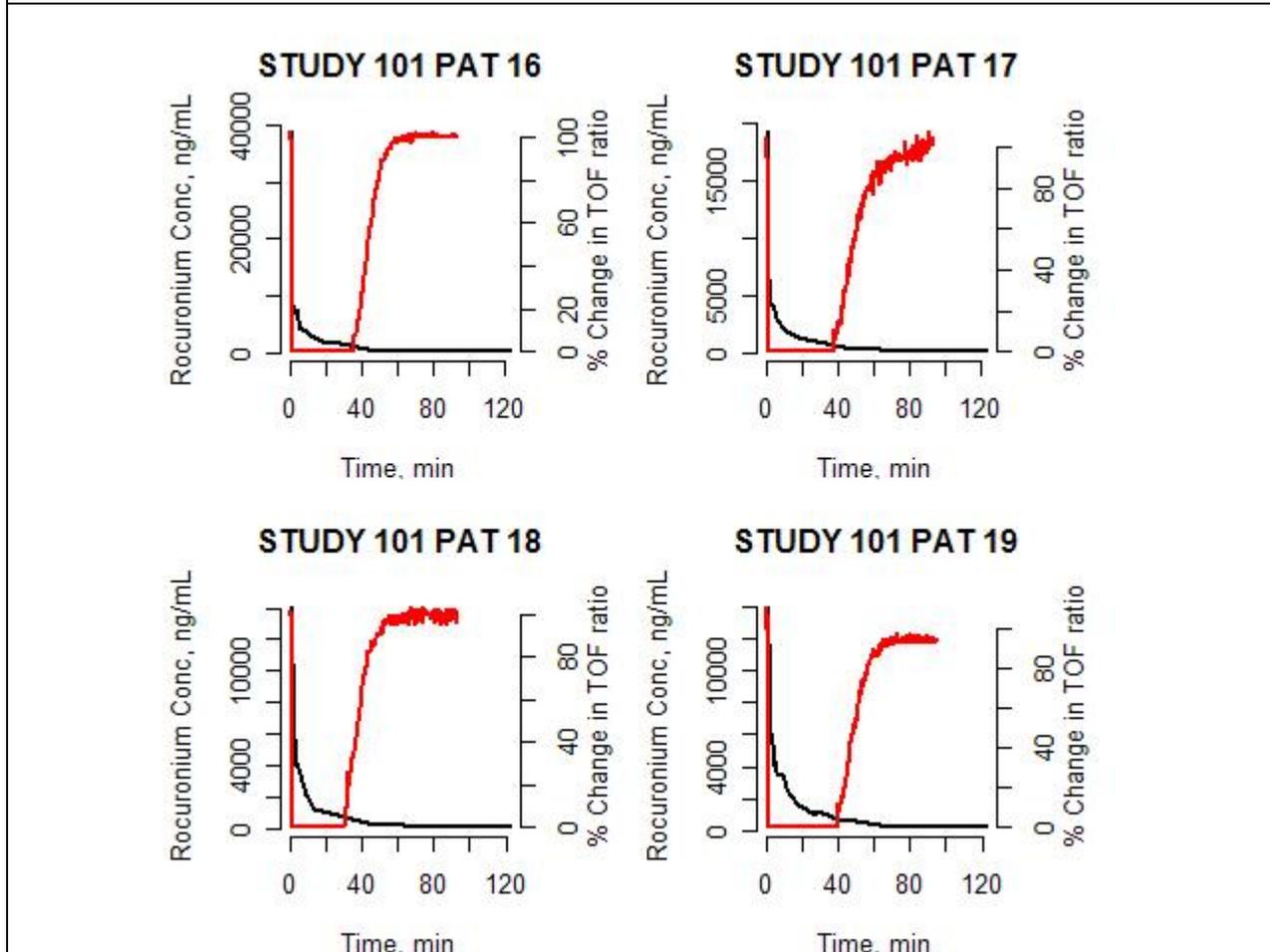
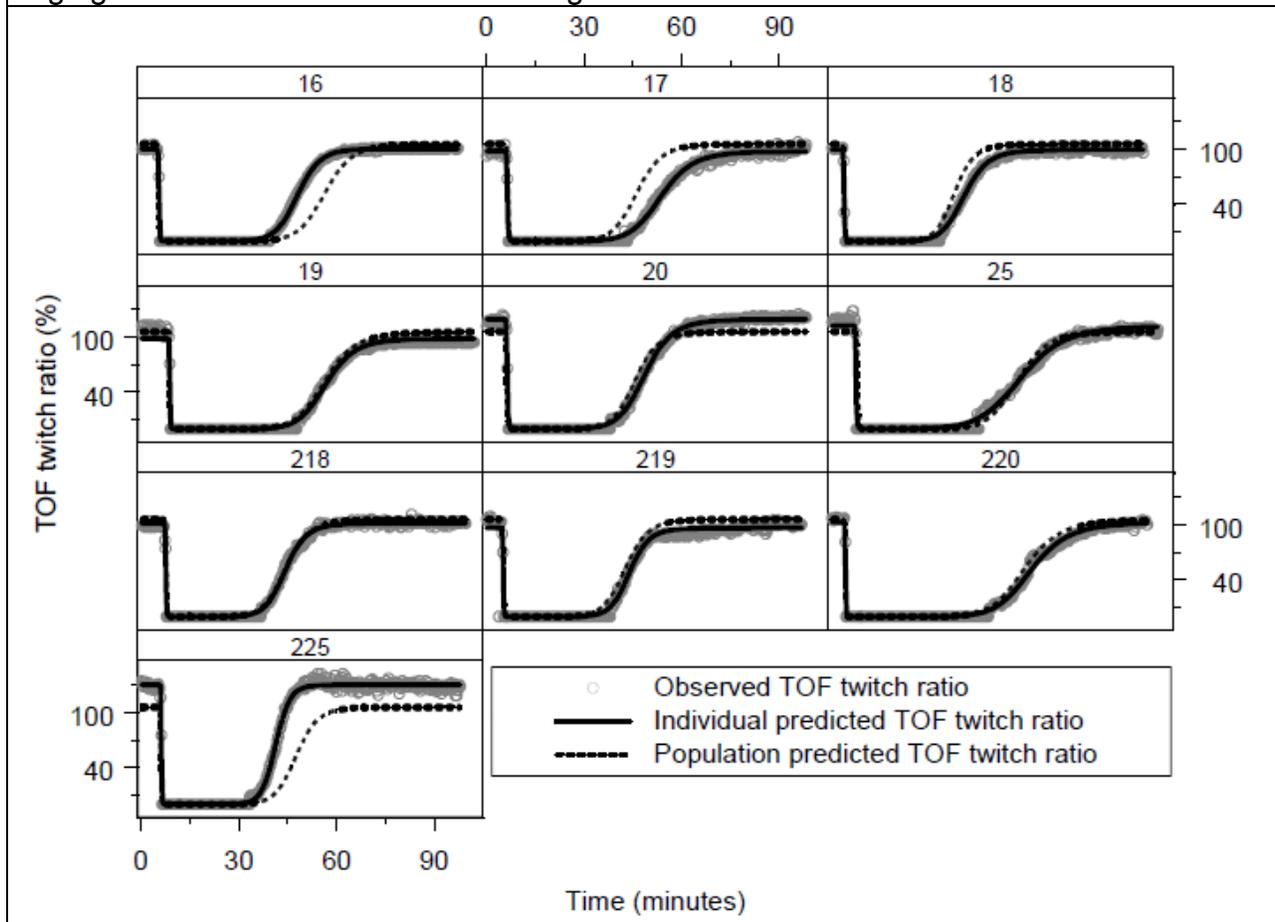


Figure 22 shows the observed, individual and population predicted changes in changes in % TOF twitch ratio. The model fits the data adequately.

Figure 22. Individual and population predicted rocuronium induced neuromuscular block represented by the TOF twitch ratio observed in study CT 19.4.101 after 0.6 mg/kg rocuronium to volunteers under general anaesthesia.



The model was updated with data from describe the PD data of the studies CT 19.4.101, CT 19.4.201, CT 19.4.202 and CT 19.4.205. The estimated parameters are shown in Table 29 below.

Table 29. Estimated structural and stochastic parameter values for the updated PK-PD model for TOF ratio (PK.PD.ROC.B2).

Parameter	Value	Se <sup>a</sup>	CV(%) <sup>b</sup>	LLCI <sup>c</sup>	ULCI <sup>d</sup>
Fixed effects					
E <sub>0</sub> (%)	105	1.91	1.8	101.3	108.7
EC <sub>50</sub> (ng/mL)	836	37.7	4.5	762	910
ke <sub>0</sub> (min <sup>-1</sup> )	0.915	0.102	11.1	0.715	1.115
γ	6.22	0.377	6.1	5.48	6.96
Random effects (inter-individual (IIV))					
ω <sup>2</sup> <sub>E<sub>0</sub>(IIV)</sub>	0.00963	0.00331	34.4	0.00314	0.01612
ω <sup>2</sup> <sub>EC<sub>50</sub>(IIV)</sub>	0.0495	0.0108	21.8	0.02833	0.07067
ω <sup>2</sup> <sub>ke<sub>0</sub>(IIV)</sub>	0.324	0.0682	21.0	0.19033	0.45767
Residual error					
σ <sub>1</sub> <sup>2</sup> (additive)	23.6	5.56	23.6	12.7	34.5
<sup>a</sup> Standard error of parameter estimate <sup>b</sup> Coefficient of variation <sup>c</sup> Lower limit of 95% confidence interval <sup>d</sup> Upper limit of 95% confidence interval					

In the PK/PD model, the effect compartment was linked to the first peripheral compartment instead of the central compartment. The decision for this link was based on statistical reasons (lower objective function) and not based on pharmacological principles. The parameters are estimated with good precision. The estimated value of 0.915 min<sup>-1</sup> the rate constant for delay implies that it takes about 3-5 minutes to reach steady state for effect after rocuronium administration. No evaluation for identification of prognostic factors affecting the EC<sub>50</sub> or E<sub>max</sub> was conducted.

## PK Interaction Model for Org 25969 and Rocuronium

The sponsor developed a PK model based on (A) Instantaneous (B) Dynamic equilibrium principles to explain the binding between Org 25969 and Rocuronium. X-ray crystallography of the Org 25969–rocuronium complex formation showed that Org 25969 and rocuronium bind in equimolar quantities. It is hypothesized that after administration of Org 25969 the Org 25969-rocuronium complex is cleared from plasma via the Org 25969 clearance pathway, whereas the remaining fraction unbound of rocuronium is cleared via the rocuronium elimination pathway. The sponsor concluded that the dynamic equilibrium model provided better description of the data compared to the model which assumes instantaneous equilibrium.

Figure 23 shows the time course of rocuronium concentrations in Study 19.4.101 where patients were administered 0.1-8 mg/kg Org 25969 three minutes after 0.6 mg/kg rocuronium. Shown are the model fitted line when analyzed using instantaneous (EQ1, EQ2) and dynamic equilibrium models.

Figure 23. Time course of rocuronium plasma concentrations and model fitted line derived using (A) Instantaneous (B) Dynamic equilibrium models. Shown in the right hand side figure are two lines (red and blue) which are for concentrations of rocuronium with and without Org 25969. For comparison purposes between models, the green and red lines should be compared.

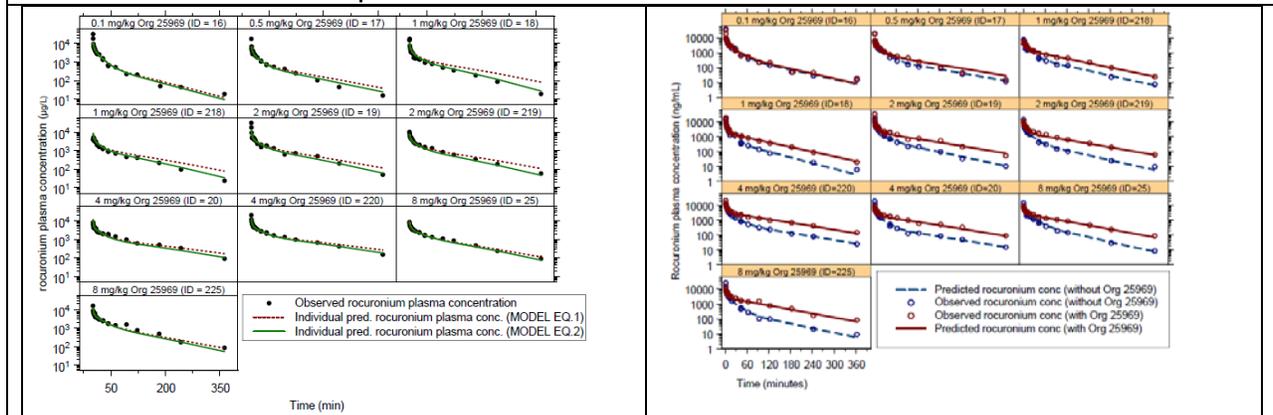


Figure 24 shows the comparison between observed and model predicted AUC(0-tlast) which indicates that the bias is minimal for the dynamic equilibrium model.

Figure 24. Observed versus predicted AUC[0-tlast] for model EQ.1 with a Kd value that was fixed to 0.1  $\mu\text{M}$  (open circles), model EQ.2 (closed boxes) in which the Kd was optimized value and the most optimal dynamic interaction model DIM.C.2 (open triangles). The AUC[0-tlast] was calculated using the trapezoidal rule. For the calculation of the observed AUC[0-tlast) data from part II of the study CT 19.4.101 was used.

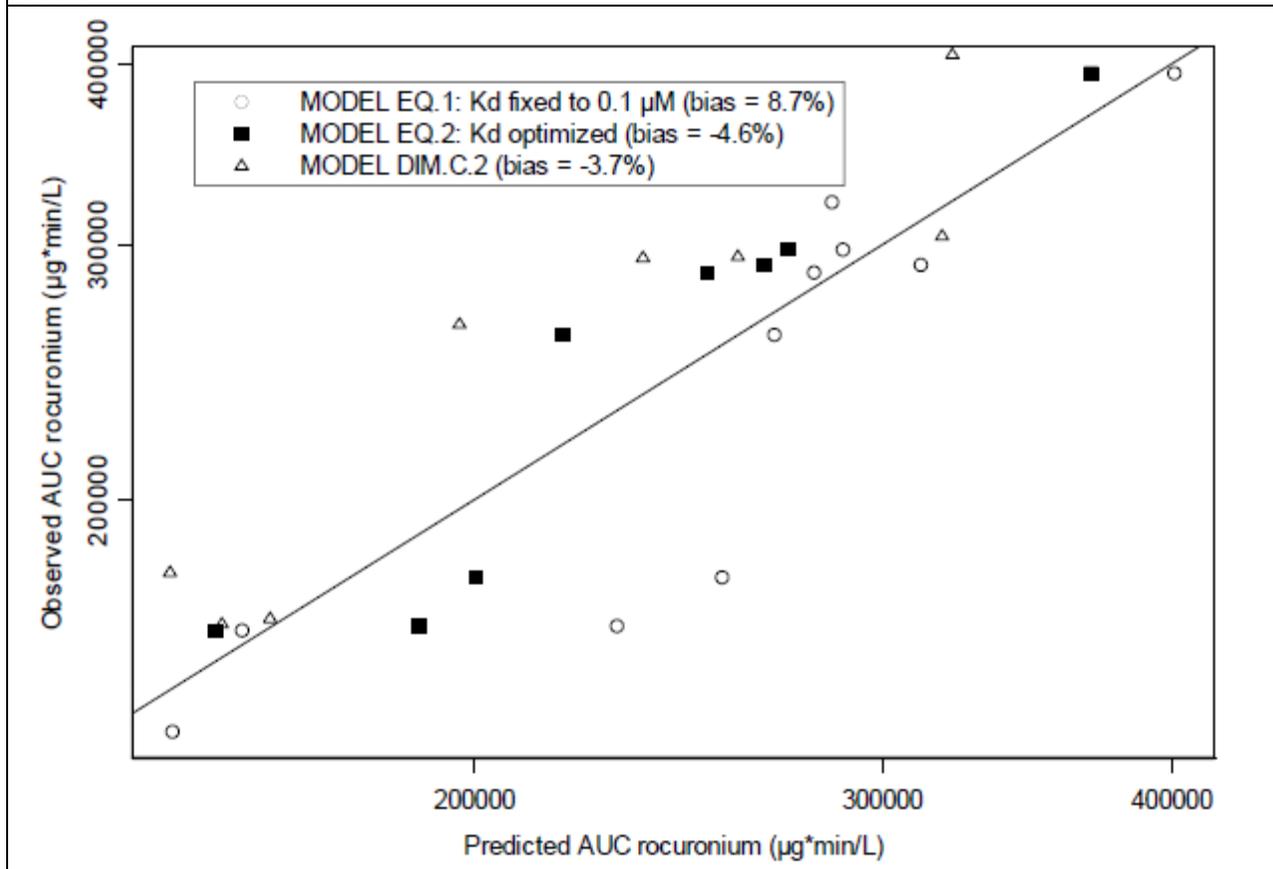


Figure 25 and Figure 26 shows the diagnostic plots which indicate that the model fits the data adequately.

Figure 25. Diagnostic plots for rocuronium data predicted by the PK interaction model (DIM.1.2.FOCE) (A) Observed versus individual predicted rocuronium plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations. Solid line represents a loess smooth through the data. Dashed line is the unity line.

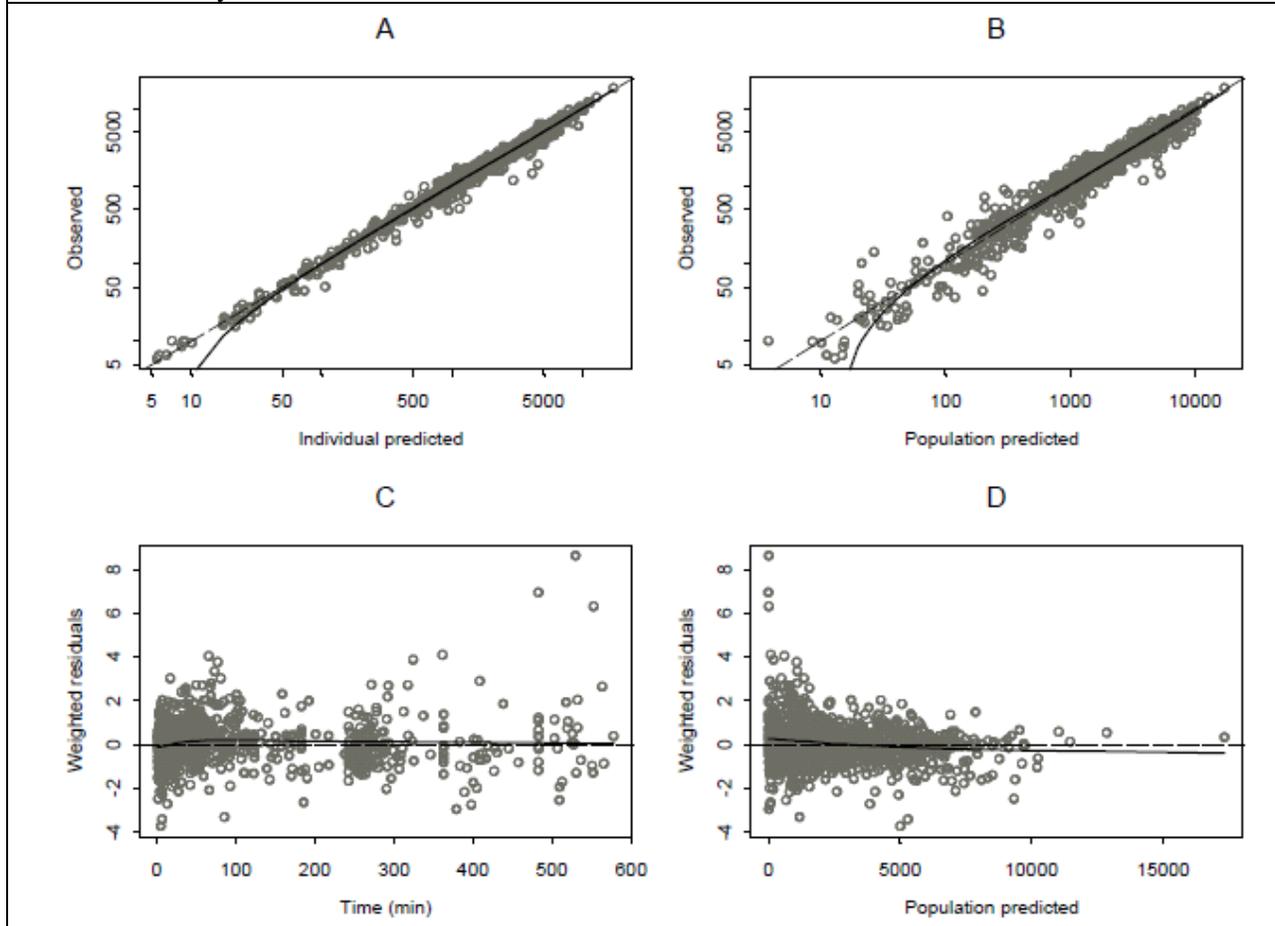
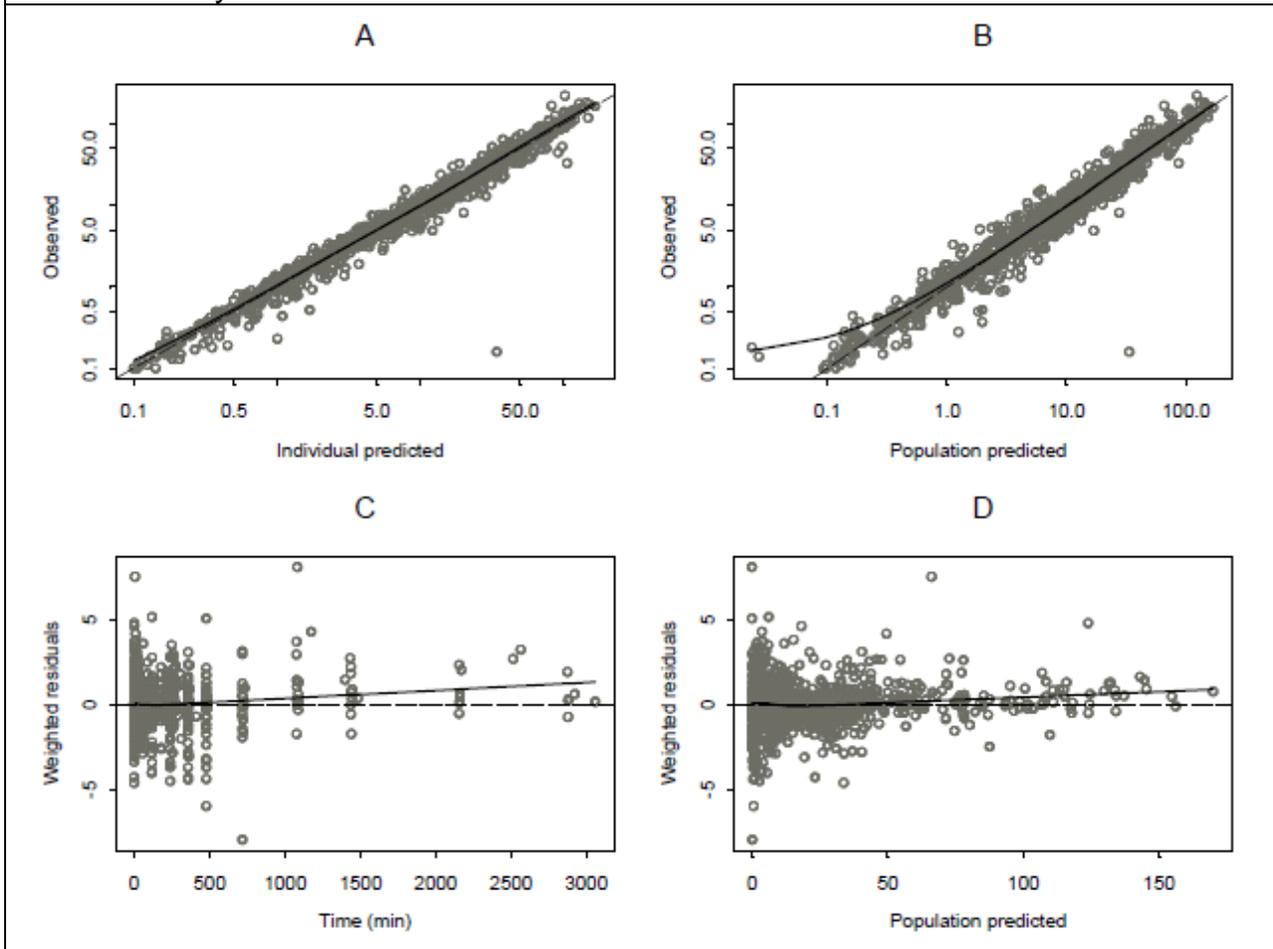


Figure 26. Diagnostic plots for Org 25969 data predicted by the PK interaction model (DIM.I.2.FOCE) (A) Observed versus individual predicted rocuronium plasma concentrations, (B) Observed versus population predicted plasma concentrations, (C) Weighted residuals versus time, (D) Weighted residuals versus population predicted plasma concentrations. Solid line represents a loess smooth through the data. Dashed line is the unity line.



The estimates of the pharmacokinetic parameters for rocuronium and Org 25969 are shown in Table 30 below.

Table 30. Estimated structural and stochastic parameter values for the updated PK interaction model (DIM.I.2.FOCE)

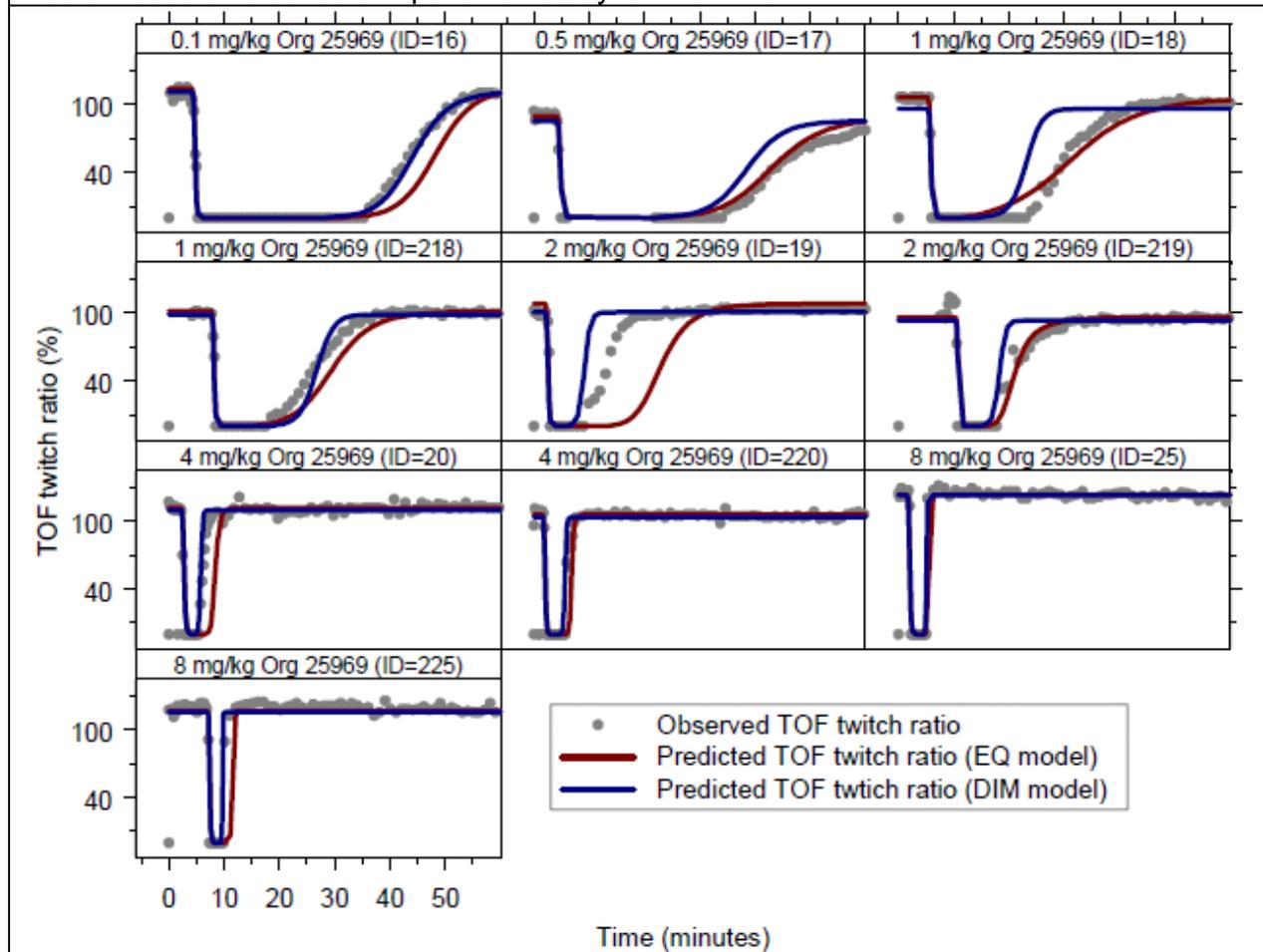
Parameter	Value	Se <sup>a</sup>	CV(%) <sup>b</sup>	LLCF <sup>c</sup>	ULCF <sup>d</sup>
Fixed effects					
Duration infusion (min) ID=2, 4, 5, 10-13	6.07 FIX				
Duration infusion (min) ID=15	22.1 FIX				
Duration infusion (min) ID=6	11.5 FIX				
Cl Org 25969 alone (L/min)	0.119	0.00428	3.6	0.1106	0.1274
Cl Org 25969 + rocuronium (exponential. difference)	-0.268	0.0513	19.1	-0.3685	-0.1675
Cl Org 25969 + rocuronium (L/min)	0.091				
Cl Org 25969 renal impaired (exponential. difference)	-2.34	0.176	7.5	-2.6850	-1.9950
Cl Org 25969 + rocuronium renal impaired (L/min)	0.00877				
Cl complex Org 25969-rocuronium (exponential. difference)	-0.14	0.0506	36.1	-0.2392	-0.0408
Cl complex Org 25969-rocuronium (L/min)	0.079				
Vc Org 25969 alone (L)	5.72	0.446	7.8	4.846	6.594
Vc Org 25969 + rocuronium (exponential. difference)	-0.438	0.0928	21.2	-0.6199	-0.2561
Vc Org 25969 + rocuronium (L)	3.69				
Vc complex Org 25969-rocuronium (exponential. difference)	-0.363	0.0698	19.2	-0.4998	-0.2262
Vc complex Org 25969-rocuronium (L)	2.57				
Q2 Org 25969 alone (L/min)	0.481	0.0307	6.4	0.4208	0.5412
Q2 Org 25969 renal impaired (exponential. difference)	-0.339	0.111	32.7	-0.5566	-0.1214
Q2 Org 25969 renal impaired (L/min)	0.343				
V2 Org 25969 alone (L)	2.73	0.567	20.8	1.619	3.841
V2 Org 25969 + rocuronium (exponential. difference)	0.799	0.193	24.2	0.4207	1.1773
V2 Org 25969 + rocuronium (L)	6.07				
V2 Org 25969 renal impaired (exponential. difference)	0.912	0.182	20.0	0.5553	1.2687
V2 Org 25969 renal impaired (L)	15.1				
Q3 Org 25969 alone (L/min)	0.0819	0.00999	12.2	0.0623	0.1015
Q3 Org 25969 renal impaired (exponential. difference)	-1.53	0.209	13.7	-1.940	-1.120
Q3 Org 25969 renal impaired (L/min)	0.0177				
V3 Org 25969 alone (L)	6.06	0.453	7.5	5.17	6.95
V3 Org 25969 + rocuronium (exponential. difference)	-0.228	0.198	86.8	-0.6161	0.1601
V3 Org 25969 + rocuronium (L)	4.82				
V3 Org 25969 renal impaired (exponential. difference)	-1.27	0.331	26.1	-1.9188	-0.6212
V3 Org 25969 renal impaired (L)	1.35				
<i>Equilibrium constant for the interaction Org 25969 - rocuronium</i>					
Kd (μM)	0.0559 FIX				
k2 (min <sup>-1</sup> )	0.00263	0.000494	18.8	0.0017	0.0036
Random effects (inter-individual (IIV))					
Total ω <sup>2</sup> <sub>Cl(IIV)</sub> = θ <sub>11</sub>					
θ <sub>11</sub>	0.0805	0.012	14.9	0.0570	0.1040
Residual error					
σ <sub>1</sub> <sup>2</sup> (proportional) rocuronium	0.0215	0.00277	12.9	0.0161	0.0269
σ <sub>2</sub> <sup>2</sup> (proportional) Org 25969	0.0444	0.00602	13.6	0.0326	0.0562

## PK-PD Interaction Model for Org 25969 and Rocuronium

The PK/PD interaction model was developed initially using data from Study 19.4.101. The PK and PD parameters were fixed to the estimates derived from the Rocuronium-Org 25969 PK interaction and Rocuronium PK/PD model respectively.

Figure 27 shows the simulated time course of % TOF ratiogoodness of fit in individuals using the two models. The dynamic equilibrium model was selected as the final model as the model describes the data well in the dose ranges for which approval is being sought. (> 1 mg/kg).

Figure 27. Individual predicted reversal of rocuronium-induced neuromuscular blockade after 0.1–8 mg/kg Org 25969 administered 3 minutes after 0.6 mg/kg by model PKPD.EQ.A (Instantaneous equilibrium; red line) and model PKPD.DIM.A (Dynamic equilibrium; blue line). Symbols represent the observed reversal of rocuronium-induced neuromuscular blockade in part II of study CT 19.4.101.

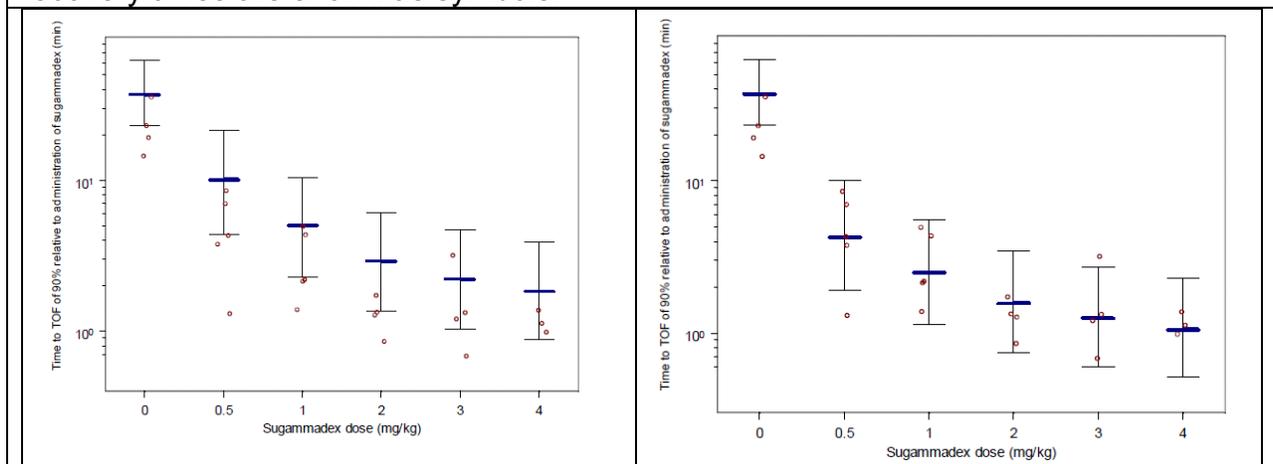


The dynamic equilibrium model was further evaluated using simulations using data from Study 19.4.201, 19.4.202 and 19.4.205. No parameters were estimated but the model

was checked for its predictive ability for the new studies using simulations. Evaluation of the assumption of linking central, first peripheral and second peripheral concentrations of rocuronium to the PD effect was checked using simulations. The simulations suggested that the updated model was biased due to changes in parameter estimates of peripheral volume of distribution. In order to correct for this bias, the sponsor chose to use a ratio of the first peripheral volume of distribution between the previous model and the updated model.

Figure 28. VPC for the PK-PD interaction the previously developed PK-PD interaction model (A) and models PK.PD.DIM.V2 (B), PK.PD.DIM.V1 (C) and PK.PD.DIM.V3 (D); observed and predicted variability in time to recovery of the TOF ratio to 0.9 (recovery time) after 0 – 4 mg/kg Org 25969 administered 3 minutes after 0.6 mg/kg rocuronium in the study CT 19.4.202.

The time to reappearance of T2 after administration of rocuronium was simulated using model PK.PD.F.T2. The bold horizontal line represents the predicted median recovery time, whereas the horizontal above and below the median shows the predicted recovery time for 95% and 5% of the population, respectively. As a result, the range between these lines represents the expected variability in 90% of the population. The observed recovery times are shown as symbols.



### **Reviewer Comments**

The sponsor developed a mechanism based PK model describing the interaction between rocuronium and Org 25969 and integrated it with the pharmacodynamic data. Overall, the reviewer agrees with the modeling approach.

#### 4.4 OCP Filing and Review Form

Office of Clinical Pharmacology New Drug Application/Biologics License Application Filing and Review Form				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	22-225	Brand Name	(b) (4)	
OCPB Division (I, II, III)	DCP2	Generic Name	Sugammadex Sodium (Org 25969)	
Medical Division	DAARP	Drug Class	Selective relaxant binding agent	
OCP Reviewers	Lei Zhang, Ph.D. Atul Bhattaram, Ph.D. (PM)	Indication(s)	Routine reversal of shallow or profound neuromuscular blockade induced by rocuronium or vecuronium and for immediate reversal of neuromuscular blockade at 3 min after administration of rocuronium.	
OCP Team Leaders	Suresh Doddapaneni, Ph.D Jogarao Gobburu, Ph.D. (PM)	Dosage Form	Injection Solution (100 mg/mL)	
		Dosing Regimen	<p>Routine Reversal :</p> <ul style="list-style-type: none"> <li>A dose of 4.0 mg/kg (b) (4) <sup>TM</sup> is recommended if recovery has reached 1-2 post tetanic counts (PTC) (profound blockade) following administration of rocuronium or vecuronium induced blockade.</li> <li>A dose of 2.0 mg/kg (b) (4) <sup>TM</sup> is only recommended if spontaneous recovery has reached the reappearance of T2 (shallow blockade) following rocuronium or vecuronium induced blockade.</li> </ul> <p>Immediate reversal :</p> <ul style="list-style-type: none"> <li>If there is a clinical need for immediate reversal at 3 minutes following administration of rocuronium, a dose of 16.0 mg/kg (b) (4) <sup>TM</sup> is recommended.</li> </ul>	
Date of Submission	10/30/2007	Route of Administration	Intravenous as a single bolus injection	
Estimated Due Date of OCP Review	6/10/2008 (AC meeting 3/11/08)	Sponsor	Organon	
PDUFA Due Date	7/30/2008	Priority Classification	1P	
Division Due Date	6/13/2008		IND 68,029	
<u>Clin. Pharm. and Biopharm. Information</u>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>				
Mass balance:	X	1	1	19.4.107 (14C-labeled)
Isozyme characterization:				
Blood/plasma ratio:	X	1	1	NL0047787 (Erythrocyte)
Plasma protein binding:	X	1	1	NL0046285
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>1) Healthy Volunteers-</b>				
single dose:	X	4	3	19.4.101 (25 mg/mL, male only) 19.4.102 (100 mg/mL) 19.4.106 (100 mg/mL) 19.4.108 (pilot safety study for QT evaluation)
multiple dose:				
<b>2) Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:	X	(3)		19.4.101 (25 mg/mL, male only) 19.4.102 (100 mg/mL) 19.4.106 (100 mg/mL)
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	1	1	050351 Metabolite profiling in plasma and urine (ex vivo)
In vitro and in silico:	X	8	8	8 study reports are submitted to show validation and utility of PK-PD interaction model for drug interaction assessment
<b>Subpopulation studies -</b>				
ethnicity:	X	(1)		19.4.102 (Caucasian and Japanese)
gender:				
pediatrics:	X	1		19.4.306 (100 mg/mL for adults and 25 mg/mL for infants)- Sparse sampling for PK Sponsor is not seeking pediatric indication for this application
geriatrics:	X	1	1	19.4.305 (100 mg/mL)-Sparse sampling for PK
renal impairment:	X	1	1	19.4.304 (100 mg/mL)-Dense PK and PD evaluation
hepatic impairment:	X	1	1	Drug is not metabolized. Clinical trial simulation was conducted to predict the likely effect in patients with liver impairment.
<b>PD:</b>				
Phase 2:	X	4	4	19.4.206 (100 mg/mL)-No PK sampling 19.4.209A (Japanese) 19.4.209B (Caucasians) 19.4.210 (100 mg/mL)-No PK sampling

Phase 3:	X	1	1	19.4.312-No PK sampling
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:	X	6	6	19.4.201 (25 mg/mL) 19.4.202 (25 mg/mL) 19.4.205 (100 mg/mL) 19.4.207 (25 mg/mL) 19.4.208A (100 mg/mL) (Japanese subjects) 19.4.208B (100 mg/mL) (Caucasian subjects)
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:	X	(1)		19.4.207 (25 mg/mL)
Data sparse:	X	(5)		19.4.201 (25 mg/mL) 19.4.202 (25 mg/mL) 19.4.205 (100 mg/mL) 19.4.208A (100 mg/mL) (Japanese subjects) 19.4.208B (100 mg/mL) (Caucasian subjects)
	X	1	1	3 population PK/PD reports for model development and validation
<b>II. Biopharmaceutics</b>				
Absolute bioavailability:				Not applicable. IV drug.
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				Not applicable. IV drug.
Dissolution:				Not applicable. IV drug.
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
QT/QTc Evaluation	X	2	2	19.4.105 19.4.109 (Thorough)
In vitro dialysis study	X	1	1	19.4.006
Possible interferences of Org 25969 and Org 48302 in clinical chemistry tests	X	2	2	19.4.004 19.4.007
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan	X	1		Request a deferral for age from birth to 17.
Literature References	X	1	1	
<b>Total Number of Studies</b>		<b>39</b>	<b>36</b>	

<b>Fiability and QBR comments</b>		
	"X" if yes	Comments
<b>Application filable?</b>	X	
<b>Comments sent to firm?</b>	X	Information request for electronic datasets and control files.
<b>QBR questions (key issues to be considered)</b>		<ul style="list-style-type: none"> <li>• <b>Have the single dose PK been adequately characterized in healthy subjects?</b></li> <li>• <b>Is PK dose proportional?</b></li> <li>• <b>Have the analytical methods been adequately validated?</b></li> <li>• <b>What is ADME of sugammadex?</b></li> <li>• <b>Has drug interaction potential of sugammadex with other drugs been adequately evaluated?</b> <ul style="list-style-type: none"> <li>○ <b>Any potential for non-specific inclusion of other co-administered drugs?</b></li> <li>○ <b>If so, how to manage this drug interaction clinically?</b></li> </ul> </li> <li>• <b>What are the effects of intrinsic and extrinsic factors on PK or PD of sugammadex?</b> <ul style="list-style-type: none"> <li>○ <b>Is there a need for dose adjustment?</b></li> </ul> </li> <li>• <b>How PD of sugammadex is evaluated? Is PK/PD modeling acceptable?</b></li> <li>• <b>Is POP-PK/PD analysis acceptable?</b> <ul style="list-style-type: none"> <li>○ <b>What are main covariates?</b></li> <li>○ <b>Is there a need for dose adjustment?</b></li> </ul> </li> <li>• <b>Does exposure-response support the dose recommendation?</b></li> <li>• <b>Is clinical trial simulation conducted by the sponsor acceptable?</b></li> </ul>
<b>Other Comments or information not included above</b>		
<b>Primary reviewer Signature and Date</b>	Lei Zhang	
<b>Secondary reviewer Signature and Date</b>	Suresh Doddapaneni	

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/s/

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