

Statistical Parameter	Age / Treatment Group						
	Neonates (< 29 days)		Children (> 29 days to < 2 years)		Children (> 2 years to < 13 years)		
	Org 9487 (mg/kg)		Org 9487 (mg/kg)		Org 9487 (mg/kg)		Mivacurium Chloride (mg/kg)
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
<b>Peak Effect (T1, % of Control)</b>							
N	5	4	14	16	23	21 <sup>a</sup>	23
Mean ± SD	1.1±2.4	3.3±6.5	4.4±12.4	0.8±3.0	0.3±1.3	0.2±1.9	1.5±4.2
Median	0	0	0	0	0	0	0
Min - Max	0-5.4	0-13.0	0-46.0	0-12.0	0-6.0	0-4.0	0-20.0
<b>Onset Time (seconds)<sup>b</sup></b>							
N <sup>a</sup>	5	4	14	16	23	21 <sup>a</sup>	22
Mean ± SD	98±95	190±261	88±73	84±66	53±16	67±44	155±92
Median	39	75	73	55	50	59	140
Min - Max	20-220	30-580	20-300	20-250	32-100	10-228	50-450
<b>Recovery Rate from 25% to 75% T1 (Minutes)</b>							
N <sup>b</sup>	1	1	9	8	19	12	15
Mean ± SD	7.5	4.0	6.9±3.9	13.4±10.8	6.3±3.9	11.1±6.2	3.8±1.1
Median	7.5	4.0	5.6	9.5	5.3	9.5	3.7
Min - Max	7.5-7.5	4.0-4.0	3.0-15.1	4.0-37.0	2.5-18.3	4.7-24.5	2.5-6.3
<b>Duration to 70% T4/T1 (Minutes)<sup>c</sup></b>							
N	4	4	12	16	21	19	22
Mean ± SD	25.0±10.9	22.8±5.9	19.5±6.9	34.3±13.2	25.5±9.1	37.1±9.4	16.2±3.9
Median	21.3	23.0	18.1	29.3	22.6	34.0	15.4
Min - Max	16.5-41.0	16.5-28.7	10.7-29.9	17.5-57.9	17.5-50.5	22.5-54.2	9.4-23.9

Sponsor's Table 14 Vol99 p 0074

1. Maximum Block (Peak Effect): The value of the first T1 which shown no further decline over 3 consecutive TOF following administration of muscle relaxant.
2. Onset Time: the time interval between completion of the injection and the time to Peak Effect. In the neonates, time to peak effect was longer in the 2.0mg/kg group (75 sec) than in the 1.0 mg/kg group (39 sec) while in the Children < 2 years, time to peak effect was longer in the 1.0 mg/kg (73 sec) than in the 2.0 mg/kg (55sec). These differences were found not to be statistically significant. The subjects administered mivacurium chloride had a median time to peak effect of 140 sec which was significantly ( $p<0.01$ ) longer than both Org 9487 dose groups.
3. Recovery Rate (25-75% T1): Time of recovery from 25% to 75% of control T1. There were only 2 subjects in the neonates with recovery rate data. In children < 2 years, the differences in recovery rates between the 2 groups were not statistically significant. The differences in Recovery Rate between each Org 9487 group in the group of children  $\geq 2$  to <13 was statistically significantly longer when compared to the mivacurium chloride group.
4. Duration to 70% T4/T1: The time interval between the administration of relaxant and the return to 70% T4/T1. The difference between the 1.0 and 2.0 mg/kg Org 9487 in children < 2 years was statistically significant. In children  $\geq 2$  years to <13 years, the differences between each Org 9487 group (2.0 and 3.0 mg/kg) were statistically significant.

#### SECTION 9.4.1.5 SPONSOR'S SUMMARY OF EFFICACY:

A profound mean maximum (>95%) neuromuscular blockade was observed in all treatment groups. In neonates, the 1.0 mg/kg group had a median onset of < 1 min and a median clinical duration of 9.7 min with a spontaneous recovery to 70% T4/ T1 of 21.3 min. The higher dose (2.0mg/kg) had an onset of 1.25 min and a clinical duration of 13.4 min with a recovery time to 70% T4/T1 of 23 in. The children < 2 years had a very similar response to Org 9487 with median onset times of  $\leq$  1.2 min. Clinical duration was longer in the higher dose group with a spontaneous recovery to 70% T4/T1 of 18.1 min and 29.3 min in the 1.0 mg/kg and 2.0 mg/kg dose groups, respectively.

In children  $\geq$  2 years the 2.0 mg/kg and 3.0 mg/kg dose groups had median onset times <1 min and clinical durations of 12.7 min and 17.4 min, respectively. The higher dose group had substantially longer median spontaneous recovery to 70% T4.T1 of 34 min as compared to 22.6 min in the 2.0 mg/kg dose group.

Onset of mivacurium chloride was slower (median=2.3 min) with a shorter clinical duration (median=9.5 min) and a shorter spontaneous recovery to 70% T4/T1 (15.4 min) than the 2.0 mg/kg and 3.0 mg/kg dose groups.

#### SECTION 9.4.1.6 REVIEWER'S EFFICACY DISCUSSION

For this open label study the sponsor chose two primary efficacy variables, the T1 at 60 seconds and the time to recovery of T1 at 25% of control (Clinical Duration). The demonstration of efficacy was the ability of Org 9487 to produce changes to electromyographic parameters. Clinical measures of effect, such as adequate relaxation for surgery or endotracheal intubation, were not investigated. However, the noted surrogate EMG endpoints usually are a valid correlate of clinical efficacy.

There were numerous secondary efficacy variables. The sponsor's conclusions regarding time of onset and clinical duration of Org 9487 in comparison to mivacurium chloride were based on surrogate measures of EMG parameters. Actual clinical evaluations may be required to sustain these claims.

While the neonate group and the children < 2 years group did not involve placebo or active controls, the effects on the EMG most likely resulted from the action of Org 9487. The anesthetic technique involved in the study does not cause the EMG effects that are known to correlate with non-depolarizing neuromuscular blocking agents. In the group children  $\geq$  2 years < 13 years, the effects of Org 9487 on the EMG were compared to another known effective neuromuscular blocking agent, mivacurium chloride. These effects were qualitatively similar.

This reviewer is of the opinion that Org 9487, as measured by surrogate means, is an effective neuromuscular blocking agent in the population studied. The design of this

study does not enable this reviewer to support any claims of clinical superiority of Org 9487 over other neuromuscular blocking agents.

## **SECTION 9.5.1 STUDY 174208**

### **SECTION 9.5.1.1 PROTOCOL REVIEW SUMMARY:**

**TITLE:** A Dose Ranging Study of Org 9487 in Pediatric Patients

**OBJECTIVE:**

**Primary:** To evaluate the intubation scores at 60 seconds after administration of various doses of Org 9487 in neonates, infants, and children

**Secondary:** 1. To evaluate in an uncalibrated fashion, the time course of action (time to reappearance of the third twitch and/or duration until T4/T1 ratio recovery to 0.7) of various doses of Org 9487, in neonates, infants and children.

2. To collect sparse samples (blood and urine) in a number of subjects for population based pharmacokinetic analysis.

3. To collect safety data on various doses of Org 9487 in this patient population.

**STUDY DESIGN:** Open label, parallel group, comparative, randomized multicenter phase IIb study enrolling 165 pediatric patients: 15 neonates, 50 infants, and 100 children (50 children 1-6 years and 50 children 7-12 years). The subjects were enrolled at three study sites in Germany, United Kingdom, and Finland. The infants, children 1-6 years and children 7-12 years were randomized to one of 5 dose groups: 0.5, 1.0, 1.5, 2.0 and 2.5 mg/kg Org 9487.

The neonates were randomized to one of 3 dose groups:  
0.5, 1.0, and 1.5 mg/kg Org 9487.

Interim analysis of the data after completion of the first 2 subjects for each dose group for each age group was performed. The purpose of this analysis was to assess if the tested dose ranges were appropriate. Based upon the results of this analysis the dose ranges for the children and for the infants were adapted. It was decided to eliminate the 0.5 mg/kg dose in both the children groups (1-6 yr and 7-12 yr) and the 2.5 mg/kg dose in the infants.

**INCLUSION CRITERIA:**

- Male or female pediatric patients up to and including 12 years of age.
- Patients of ASA Class 1 or 2 scheduled for elective surgery

**EXCLUSION CRITERIA:**

- Patients of 13 years or over; neonates must be full term ( $\geq 38$  to 42 weeks of gestation)
- Patients of ASA Class 3,4, or 5 and/or patients not scheduled for elective surgery
- Patients with clinical signs predicting difficult tracheal intubation
- Patients with a body weight less than 80% or over 130% of normal body weight
- Patients with known significant renal or hepatic or neuromuscular disorders
- Patients with known allergy to narcotics or other medications used during anesthesia
- Patients chronically receiving anticonvulsants or aminoglycoside or polypeptide antibiotics in a dosage regimen known to modify the action of neuromuscular blockers
- Patients in whom a rapid sequence intubation is required
- Patients participating as research subjects in another study not preapproved by Organon within 30 days of entering into this study
- Patients for whom proper informed written parental consent cannot be obtained

**DOSING SCHEDULE:**

Org 9487 was dosed on actual body weight. The drug was administered as a rapid 5 sec bolus into an iv line located in the forearm and immediately flushed afterwards. In neonates, Org 9487 was permitted to be administered through a butterfly rather than through an iv line. It was also allowed to administer the drug via a line or butterfly located other than in the forearm.

**STUDY FLOW:**

Agents and doses used for the anesthetic management of subjects enrolled in this study could be adjusted when necessary to provide optimal patient care.

**Premedication:**

No premedication was given in neonates. Children were allowed to receive midazolam orally 0.5mg/kg before induction of anesthesia; infants were allowed to receive midazolam intranasally 0.2 mg/kg.

**Induction:**

Anesthesia was induced with 5-8 mg/kg thiopental followed by inhalation of a mixture of 66% nitrous oxide in oxygen. Some subjects received more than 8 mg/kg of thiopental as induction dose (defined as the first dose of thiopental). Other subjects received more than the maximum allowed dose before intubation divided into 2 or more doses. No Emla cream was used and no opioids were given before intubation of the subject.

**Administration of Muscle Relaxant:**

In neonates the randomly assigned intubating dose of Org 9487 was administered immediately after the induction with thiopental. In infants and children the randomly assigned intubating dose of Org 9487 was administered upon loss of eyelid reflex. Laryngoscopy started at 45-50 sec after administration of Org 9487, followed by intubation at 70 sec. The actual intubating time was recorded. The intubation conditions were scored using a 4 step score. Scoring was assessor blinded. If intubation was not possible at 60 sec, an intubating dose of vecuronium or atracurium could be administered.

#### Maintenance of Anesthesia:

Adequate depth of anesthesia was maintained with nitrous oxide in oxygen at concentrations determined by clinical need. Inhalational agents were given after the subject's spontaneous recovery from muscle relaxation. Doses of alfentanil could be administered as clinically indicated.

#### Maintenance of Muscle Relaxation:

After receiving the intubating dose of Org 9487, the subjects were allowed to recover spontaneously to a T4/T1 ratio of 0.7 before a maintenance dose of muscle relaxant was administered. Muscle relaxation was maintained during surgery when clinically required by maintenance doses of atracurium, rocuronium or vecuronium.

#### Reversal of Neuromuscular Blockade:

Reversal of residual neuromuscular block was allowed when clinically indicated but not before spontaneous recovery to a T4/T1 ratio of 0.7 after the intubating dose of Org 9487. The post study period started at transfer of the subjects to the recovery room and ended after the post study assessment.

#### Study Assessments:

##### 1. Intubation Scores:

Intubating conditions were scored at 60 seconds as follows:

Excellent: jaw relaxed, vocal cords immobile, no diaphragmatic movement

Good: jaw relaxed, vocal cords moving but not closing, minor diaphragmatic movement

Poor: jaw relaxed, vocal cords closing, marked coughing/"bucking" or

Jaw not relaxed, vocal cords immobile, no or minor diaphragmatic movement

Impossible: jaw not relaxed, vocal cords not visualized or

jaw relaxed or not relaxed and vocal cords closed

NA: Intubation impossible due to anatomical malformation.

If the administration of an intubating dose of atracurium or vecuronium was necessary, the intubating conditions following this dose of muscle relaxant were not recorded.

##### 2. Neuromuscular Assessments:

Neuromuscular function was monitored using a TOF Guard AG. The ulnar nerve was stimulated at the wrist through surface electrodes with Train of Four (TOF) supramaximal square wave impulses of 0.2 msec duration administered at 2 Hz. A constant current stimulator was used to deliver TOF every 15 sec.

## SECTION 9.5.1.2 PROTOCOL AMENDMENTS

### Amendment 1

After an interim analysis, it was decided to eliminate the 0.5 mg/kg dose for the children (1-6 years)

### Amendment 2

In order to facilitate treatment and handling of the infants, it was allowed to administer midazolam 0.2 mg/kg intranasally as premedication. In one of the centers, rocuronium was also allowed for maintenance of muscle relaxation.

### Amendment 3

After an interim analysis, it was decided to eliminate the 0.5 mg/kg dose for the children. After an interim analysis, it was decided to eliminate the 2.5 mg/kg dose for the infants.

### Amendment 4

In order to increase the overall enrollment rate it was decided to decrease the number of infant subjects to be studied in the German center from 25 subjects to 10 subjects and to increase the number of infants in the Finland center from 25 subjects to 40 subjects.

### Amendment 5

In order to increase the overall enrollment rate, it was decided to decrease the number of infant subjects in the Finland center by 10 subjects to 30 subjects; these 10 subjects were enrolled in the UK center in a new age group.

## SECTION 9.5.1.3 STATISTICAL AND ANALYTICAL METHODS

### Sample Size:

Sample size for the infants and children was estimated based on the anticipated success rate of 96% for succinylcholine. Having 30 subjects per dose group (10 infants and 20 children), one subject with failure (poor or impossible intubating conditions) would still mean 96.7% success (excellent or good).

### Study Parameters:

Data was summarized by descriptive statistics. Data was summarized by age group and within age group by dose group. The success rate of clinically acceptable intubation conditions were calculated together with a one sided 95% CI.

### Blind Broken During Study:

Not applicable.

### Protocol Violations:

A violation of the protocol is defined as a lack of compliance with the protocol interfering with the assessment of efficacy. Major violations lead to the exclusion of all efficacy data for a subject from the Per protocol analysis. Minor violations result in exclusion of some but not all efficacy data from the Per Protocol analysis. A protocol deviation is defined as a lack of compliance with the protocol not having impact on the assessment of efficacy. Subjects who violated the eligibility criteria, who received study medication not conforming to the randomization schedule, who received disallowed concomitant medication, and/or subjects from whom efficacy parameters were missing, were considered non-evaluable.

**Subject Data Sets:**

4 subject groups were distinguished:

- ASR: all subjects who were randomized
- AST: all randomized subjects who received at least one dose of study medication
- ITT: all subjects who received at least one dose of study medication and had at least one post baseline efficacy assessment
- PP: all subjects included in the ITT group and who did not have any major protocol violations.

**SECTION 9.5.1.4 CONDUCT OF STUDY**

**Disposition of Subjects:**

Table 33 Disposition of Enrolled Subjects

Age Group	Data Set	Dose mg/kg					Total
		0.5	1.0	1.5	2.0	2.5	
Neonates	ASR	5	5	5			15
	AST	5	5	5			15
	ITT	5	5	5			15
	PP	5	5	5			15
Infants	ASR	14	12	11	11	2	50
	AST <sup>1</sup>	13	13	11	11	2	50
	ITT	14	12	11	11	2	50
	PP	13	12	11	11	2	49
Children <sup>2</sup> (1-6 years)	ASR	2	12	12	12	12	50
	AST	2	12	13	12	12	51
	ITT	2	12	12	12	12	50
	PP	2	12	12	12	12	50
Children <sup>2</sup> 7-12 years)	ASR	3	12	12	11	12	50
	AST	3	12	11	11	12	49
	ITT	3	12	12	11	12	50
	PP	3	12	11	11	12	49

Modified Sponsor's Table 7 Vol 87 p. 0042

1. One infant was given 1.0 mg/kg of Org 9487 instead of 0.5 mg/kg
2. One subject was allocated to the children (7-12 years); however the subject was only 6 years and 10 month of age

## Disposition of Subjects by Center:

Table 34 Disposition of Subjects by Center

Age	Center	Dose mg/kg					Total
		0.5	1.0	1.5	2.0	2.5	
Neonates 0-1 month	UK	5	5	5	0	0	15
Infants 1-11 month	Germany	3	3	2	2	0	10
	UK	3	2	3	2	0	10
	Finland	7	8	6	7	2	30
Children 1-6 years	Germany	0	5	6	5	5	21
	UK	1	2	3	2	2	10
	Finland	1	5	4	5	5	20
Children 7-12 years	Germany	1	5	4	4	5	19
	UK	1	2	2	2	3	10
	Finland	1	5	5	5	4	20

Modified Sponsor's Table 8 Vol 87 p. 0043

## Protocol Violations:

Major Protocol Violations:  
2 subjects

Table 35 Minor Protocol Violations:

Age group	Subject	Dose (mg/kg)	Excluded from evaluation of data with respect to:		Violation
			intubation	time course of action	
Neonates	202	1.0	No	Yes	Memory card not in situ
	203	1.5	No	Yes*	Inhalational anesthetic started prior to recovery of T <sub>4</sub> /T <sub>1</sub> to 0.7
	208	1.0	No	Yes	Electrode off
Infants	107, 110, 430	0.5	Yes	No	Subjects received too much thiopental before administration of study drug
	104, 106, 109				
	315, 428	1.0			
	427	1.5			
	108, 324	2.0			
Children (1-6 yrs)	136, 145	1.0	Yes	No	Subjects received too much thiopental before administration of study drug
	137, 147	1.5			
	131, 138, 140				
	150	2.0			
	132, 135, 142				
	145, 149	2.5			
331	2.5	No	Yes*	Inhalational anesthetics started prior to recovery of T <sub>4</sub> /T <sub>1</sub> to 0.7	
Children (7-12 yrs)	164	0.5	Yes	No	Subjects received too much thiopental before administration of study drug
	177	1.0			
	167, 262	2.0			
	162, 175	2.5			
	37E	2.0	No	Yes*	Inhalational anesthetics started prior to recovery of T <sub>4</sub> /T <sub>1</sub> to 0.7

Sponsor's Table 10 Vol 87 p. 0044

30 subjects received thiopental above the upper protocol limit (i.e. more than 8.4 mg/kg for induction). It was assumed that a relationship exists between the intubation conditions and anesthetic depth in balanced anesthesia. Intubation conditions may be improved by administration of supplemental doses of thiopental. Therefore these subjects were not included in the Per Protocol group. For 3 subjects, the administration of inhalational anesthetics started after the reappearance of the third twitch but before the T<sub>4</sub>/T<sub>1</sub> ratio had regained to over 0.7. As volatile inhalational agents are known to potentiate and increase the duration of action of neuromuscular blocking drugs, these subjects were excluded from the Per Protocol group for the analysis of duration 0.7.

Baseline Characteristics:

All subjects were Caucasian. Only one subject (an infant) had a preexisting medical condition. No subjects were treated with vasoactive drugs, antiasthmatics, anticonvulsants, antibiotics, systemic corticosteroids or antihistaminics during the pre-study period. No opioids were given before intubation of the subjects.

PER PROTOCOL EVALUATION:

Table 36 Intubation Scores: Per Protocol Group

AGE	SCORE	DOSE mg/kg									
		0.5		1.0		1.5		2.0		2.5	
		N	%	N	%	N	%	N	%	N	%
Neonate 0-1Month	Excellent	1	20	1	20	5	100				
	Good	0	0	2	40	0	0				
	Poor	4	80	2	40	0	0				
	Impossible	0	0	0	0	0	0				
Infants 1-11Month	Excellent	1	10	3	43	8	80	9	100	2	100
	Good	3	30	4	57	2	20	0	0	0	0
	Poor	6	60	0	0	0	0	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
Children 1-6yr	Excellent	0	0	3	30	5	50	4	50	5	71
	Good	0	0	2	20	3	30	4	50	2	29
	Poor	2	100	5	50	2	20	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
Children 7-12 yr	Excellent	0	0	0	0	3	27	6	67	5	50
	Good	0	0	6	55	7	64	3	33	5	50
	Poor	1	50	4	36	1	9	0	0	0	0
	Impossible	1	50	1	9	0	0	0	0	0	0

Sponsor's Table 21 Vol 87 p.0053

ITT EVALUATION:

Table 37 Intubation Scores: ITT Group

AGE	SCORE	DOSE mg/kg									
		0.5		1.0		1.5		2.0		2.5	
		N	%	N	%	N	%	N	%	N	%
Neonate 0-1Month	Excellent	1	20	1	20	5	100				
	Good	0	0	2	40	0	0				
	Poor	4	80	2	40	0	0				
	Impossible	0	0	0	0	0	0				
Infants 1-11Month	Excellent	2	14	5	45	8	73	11	100	2	100
	Good	5	36	6	55	3	27	0	0	0	0
	Poor	7	50	0	0	0	0	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
	Not Applic	0		1		0		0		0	
Children 1-6yr	Excellent	0	0	4	33	6	50	8	67	10	83
	Good	0	0	2	17	3	25	4	33	2	17
	Poor	2	100	6	50	3	25	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0	0	0
Children 7-12 yr	Excellent	0	0	1	8	3	25	8	73	7	58
	Good	0	0	6	50	8	67	3	27	5	42
	Poor	2	67	4	33	1	8	0	0	0	0
	Impossible	1	33	1	8	0	0	0	0	0	0

Sponsor's Table A.11 Vol 87 p. 0249

## NEUROMUSCULAR PARAMETERS:

Table 38 Time Course of Action  
Neonates: PP Group

		DOSE mg/kg		
		0.5	1.0	1.5
Time to Reappearance of Third twitch (Min)	N	1	2	5
	MEDIAN	3.3	7.1	11
	MEAN	3.3	7.1	11.7
	SD		1.6	2.3
	MIN	3.3	6.0	9.0
	MAX	3.3	8.3	15.3
DUR 0.7 (Min)	N	5	3	4
	MEDIAN	7.5	14	20.0
	MEAN	6.6	13.7	19.7
	SD	2.0	1.0	3.7
	MIN	4.0	12.5	15.5
	MAX	9.0	14.5	23.3

Sponsor's Table 24 Vol 87 p. 0057

**Table 39** Time Course of Action  
Infants: PP Group

		DOSE mg/kg				
		0.5	1.0	1.5	2.0	2.5
Time to Reappearance of Third twitch Min	N	6	11	11	11	2
	MEDIAN	2.6	5.5	6.5	10.3	15.4
	MEAN	2.8	6.4	7.6	10.5	15.4
	SD	1.3	2.7	2.5	2.8	3.7
	MIN	1.0	2.5	5.5	7	12.8
	MAX	4.8	11.5	12.3	16.8	18
DUR 0.7 Min	N	12	12	11	11	2
	MEDIAN	6.3	10.4	13.3	21	29.5
	MEAN	6.2	11.5	15.7	20.9	29.5
	SD	1.9	3.6	4.2	4.8	9.2
	MIN	3.0	7.5	12	14.8	23
	MAX	9.0	18.8	23	30.3	36

Sponsor's Table 25 Vol 87 p. 0058

**Table 40** Time Course of Action  
Children 1-12 Years: PP Group

		DOSE mg/kg				
		0.5	1.0	1.5	2.0	2.5
Time to Reappearance of Third twitch	N	0	11	21	23	22
	MEDIAN		5.0	7.3	7.8	10.4
	MEAN		4.9	7.2	8.3	10.3
	SD		1.7	2.6	2.7	2.6
	MIN		2.0	2.8	2.8	5.8
	MAX		7.3	11.3	14.5	15.8
DUR 0.7 Min	N	5	23	21	21	23
	MEDIAN	5.0	10.3	14.5	15.5	21.8
	MEAN	5.3	10.7	15.5	17.2	22.2
	SD	1.2	2.4	5.8	5.8	6.4
	MIN	3.8	6.3	8.3	5.8	12.3
	MAX	6.8	16.8	32.3	31.8	34.5

Sponsor's Table 28 Vol 87 p. 0059

#### SECTION 9.5.1.5 SPONSOR'S EFFICACY DISCUSSION

The primary objective of the study was to evaluate the intubation scores at 60 seconds after administration of various doses of Org 9487 in neonates, infants and children. The results indicate that with a dose of 1.5 mg/kg clinically acceptable intubating conditions by 60 sec can be achieved in neonates, whereas for the infants a dose of  $\geq 1.0$  mg/kg and for the children, both age groups, a dose of  $\geq 2.0$  mg/kg provides the same acceptable conditions. The main objective of the study was to find a dose which provides a success rate of 96% (which is equal to the anticipated success rate of succinylcholine [excellent

or good intubating conditions]). The results suggest that this objective can be met by giving the mentioned doses of Org 9487 to the different age groups.

A secondary objective was to evaluate, in an uncalibrated fashion, the time course of action (time to reappearance of the third twitch and/or duration until T4/T1 ratio recovery to 0.7). The time course of action data show dose dependency (not statistically tested) of the neuromuscular parameters: time to reappearance of the third twitch (T3) and time to recovery of the T4/T1 ratio to 0.7. Increase of the dose gives an increase in T3 and dur 0.7. Applying the dose for clinical acceptable intubating conditions (1.5, 1.0, 2.0 and 2.0 mg/kg for the neonates, infants, children 1-6 years and children 7-12 years respectively) gave the following values for the Per Protocol group:

	Dose (mg/kg)	T3 (min) Median	Dur 0.7 (min)
Neonates	1.5	11.5	20
Infants	1.0	5.5	10.4
Children (1-6 yr)	2.0	8.1	14.5
Children (7-12 yr)	2.0	7.0	17

For neonates, a dose of 1.5 mg/kg resulted in 5 of the 5 patients studied on this dose in clinically acceptable intubation conditions. This dose provided a short duration of action: median time to reappearance of the T3 was 11.5 min.

In the infant group, clinically acceptable intubating conditions in 100% of the subjects were found with a dose of Org 9487  $\geq$  1.0 mg/kg. The 1.0 mg/kg resulted in an ultrashort duration of action: median time to reappearance of T3 was 5.5 min.

In both children groups (1-6 and 7-12 years) clinically acceptable intubating conditions in 100% of the patients were found with a dose of Org 9487  $\geq$  2.0mg/kg. The 2.0 mg/kg dose resulted in an ultrashort duration of action: median times to reappearance of T3 were 8.1 and 7.0 min respectively.

#### SECTION 9.5.1.6 REVIEWER'S EFFICACY DISCUSSION:

The main objective of this study was to evaluate the intubation scores at 60 seconds after administration of various doses of Org 9487 in neonates, infants, and children. Acceptable (Good or Excellent) intubation conditions occurred in 100% of the subjects at or above the following doses:

Neonates	1.5 mg/kg
Infants	1.0 mg/kg
Children 2-6 years	2.0 mg/kg
Children 7-12 years	2.0 mg/kg

While the results support a conclusion for 100% Acceptable intubation conditions at or above the noted doses, this non-comparative study is unable to make any inference regarding equivalence with succinylcholine.

The sponsor's use of the terms "short" and "ultrashort" for describing the duration of Org 9487 is not appropriate. Sponsor acknowledges (Vol 149, p. 0018) FDA criteria for definition of clinical duration. These criteria as published by Bedford (Anesthesiology, V82 Jan 1995) defined duration (ultrashort, short, intermediate, long-acting) in terms of return to 25% of control twitch height. This study defined duration in terms of 1) Time to Reappearance of Third Twitch and 2) Duration to T4/T1 Recovery Ratio 0.7%. Duration to T4/T1 70% and 25% control twitch height are not interchangeable measurements. While return to 25% control twitch height and Reappearance of Third Twitch are both commonly used to define Clinical Duration, no data has been presented in this study to validate equivalence for these two measurements for Org 9487. Consequently, use of the terms "short" and "ultrashort" is not supported by the data from this study.

## SECTION 9.6.1 STUDY 174303

### SECTION 9.6.1.1 PROTOCOL REVIEW SUMMARY:

**TITLE:** Evaluation of the Intubating Conditions Provided with Org 9487 and Succinylcholine When Used in Elective Rapid Sequence Induction

**OBJECTIVE:** To evaluate the intubating conditions provided with Org 9487 and succinylcholine when used in a rapid sequence induction in patients scheduled for elective surgery using general anesthesia.

**STUDY DESIGN:** This study was an open label, parallel group comparative, assessor blinded, randomized multicenter Phase III study. The study was carried out in 5 centers in Germany and Austria.

**SUBJECT SELECTION:** The study was designed to enroll 160 ASA Class 1 and 2 patients with normal body weight, as well as 160 obese patients. Patients (ASA class 1 and 2, with normal body weight as well as

Immediately thereafter either Org 9487 1.5mg/kg (study groups 1 and 2) or succinylcholine 1.0 mg/kg (study groups 3 and 4) were to be given over 5 sec.

Table 41 Treatment Groups

Treatment Group	
1	FENTANYL 2-3µg/kg+THIOPENTAL 5-6mg/kg+ORG 9487 1.5mg/kg
2	ALFENTANIL 20 µg/kg+PROPOFOL/1.5-2 mg/kg +ORG 9487 1.5mg/kg
3	FENTANYL 2-3µg/kg+THIOPENTAL 5-6mg/kg+SUCCINYLCHOLINE1.0 mg/kg
4	ALFENTANIL/20 µg/kg+PROPOFOL/1.5-2 mg/kg +SUCCINYLCHOLINE1.0 mg/kg

#### INTUBATION:

Laryngoscopy was to be started at 50 sec after the end of administration of either Org 9487 or succinylcholine followed by intubation at 60 sec or less. Endotracheal tubes sizes were 7.0 for women and 8.0 for men. The intubating conditions were to be evaluated and scored assessor blinded, by one and the same assessor at each of the study sites. If intubation was not possible at the first attempt, a second attempt was to be made as soon as possible. The actual intubating time was to be recorded.

#### MAINTENANCE OF ANESTHESIA:

During the first 10 minutes following administration of the muscle relaxant, anesthesia was to be maintained in groups 1 and 3 with isoflurane 0.2- 0.4 % and N<sub>2</sub>O 2/1, and in groups 2 and 4 with propofol 150 µg/kg/min, alfentanil 1 µg/kg/min and N<sub>2</sub>O 2/1. No further muscle relaxants were to be given. After the 10 min cardiovascular assessment adequate depth of muscle relaxation were to maintained as clinically required.

#### SECTION 9.6.1.2 PROTOCOL AMENDMENTS

Table 42

Amendment 1 5/6/96	According to the protocol, anesthesia should be induced with 5-6 mg/kg of thiopental. However, dose requirements for induction of anesthesia with thiopental are less for the obese subjects than for subjects with normal body weight. Therefore, in order to optimize the care for the subjects, it was decided to allow induction of anesthesia (in groups 1 and 3) with 3-6 mg/kg of thiopental in the obese subjects
Amendment 2 5/9/96	Recruitment of the obese subjects turned out to be more difficult than was originally estimated before the start of the study. Sample size calculations were done without accounting for a possible interaction of body weight, as such an interaction was not to be expected. Therefore the ratio of subjects of normal body weight vs obese subjects was changed from 160 vs 160 to 220 vs 100.
Amendment 3 9/3/96	The enrollment for this study was slower than originally expected before the start of the study. Therefore the following changes were incorporated in the conduct of the study: <ul style="list-style-type: none"> <li>• The number of subjects to be enrolled was no longer restricted to 80 subjects per site.</li> <li>• The Innsbruck center, which had enrolled 80 subjects, was allowed to enroll additional subjects</li> <li>• Another individual was added as co-investigator in Giessen and was allowed to enroll additional subjects</li> </ul>
Amendment 4 9/16/96	One batch of Org 9487 was replaced with another batch because of a fall in specifications
Amendment 5 9/17/96	The enrollment for this study was slower than originally expected before the start of the study. Therefore, an additional investigator was added and additional subjects were added

Modified Sponsor's Table 5, Vol 106 p 0034

### SECTION 9.6.1.3 STATISTICAL AND ANALYTICAL METHODS

Intubating conditions were to be scored at 60 sec or less following the end of administration of either Org 9487 or succinylcholine. Intubating conditions were to be evaluated and scored as proposed by Viby-Mogensen:

Table 43 Viby-Mogensen Definitions

	CLINICALLY ACCEPTABLE		
	Excellent	Good	Poor
Vocal Cord Position	Abducted	Intermediate	Closed
Vocal Cord Movement	None	Moving	Closing
Easiness of Laryngoscopy*	Easy	Fair	Difficult
Airway Reaction	None	Diaphragm	Sustained >10 sec
Movement of the Limbs	None	Slight	Vigorous

Modified Sponsor's Table 5 Vol 121 p. 0037

\* Easy: Jaw relaxed; No resistance

Fair: Jaw relaxed, Slight Resistance

Excellent Score: All items excellent

Good Score: All items excellent or good

Poor Score: Any item poor makes score poor

The intubating conditions on the first attempt were to be recorded on the CRF even in the unlikely event of intubation not being possible at the first attempt.

#### ADVERSE EXPERIENCES:

Any adverse experiences that occurred were to be reported, whether or not the adverse experience was thought to be drug related. All histamine release symptoms and all symptoms of local intolerance at the site of injection of study medication were to be regarded as adverse experiences.

#### STATISTICAL METHODS:

For this study it was anticipated that the rate of acceptable (excellent or good) intubating conditions with Org 9487 is 96%, i.e. equal to that of succinylcholine. Using a power of 80% and a significance of 0.05, a sample size of 130 per muscle relaxant was estimated to be sufficient to detect a difference of 10% or more in frequency of excellent or good intubation scores. To allow for subjects being non-evaluable, and to allow equal randomization in each study site, group sizes were to be increased to 160.

The intubation conditions were the primary objective of the study. The hypotheses (null and alternative) that have been tested, were formulated as follows:

If  $P_{org}$  and  $P_{six}$  are the rates of clinically acceptable (excellent or good) intubation conditions, the null hypothesis and the alternative hypothesis were defined as follows:

$H_0: P_{org} = P_{six}$  and  $H_1: P_{org} \neq P_{six}$

Statistical testing was done two-sided, using a significance level of 0.05.

The influence of the anesthetic technique on the intubation conditions was the secondary objective and was investigated for Org 9487 treatment groups with the same statistical methods as mentioned above.

**BLIND BROKEN DURING STUDY:**

Not applicable

**DISCONTINUED SUBJECTS:**

Discontinued subjects were to be reported

**SUBJECT DATA SETS:**

For evaluation of the data four subject data sets were defined:

- the all-subjects-randomized (ASR) group, which includes all subjects who were randomized (i.e. subject study number was assigned);
- the all-subjects-treated (AST) group, which includes all randomized subjects who received the dose of study medication;
- the intent-to-treat (ITT) group, which includes all subjects who received the dose of study medication and had at least one post baseline efficacy assessment; and
- the per-protocol (PP) group, which includes all subjects that are included in the intent-to-treat group and who did not have any major protocol violations.

With respect to the intent-to-treat and all-subjects-randomized groups, subjects with incorrect randomization (assigned to wrong treatment group) were included under the planned treatment group as per randomization schedule. With respect to the all-subject-treated group, subjects with incorrect randomization (assigned to wrong treatment group) were included under the actual treatment group.

**PROTOCOL VIOLATIONS:**

A violation of the protocol is defined as a lack of compliance with the protocol interfering with the assessment of efficacy. A protocol deviation is defined as a lack of compliance with the protocol not having impact on the assessment of efficacy.

Protocol violations are of two types: major and minor. Major violations lead to the exclusion of all efficacy data for a subject from the per-protocol analysis. Minor violations result in exclusion of some but not all efficacy data for a subject from the per-protocol analysis.

**Major Protocol Violations:**

- Incorrect body mass index, BMI outside the borders of the in- and exclusion criteria
- Incorrect body mass index; subjects have been assigned to the incorrect subject group
- Pregnant subject

- Incorrect dose of study medication
- Paravenous injection
- Incorrect randomization
- Incorrect induction of anesthesia (incorrect dose of fentanyl)
- Incorrect randomization ("double subjects")

Since intubation score is the only parameter which assesses efficacy, only major protocol violations could occur.

Minor Protocol Violations:  
None

#### SECTION 9.6.1.4 STUDY CONDUCT

#### DISPOSITION OF SUBJECTS:

Table 44 Disposition of Subjects

Center	Normal Body Weight				Obese				Total
	Org 9487		Succinylcholine		Org 9487		Succinylcholine		
	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	
1	11	11	10	10	1	1	1	1	46
2	13	13	13	13	3	4	4	3	66
3	14	15	15	14	4	5	6	5	78
4	17	17	16	16	11	12	12	12	113
5	4	4	4	4	4	4	4	4	32
Total	59	60	58	57	23	26	27	25	335

Modified Sponsor's Table 6, Vol 106 p 0045

In total 335 subjects were enrolled in the study: 101 obese subjects and 234 subjects with normal body weight. 168 subjects were assigned to the Org 9487 group and 167 to the succinylcholine group.

#### MAJOR PROTOCOL VIOLATIONS:

Table 45 Major Protocol Violations

Major Protocol Violation	Org 9487		Succinylcholine	
	Fen/thio	Alf/prop	Fen/thio	Alf/prop
Incorrect body mass index: Outside border of inclusion/exclusion Criteria	1		2	
Incorrect body mass index: Subjects assigned to wrong treatment group			1	1
Pregnant subject	1			
Paravenous injection	1			
Incorrect Randomization	1			
Incorrect induction of anesthesia Incorrect dose of fentanyl			2	
Incorrect randomization (double subjects)			2	
Total	6	2	10	1

Modified Sponsor's Table 7 Vol106 p 0047

Table 46 Protocol Deviations

Protocol Deviation	Org 9487		Succinylcholine	
	Fentanyl/Thio	Alf/Prop	Fentanyl/Thio	Alf/Prop
Subjects received premedication	14	20	19	20
Fentanyl outside $\pm 10\%$ of Protocol range	7		8	
Alfentanil outside $\pm 10\%$ of protocol dose				1
Propofol outside $\pm 10\%$ of protocol range		1		1
Thiopental outside $\pm 10\%$ of protocol range	1			
Maintenance of anesthesia did not start within 1 minute after the administration of the study drug	8	11	7	8
Isoflurane outside protocol range or no isoflurane given during the first 10 min after administration of the study drug	8		7	
Additional thiopental given during the first 10 min after administration of the study drug	1		3	
No propofol given during the first 10 min after administration of the study drug or prematurely stopped infusion		5		2
No alfentanil given during the first 10 min after administration of the study drug or prematurely stopped infusion		11		12
No N <sub>2</sub> O in O <sub>2</sub> given during the first 10 min after administration of the study drug		1		
Incorrect tube size	5	6	1	3

Modified Sponsor's Table 8, Vol 106 p. 0048

According to the protocol, premedication was not permitted. Some investigators deemed it necessary to give premedication in a number of cases. 73 subjects received premedication, which consisted mainly of potassium clorazepate (20-25mg) and/or midazolam (7.5mg). The premedications were small doses of sedating agents that the sponsor regarded as having no influence on the outcome of the study.

## SUBJECT DATA SETS:

Table 47 Subject Data Set

Subject Data Set	Normal Body Weight				Obese				Total
	Org 9487		Succinylcholine		Org 9487		Succinylcholine		
	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	Fen/thio	Alf/prop	
ASR <sup>1</sup>	59	60	58	57	23	26	27	25	335
AST <sup>1</sup>	58	61	57	58	23	26	28	24	335
ITT	59	60	57	58	23	26	26	26	335
PP	55	58	52	57	21	26	23	24	316

Modified Sponsor's Table 9, Vol 106 p. 0049

1. There were 2 cases in which the same subject number was given to 2 subjects. These subjects are included for the ASR and AST group under treatment fentanyl/thiopental/succinylcholine and for the ITT group under treatment alfentanil/propofol/succinylcholine.

## DEMOGRAPHICS:

Table 48 Demographics

		Normal Body Weight				Obese			
		Org 9487		Succinylcholine		Org 9487		Succinylcholine	
		Fen/thio	Alf/pro p	Fen/thio	Alf/pro p	Fen/thio	Alf/pro p	Fen/thio	Alf/pro p
Age	N	58	61	57	58	23	26	28	24
	Mean(SD)	37 (12)	36(13)	36 (12)	37(13)	45(14)	39(13)	43(11)	40(10)
	Median	35	32	36	34	49	38	46	41
Wt (kg)	N	58	61	57	58	23	26	28	24
	Mean(SD)	74(11)	76(10)	77(11)	74(10)	98(13)	100(19)	103(17)	95(17)
	Median	73	75	75	73	96	93	100	93
Ht (cm)	N	58	61	57	58	23	26	28	24
	Mean(SD)	176(9)	177(9)	177(8)	175(8)	170(10)	170(9)	171(7)	167(10)
	Median	176	179	178	175	170	168	170	165
Sex	Female	11 (19)	16(26)	9(16)	16(28)	13(57)	13(50)	13(46)	14(58)
	Male	47(81)	45(74)	48(84)	42(72)	10(43)	13(50)	15(54)	10(42)
Race N(%)	Caucasian	57(98)	60(98)	56(98)	58(100)	23(100)	25(96)	28(100)	24(100)
	Asian	0	1(0)	0	0		0	0	0
	Black Other	1(2)	0	1(2)		1(4)			
ASA N(%)	1	49 (84)	48(79)	50(88)	42(72)	6(26)	11(42)	10(36)	10(42)
	2	9 (16)	13(21)	7(12)	16(28)	17 (74)	15(58)	18(64)	14(58)

Modified Sponsor's Tables 10 and 11 Vol 106 p 0050

No statistical analysis was done comparing the 4 treatment groups with regard to baseline characteristics. Within the subject groups (normal weight and obese), the 4 treatment groups were comparable with respect to age, height, weight, gender, race and ASA class. In the normal weight group, more males were enrolled while in obese subject group the distribution of males to females was about equal.

Table 49 Pre-existing Medical Conditions

		Normal Body Weight				Obese			
		Org 9487		Succinylcholine		Org 9487		Succinylcholine	
		Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)
Cardiac System	Hypertension	1 (1%)	3 (5)	1 (2)	1 (2)	5 (22)	5 (19)	7 (25)	4 (17)
	Ischemic dis								
	Valve dis								
	Arrhythmia								
	Congenital								
	Misc	3 (3)	1 (2)	2 (4)		1 (4)		2 (7)	1 (4)
Resp System	Asthma	1 (2)				1 (4)			
	COPD					1 (4)		1 (4)	
	Misc	1 (2)	2 (3)	1 (2)		1 (4)	2 (8)	1 (4)	2 (8)
Asthma	Childhood								
	Recent					1 (4)			
Renal Failure									
Hepatic Disease									
Other	Obesity								
	Current Smoker	3 (5)	4 (7)		2 (3)	2 (9)	2 (8)	4 (14)	1 (4)
	Misc	1 (2)			1 (2)				

Modified Sponsor's Tables 12a,b, 13a,b Vol 106 pp0051-0054

No subjects were treated with anticonvulsants, selected antibiotics or systemic corticosteroids during the pre-study period; the number of subjects treated with vasoactive drugs, anti-asthmatics and antihistamines was low, and these medications were regarded to have no influence on the outcome of the study.

## SECTION 9.6.1.5 EFFICACY RESULTS

Table 50 Intubation Scores, Per Protocol Group

Center	Intubation Score	Normal Body Weight				Obese			
		Org 9487		Succinylcholine		Org 9487		Succinylcholine	
		Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)	Fen/thio N (%)	Alf/prop N (%)
1	Excellent Good Poor	9 (81.8) 2 (18.2) 0	8 (72.7) 3 (27.3) 0	7 (77.8) 2 (22.2) 0	7 (70) 3 (30) 0	1 (100) 0 0	1 (100) 0 0	1 (100) 0 0	1 (100) 0 0
2	Excellent Good Poor	4 (36.4) 7 (63.6) 0	6 (54.5) 4 (36.4) 1 (9.1)	8 (66.7) 3 (25) 1 (8.3)	9 (69.2) 3 (23.1) 1 (7.7)	1 (33.3) 1 (33.3) 1 (33.3)	0 2 (50) 2 (50)	2 (66.7) 1 (33.3) 0	1 (33.3) 2 (66.7) 0
3	Excellent Good Poor	3 (23.1) 4 (30.8) 6 (46.2)	6 (40) 7 (46.7) 2 (13.3)	10 (77.8) 3 (22.2) 0	11 (78.6) 3 (21.4) 0	1 (33.3) 1 (33.3) 1 (33.3)	3 (60) 2 (40) 0	3 (100) 0 0	2 (40) 2 (40) 1 (20)
4	Excellent Good Poor	8 (50) 7 (43.8) 1 (6.3)	7 (41.2) 9 (52.9) 1 (5.9)	12 (85.7) 2 (14.3) 0	12 (75) 4 (25) 0	4 (36.4) 6 (54.5) 1 (9.1)	10 (83.3) 2 (16.7) 0	8 (66.7) 4 (33.3) 0	9 (81.8) 2 (18.2) 0
5	Excellent Good Poor	0 (0) 4 (100) 0	3 (75) 0 1 (25)	1 (25) 2 (50) 1 (25)	3 (75) 1 (25) 0	3 (100) 0 0	3 (75) 1 (25) 0	4 (100) 0 0	3 (75) 1 (25) 0
OVERALL	Excellent Good Poor	24 (43.6) 24 (43.6) 7 (12.7)	30 (51.7) 23 (39.7) 5 (8.6)	38 (73.1) 12 (23.1) 2 (3.8)	42 (73.7) 14 (24.6) 1 (1.8)	10 (47.6) 8 (38.1) 3 (14.3)	17 (65.4) 7 (26.9) 2 (7.7)	18 (78.3) 5 (21.7) 0	16 (66.7) 7 (29.2) 1 (4.2)
	Acceptable <sup>1</sup>	48 (87.3)	53 (91.4)	50 (96.2)	56 (98.2)	18 (85.7)	24 (92.3)	23 (100)	23 (95.8)
	Not Acceptable <sup>2</sup>	7 (12.7)	5 (8.6)	2 (3.8)	1 (1.8)	3 (14.3)	2 (7.7)	0	1 (4.2)

Modified Sponsor Tables 19, 20 Vol 106 pp 0063-0064

1. Acceptable: Excellent or good intubation scores
2. Not Acceptable: Poor intubation scores

For subjects who received Org 9487 for muscle relaxation, no statistically significant differences between the two anesthetic techniques were observed with respect to clinically acceptable and excellent intubation conditions.

After administration of succinylcholine the percentage of clinically acceptable intubation conditions was 97.4% with 95% CI ranging from 93.6% to 99.3%. After administration of Org 9487 the percentage of clinically acceptable intubation conditions was 89.4% with 95% CI ranging from 83.5% to 93.7%. It was found that the percentage of clinically acceptable intubation conditions was statistically higher in the succinylcholine group as compared to those in the Org 9487 group: estimated difference between succinylcholine and Org 9487 was 8.1 % with 95% CI ranging from 2.0 % to 14%. Excellent intubation conditions were observed in 73.1% of the subjects in the succinylcholine group (95% CI 65.4-79.9%) and in 50.6% of the subjects in the Org 9487 group (95% CI 42.6-58.5%). Estimated difference between succinylcholine and Org 9487 was 22.5% with 95% CI ranging from 11.4 % to 33.5%.

**Table 51 Acceptable and Excellent Intubation Conditions, Per Protocol Group**

Intubation Condition	Treatment Group		Difference %	2 Sided 95% CI %	p-Value
	Org 9487 N (%)	Succinylcholine N (%)			
Acceptable	143 (89.4)	152 (97.4)	8.1	(2.0, 14.1)	<0.01
Not Acceptable	17 (10.6)	4 (2.6)			
Excellent	81 (50.6)	114 (73.1)	22.5	(11.4, 33.5)	<0.01
Not Excellent	79 (49.4)	42 (26.8)			

Modified Sponsor's Table 22 Vol 106 p. 0066

**Per Protocol Comparison With Intent to Treat Evaluation:**

For the estimates, with 95% CI, for the difference between the two treatment groups, similar results for the ITT and PP groups were observed:

**Table 52 Results: ITT vs Per Protocol**

	Acceptable Intubating Conditions		Excellent Intubating Conditions	
	Difference	95% CI	Difference	95% CI
ITT Analysis	7.7%	(1.8%, 13.7%)	22.5%	(11.8%, 33.1%)
PP Analysis	8.1%	(2.0%, 14.1%)	22.5%	(11.4%, 33.5%)

**SECTION 9.6.1.6 REVIEWER'S EFFICACY DISCUSSION:**

The objective of this study was to evaluate the intubating conditions provided with Org 9487 and succinylcholine when used in a rapid sequence induction in patients scheduled for elective surgery. 335 subjects were enrolled in this study: 101 obese subjects and 234 subjects with normal body weight. 168 subjects were assigned to the Org 9487 group and 167 were assigned to the succinylcholine group. The comparison between clinically acceptable intubating conditions (excellent and good) and clinically non-acceptable intubating conditions (poor) was the subject of interest. Intubating conditions were to be determined at 60 sec after administration of the muscle relaxant; laryngoscopy was to be performed at 50 sec after the administration of the muscle relaxant.

The results of this study reveal that the percentage of clinically acceptable intubation conditions was statistically significantly higher in the succinylcholine group as compared to the Org 9487 group. With respect to excellent intubating conditions, succinylcholine provides a far higher percentage of excellent intubating conditions than Org 9487. Sponsor states the observed differences in percentages of clinically acceptable intubating conditions cannot be explained by differences between the treatment groups with respect to body mass index, administration of a premedication or protocol deviations in induction agents. A possible explanation offered by the sponsor is the time to completion of intubation. Following Org 9487, more subjects were intubated within 65 sec than following succinylcholine (75% vs 67%). Most of the unacceptable intubating conditions

for Org 9487 were scored within 65 sec (65%) whereas following succinylcholine only a minority of the unacceptable intubation conditions were scored within 65 sec (25%).

In conclusion, the data demonstrate Org 9487 is an efficacious neuromuscular blocking agent for rapid sequence intubation. However, in this situation, Org 9487 is not as capable as succinylcholine in establishment of excellent or acceptable intubating conditions.

## **SECTION 9.7.1 STUDY 070006**

### **SECTION 9.7.1.1 PROTOCOL REVIEW SUMMARY**

**TITLE:** A Study to Compare the Neuromuscular Blocking Effects and Safety of Org 9487 To Succinylcholine in a Rapid Sequence Induction in Subjects Undergoing Elective Surgery for Cesarean Section.

#### **OBJECTIVES**

**Primary:** To compare the neuromuscular parameters, clinical responses and safety of 2.5mg/kg of Org 9487 to 1.5 mg/kg of succinylcholine in a rapid sequence induction in subjects undergoing elective Cesarean surgery with general anesthesia.

**Secondary:** 1. To determine maternal plasma and newborn umbilical levels of Org 9487 and metabolites at delivery. 2. A population based pharmacokinetic analysis was to be done on subjects receiving Org 9487.

#### **STUDY DESIGN**

This was to be an assessor blinded, randomized, Phase IIb/III, multicenter study of 120 subjects undergoing a rapid sequence induction for Cesarean section surgery with general anesthesia at a total of 10 sites. Subjects were to be randomized to receive either 2.5 mg/kg of Org 9487 or 1.5 mg/kg of succinylcholine (60 subjects per treatment group). Each site was scheduled to enroll 12 subjects (6 subjects per treatment group). If any site could not enroll a reasonable number of subjects in a timely manner, then with the written authorization of Organon Inc, more subjects were to be enrolled by the other sites. Enrollment was to proceed at each site according to separate randomization schedules

with provisions for randomization of more than the initially scheduled number of subjects per site.

### SUBJECT SELECTION

120 subjects undergoing elective Cesarean section surgery suited for general anesthesia in which rapid sequence induction is used were to be enrolled at 10 sites. An interim analysis was to be conducted to determine the safety of Org 9487 after about one third of non-high risk subjects had been enrolled. High risk subjects were to be enrolled if the results of the interim analysis demonstrated adequate safety with the use of Org 9487.

Table 53 INCLUSION CRITERIA

Criteria for Non-High Risk Subjects	Criteria for High Risk Subjects
Subjects between 18-45 years old	Subjects from 15 years old
ASA Class 1 and 2	ASA Class 1, 2, or 3
Subjects in whom a rapid sequence induction with thiopental is required	Subjects in whom a rapid sequence induction with thiopental is required
Subjects undergoing primary or repeat non-emergent C-section; and	Subjects undergoing primary or repeat non-emergent C-section; and
Subjects in whom the gestational age is 36 weeks or more	Subjects in whom the gestational age is 34 weeks or more

Modified Sponsor's Table 2, Vol 121 p. 0026

Table 54 EXCLUSION CRITERIA

<b>Exclusion for Non High Risk Subjects</b>	<b>Exclusion Criteria for High Risk Subjects</b>
Subjects < 18 or > 45 years of age	Subjects < 15 years of age
ASA Class 3,4, or 5	ASA Class 4 or 5
Subjects undergoing C-section for fetal death, suspected or known congenital anomaly, maternal or fetal distress, overt fetal distress,(e.g. persistent fetal heart rate below 100 beats per minute or scalp pH less than 7.2) and multiple gestations	Subjects undergoing C-section for fetal death, maternal or fetal distress, overt fetal distress,(e.g. persistent fetal heart rate below 100 beats per minute or scalp pH less than 7.2) and multiple gestations
Subjects undergoing emergent C-section	Subjects undergoing emergent C-section
Subjects in whom the gestational age is less than 36 weeks	Subjects in whom the gestational age is less than 34 weeks
Subjects with known or suspected airway abnormalities or airway obstructions that would preclude visualization of the vocal cords or intubation of the trachea	Subjects with known or suspected airway abnormalities or airway obstructions that would preclude visualization of the vocal cords or intubation of the trachea
Subjects with known allergy to narcotics or other medications used during anesthesia	Subjects with known allergy to narcotics or other medications used during anesthesia
Subjects receiving drugs in doses known to modify the action of neuromuscular blockers	Subjects receiving drugs in doses known to modify the action of neuromuscular blockers
Subjects with history of heart disease, severe pregnancy induced hypertension, severe anemia or hemorrhage	Subjects with a history of congenital or valvular heart disease, other than asymptomatic mitral valve prolapse
Subjects participating as research subjects in another drug study within the prior 30 days which has not been preapproved by Organon Inc	Subjects participating as research subjects in another drug study within the prior 30 days which has not been preapproved by Organon Inc
Subjects for whom written informed consent cannot be obtained	Subjects for whom written informed consent cannot be obtained
Subjects with known significant hepatic or renal dysfunction (as determined by elevated liver enzymes and/or renal function tests, physical exam or medical history) or neuromuscular disorders (as determined by physical exam or medical history, including a family history of malignant hyperthermia)	Subjects with known neuromuscular disorders (as determined by physical exam or medical history, include a family history of malignant hyperthermia) and
Subjects receiving magnesium sulfate	Subjects with eclampsia
Subjects with insulin dependent mellitus and	
Subjects who are morbidly obese	

Modified Sponsor's Table 3, Vol 121, p 002

## DOSING SCHEDULE

### Premedication

Subjects may have received 10 to 30 cc of an oral solution of sodium citrate/citric acid (Bicitra) and/or 10 mg of metoclopramide i.v. or orally prior to surgery.

### Rapid Sequence Induction

All subjects were to have a rapid sequence induction (preoxygenation, i.v. induction followed immediately by application of cricoid pressure and administration of the muscle relaxant). After preoxygenation with 100% oxygen for three minutes anesthesia was to be induced with 5 mg/kg thiopental administered through a rapidly flowing i.v. line. No precurarization was to be performed. Following the administration of thiopental cricoid pressure was to be applied.

### Administration of Muscle Relaxant

The investigator administering the contents of the syringe was not to score the intubation conditions. Immediately after the administration of the thiopental, the electromyograph (EMG) was to be turned on and the dose of Org 9487 or succinylcholine was to be administered as a bolus injected within 5 seconds close to a forearm vein into a fast flowing i.v. infusion line through an 18 gauge needle (preferably). The time the administration of the muscle relaxant was completed was to be recorded.

### Intubation

Laryngoscopy was to be initiated at 50 seconds after the administration of the muscle relaxant followed by intubation by 60 seconds after the end of administration of the muscle relaxant. If intubation was not possible by 60 seconds, another attempt was to be made as soon as possible. The intubation conditions by 60 seconds (or at the second attempt) was to be scored by an investigator blinded to the randomization code and to the contents of the syringe. Lidocaine was not to be used to facilitate intubation. If intubation was impossible after a second attempt, succinylcholine or another muscle relaxant other than Org 9487 was to be administered to facilitate intubation. The anesthetic management was to be adjusted to provide optimal care for the subject. No further neuromuscular data was to be collected if a neuromuscular blocking agent other than the initial intubating dose of Org 9487 or succinylcholine was used.

- Maintenance of Anesthesia

Adequate depth of anesthesia was to be maintained with at least 50% nitrous oxide in oxygen with 0.50-0.75% isoflurane until the baby was delivered. Oxygen saturation and pCO<sub>2</sub> was to be continually monitored. Postdelivery, the concentration of

The duration to 70% T4/T1 was defined as the time interval between the administration of the dose and the return to 70% T4/T1 of the TOF. The time at which the T4/T1 returns to 70% was to be recorded only for subjects receiving Org 9487.

- **Clinical Signs of Recovery of Neuromuscular Function**

The time of clinical signs of recovery, i.e., head lift for five seconds, hand squeeze and tongue extension was to be recorded.

- **Intubation**

Intubating conditions by 60 seconds (or at second attempt) after the completion of administration of the randomized dose was to be recorded on the case report form and evaluated by an investigator blinded to the randomization code. The evaluation was to be scored as proposed by Viby-Mogensen and co-investigators (Viby-Mogensen et al., 1995) as presented in Table 55.

Table 55 Criteria for Scoring Intubating Conditions

	CLINICALLY ACCEPTABLE		
	Excellent	Good	Poor
Vocal Cord Position	Abducted	Intermediate	Closed
Vocal Cord Movement	None	Moving	Closing
Easiness of Laryngoscopy*	Easy	Fair	Difficult
Airway Reaction	None	Diaphragm	Sustained >10 sec
Movement of the Limbs	None	Slight	Vigorous

Modified Sponsor's Table 5 Vol 121 p. 0037

\* Easy: Jaw relaxed; No resistance

Fair: Jaw relaxed, Slight Resistance

Excellent Score: All items excellent

Good Score: All items excellent or good

Poor Score: Any item poor makes score poor

Subjects who could not be intubated due to anatomical malformation were to receive a score of NA.

#### OBSTETRIC OBSERVATIONS

The presence or absence of maternal labor was to be recorded on the CRF. The newborn assessments at the time of delivery and post-delivery were to be recorded. The time of delivery was to be defined as the time the newborn was removed from the uterus.

#### Newborn Observations:

- **Time to Sustained Respiration:**

the time interval between the time of delivery and sustained respiration of

the newborn was to be defined as the time to sustained respiration.

- **Apgar Score:**  
Apgar Scores were to be recorded at 1 and 5 minutes after delivery.
- **Neuroadaptive Capacitive Score (NAC)**  
These scores were to be recorded at 15 min, 2 hours, and 24 hours after delivery.
- **Newborn Assessment:**  
The investigator was to record the medical condition of the newborn at delivery and 24 hours after delivery.

#### PHARMACOKINETIC ASSESSMENTS

Umbilical cord venous and arterial blood were to be collected from all infants. All subjects were to have plasma samples collected prior to the administration of the relaxant, within 5 minutes after the administration of the relaxant and at delivery.

### SECTION 9.7.1.2 STATISTICAL AND ANALYTICAL METHODS

#### STUDY POPULATION

##### Disposition of Subjects

The total number of subjects randomized in the study, the number of subjects treated with study drug, the number of subjects in the Intent-To-Treat (ITT) Group, and the number of subjects in the Per-Protocol (PP) Group were tabulated by treatment group. The distribution of the treated subjects enrolled at the eleven centers were also presented.

##### Subject Discontinuations:

Subjects randomized in the study but not treated with study drug were considered discontinued. Subjects with incomplete data as indicated on the End-of-Trial page of the CRF were listed along with the comment.

##### Blind Broken During the Study:

This was an assessor-blinded study. The only reason for breaking the blind was if the information was important for the medical management of the subject. In case of a medical emergency, the assessor was to contact the investigator who had prepared and dispensed the syringes per the randomization schedule in order to break the blind for a particular subject. Subjects for whom the blind was broken (if any) were to be listed along with the reason for breaking the blind.

##### Protocol Violations:

A violation of the protocol is defined as a lack of compliance with the protocol interfering with the assessment of efficacy. Protocol violations are of two types. Major violations lead to the exclusion of all efficacy data for a subject from the Per-

Protocol analysis. Minor violations result in the exclusion of some, but not all, efficacy data for a subject from the Per-Protocol analysis.

A deviation from the protocol is defined as a lack of compliance with the protocol not having an impact on assessment of efficacy.

All subjects treated with study drug were to be screened for protocol violations and deviations with respect to inclusion/exclusion criteria, dosing regimens of anesthetic agents and muscle relaxants, use of contraindicated medications, and noncompliance of scheduled assessments.

#### Protocol Violations:

The following occurrences constituted a major protocol violation:

- Dose of muscle relaxant greater than  $\pm 10\%$  of planned dose.
- Violation of exclusion criteria.

The following occurrences constituted a minor protocol violation:

- Dose of thiopental greater than  $\pm 10\%$  of planned dose 5 mg/kg.

The following occurrences constituted protocol deviations:

- Isoflurane concentration greater than 0.75%

#### All-Subjects-Randomized Group:

The All-Subjects-Randomized Group consists of all subjects admitted to the study who were randomized.

#### All-Subjects-Treated Group

The All-Subjects-Treated Group consists of all randomized subjects who received at least one dose of study medication.

#### Intent To-Treat Group

The Intent-to-Treat Group consists of all subjects treated who had at least one post-baseline assessment of the primary efficacy variable.

#### Per-Protocol Group

The Per-Protocol Group consists of all subjects in the Intent-to-Treat Group with no major protocol violations.

#### Efficacy Parameters

Efficacy analyses were done using the Intent-to-Treat Group and the Per-Protocol Group. Due to slow enrollment, the study was prematurely terminated after one third of the planned number of subjects were entered. Only summary statistics were calculated.

## SECTION 9.7.1.3 PROTOCOL AMENDMENTS

No amendments to the Protocol are noted.

## SECTION 9.7.1.4 STUDY CONDUCT

Table 56 Disposition of Subjects

Subject Data Set	Treatment Group	
	Org 9487 2.5 mg/kg	Succinylcholine 1.5 mg/kg
All Subjects Randomized	21	22
All Subjects Treated <sup>1</sup>	20	22
Intent To Treat	20	22
Per Protocol <sup>2</sup>	17	20

Modified Sponsor's Table 6 Vol 121 p. 0054

1. One subject (Org 9487) was discontinued prior to administration of muscle relaxant since the case was canceled per surgeon's orders
2. Three Subjects (Org 9487), two subjects (Succinylcholine) were excluded due to major protocol violations.

Although 11 sites were planned, only 4 sites actually enrolled subjects. The Study was prematurely terminated after enrollment of subjects at these sites stopped due to the increasingly standard use of regional anesthesia in all but emergency cesarean section cases. No high-risk subjects were enrolled in the study.

Table 57 Distribution of Subjects by Center

Center Number	Treatment Group	
	Org 9487 2.5 mg/kg N=20	Succinylcholine 1.5mg/kg N=22
1	8	8
2	1	1
3	9	10
4	2	3
Total	20	22

Modified Sponsor's Table 7 Vol 121 p. 0055

## SUBJECT DISCONTINUATIONS:

Subjects were considered prematurely discontinued if they received an allocation number but did not receive study medication. One Org 9487 subject was discontinued prior to administration of relaxant since the case was canceled per surgeon's orders.

No subjects were discontinued due to an adverse event. One Org 9487 patient did not complete the study due to the adverse event of esophageal intubation. Intubation conditions were assessed as excellent; however the resident intubating the subject inserted the intubating tube into the esophagus.

#### BLIND BROKEN:

This was an assessor blinded study. The intubating condition was assessed by an individual blinded to the randomization code and to the contents of the syringe. The blind was not broken prior to scoring intubation conditions for any subjects.

#### PROTOCOL VIOLATIONS:

Table 58 Major Protocol Violations

Major Protocol Violation	Treatment Group	
	Org 9487 2.5mg/kg	Succinylcholine 1.5mg/kg
Dose of relaxant greater than $\pm$ 10% of planned dose	2	2
Violation of Exclusion Criteria (Chronic Use of Anticonvulsants)	1	0

Modified Sponsor's Table 8 Vol 121 p.0056

Table 59 Minor Protocol Violations

Minor Protocol Violation	Efficacy Data Excluded	Treatment Group	
		Org 9487	Succinylcholine
Dose of thiopental Greater the $\pm$ 10% Planned (5mg/kg)	Intubation Score	2	1

Modified Sponsor's Table 9 Vol 121 p.0059

Table 60 Protocol Deviations

Protocol Deviation	Treatment Group	
	Org 9487	Succinylcholine
Isoflurane Concentration Greater than 0.75%	N=3 Concentration: 1%; 2%; 1-2%	N=4 Concentration 1.5%; 1%; 1.4%; 1.2%
Maintenance agents other than Specified in protocol	N=3 Agents: Thiopental	N=4 Agents: Thiopental; Sevoflurane

Modified Sponsor's Table 10 Vol 121 p.0056

## DEMOGRAPHIC DATA:

Table 61 Demographic Data

Demographic Parameter	Treatment Group	
	Org 9487 2.5mg/kg	Succinylcholine 1.5mg/kg
Age		
Mean $\pm$ SD	28 $\pm$ 6	31 $\pm$ 6
Median (Min-Max)	29 (19-39)	30 (18-42)
Weight (kg)		
Mean $\pm$ SD	79 $\pm$ 11.1	76.2 $\pm$ 11.1
Median (Min-Max)	77.4 (60-99)	73.1 (62.3-97)
Height (cm)		
Mean $\pm$ SD	160.3 $\pm$ 5.9	156.3 $\pm$ 6.6
Median (Min-Max)	158.8 (152-178)	155.5 (142-170.2)
Race n (%)		
Caucasian	1 (5%)	3 (14%)
Asian	0	0
Black	2 (10%)	3
Other	17 (85%)	16 (73%)
ASA Class n (%)		
1	6 (30%)	12 (55%)
2	14 (70%)	10 (45%)
3	0	0

Modified Sponsor's Table 11 Vol 121 p.0059

## PRE-EXISTING MEDICAL CONDITIONS/MEDICATIONS:

The subjects in this study were generally young and healthy and as such were taking few medications other than prenatal vitamins and iron supplements.

Most subjects in both treatment groups received sodium citrate and/or metoclopramide to decrease gastrointestinal acidity and to prevent reflux. The median dose of thiopental administered for induction was 5 mg/kg as per protocol with all but 3 subjects receiving doses within 10% of the planned dose. Most subjects had anesthesia maintained with isoflurane per protocol with doses of fentanyl or other agents administered as clinically indicated.

Only 2 of the subjects in the Org 9487 group had another muscle relaxant administered while 15 of the succinylcholine subjects required additional muscle relaxant. The majority of the Org 9487 subjects were administered neostigmine for reversal and half of the succinylcholine subjects received a reversal agent.

## EXTENT OF EXPOSURE TO OTHER ANESTHETIC AGENTS

Table 62 Exposure to Anesthetic Agents

Agent	Treatment Group	
	Org 9487 2.5 mg/kg N=20 (%)	Succinylcholine 1.5mg/kg N=22 (%)
Sodium Citrate	18 (90)	17 (77)
Metoclopramide	9 (45)	10 (45)
Thiopental (mg/kg) Median (min-max)	5 (4.4-5.9)	5 (4.8-6)
Maintenance Agents		
N2O/O2	19 (95)	22 (100)
Isoflurane	19 (95)	22 (100)
Fentanyl	15 (75)	18 (82)
Thiopental	2 (10)	0
Sevoflurane	0	1 (5)
Sufentanil	1 (5)	0
Ketamine	0	3 (14)
Neuromuscular Relaxants (other than study drug)		
Vecuronium	2 (10)	8 (36)
Mivacurium	0	3 (14)
Rocuronium	0	3 (14)
Succinylcholine	0	1 (5)
Reversal Agents		
Neostigmine	19 (95)	11 (50)

Modified Sponsor's Table 14 Vol 121 p. 0062

## SECTION 9.7.1.5 SPONSOR'S EFFICACY RESULTS

## INTUBATION

Table 63 Intubation Scores, Per Protocol

Intubation Score	Intubation Scores, Per Protocol	
	Org 9487 2.5mg/kg N=15 <sup>1</sup>	Succinylcholine 1.5mg/kg N=19 <sup>1</sup>
Excellent	10 (67%)	13 (68%)
Good	4 (27%)	4 (21%)
Poor	1 (7%)	2 (11%)
Acceptable (Excellent or Good)	14 (93%)	17 (89%)
Unacceptable (Poor)	1 (7%)	2 (11%)

Modified Sponsor's Table 16 Vol 121 p. 0065

1. 2 Org 9487 subjects and 1 Succinylcholine subject had minor protocol violations and were excluded.

Table 64 Intubation Scores, Intent-To-Treat

Intubation Score	Org 9487 2.5mg/kg	Succinylcholine 1.5mg/kg
	N=20	N=22
Excellent	15 (75%)	16 (73%)
Good	4 (20%)	4 (18%)
Poor	1 (5%)	2 (9%)

## SECONDARY EFFICACY PARAMETERS

- **Return of the First Twitch:**  
Recovery from neuromuscular block was allowed to occur spontaneously and the time for the recovery of the first twitch was recorded. Return of the first twitch is defined as the time from end of administration of the intubating dose to return to the first twitch (T1)

Table 65 Return of First Twitch, Per Protocol

Parameter	Treatment Group	
	Org 9487 2.5mg/kg	Succinylcholine 1.5mg/kg
N	13 <sup>1</sup>	18 <sup>1</sup>
Mean $\pm$ SD	16.9 (5.9)	9.6 (4.3)
Median	15.4	9.8
Min-Max	8.8-2.8	2.3-18

Modified Sponsor's Table 17 Vol 121 p. 0066

1. Time to return of First Twitch was not available for 4 subjects in Org 9487 group and 2 subjects in succinylcholine group
- **Duration to 70% T4/T1 (Org 9487 only):**  
This is defined as the time interval between the administration time of the muscle relaxant and the return to 70% T4/T1. This parameter was not recorded since 19 of the 20 subjects in the Intent To Treat group were administered the reversal agent neostigmine prior to recovery to T4/T1 of 70%.
  - **Clinical Signs of Recovery:**

Table 67 Study Design

Dose	Reversal
1.5 mg/kg Org 9487 60 subjects	No reversal agent N= 12
	Reversal with 0.05 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.05 mg/kg neostigmine at 5 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 5 min after Org 9487 administration N=12
2.5 mg/kg Org 9487 60 subjects	No reversal agent N= 12
	Reversal with 0.05 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 2 min after Org 9487 administration N=12
	Reversal with 0.05 mg/kg neostigmine at 5 min after Org 9487 administration N=12
	Reversal with 0.07 mg/kg neostigmine at 5 min after Org 9487 administration N=12

Modified Sponsor's Table Vol96 p 0027

**SUBJECT SELECTION:**

**INCLUSION CRITERIA:**

- Male or non-pregnant female subjects from  $\geq 18$  to  $< 65$  years of age;
- Subjects of ASA Class 1, 2, or 3 undergoing surgery under general anesthesia who do not require continuous muscle relaxation; and
- Subjects with body weight within 30% of ideal body weight and not exceeding 80 kg.

**EXCLUSION CRITERIA:**

- Subjects under 18 years of age and  $\geq 65$  years of age; Subjects of ASA Class 4 and 5;
- Pregnant females as determined by history, physical exam or urine or serum HCG test;

- Subjects with body weight that was  $\pm$  30% of ideal body weight or greater than 80 kg;
- Subjects requiring continuous muscle relaxation:
- Subjects with known hepatic or renal dysfunction (as determined by elevated liver enzymes and/or renal function tests, physical exam or medical history) or neuromuscular disorders (as determined by physical exam or medical history, including a family history of malignant hyperthermia);
- Subjects with a known allergy to narcotics or other medications used during anesthesia;
- Subjects with known airway abnormalities or airway obstructions that would preclude visualization of the vocal cords or intubation of the trachea;
- Subjects receiving drugs (antibiotics or anticonvulsants) in doses known to modify the action of neuromuscular blockers;
- Subjects participating as research subjects in another study within the prior 30 days which has not been approved by Organon Inc.; and
- Subjects for whom written informed consent could not be obtained.

#### DOSING SCHEDULE:

After a 3 minute standardization of baseline twitch stimulation the randomized dose of Org 9487 was to be administered as a rapid bolus within 5 seconds close to a forearm vein into a fast flowing I.V. infusion line (preferably through an 18 gauge needle). Subjects were to receive neostigmine 2 minutes or 5 minutes after muscle relaxant administration or they received no reversal agent. Glycopyrrolate (0.01 mg/kg) was to be administered I.V. along with the neostigmine dose.

#### Premedication

Subjects may have received 1.0 - 5.0 mg of midazolam I.V. before induction of anesthesia as clinically indicated.

#### Induction

Subjects were to be preoxygenated for a maximum of three minutes with 100% oxygen. At the start of preoxygenation, appropriate doses of fentanyl (2-5 mcg/kg) were to be administered. At the end of preoxygenation anesthesia was to be induced with propofol (1.0-3.0 mg/kg) administered I.V.

#### Administration of Muscle Relaxant

Calibration of the monitoring equipment was to be done using a single twitch at 1 Hz starting after induction of anesthesia. After a three minute standardization of baseline

twitch stimulation, the stimulation mode was to be switched to Train-of-Four (TOF) and the randomized dose of Org 9487 was to be administered.

#### Intubation

Sixty seconds after the administration of Org 9487, the subject may have been intubated.

#### Maintenance of Anesthesia

Ventilation was to be assisted or controlled as necessary to maintain adequate oxygenation and an end tidal  $p\text{CO}_2$  between 32-42 mmHg. Adequate depth of anesthesia was to be maintained with 60%-70% nitrous oxide in oxygen and with an infusion or bolus doses of fentanyl and/or propofol as clinically indicated. No volatile inhalational agents were to be administered until recovery to 80%  $T_4/T_1$ .

Glycopyrrolate (0.01 mg/kg) was to be administered I.V. along with the neostigmine dose.

#### Maintenance of Muscle Relaxation

Subjects were to be allowed to recover to 90% of control  $T_1$  or to 80%  $T_4/T_1$  whichever time period is longer, before an additional dose of another muscle relaxant was administered.

#### Monitoring:

Neuromuscular monitoring was to be done using a mechanomyograph (MMG) with single twitch stimulation starting after induction of anesthesia and continuing for three minutes to obtain baseline stabilization. Thereafter stimulation was to be switched to TOF so that  $T_1$  was measured continuously. The ulnar nerve was to be stimulated at the wrist through surface electrodes at 1 Hz for single twitch stimulation and with train-of-four (TOF) supramaximal (plus 15% to 20% at maximal response) square wave impulses of 0.2 msec duration administered at 2 Hz. The isometric twitch responses of the adductor pollicis were to be recorded with a preload of 200-300 g (with a maximum variation of  $\pm 25\%$ ). A constant current stimulator was to be used to deliver TOF with intervals of 10 sec and continuously recorded. A copy of this recording was to be retained as a source document. The arm used for neuromuscular monitoring was to be kept warm (peripheral skin temperature above monitored muscle  $\geq 32^\circ\text{C}$  and central temperature  $\geq 35^\circ\text{C}$ ) during the neuromuscular monitoring. End Tidal  $\text{CO}_2$  was to be monitored and maintained between 32-42 mmHg. Oxygen saturation was to be monitored by pulse oximeter and maintained at  $\geq 95\%$ .

The following parameters were to be recorded.

#### Block at 2 minutes after Org 9487 administration

The  $T_1$  at 2 minutes after the end of administration of the Org 9487 dose (prior to the administration of neostigmine) was to be recorded (if randomized to this group).

#### Block at 5 minutes after Org 9487 administration

The T1 at 5 minutes after the end of administration of the Org 9487 dose (prior to the administration of neostigmine) was to be recorded (if randomized to this group).

#### Time to Recovery to 25%, 50%, 75% and 90% T1

The time to recovery to 25%, 50%, 75% and 90% T1 was to be recorded. The time intervals between the administration of Org 9487 and the return of the twitch tension to 25% of control T1, to 50% of control T1, to 75% of control T1, and to 90% of control T1 were to be calculated (using the final control as control T1).

#### Time to 70% T4/T1

The time at which T4/T1 returns to 70% was to be recorded. The time interval between the administration of Org 9487 and the return to 70% T4/T1 of the TOF was to be calculated.

#### Time to 80% T4/T1

The time at which T4/T1 returns to 80% was to be recorded. The time interval between the administration of Org 9487 and the return to 80% T4/T1 of the TOF was to be calculated.

### SECTION 9.8.1.2 PROTOCOL AMENDMENTS

There were no protocol amendments to this study.

### SECTION 9.8.1.3 STATISTICAL ANALYSIS

Descriptive statistics (Mean, SD, Median, Minimum, and Maximum) were calculated by treatment group. Three-way analysis of variance (ANOVA) was used for comparing the groups, with Org 9487 dose, reversal agent (time and dose), and center as the three factors, including the interaction terms. Ninety five percent confidence intervals were calculated for pre-defined pairs of treatment groups (e.g., subjects intubated with the same dose of Org 9487 but reversed at 2 minutes versus those at 5 minutes with 0.07 mg/kg of neostigmine, subjects reversed at 2 or 5 minutes versus those who recovered spontaneously, etc.) using the t-distribution. The estimate of the difference between the two groups, standard error, and the degrees of freedom were estimated using the additive model of the three way ANOVA on the untransformed data.

The primary efficacy parameters:

1. Recovery time to 25% of T1 and recovery index. The recovery time to 25% of T1 was defined as the time interval from administration of Org 9487 to return of T1 to 25% of control.
2. The recovery index was defined as the time interval of return of T1 from 25% to 75% of control.

The secondary efficacy parameters:

1. Recovery time to 50%, 75%, and 90% of T1 - defined as the time interval from administration of Org 9487 to return of T1 to 50%, 75%, and 90% of control;
2. Recovery time to 70% (80%) T4/T1 - defined as the time interval from administration of Org 9487 to return of 70% (80%) T4/T1.

T1 prior to neostigmine administration - defined as T1 at 2 or 5 minutes after the end of administration of the Org 9487 dose (prior to administration of neostigmine), according to the neostigmine reversal time (i.e., 2 min or 5 min) the subject was randomized to.

#### Protocol Violations:

A violation of the protocol is defined as a lack of compliance with the protocol interfering with the assessment of efficacy. Protocol violations are of two types- major and minor. Major violations lead to the exclusion of all efficacy data for a subject from the per protocol analysis. Minor violations result in the exclusion of some, but not all, efficacy data for a subject from the per protocol analysis. A deviation from the protocol is defined as a lack of compliance with the protocol not having an impact on assessment of efficacy.

#### MAJOR PROTOCOL VIOLATIONS:

The following were considered major protocol violations.

- Neostigmine dose exceeding 5 mg; Violation of eligibility criteria
- Dose of Org 9487 is greater than or less than 10% of planned dose;
- Dose of neostigmine is greater than or less than 10% of planned dose;
- Time between muscle relaxant and neostigmine is greater than or less than 5% of the randomized time (in seconds);

#### Minor Protocol Violations:

No minor protocol violations were noted.

#### Protocol Deviations:

The following were considered protocol deviations:

- Dose of fentanyl or propofol above or below 10% of planned dose;
- Dose of glycopyrrolate greater than or less than 10% of planned dose.

#### DATA SETS:

The All-Subjects-Randomized Group consists of all subjects who were randomized. The All-Subjects-Treated Group consists of all randomized subjects who received at least one dose of Study medication. Subjects with deviations from the randomization schedule (e.g., wrong dose of Org 9487 or neostigmine, or reversed at a time different from the planned time) were included in treatment groups as per randomization schedule. The Intent-to-Treat Group consists of all subjects treated with study drug and at least one post baseline efficacy assessment of at least one of the primary efficacy variables. The Per Protocol Group consists of all subjects in the Intent-to-Treat Group and with no major

protocol violations. Subjects with incorrect randomization were considered major protocol violators and were excluded from the Per Protocol Group.

### SECTION 9.8.1.4 STUDY CONDUCT

Table 68 Disposition of Subjects by Treatment Group

Data Set	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg					Total
	No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		
		Neostigmine Dose mg/kg					Neostigmine Dose mg/kg				
		.05	.07	.05	.07		.05	.07	.05	.07	
ASR <sup>1</sup>	13	11	12	12	12	12	12	12	11	11	118
AST <sup>2</sup>	13	11	12	12	12	11	12	12	11	11	117
ITT <sup>3</sup>	13	11	12	12	12	11	12	12	11	11	117
PP <sup>4</sup>	11	7	10	12	9	10	12	9	8	9	97

Modified Sponsor's Table 3 Vol 96 p. 0052

1. All Subjects Randomized
2. All Subjects Treated. One subject was discontinued prior to administration of study medication and was excluded from this group
3. Intent to Treat
4. Per Protocol

Table 69 All Subjects Treated Group by Site

Center	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg					Total
	No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		
		Neostigmine Dose mg/kg					Neostigmine Dose mg/kg				
		.05	.07	.05	.07		.05	.07	.05	.07	
1	8	7	8	7	7	7	8	7	7	7	73
2	1	0	0	1	1	1	0	0	0	0	5
8	4	4	4	4	4	3	4	4	4	4	39
TOTAL	13	11	12	12	12	11	12	12	11	11	117

Modified Sponsor's Table 4 Vol 96 p. 0052

There were 20 subjects with major protocol violations. All efficacy data for these subjects were excluded from the Per Protocol efficacy analysis. 11 subjects who received Org 9487 1.5mg/kg and 9 subjects who received Org 9487 2.5 mg/kg were excluded from the Per Protocol Group. There were no minor protocol violations in this study.

Table 70 Protocol Deviations

Protocol Deviation	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min		No Reverse	Neostigmine @ 2 Min		Neostigmine @ 5 Min	
		Neostigmine Dose mg/kg					Neostigmine Dose mg/kg			
		.05	.07	.05	.07		.05	.07	.05	.07
Fentanyl > ± 10% Planned	2	4	4	3	3	4	3	3	1	1
Propofol > ± 10% Planned	1	0	0	1	0	0	0	0	0	0
Glycopymolate > ± 10% Planned		1	5	1	2		2	4	3	4

Modified Sponsor's Table 6 Vol 96 p. 0057

Table 71 Demographic Characteristics: All Subjects Treated Group

Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal (n=13)	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal (n=11)	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05 (n=11)	0.07 (n=12)	0.05 (n=12)	0.07 (n=12)		0.05 (n=12)	0.07 (n=12)	0.05 (n=11)	0.07 (n=11)
Age (yrs)										
Mean	42.8	38.1	41.5	35.7	40.8	36.5	43.7	38.8	38.8	38.3
SD	18.7	13.2	10.1	8.8	8.4	10.6	11.9	12.8	12.3	12.8
Median	41.8	34.0	41.8	33.5	42.8	34.0	45.8	38.5	37.8	37.8
Minimum	20.8	20.0	29.8	27.0	28.0	23.0	23.0	19.0	20.0	20.0
Maximum	88.0	61.0	55.0	48.0	55.0	66.0	82.0	68.0	61.0	58.0
Weight (kg)										
Mean	82.5	83.8	85.8	88.8	84.5	85.8	82.8	83.4	83.4	81.4
SD	8.8	8.1	8.1	7.8	8.8	8.8	9.8	8.2	12.8	12.3
Median	80.3	84.0	85.8	88.5	82.5	86.0	80.5	82.5	84.0	81.4
Minimum	52.0	65.0	49.0	47.8	56.0	54.0	47.2	52.0	48.0	45.5
Maximum	77.8	72.0	87.0	70.0	79.5	79.5	77.0	80.0	80.0	79.5
Height (cm)										
Mean	181.3	183.9	188.8	183.4	185.0	183.8	187.8	185.1	180.9	184.8
SD	4.5	7.0	6.8	6.7	8.4	8.3	8.8	9.8	8.7	11.5
Median	182.0	185.0	188.0	181.5	181.0	182.0	188.0	184.5	182.5	183.0
Minimum	152.0	152.5	151.0	154.9	157.8	152.0	155.0	145.0	142.0	147.0
Maximum	188.0	173.0	173.0	175.8	188.0	173.0	177.8	183.0	172.0	188.0
Gender (n%)										
Male	0	1(9%)	0	1(8%)	1(8%)	1(9%)	2(17%)	3(25%)	2(18%)	2(18%)
Female	13(100%)	10(81%)	12(100%)	11(82%)	11(82%)	10(91%)	10(83%)	8(73%)	9(82%)	9(82%)

Sponsor's Table 7 Vol 96 p. 070010

Table 72 Demographic Characteristics by Race And ASA Status All Subjects Treated Group

Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal (n=13)	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal (n=11)	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05 (n=11)	0.07 (n=12)	0.05 (n=12)	0.07 (n=12)		0.05 (n=12)	0.07 (n=11)	0.05 (n=11)	0.07 (n=11)
Race n(%)	13(100%)	11(100%)	9(75%)	9(75%)	9(75%)	10(91%)	11(82%)	9(75%)	10(91%)	9(73%)
Caucasian	0	0	3(25%)	3(25%)	3(25%)	0	0	3(25%)	0	2(18%)
Asian	0	0	0	0	1(8%)	0	1(8%)	0	0	0
Black	0	0	0	0	0	1(9%)	0	0	1(9%)	1(9%)
Other	0	0	0	0	0	0	0	0	0	0
ASA Class n(%)										
1	18(77%)	7(64%)	9(75%)	10(75%)	9(50%)	9(82%)	9(75%)	7(58%)	7(64%)	9(55%)
2	3(23%)	4(36%)	3(25%)	2(17%)	4(24%)	1(9%)	3(25%)	5(42%)	4(36%)	4(45%)
3	0	0	0	0	0	1(9%)	0	0	0	0

Sponsor's Table 7 Vol 96 p 0060

## SECTION 9.8.1.5 SPONSOR'S EFFICACY RESULTS

For those subjects receiving reversal treatment, T1 was assessed just prior to neostigmine administration. The time of neostigmine administration was either 2 minutes or 5 minutes after muscle relaxant administration. T1 prior to neostigmine administration was 0% for all subjects with the exception of 3 subjects. The 3 subjects with T1 greater than 0% had values of 3, 2 and 1.3%. [Reviewer note: T1 values this low indicate the subjects had a profound degree of neuromuscular blockade.]

Table 73 Recovery Time to 25% of T1: Per Protocol Group

Statistical Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	11	7	10	12	9	10	12	9	8	9
Mean	17.3	8.0	7.6	9.1	9.4	24.0	11.7	12.3	12.4	11.7
SD	5.1	1.9	1.3	1.0	1.4	6.0	1.8	2.2	2.7	2.2
Median	17.1	7.6	7.3	9.3	9.2	24.5	11.7	12.3	12.8	11.8
Minimum	10.8	6.2	6.2	7.4	7.5	16.0	9.3	8.9	7.1	7.9
Maximum	25.7	9.9	10.0	10.8	11.8	32.3	14.0	15.3	15.8	14.7

Sponsor's Table 12 Vol 96 p. 070010

The range of mean recovery times to 25% of T1 for the neostigmine reversal groups vs the no reversal groups was 7.6-9.4 vs 17.3 min and 11.7-12.4 vs 24 min for the Org 9487 1.5 and 2.5 mg/kg dose groups, respectively. Within each dose group of Org 9487 (1.5 and 2.5 mg/kg), the recovery time to 25% of T1 was significantly shorter ( $p < 0.01$ ) for subjects in all of the neostigmine reversal groups relative to that observed in the no reversal groups. Reversal at profound block at 2 or 5 min following 1.5 and 2.5 mg/kg of Org 9487 reduced the recovery time to 25% of T1 by approximately 8 to 12 minutes.

Table 74 Recovery Index (Time to Return of T1 from 25-75%)  
Per-Protocol Group

Statistical Parameter	Org 9427 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	10 <sup>a</sup>	7	10	12	9	10	12	9	8	9
Mean	12.1	4.9	7.0	5.3	6.4	14.8	8.8	11.6	8.5	8.0
SD	5.4	1.1	3.9	2.6	2.3	6.0	3.6	4.6	3.1	3.0
Median	12.0	4.5	5.7	5.2	5.6	12.1	7.4	12.5	8.5	7.3
Minimum	4.1	3.6	3.8	2.5	3.3	10.0	3.0	4.2	3.7	5.0
Maximum	21.6	6.7	16.7	12.7	10.7	27.7	15.2	17.2	13.8	15.5

<sup>a</sup> Subject 172 (Org 9487 1.5 mg/kg, no reversal) was reversed prior to completing neuromuscular function measurements (since surgery terminated earlier than anticipated) therefore the time to return of T1 to 75% was not recorded.

Sponsor's Table 14, Vol 96 P. 0074

The range of mean recovery indices for the neostigmine reversal groups vs. the no reversal groups was 4.9 - 7.0 vs. 12.1 minutes and 8.0 - 11.6 vs. 14.8 minutes for the Org 9487 1.5 and 2.5 mg/kg dose groups, respectively. Within each dose group of Org 9487 (1.5 and 2.5 mg/kg), the recovery index was significantly shorter ( $p < 0.05$ ) for subjects in each of the neostigmine reversal groups relative to that observed in the no reversal groups with the exception of the Org 2.5, neo 0.07 @ 2 min group. In this group, reversal assisted recovery reduced the 25% to 75% recovery time by approximately four minutes compared to 5 to 7 minutes in the other groups.

Summary of Recovery Time (min) to 70% T4/T1, Per Protocol  
Table 75 Recovery Time

Statistical Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	10 <sup>a</sup>	7	10	12	8 <sup>b</sup>	8 <sup>c</sup>	12	9	8	9
Mean	37.9	17.1	15.3	18.5	18.8	56.3	25.8	34.8	32.2	28.1
SD	10.4	4.2	3.2	3.2	7.5	12.5	6.6	8.2	13.4	9.3
Median	42.4	15.8	14.7	16.4	15.4	56.2	23.0	35.4	32.5	27.2
Minimum	23.3	12.1	10.3	11.7	11.7	34.8	17.0	22.0	14.0	16.8
Maximum	53.9	23.1	20.6	23.4	34.9	79.0	39.5	50.0	60.1	47.6

- <sup>a</sup> Does not include Subject 172 because surgery terminated earlier than anticipated and the subject was reversed after T<sub>1</sub> had returned to 50% of control.
- <sup>b</sup> Does not include Subject 203 because the subject's arm was accidentally moved by a surgeon.
- <sup>c</sup> Does not include Subject 131, for whom recovery data was available only to 66% of train-of-four due to completion of surgery prior to full recovery of neuromuscular function, and Subject 204, for whom additional muscle relaxant was required by the surgeon prior to the recovery of T<sub>4</sub>/T<sub>1</sub> to 70%.

Sponsor's Table 16 Vol 96 p. 0078

Table 76 Summary of Recovery Time (min) to 80% T<sub>4</sub>/T<sub>1</sub>, Per Protocol

Statistical Parameter	Org 9487 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
N	8 <sup>a</sup>	7	8 <sup>b</sup>	12	8 <sup>c</sup>	7 <sup>d</sup>	12	9	8	9
Mean	42.9	20.3	20.8	19.2	24.4	59.6	30.5	40.7	38.4	35.7
SD	12.2	5.0	7.3	3.9	7.9	10.5	7.8	9.5	18.4	11.7
Median	49.4	21.3	17.7	19.0	22.9	59.3	27.0	40.5	37.5	31.8
Minimum	28.6	13.3	13.4	13.0	16.3	38.3	19.0	25.7	16.4	21.3
Maximum	62.5	26.4	35.3	28.0	41.9	70.2	44.3	58.0	79.1	63.6

- <sup>a</sup> Does not include Subject 172 because surgery terminated earlier than anticipated and the subject was reversed after T<sub>1</sub> had returned to 50% of control, and Subject 165, for whom relaxation was required for surgery after recovery to 70% T<sub>4</sub>/T<sub>1</sub>.
- <sup>b</sup> Does not include Subject 141 due to recording instrument gain becoming erratic and variable after recovery to 70% T<sub>4</sub>/T<sub>1</sub>.
- <sup>c</sup> Does not include Subject 203 because the subject's arm was accidentally moved by a surgeon.
- <sup>d</sup> Does not include Subject 113 because the subject was awakened before recovery to 80% T<sub>4</sub>/T<sub>1</sub>, Subject 131, for whom recovery data was available only to 66% of train-of-four due to completion of surgery prior to full recovery of neuromuscular function, and Subject 204, for whom additional muscle relaxant was required by the surgeon prior to the recovery of T<sub>4</sub>/T<sub>1</sub> to 70%.

Sponsor's Table 17 Vol 96 P. 0079

The range of mean recovery times to 70% of T<sub>4</sub>/T<sub>1</sub> for the neostigmine reversal groups vs. the no reversal groups was 15.3 - 18.8 vs. 37.9 minutes and 25.8 34.8 vs 56.3 minutes for the Org 9487 1.5 and 2.5 mg/kg dose groups, respectively. The range of mean recovery times to 80% of T<sub>4</sub>/T<sub>1</sub> for the neostigmine reversal groups vs. the no reversal groups was 19.2 - 24.4 vs. 42.9 minutes and 30.5 - 40.7 vs. 59.6 minutes for the Org 9487

1.5 and 2.5 mg/kg dose groups, respectively. Within each dose group of Org 9487 (1.5 and 2.5 mg/kg), the recovery times to 70% and 80% of T4/T1 were significantly shorter ( $p < 0.05$ ) for subjects in each of the neostigmine reversal groups relative to that observed in the no reversal groups. Reversal with neostigmine (0.05 or 0.07 mg/kg) at 2 or 5 minutes after Org 9487 administration shortened the recovery time to 70% (and 80%) of T4/T1 by at least 40%.

Table 77 RECOVERY TIME TO 50%, 75% AND 90% OF T1

Statistical Parameter	Org 9427 1.5 mg/kg					Org 9487 2.5 mg/kg				
	No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min		No reversal	Neostigmine @ 2 min		Neostigmine @ 5 min	
		Neostigmine dose (mg/kg)					Neostigmine dose (mg/kg)			
		0.05	0.07	0.05	0.07		0.05	0.07	0.05	0.07
Time to 50% of T <sub>1</sub>										
N	11	7	10	12	9	10	12	9	8	9
Mean	24.1	10.2	9.9	11.0	11.7	30.7	14.6	17.7	16.1	14.6
SD	9.2	1.7	2.1	1.6	2.0	7.0	2.5	3.6	3.9	2.7
Median	21.5	10.0	9.2	11.3	12.0	30.0	14.9	16.7	16.4	14.3
Minimum	14.2	7.6	7.1	8.5	9.1	22.2	10.7	11.1	8.4	10.2
Maximum	45.0	12.8	14.5	14.7	15.0	46.9	17.5	22.9	21.3	20.2
Time to 75% of T <sub>1</sub>										
N	10	7	10	12	9	10	12	9	8	9
Mean	28.5	12.9	14.6	14.3	15.8	38.9	20.3	23.9	20.9	19.7
SD	9.3	2.2	4.8	3.4	2.8	9.1	4.2	5.8	5.6	4.6
Median	27.3	12.3	13.0	14.3	15.2	35.8	21.4	23.3	21.0	18.9
Minimum	18.3	9.8	10.5	10.0	12.5	27.8	12.3	13.1	10.8	12.9
Maximum	46.2	16.6	26.7	23.4	20.9	60.0	25.6	31.7	29.6	30.2
Time to 90% of T <sub>1</sub>										
N	10	7	10	12	9	10	12	9	8	9
Mean	33.3	15.5	17.4	16.6	18.9	44.8	24.8	31.3	29.8	24.3
SD	9.8	2.8	5.9	3.7	3.8	11.2	5.2	8.0	12.4	6.3
Median	31.3	15.5	15.4	16.9	17.8	40.6	24.3	31.0	27.2	22.8
Minimum	21.8	11.9	12.3	11.6	14.2	33.0	14.3	15.9	14.0	15.2
Maximum	53.3	20.1	31.5	25.5	25.4	71.2	33.0	39.0	57.4	38.7

Sponsor's Table 20 Vol 96 p. 0086

Within each dose group of Org 9487 (1.5 and 2.5 mg/kg), the mean recovery times to 50% (and 75% and 90%) were shorter for each of the neostigmine reversal groups than the recovery times for the corresponding no reversal groups. For the Org 1.5 mg/kg dose group, the range of mean recovery times to 50%, 75%, and 90% of T1 for the neostigmine reversal groups vs. the no reversal groups was 9.9 - 11.7 vs. 24.1 minutes, 12.9 - 15.8 vs. 28.5 minutes, and 15.5 - 18.9 vs. 33.3 minutes, respectively. For the Org 9487 2.5 mg/kg dose group, the range of mean recovery times to 50%, 75% and 90% of T1 for the neostigmine reversal groups vs. the no reversal groups was 14.6 - 17.7 vs. 30.7

minutes, 19.7 - 23.9 vs. 38.9 minutes, and 24.3 - 31.3 vs, 44.8 minutes, respectively. Within each group, reversal at profound block reduced the mean recovery time to 90% of T1 by approximately 15 minutes.

Table 78 Treatment Differences at 95% Confidence Intervals  
Per Protocol and Intent to Treat Groups

Efficacy parameter	Subject data set	Estimate of difference (95% confidence interval)			
		Neostigmine 0.05 mg/kg @ 2 min vs. No reversal	Neostigmine 0.07 mg/kg @ 2 min vs. No reversal	Neostigmine 0.05 mg/kg @ 5 min vs. No reversal	Neostigmine 0.07 mg/kg @ 5 min vs. No reversal
<b>Org 9487 1.5 mg/kg</b>					
Recovery time to 25% of T <sub>1</sub>	Per Protocol	-8.3 [-13.2, -4.4]	-8.8 [-13.1, -4.4]	-8.3 [-11.2, -6.5]	-7.9 [-11.4, -4.4]
	Intent-to-Treat	-8.8 [-11.8, -6.8]	-9.2 [-12.0, -6.3]	-7.9 [-10.6, -6.1]	-7.4 [-10.4, -4.4]
Recovery index	Per Protocol	-7.2 [-11.8, -2.8]	-8.1 [-9.7, -6.5]	-8.9 [-10.8, -3.1]	-8.8 [-9.8, -1.4]
	Intent-to-Treat	-8.5 [-10.2, -2.8]	-8.1 [-9.1, -1.0]	-8.7 [-10.4, -3.0]	-6.5 [-8.5, -1.8]
Recovery time to 80% of T <sub>1</sub>	Per Protocol	-22.1 [-34.0, -12.3]	-22.3 [-32.7, -11.8]	-24.2 [-32.2, -16.3]	-18.2 [-29.5, -6.9]
	Intent-to-Treat	-19.8 [-28.6, -11.0]	-20.2 [-29.2, -11.2]	-23.6 [-31.1, -16.2]	-19.4 [-28.6, -10.1]
<b>Org 9487 2.5 mg/kg</b>					
Recovery time to 25% of T <sub>1</sub>	Per Protocol	-12.3 [-18.4, -6.2]	-12.4 [-18.9, -9.0]	-12.0 [-16.2, -7.8]	-12.4 [-16.4, -6.6]
	Intent-to-Treat	-11.2 [-14.9, -7.5]	-11.3 [-15.0, -7.7]	-10.7 [-14.7, -6.9]	-11.1 [-15.3, -6.9]
Recovery index	Per Protocol	-8.3 [-10.7, -1.8]	-3.6 [-9.0, 1.8]	-8.8 [-11.7, -1.8]	-8.8 [-11.7, -2.0]
	Intent-to-Treat	-8.1 [-10.3, -1.8]	-3.8 [-8.0, 0.4]	-8.0 [-10.0, -1.8]	-8.2 [-10.6, -1.8]
Recovery time to 80% of T <sub>1</sub>	Per Protocol	-29.1 [-38.2, -19.9]	-19.8 [-31.0, -8.5]	-21.2 [-30.4, -2.9]	-23.2 [-35.1, -11.2]
	Intent-to-Treat	-29.1 [-38.2, -19.9]	-22.5 [-32.4, -12.6]	-22.1 [-37.0, -7.2]	-24.3 [-37.1, -11.5]

Sponsor's Table 21 Vol 96 p. 0088

For the efficacy parameters recovery time to 25% of T<sub>1</sub>, recovery index, and recovery time to 80% T<sub>4</sub>/T<sub>1</sub>, the estimated treatment differences and the corresponding 95% confidence intervals using the Per Protocol Group and Intent-to-Treat Group yield similar results.

#### SECTION 9.8.1.6 REVIEWER'S EFFICACY DISCUSSION:

The objective of this study was to compare spontaneous recovery of 1.5 mg/kg Org 9487 and 2.5 mg/kg Org 9487 using electromyographic parameters after reversal with 0.05 and 0.07 mg/kg neostigmine at two minutes and five minutes. The parameters of recovery to 25% T<sub>1</sub>, recovery index (defined as the time to return of T<sub>1</sub> from 25% to 75%), recovery to 50%, 75%, and 90% T<sub>1</sub>, and recovery to 70% and 80% T<sub>4</sub>/T<sub>1</sub> were evaluated for each Org 9487 dose group based either on spontaneous recovery or on reversal. The Per Protocol group consisted of 97 out of 117 subjects treated.

The mean recovery time to 25% of T<sub>1</sub> for both the 1.5 and 2.5 mg/kg Org 9487 dose groups was significantly shorter ( $p < 0.01$ ) when compared to the spontaneous recovery group. The time to recovery of 25% of T<sub>1</sub> is sometimes noted as the Clinical Duration. When the neuromuscular activity returns to 25% of control, a maintenance dose or an

infusion of the neuromuscular blocking agent can be administered if further relaxation is required.

The Recovery Index for the 1.5 mg/kg Org 9487 reversal dose groups was significantly shorter ( $p < 0.05$ ) than the spontaneous recovery group. Except for the 2 minute neostigmine 0.07 mg/kg subgroup, the 2.5 mg/kg Org 9487 reversal groups had a significantly shorter ( $p < 0.05$ ) Recovery Index when compared with the spontaneous recovery group. The Recovery Index is a useful parameter to compare the rapidity of recovery with different agents.

The recovery time to 70% and 80% T4/T1 (TOF) ratio is the most clinically useful parameter of the study. These parameters signal that there is satisfactory clinical recovery, that the airway is protected, and ventilatory regulation has recovered adequately. Some earlier studies have reported adequate recovery at a T4/T1 ratio of 70%. Newer data suggests adequate clinical recovery correlates with a TOF ratio of 75 or 80%. For the TOF to 80%, both the 1.5mg/kg and 2.5 mg/kg Org 9487 dose groups had significantly shorter ( $p < 0.05$ ) recovery times than the spontaneous recovery groups.

Reversal with either 0.05 or 0.07 mg/kg neostigmine at either 2 or 5 minutes after administration of 1.5 or 2.5 mg/kg Org 9487 significantly shortened the time to recovery compared to spontaneous recovery.

## **SECTION 9.9.1 OTHER SUPPORTING CLINICAL TRIALS**

### **SECTION 9.9.1.1 STUDY 070005**

**TITLE:** A Parallel Group Comparative, Randomized, Multi-Center Study to Compare the Time Course of the Neuromuscular Effects and Safety of Two Org 9487 dose Groups, Mivacurium, and Succinylcholine in Adult Subjects

This study was designed to compare the time course of two intubating doses of Org 9487 with those of the recommended intubating doses of mivacurium chloride (0.25 mg/kg in divided doses) and succinylcholine (1 mg/kg). The cardiovascular parameters of the 2 doses of Org 9487 were compared to those of mivacurium and succinylcholine until 10 min after administration of the relaxant. Plasma samples from selected subjects were also used for a population based PK analysis.

The study was an open label, parallel group, comparative randomized multi-centered study conducted at four sites. 125 subjects received study medication as follows: 33 subjects to the 1.5mg/kg Org 9487 group, 29 subjects to the 2.5 mg/kg Org 9487 group, 31 subjects to the succinylcholine group, and 32 subjects to the mivacurium group. ASA

Class 1, 2, or 3 adults  $\geq$  18 years underwent surgery under balanced anesthesia consisting of propofol, fentanyl, and nitrous oxide were included. Org 9487 and succinylcholine were to be administered as single boluses over 5 seconds, while mivacurium was given in 2 divided doses (0.15 mg/kg followed in 30 sec by 0.10 mg/kg).

The following criteria were evaluated: block at 60 sec; time to 80% depression of T1; maximum block (peak effect); onset time; clinical duration (time of recovery to 25% of control twitch); recovery rate (25-75% T1); duration to 70% T4/T1; and duration to 80% T4/T1 (for Org 9487 and mivacurium) and duration to 90% T1. Cardiovascular function was also evaluated.

Efficacy analysis demonstrated the following:

- Mean time to 80% depression of T1 was not significantly different from succinylcholine (48.4 sec) for either the 1.5 mg/kg Org 9487 dose (56.2 sec) or the 2.5 mg/kg Org 9487 dose (47.7 sec).
- The mean Onset Time for succinylcholine (66.5 sec) was comparable to the 2.5 mg/kg Org 9487 dose (68.2 sec) and shorter than the 1.5 mg/kg dose (97.6 sec;  $p < 0.01$ ).
- The recovery profile of both Org 9487 dose groups was longer compared to succinylcholine ( $p < 0.01$  for all comparisons). Mean Clinical Duration (return of T1 to 25%) was 15.4 min for the 1.5 mg/kg Org 9487 dose and 25.0 min for the 2.5 mg/kg Org 9487 dose compared to 9.0 min for succinylcholine.
- Recovery time to 90% T1 was 27.4 min for Org 9487 1.5 mg/kg, 41.6 min Org 9487 2.5 mg/kg, and 11.5 min for succinylcholine.
- Mean recovery rate (time from 25% to 75% block) was 8.3 min for the 1.5 mg/kg Org 9487 group and 13 min for the 2.5 mg/kg Org 9487 group and 2.1 min for succinylcholine.

#### SECTION 9.9.1.2 STUDY 174305

**TITLE:** The effects of Org 9487, succinylcholine, and vecuronium on the intraocular pressure, blood pressure and heart rate.

This was an open label, parallel group, comparative, randomized, single center study. The purpose was to compare the effects of Org 9487, succinylcholine and vecuronium on the intraocular pressure, blood pressure and heart. The study involved healthy adult subjects undergoing elective ophthalmic surgery under general anesthesia. There were a total of

25 subjects enrolled with 9 being exposed to a single bolus dose of Org 9487 at 1.5 mg/kg.

The following results were noted:

- In the subjects in the succinylcholine group, an increase in intraocular pressure was observed following succinylcholine, while in subjects in the Org 9487 group, a decrease in intraocular pressure was recorded. Over a period of 3 minutes following the administration of the muscle relaxant, the mean percentage change of the IOP from base line was statistically significant different for subjects in the succinylcholine group as compared to those in the Org 9487 group.
- No statistically significant differences in percentage change of the IOP from baseline /pre-intubation value were observed between Org 9487 and vecuronium.
- Sponsor states (Reviewer agrees) no firm conclusions can be drawn from this study because of the small number of subjects participating (succinylcholine N=7; Org 9487 N= 8) in the Per Protocol analysis and because of the high variability observed within the treatment groups at the various time points of assessment.
- Reviewer notes that no non-depolarizing relaxant was administered prior to succinylcholine. This is a common clinical practice used to attenuate the known increase in intraocular pressure from succinylcholine.

### SECTION 9.9.1.3 STUDY 070003

**TITLE:** A Study to Determine the Pharmacokinetics and Pharmacodynamics of Org 9487 in Adults With Renal Failure Compared to Adult Volunteers With Normal Renal Function.

This was an open label, non-randomized, single center study enrolling 10 adult end stage renal disease subjects undergoing elective surgery (shunt surgery or cannula insertion) under propofol anesthesia and 10 volunteers with normal renal function. A dose of 1.5 mg/kg of Org 9487 was administered as a rapid 5 sec bolus. The primary efficacy parameters that were studied were onset time and clinical duration. The secondary efficacy parameters were T1 at 60 sec, maximum block (peak effect), recovery rate, and duration to 70% and 80% T4/T1. Efficacy analyses compared assessments measured at the adductor pollicis of the normal volunteers to corresponding assessments of the renal subjects.

Efficacy analysis demonstrated the following:

- For the normal volunteers, onset time was 66 sec, a clinical duration of 12.8 min, a recovery rate of 8.2 min, duration to 70% T4/T1 of 28.4 min, and duration to

80%T4/T1 of 31.3 min. For the renal subjects, onset time was 83 sec, a clinical duration of 11.8 min, a recovery rate of 12.2 min, duration to 70% T4/T1 of 33.1 min and duration to 80% T4/T1 of 39.6 min.

- Although mean pharmacodynamic parameters were generally greater for the renal patients, there were no statistically significant differences between the normal volunteers and the renal subjects for any of these parameters.

#### SECTION 9.9.1.4 STUDY 174309

**TITLE:** Evaluation of the Neuromuscular Parameters and the Pharmacokinetics of Org 9487 in Patients with Liver Cirrhosis

This was an open label, parallel group comparative, non-randomized, single center study that involved a single bolus dose of 1.5 mg/kg Org 9487 in cirrhotic patients compared with healthy controls. The patients were adults scheduled for elective peripheral surgery or endoscopy under general anesthesia. The study enrolled 6 evaluable cirrhotic and 7 evaluable control subjects. The patients underwent general anesthesia with thiopental, fentanyl, nitrous oxide/oxygen. 100% of patients received isoflurane after intubation until T4/T1 reached a level of 0.8.

Efficacy criteria evaluated were onset time, maximum block, intubation score, T1 at time of intubation, time to T1 25% recovery, recovery time (25-75), time to T1 90% recovery, time to T4/T1 0.7 and 0.8 recovery.

Efficacy analysis demonstrated the following:

- For the neuromuscular parameters, no statistically significant difference was observed between the control and the cirrhotic subjects.
- This reviewer finds this study to be of very limited usefulness. There were only 4 or 5 cirrhotic patients evaluable for the neuromuscular parameters or intubating conditions. In addition, isoflurane, a known potentiator of non-depolarizing relaxants, was administered until T4/T1 recovery reached 0.8. This obscures any conclusions that can be reached regarding duration of action in this patient population.

#### SECTION 9.9.1.5 STUDY 070002

**TITLE:** A Study to Determine the Potency and Safety of Org 9487 in Children and Neonates.

This was an open label, parallel group, comparative, randomized, study at 2 sites involving 75 subjects undergoing elective surgery under I.V. anesthesia. The study involved 15 neonates, 30 infants, and 30 children ( $\geq 1$  year to  $< 13$  year). The primary efficacy objective was to estimate the potency of Org 9487 by determining the ED50 (dose which produces a 50% depression of twitch height). Also evaluated were peak effect (maximum depression of T1) and onset time. The ED50 was determined in 3 ways: linear regression of probit of percent twitch depression on log dose, linear interpolation, and non-linear regression (Hill Equation). Subjects were randomized into one of 3 dose groups: 0.3, 0.6, or 0.9 mg/kg Org 9487. The dose was administered as a rapid 5 second bolus injection after induction with propofol or thiopental (maintenance with propofol, thiopental, N2O).

Efficacy analysis demonstrated the following:

- Table 79 ED50 Estimate

Group	N	Probit	Linear Interpolation	Hill Equation
Neonates	15	0.32 [0.15-0.61]	0.38	0.33
Infants	28	0.28 [0.11-0.61]	0.35	0.32
Children	30	0.39 [0.17-0.85]	0.42	0.39

Sponsor's Table 12 Vol 79 p. 0060

The estimate of ED50 of Org 9487 was approximately 0.3 mg/kg in the Neonates and Infants groups. The ED50 of the Children's group was estimated to be 0.4 mg/kg.

• Table 80 Percent Twitch Depression (Per Protocol)

Parameter	Dose Group		
	0.3 mg/kg	0.6 mg/kg	0.9 mg/kg
Neonates N=15			
N	5	5	5
Mean ± SD	34 ± 28	98 ± 3	99 ± 2
Median	27	100	100
Min-Max	10-80	92-100	97-100
Infants N=28			
N	8	9	11
Mean ± SD	41 ± 34	96 ± 7	100 ± 1
Median	26	100	100
Min-Max	17-100	80-100	97-100
Children N=30			
N	9	10	11
Mean ± SD	29 ± 23	83 ± 112	90 ± 16
Median	25	88	100
Min-Max	4-73	63 - 95	55-100

Sponsor's Table 13 Vol79 p. 0061

• Table 81 Onset Time (Per Protocol)

Parameter (Seconds)	Dose Group		
	0.3 mg/kg	0.6 mg/kg	0.9 mg/kg
Neonates N=15			
N	5	5	5
Mean ± SD	95 ± 18	84 ± 35	57 ± 20
Median	92	62	46
Min-Max	72-113	54-134	42-90
Infants N=28			
N	8	9	11
Mean ± SD	108 ± 51	83 ± 37	62 ± 29
Median	101	73	52
Min-Max	42-216	31-140	34 - 132
Children N=30			
N	9	10	11
Mean ± SD	128 ± 70	112 ± 25	96 ± 33
Median	121	110	89
Min-Max	60-298	77 - 170	50 - 143

Sponsor's Table 14 Vol 79 p. 0062

Higher doses of Org 9487 result in a faster onset. In the Neonate group, the onset time decreased from 92 sec to 46 sec when the dose was increased from 0.3 m/kg to 0.9 mg/kg. In the Infants group, the onset time decreased from 101 sec to 52 sec when the

dose was increased from 0.3 to 0.9 mg/kg. In the Children's group the onset time decreased from 121 sec to 89 sec when the dose was increased from 0.3 to 0.9 mg/kg.

#### SECTION 9.9.1.6 STUDY 070004

**TITLE: A Study to Determine the Potency and Safety of Org 9487 in Geriatric and Non-Geriatric Adults.**

This was an open label, randomized, single dose study done at 2 sites. The primary efficacy objective was to determine the ED<sub>50</sub> (potency), peak effect, and onset of Org 9487 in adult subjects undergoing elective general surgery under propofol and alfentanil anesthesia. The ED<sub>50</sub> was determined separately for 11 geriatric ( $\geq 65$  years) and 29 non-geriatric adults ( $18 < 65$ ). One of 3 doses (0.3 mg/kg, 0.6 mg/kg, or 0.9 mg/kg) of Org 9487 was to be randomly administered as a rapid 5 sec bolus after intubation and a stable anesthetic level had been achieved.

Efficacy analysis demonstrated the following:

- ED<sub>50</sub>: This parameter was calculated using probit values, linear interpolation and the Hill equation:

Table 82: ED<sub>50</sub> (mg/kg) Estimate (95% CI) Per Protocol Group

GROUP	N	PROBIT	LINEAR	HILL
Non Geriatric	29	0.33 [0.16,0.62]	0.35	0.32
Geriatric	11	0.2 [Not estimable]	NE	0.27
All	40	0.3 [0.12, 0.69]	0.32	0.31

Sponsor's Table 11 Vol82, p 0060

The ED<sub>50</sub> in non-geriatric adults ranged from 0.32-0.35 mg/kg; for geriatric adults, the ED<sub>50</sub> ranged from 0.20-0.27 mg/kg. Sponsor proposes 0.3 mg/kg as a reasonable estimate of ED<sub>50</sub> given the proximity of the estimate and the observed median values for twitch depression of 46% for the non-geriatric and 51% for the geriatric subject groups [see following table on Twitch Depression].

- Percent Twitch Depression was summarized for each dose group and presented in the following table: