

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20984

MEDICAL REVIEW(S)

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

<u>Brand Name:</u>	Raplon
<u>Generic Name:</u>	Rapacuronium Bromide
<u>Indication:</u>	Neuromuscular Blocking Agent
<u>NDA Classification:</u>	1S
<u>NDA Number:</u>	20-984
<u>Original Receipt Date:</u>	29 June 1998
<u>Clinical Reviewer:</u>	Charles R. Cortinovic, MD MPH
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SECTION 1.0 MATERIALS USED IN REVIEW

Table 1 MATERIALS UTILIZED IN REVIEW

ITEM	DATE	MATERIAL
Volume 1,2,3	29 June 98	Summary and Proposed Labeling
Volumes 77-198	29 June 98	Clinical Data
Volume 1.1	27 October 98	120 Day Safety Update
Volume 1.1	24 February 99	Additional Draft Labeling
Amendment	15 September 98 (Stamp)	Additional Information Study 070007
Amendment	19 October 98 (Stamp)	Additional Information Study 174308
By Fax	2 February 99	Demographic Table
By Fax	24 February 99	EMG Definitions/Descriptions
By Fax	25 February 99	WHOART Definitions
By Fax	1 March 99	Creatine Kinase Material
By Fax	17 March 99	CRF Intracranial Pressure Study

SECTION 2.0 BACKGROUND

SECTION 2.1 INDICATION

Raplon™ is a nondepolarizing neuromuscular blocking agent indicated for outpatients and inpatients as an adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgical procedures.

SECTION 2.2 RELATED NDA'S AND IND'S

There are no related NDA's. The only IND is

SECTION 2.3 PROPOSED DIRECTIONS FOR USE

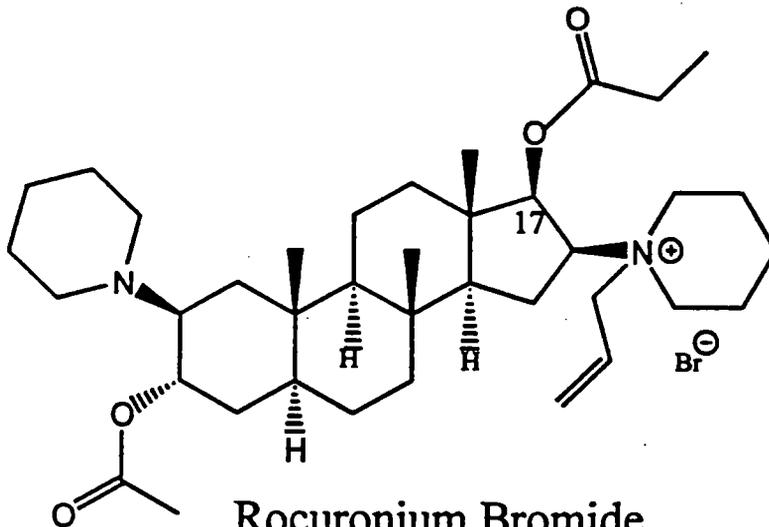
Raplon™ is intended for intravenous use only. The recommended dose of Raplon™ in adult and geriatric patients is 1.5 mg/kg. In pediatrics (ages 2 months to 12 years), initial doses of 2 mg/kg intravenously under halothane anesthesia produce acceptable intubating conditions within 60 seconds.

SECTION 2.4 FOREIGN MARKETING

Rapacuronium is not marketed anywhere in the world.

SECTION 3.0 CHEMISTRY

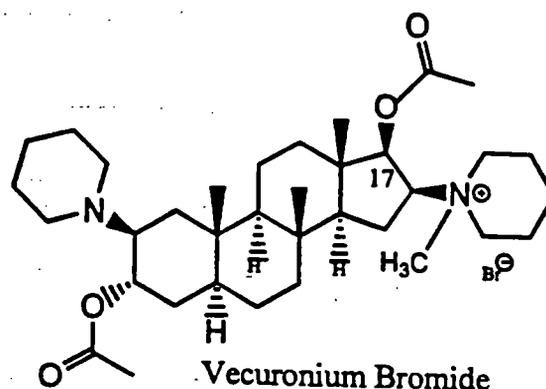
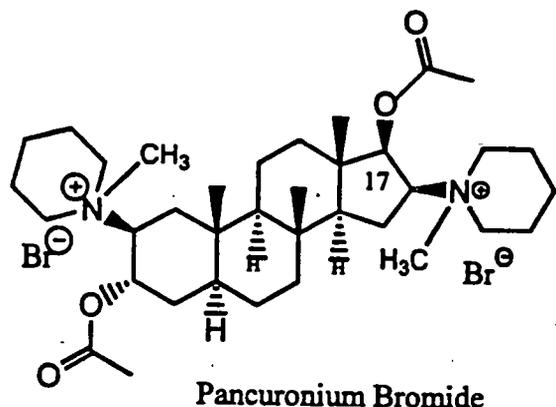
Raplon™ (Rapacuronium bromide) is chemically designated as a synthetic steroid molecule with a mono-quaternary ammonium structure. This chemical structure has a basic steroid framework similar to other neuromuscular blocking agents like vecuronium, pancuronium, rocuronium, and pipecuronium. Rapacuronium is closest in structure to vecuronium and pancuronium. It differs from vecuronium at the quaternary ammonium site and at the 17-hydroxy ester. Pancuronium is the di-quaternary ammonium salt of vecuronium.



Rocuronium Bromide

Chemical formula: $C_{37}H_{61}BrN_2O_4$

Molecular Weight: 667.79



The drug product is supplied as a sterile lyophilized cake in strengths of 100 mg/ 5 mL vial and 200 mg /10 mL vial. However, when each of these vials are appropriately reconstituted with bacteriostatic water (5 mL and 10 mL, respectively), the product obtained contains 20 mg per mL of rapacuronium bromide. The lyophilized cake contains the following inactive ingredients: citric acid anhydrous, mannitol, sodium phosphate buffer, and either sodium hydroxide or phosphoric acid to buffer and adjust the pH. Each of the reconstituted solutions is isotonic and has a pH of 4. It should be noted that the solution is not preserved and therefore is meant for single use only.

SECTION 4.0 ANIMAL PHARMACOLOGY/TOXICOLOGY

The following is a summary of the pharmacology/toxicology information provided by the sponsor:

General toxicity studies comprised both acute and subacute treatment regimens in four animal species: rat, rabbit, cat and dog. Special toxicity studies included induction of malignant hyperthermia in swine and local irritation in rabbits. Impurities and degradation products of Org 9487 were tested in a separate acute toxicity study in dogs. Intracellular distribution of Org 9487 and effects on cellular functions were investigated using rat hepatocytes. Developmental toxicity studies comprised treatment of pregnant rats and rabbits with assessment of effects on embryonic and fetal development. Genotoxic activities of Org 9487 were evaluated in a series of tests for mutagenicity and clastogenicity. ¹⁴C-labeled Org 9487 were performed to determine the distribution, metabolism and excretion of Org 9487.

In anesthetized cats, pigs, and monkeys, Org 9487 (90% and 2-3 times the 90% blocking doses) produced no effect or consistent small, dose-dependent decreases in arterial pressure and either no effect or a small increase in heart rate.

A screening study was conducted in rats to determine if Org 9487 possessed any estrogenic, androgenic, anabolic, gonad inhibiting, glucocorticoid-like or related hormonal activities. Org 9487 was administered at 1.22 and 2.45 mg/kg/day subcutaneously for 7 days. At the daily doses administered, Org 9487 was not considered to possess any relevant hormonal activity.

Two studies on local irritation were conducted using rabbits. The first was an IM study designed to support an IM study in infants. The second study was a more extensive study using the proposed and accidental routes of administration. IM injection of Org 9487 caused no compound specific signs of local irritation. The second study was to assess the irritation potential following the intended IV and IM routes as compared to accidental intra-arterial or paravenous routes of administration. The results displayed signs of local irritation characteristic for mechanical injury caused by the injection procedure.

A study was carried out to assess whether Org 9487 will trigger malignant hyperthermia (MH) in known malignant hyperthermia susceptible swine. Org 9487 was not a MH trigger in susceptible swine.

Subacute systemic and local toxicity of Org 9487 were evaluated in anesthetized mechanically ventilated dogs and cats following IV bolus injection for twice a week for three doses 30 minutes apart. High dose treatment (3 x 6.0mg/kg) in dogs caused no ECG changes following the initial dose. However, QT prolongation was observed pre-dose after 4 weeks. Sponsor claims the appearance of drug related changes after 4 weeks could not be related to drug accumulation because of stable plasma concentration-versus-time curves during the first to fourth week. Sponsor also states the QT effects have no clinical relevance for humans because Org 9487 is a single use drug (single bolus dose, or bolus and maintenance doses); the QT prolongation is a mild adverse effect; there is no correlation with any histopathological effect; and the effects were observed at the high dose of 3 x 6 mg/kg but not at the intermediate or low dose.

Reproductive toxicity studies were performed in pregnant rats and rabbits during the period of organogenesis of the developing embryo. A variety of genotoxicity studies were carried out. Org 9487 displayed no teratogenic or genotoxic properties.

Plasma protein binding was established for dog, cat and human plasma by equilibrium dialysis. The protein binding was rather variable which was at least partly due to hydrolysis of Org 9487 to its 3-hydroxy metabolite Org 9488. For all species tested the in-vitro plasma protein binding of Org 9487 was < 90%.

SECTION 5.0 SUMMARY OF HUMAN PHARMOKINETICS

The pharmacokinetic profiles of Org 9487 and Org 9488 were based on data from 24 US and Non-US studies involving 397 subjects. The sponsor has summarized the human pharmacokinetics and bioavailability data as follows:

"Raplon™ for injection plasma concentration data were best described by a three compartment mammillary model. The pharmacokinetic model was parametrized in clearances and volumes. Estimates of these parameters were used subsequently to calculate volume. The volume of distribution for Raplon™ at steady state was 292 mg/kg

in adult patients. The rapid distribution half-life was 4.56 minutes and the slow distribution half-life was 27.8 minutes. Based on urinary excretion data, it is estimated that less than 10% of administered Raplon™ is metabolized to the 3-OH metabolite of Raplon™. The highest plasma levels of this metabolite occur within the first 10 minutes after Raplon™ administration and decreases rapidly, parallel to the decrease of Raplon™ during the first hour, after which the 3-OH metabolite decreases more slowly than Raplon™.

"Mean clearance value of Raplon™ for adult patients was 6.56 mg/kg/min while the $T_{1/2\beta}$ elimination half-life was 141 minutes. Approximately 7.5% of the administered Raplon™ was recovered from urine up to 48 hours after dosing as unchanged Raplon™ and approximately 5% as the 3-OH metabolite. Almost all of the Raplon™ excreted in the urine appears within the first 6 hours, while < 50% of the excreted 3-OH metabolite is recovered within this period.

"Special Populations:

Geriatrics: Total plasma clearance of Raplon™ decrease with increasing age; however, no dosage adjustments were determined to be necessary for geriatric patients.

Pediatrics: In pediatric patients with ages ranging from 0.025 to 12 years (median 3 years), the plasma concentration data were best described by a three compartment model in which all PK parameters were proportional to body weight. The volume of distribution at steady state is 495 ml/kg and the elimination half-life is 262 min.

Gender: Studies do not reveal any differences in pharmacokinetics of Raplon™ due to gender.

Race: Race was not examined as a covariate in the pooled pharmacokinetic analysis of Raplon™."

In renal insufficiency, an open label, single center, single dose of 1.5 mg/kg IV Org 9487 was conducted in 20 adult subjects (10 with end-stage renal failure). The renal group had a lower total plasma clearance (3.41 vs. 22.2 mg/kg/min renal vs. normal respectively). The renal failure patients also had a longer elimination half-life (1052 vs 170 min) as compared with normal subjects.

In hepatic insufficiency, an open label non-randomized, single center study was performed in 10 subjects with cirrhosis and 10 control subjects with normal liver function. Subjects received a single 1.5 mg/kg bolus dose of Org 9487. Plasma clearance and volume of distribution at steady state were found to be greater in cirrhotic patients compared to patients with normal liver function. Sponsor states that the higher clearance in cirrhotics is difficult to explain.

An excretion balance study (174104) was performed to determine the amount of radioactivity in urine, feces and expired air by injecting ¹⁴C-labeled Org 9487. This investigation was a single center, open-label, single dose of 1.5 mg/kg ¹⁴C-labeled Org.

Six healthy male subjects, aged 28 to 41 years with a body mass between 70 and 89 kg were enrolled into the trial; all completed the study without significant adverse effects. On the morning before anesthesia, the subjects received sublingual lorazepam (1.25 mg). Atropine 0.25 mg IM was administered a few minutes before anesthesia. Induction of anesthesia was obtained in all the subjects with alfentanil (0.5-1 mg), propofol (160-200mg) and lidocaine 20 mg. The subjects were mechanically ventilated with O₂ enriched room air via a laryngeal mask. Anesthesia was maintained until the ventilatory function was recovered to an adequate level.

The radiocarbon label was excreted to about the same extent in urine and feces at a very slow rate. Mean total recovery of radiocarbon after 13 ½ days was 56.1%. The estimated total amount of radiocarbon excreted over 24 hours in expired carbon dioxide was 0.6% (mean) of the administered dose. The apparent elimination half-life was estimated to be approximately 22 days, suggesting that the excretion could be achieved after several weeks. Radiocarbon was still detected in urine and feces up to 6 weeks after injection.

SECTION 6.0 DESCRIPTION OF CLINICAL DATA SOURCES

The clinical development plan for the development of Org 9487 was conducted jointly by Organon Inc (US) and Organon Teknika (The Netherlands). Nineteen controlled clinical studies are presented in the Integrated Summary of Effectiveness Data and an overall summary of safety data of twenty seven controlled clinical studies are presented in the Integrated Summary of Safety Information. A separate Summary of Controlled Clinical Studies was not submitted with the Application.

SECTION 7.0 DEMOGRAPHICS

See Section 10.2

SECTION 8.0 EXTENT OF EXPOSURE

See Section 10.1

SECTION 9.0 EFFICACY FINDINGS

SECTION 9.1 OVERVIEW OF CLINICAL STUDIES:

Nineteen completed clinical studies (9 US, 10 Non-US) were presented in the Integrated Summary of Effectiveness in support of efficacy claims for this Application. No specific studies were described or claimed as pivotal for the submission.

SECTION 9.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY:

SECTION 9.2.1 STUDY 070007

SECTION 9.2.1.1 PROTOCOL REVIEW SUMMARY:

TITLE: Evaluation of the Intubating Conditions Provided With Org 9487 and Succinylcholine

OBJECTIVES:

Primary: To evaluate the intubating conditions provided with Org 9487 and succinylcholine when used in subjects scheduled for elective surgery using general anesthesia.

Secondary: 1. To evaluate, in an uncalibrated mode, the time course of action: Time to return of the first twitch (for subjects receiving Org 9487 and succinylcholine), time to return of the third twitch (for subjects receiving Org 9487 only), duration to 90% T1 and time to full recovery. 2. Plasma samples from subjects receiving Org 9487 will be used for a population based pharmacokinetic analysis.

STUDY DESIGN:

This was an assessor blinded, parallel group, randomized, positive-controlled, Phase III multicenter study enrolling 280 subjects (140 per muscle relaxant group) undergoing elective surgery under nitrous oxide/fentanyl/propofol anesthesia at a total of 5 sites. Sixty of the assigned subjects were to be geriatric subjects (≥ 65 years of age). Subjects were to randomly receive either 1.5 mg/kg of Org 9487 or 1 mg/kg of succinylcholine. Each of the 5 sites was scheduled to enroll 56 subjects, 28 per muscle relaxant group. Twelve of the 56 subjects at each site were to be geriatric subjects (6 per muscle relaxant group). Amendment No. 1 was written to increase the number of subjects from 280 to 336. The additional subjects were to be enrolled at 4 of the 5 centers (14 subjects [11 adult, 3 geriatric] per center). Blood and urine samples were to be collected for a population based pharmacokinetic analysis from 70 subjects (45 adults, 15 geriatrics) receiving Org 9487 and 60 subjects (45 adults, 15 geriatrics) receiving succinylcholine. Twenty-four subjects (12 Org 9487 [9 adults, 3 geriatrics], 12 succinylcholine [9 adults, 3 geriatrics]) at each site were to have samples drawn.

Patients eligible for inclusion were male or non-pregnant female subjects 18 years or older and ASA Class 1, 2, 3, or 4. Included patients underwent surgery under nitrous oxide/fentanyl/propofol anesthesia. Excluded patients were the following:

- Subjects with known renal or hepatic dysfunction or neuromuscular disorder (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 in doses known to modify the action of neuromuscular blockers [Call to sponsor by this reviewer 3 Sept 1998 and reply by sponsor 14 Sept 1998 define the drugs known to modify the action of neuromuscular blockers as aminoglycosides, polypeptides and anticonvulsants].
- Subjects requiring rapid sequence tracheal intubation
- Subjects participating as research subjects in another study within the prior 30 days which has not been preapproved by Organon
- Subjects for whom written informed consent cannot be obtained.

DOSING SCHEDULE

The randomized 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, preferably through an 18 gauge needle. The randomized dose was to be administered four to five minutes after the administration of fentanyl. The time the dose was administered was to be recorded on the case report form. The investigator scoring the intubation conditions was to be blinded to the contents of the syringe.

STUDY SCHEMATA

Table 2

PROCEDURE	METHODOLOGY
Pre-Study Period	One week prior to administration of Premedications. History and physical performed; conformance to entrance criteria determined 24 hrs prior to surgery
Assignment of study number and administration of premedications.	1-5mg of midazolam IV or 1-2 mg of oral lorazepam
Induction	Preoxygenate with 100% oxygen for a maximum of 3 minutes. At the start of preoxygenation administer 2-5 mcg/kg fentanyl 3 minutes after start of preoxygenation, administer 1-3mg/kg of propofol
After Induction	Start EMG monitoring, uncalibrated mode
Administration of Muscle Relaxant	4-5 minutes after administration of fentanyl (i.e., 1-2 minutes after administration of propofol).
Laryngoscopy	50 seconds after administration of muscle relaxant
Intubation	By 60 or 90 seconds after administration of muscle relaxant.

[Based on sponsor's Table 2, Vol 92 p. 0033]

Pre-study Period

The pre-study period was to start one week prior to the administration of premedications for surgery and was to end at the administration of premedications. Conformance to the entrance criteria was to be determined 24 hours prior to surgery. A medical history was to be recorded for each subject and a physical exam was to be performed and results recorded.

In-study Period

The subject's allocation number was to be assigned at the beginning of the in-study period. The in-study period was to start at the administration of premedications and was to end at the transfer of the subject to the recovery room. Those anesthetic practices not designated below were to be consistent with the routine anesthetic practices of centers participating in the study. In addition, agents and doses used for the anesthetic management of subjects enrolled in the study were to be adjusted when necessary to provide optimal care. Prior to induction, the first plasma sample was to be drawn from subjects selected for the population based pharmacokinetic analysis. A clinical chemistry specimen for creatinine, ALT/GPT, AST/GOT, albumin and bilirubin, and a hematocrit sample were also to be obtained from those selected subjects.

Premedication

Subjects may have received 1-5 mg of midazolam i.v. or 1-2 mg of oral lorazepam before induction of anesthesia as clinically indicated.

Induction

Subjects were to be preoxygenated for a maximum of three minutes with 100% oxygen. Anesthesia was to be induced with appropriate doses of fentanyl (2-5 mcg/kg) followed by propofol (1-3 mg/kg), administered i.v.

Administration of Muscle Relaxant

The investigator scoring the intubation conditions was to be blinded to the contents of the syringe. 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 randomized dose was to be administered four to five minutes after the administration of fentanyl. The time the dose was administered was to be recorded on the case report form.

Intubation

Laryngoscopy was to be done 50 seconds after the administration of the muscle relaxant followed immediately by intubation by 60 seconds after the administration of the muscle relaxant. If intubation was not possible by 60 seconds another attempt was to be made by 90 seconds. The intubation conditions were to be scored by an investigator who was blinded to the randomization code and who was unaware of the twitch response at the time of laryngoscopy. Lidocaine was not to be used to facilitate intubation. If intubation was impossible after the second attempt and another muscle relaxant was administered then no further neuromuscular data was to be collected.

Maintenance of Anesthesia

Adequate depth of anesthesia was to be maintained with nitrous oxide in oxygen at a concentration of 60~70% and with an infusion or bolus doses of fentanyl and/or propofol as clinically indicated. No volatile inhalational agents were to be administered.

Maintenance of Muscle Relaxation

The subject was to be allowed to spontaneously recover to the return of the first twitch after receiving succinylcholine or the return of 70% T4/T1 after receiving Org 9487 before a maintenance dose of muscle relaxant was to be administered. Muscle relaxation was to be maintained during surgery when clinically required preferably with either atracurium chloride or ZemuronTM. No further neuromuscular data was to be recorded after receiving a maintenance dose.

Reversal of Neuromuscular Blockade

If clinically indicated, the residual neuromuscular block was to be reversed at the end of surgery with appropriate doses of an anticholinesterase and anticholinergic.

Concomitant Medication

Relevant data was to be collected and entered on the case report form for concomitant medications administered in preparation for surgery, during surgery and up to the subject's release from the recovery room. For subjects selected for the pharmacokinetic sampling, concomitant medications were to be recorded up to the collection of the last sample. Medications taken one week prior to surgery were to be recorded as pretrial medications on the case report forms. Medications that were administered for nausea, vomiting and myalgia after release from the recovery room and up to 24 hours post surgery were to be recorded.

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 (efficacy evaluable) analysis. Minor violations result in the exclusion of some, but not all, efficacy data for a subject from the per protocol (efficacy evaluable) 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 screened for protocol violations and deviations with respect to eligibility criteria and violation of the study protocol with respect to dosing of the muscle relaxant used for intubation, dosing regimens, anesthetic agents and noncompliance of scheduled assessments.

Major Protocol Violations

The following were to be considered major protocol violations:

- Subjects for whom the randomization schedule was not followed
- Subjects for whom the answer to the inclusion/exclusion criteria question was "yes"
- Subjects for whom the time from fentanyl administration to muscle relaxant administration was greater than 6 minutes
- Subjects for whom the time from propofol administration to muscle relaxant administration was greater than 3 minutes.
- Subjects for whom the dose of lidocaine to facilitate intubation was > 50mg.

Minor Protocol Violations

The following were considered to be minor protocol violations:

- Subjects who received volatile inhalational agents for greater than 15 minutes prior to recording of some efficacy parameters

- Subjects who received a maintenance dose of muscle relaxant prior to the return of the first twitch (for succinylcholine subjects) or prior to the return to 70 0/o T4/T1 (for Org 9487 subjects).

Protocol Deviations

The following were considered to be protocol deviations:

- Subjects for whom the dose of fentanyl (for induction) was above or below 10% of the planned dose
- Subjects for whom the dose of propofol (for induction) was above or below 10% of the planned dose
- Subjects who received diazepam as a premedication
- Subjects who did not receive fentanyl for induction
- Subjects who did not receive propofol for induction.

SECTION 9.2.1.2 STATISTICAL ANALYSIS

Primary Efficacy Parameters

The primary efficacy parameter in this study is intubation score assessed by 60 seconds following the administration of the muscle relaxant. The intubating condition was evaluated using the approach suggested by Viby-Mogensen et al.

Table 3
Viby-Mogensen Intubation Scores

	Clinically Acceptable		
	Excellent	Good	Poor
Vocal Cord Position	Abducted	Intermediate	Closed
Vocal Cord Movements	None	Moving	Closing
Ease of Laryngoscopy*	Easy	Fair	Difficult
Airway Reaction	None	Diaphragm	Sustained > 10 sec
Movement of Limbs	None	Slight	Vigorous

[Based on Sponsor's Table 4 Vol92, page 0038]

- * Ease of Laryngoscopy: Easy means jaw relaxed, no resistance
Fair means jaw relaxed, slight resistance

Excellent Score: All items excellent

Good Score: All items either excellent or good
 Poor Score: Any item poor makes score poor

Using the ratings given to the five individual items, overall intubation score was evaluated for each subject as either excellent (all items excellent), or good (all items either good or excellent), or poor (at least one item with poor score). The number (percentage) of subjects with acceptable (excellent or good) and unacceptable (poor or impossible) scores were summarized by treatment group. Comparison of subjects with respect to acceptable intubation scores was carried out using CMH (Cochran-Mantel-Hanszel) test. Confidence intervals were also calculated for differences between the two groups using normal approximation.

Secondary Efficacy Parameters:

Time to the return of the first twitch defined as the time interval between the administration of the muscle relaxant to the return of the first twitch.

Time to the return of the third twitch (Org 9487 subjects only) defined as the time interval between the administration of Org 9487 and the return of the third twitch.

Duration to 70% T4/T1 (Org 9487 subjects only) defined as the time interval between the administration of Org 9487 and the return of T4/T1 to 70%.

Duration to 90% T1 defined as the time interval from the administration of the muscle relaxant to 90% T1 normalized to the final T1 value.

Time to Full Recovery defined as the first time for which there is no further increase in the height of twitches for a period of five minutes after the administration of the muscle relaxant.

Clinical Signs of Recovery - head lift for five seconds, hand squeeze, and tongue extension. Time to head lift, time to hand squeeze, and time to tongue extension were calculated as the time interval from the administration of the muscle relaxant to the respective times.

Neuromuscular monitoring was to be done using the electromyography (EMG) to measure evoked response of the adductor pollicis using a train-of four (TOF) stimulation

brvia

pattern. The ulnar nerve of the arm opposite to the injection site of the dose was to be stimulated at the wrist through surface electrodes with TOF supramaximal (plus 15% to 20% at maximal response) square wave impulses of 0.2 msec duration administered at 2 Hz. A constant current stimulator was to be used to deliver TOF with intervals of 10 seconds and continuously recorded. Stimulation was to start after induction of anesthesia. The TOF was to be recorded continuously for 40 minutes after the administration of the randomized dose or until surgery was completed (unless a muscle relaxant other than Org 9487 or succinylcholine was administered for intubation or maintenance). A copy of this recording was to be retained as a source document.

Descriptive statistics were calculated for the treatment groups (Mean, SD, Median, Minimum and Maximum). Two-way analysis of variance was used for comparing the two treatment groups, with respect to time to the return of the first twitch using treatment (Org 9487 or succinylcholine) and center as the two factors, and the interaction term. The analysis was done on rank transformed data (non-parametric approach) and untransformed data (parametric approach). Ninety five percent confidence intervals were calculated for the difference between the two treatment groups 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 (no interaction term) of the two factor ANOVA on the untransformed data.

SECTION 9.2.1.3 PROTOCOL AMENDMENTS

All modifications of the study were to be written and filed as an amendment to the protocol, maintaining original section identification. Such amendments were to be made jointly by Organon INC and the principal investigator(s) with the approval of the Institutional Review Board. Any amendments(s) in the study were to be in effect for all subsequent subjects once joint approval was made and documented.

There was one amendment written for this study. Amendment #1 dated May 20, 1997 was approved by the Institutional Review Boards at sites 02, 03, 04, and 05 on May 29, 1997, May 28, 1997, June 11, 1997 and June 12, 1997, respectively. Amendment #1 changed the total of subjects to be enrolled in the study from 280 to 336. The amendment was written because a large number of subjects from Site 01 had major protocol violations, therefore, data from these subjects would be excluded from the per protocol (efficacy evaluable) analysis. The 56 additional subjects were to be enrolled among the other 4 centers. [Call to sponsor by this reviewer 3 Sept 1998 and reply by sponsor 14 Sept 1998 discloses Amendment No 1 was written on 8 May 1997 and became effective at the last site 12 June 1997. Statistical analysis was conducted 10 Oct 1997].

SECTION 9.2.1.4 STUDY CONDUCT

DISPOSITION / DISTRIBUTION:

A total of 337 subjects (264 adults [18 to < 65 years old], 73 geriatrics [\geq 65 years old]) were enrolled in the study in five centers. One geriatric subject (# 573) at Site 05 was randomized to receive 1.5 mg/kg of Org 9487 but was discontinued from the study prior to administration of study medication. The distribution of treated subjects across the five centers were as follows: Site 01 (44 adults, 13 geriatrics), Site 02 (55 adults, 15 geriatrics), Site 03 (55 adults, 15 geriatrics), Site 04 (55 adults, 15 geriatrics) and Site 05 (55 adults, 14 geriatrics). Four of the five centers (Sites 02, 03, 04 and 05) enrolled a total of 70 subjects each. Fourteen additional subjects (11 adults, 3 geriatrics) were enrolled at each of these centers, as per Amendment #1. One center (Site 01) enrolled a total of 57 subjects. This center enrolled one additional geriatric subject in the Org 9487 treatment group. The first digit of the subject number reflects the study center in which the subject was enrolled. Subject numbers 101-144, 201-255, 301-355, 401-455, 501-555 represent adult (< 65 years) subjects, and numbers 171-183, 271-285, 371-385, 471-485, 571-585 represent geriatric (\geq 65 years) subjects.

Table 4
DISPOSITION OF SUBJECTS BY TREATMENT AND AGE GROUP

Subject Data Set	Treatment Group						TOTAL
	Org 9487 (1.5mg/kg)			Succinylcholine (1.0 mg/kg)			
	Adult	Geriatric	Total	Adult	Geriatric	Total	
Total Randomized	133	37	170	131	36	167	337
All Subject Treated ^a	133	36	169	131	36	167	336 ^a
Intent to Treat	133	36	169	131	36	167	336
Per Protocol	98	26	124	84	28	112	236

Based on Sponsor's Table 5 Vol 92 page 0051

a: ITT Group excluded one subject: Subject # 573 was discontinued from the study prior to administration of study drug but due to equipment problems the study was abandoned and the subject did not receive study medication

The following subjects were excluded from the Per Protocol Group:

Org 9487 Subjects: 102, 106, 108, 110, 112-114, 117, 120, 122, 123, 125, 127, 129, 132, 134, 135, 137, 138, 141, 142, 173, 174, 176, 177, 179, 160, 183, 317, 433, 437, 485, 501, 507-509, 514, 517, 519, 538, 543, 550, 551, 578, 553

Succinylcholine Subjects: 101, 103, 105, 107, 109, 111, 115, 116, 118, 119, 121, 124, 126, 128, 130, 131, 133, 136, 139, 140, 143, 144, 171, 172, 175, 178, 181, 182, 216, 222, 318, 321, 336, 337, 401, 412, 416, 426, 429, 438, 441, 447, 448, 451, 504, 511, 521, 522, 525, 528, 539, 545, 547, 571, 577

Table 5

Center Number	Treatment Group: All Subjects Treated (ITT)					
	Org 9487 (1.5 mg/)			Succinylcholine (1.0 mg/kg)		
	N			N		
	Adult	Geriatric	Total	Adult	Geriatric	Total
01	22	7	29	22	6	28
02	27	7	34	28	8	36
03	27	8	35	28	7	35
04	28	8	36	27	7	34
05	29	6	35	26	8	34
TOTAL	133	36	169	131	36	167

[Based on Sponsor's Table 6 Vol 92, page 0052

MAJOR PROTOCOL VIOLATIONS:

Major protocol violations led to the exclusion of all efficacy data for a subject from the protocol efficacy evaluable analysis. Since the intubation score was the primary efficacy parameter and exposure to fentanyl, propofol, or lidocaine has the potential of enhancing the intubating conditions, exposure to these agents for an extended period of time was considered to be a major protocol violation. [Call to sponsor by this reviewer 3 Sept 1998 and reply by sponsor 14 Sept 1998 discloses "extended period of time" is defined as: 1. Time from fentanyl administration to muscle relaxant administration greater than 6 minutes; 2. Time from propofol administration to muscle relaxant administration greater than 3 minutes].

Table 6

MAJOR PROTOCOL VIOLATIONS				
Protocol Violation	Treatment Group			
	Org 9487 Subjects per site		Succinylcholine (1.0 mg/kg) Subjects	
FAIL TO FOLLOW RANDOMIZATION SCHEDULE	Site 1	1	Site 1	
	Site 2		Site 2	
	Site 3		Site 3	
	Site 4		Site 4	
	Site 5	1	Site 5	
"YES" TO INCLUSION/EXCLUSION	Site 1	1	Site 1	
	Site 2		Site 2	1
	Site 3		Site 3	
	Site 4		Site 4	
	Site 5	1	Site 5	
TIME FROM FENTANYL ADMINISTRATION TO MUSCLE RELAXANT GREATER THAN 6 MINUTES	Site 1	17	Site 1	18
	Site 2		Site 2	
	Site 3	1	Site 3	4
	Site 4	2	Site 4	4
	Site 5	8	Site 5	8
TIME FROM PROPOFOL ADMINISTRATION TO MUSCLE ADMINISTRATION GREATER THAN 3 MINUTES	Site 1	27	Site 1	26
	Site 2		Site 2	1
	Site 3		Site 3	
	Site 4		Site 4	3
	Site 5		Site 5	2
LIDOCAINE ≥ 50 MG TO FACILITATE INTUBATION	Site 1		Site 1	
	Site 2		Site 2	
	Site 3		Site 3	
	Site 4	1	Site 4	5
	Site 5	4	Site 5	1
TOTAL	45		55	

[Modified Sponsor's Table 7 Vol 92, Page 0053]

Table 7

DEMOGRAPHICS

	TREATMENT GROUP			
	Org 9487 1.5mg/kg		Succinylcholine 1.0 mg/kg	
	ADULT	GERIATRIC	ADULT	GERIATRIC
AGE				
N	133	36	131	36
Mean +/- SD	42 (13)	73(6)	42(12)	72(5)
Median	41	72	40	62
Range	18-64	65-92	18-64	65-86
Weight (kg)				
N	133	36	131	36
Mean +/- SD	74.7 (17)	76.2(16.2)	74.1 (15.8)	72.7(13)
Median	71	75.5	72.1	75.5
Range	46.4-143	33.6-109	47.2-125	49-95
Height (cm)				
N	132	34	125	36
Mean +/- SD	166.5(10.1)	171.6(8.8)	165.7(13.7)	167.6(9)
Median	167.3	168	157	169
Range	132-192	155-188	72-195	146-183
Gender N (%)				
Male	41 (31%)	22 (61%)	48 (37%)	17 (47%)
Female	92 (69%)	14 (39%)	83 (63%)	19 (53%)
Race N (%)				
Caucasian	114 (86%)	34 (94%)	110 (84%)	34 (94%)
Asian	4 (3%)	1 (3%)	4 (3%)	0
Black	9 (7%)	1 (3%)	13 (10%)	2 (6%)
Other	6 (5%)	0	4 (3%)	0
ASA Class N(%)				
1	72 (54%)	4 (11%)	64 (49%)	1 (3%)
2	51 (38%)	21 (58%)	59 (45%)	27 (75%)
3	9 (7%)	11 (31%)	8 (6%)	8 (22%)
4	1 (1%)	0	0	0

[Based on Sponsor's Table 10 Vol 92Page 0057]

Table 8

MEDICAL HISTORY	TREATMENT GROUP	
	Org 9487 (1.5 mg/kg) (N=169) (%)	Succinylcholine (1.0mg/kg) (N=167) (%)
CARDIOVASCULAR		
Hypertension	31 (18.3)	24 (14.4)
Angina, MI, CAD, CHF	10 (5.9)	7 (4.2)
Arrhythmias	3 (1.8)	1 (0.6)
Congenital Heart Disease	3 (1.8)	2 (1.2)
Miscellaneous	0	0
	5 (3)	4 (2.4)
RESPIRATORY		
Asthma	11 (6.5)	15 (9)
COPD	13 (7.7)	16 (9.6)
Miscellaneous	2 (1.2)	2 (1.2)
ASTHMA^a		
Childhood Only	2 (1.2)	2 (1.2)
Recent (<3 years)	11 (6.5)	8 (4.8)
Renal Failure/Insufficiency	0	0
Hepatic Dysfunction	1 (0.6)	0
CNS		
CVA/TIA	3 (1.8)	4 (2.4)
Seizures	0	2 (1.2)
Psychiatric	12 (7.1)	18 (10.8)
Miscellaneous	1 (0.6)	0
METABOLIC		
Diabetes	9 (5.3)	6 (3.6)
Miscellaneous	9 (5.3)	15 (9)
OTHER		
Obesity	5 (3)	7 (4.2)
Smoker	22 (13)	21 (12.6)
Miscellaneous	5 (3)	6 (3.6)

[Based on Sponsor's Table 11 Vol 92, Page 0058]

a As indicated in response to specific questions on the Patient History page of the CRF, separate from the respiratory system question

Table 9 PRE-TRIAL MEDICATIONS:

PRE-TRIAL MEDICATIONS	TREATMENT GROUP	
	Org 9487 (1.5mg/kg) (N=169) (%)	Succinylcholine 1.0mg/kg (N=167) (%)
VASOACTIVE		
Beta Blockers	6 (4)	3 (2)
Calcium Channel Blockers	13 (8)	5 (3)
Misc Antihypertensives	15 (9)	13 (8)
Cardiac Glycosides	1 (1)	2 (1)
Coronary Vasodilators	2 (1)	2 (1)
ANTI-ASTHMATICS		
β Agonists Inhalants	6 (4)	5 (3)
Glucocorticoids Inhalents	1 (1)	2 (1)
Other Anti asthma agents	0	2 (1)
ANTICONVULSANTS (All Types)	1 (1)	2 (1)
ANTIBIOTICS		
Aminoglycosides	1 (1)	4 (2)
Macrolides	3 (2)	4 (2)
OTHER		
Systemic Corticosteroids	3 (2)	4 (2)
Antihistamines	20 (12)	10 (6)

[Based on Sponsor's Table 12 Vol 92 Page 0059]

SECTION 9.2.1.5 SPONSOR'S EFFICACY RESULTS

PRIMARY EFFICACY VARIABLES:

Percentage of acceptable intubation scores in the succinylcholine treatment group (95%) was higher than in the Org 9487 treatment group (87%) [8 % Difference; 95 % CI 0.1-15]. The distribution was similar for the adult subjects but the difference was smaller in the geriatric group (96% for Org 9487 and 100% for succinylcholine).

Table 10

	PER PROTOCOL GROUP		ITT GROUP	
	Org 9487 (%)	Succinylcholine (%)	Org 9487 (%)	Succinylcholine (%)
Acceptable [Acceptable = Excellent + Good]	108/124 (87)	106/112 (95)	148/169 (88)	157/167 (94)
Excellent	53/124 (43)	74/112 (66)	75/169 (44)	110/167 (66)
Good	55/124 (44)	32/112 (29)	73/169 (43)	47/167 (28)

[Based on Sponsor's Table 24 Vol 92 Page 0072]

Table 11

	AGE GROUP (PER PROTOCOL)			
	ADULT		GERIATRIC	
	Treatment Group		Treatment Group	
	Org 9487 1.5mg/kg N=98 (%)	Succinylcholine 1.0 mg/kg N=84 (%)	Org 9487 1.5 mg/kg N=26 (%)	Succinylcholine 1.0 mg/kg N=28 (%)
Excellent	40 (41)	52 (62)	13 (50)	22 (79)
Good	43 (44)	26 (31)	12 (46)	6 (21)
Poor	15 (15)	4 (5)	1 (4)	0
Impossible	0	2 (2)	0	0
Acceptable	83 (85)	78 (93)	25 (96)	28 (100)
Unacceptable	15 (15)	6 (7)	1 (4)	0

[Based on Sponsor's Table 16 Pages 0066]

SECONDARY EFFICACY VARIABLES:

1. Time to the Return of the First Twitch

The mean time to the return of the first twitch was 6.2. minute for the succinylcholine group and 9.1 min for the Org 9487 group. This difference was statistically significant ($p < 0.01$) but not clinically significant.

2. Time to the Return of the Third Twitch

The time at which the third twitch returned was recorded only for subjects receiving Org 9487 since this parameter is not measurable with a depolarizing muscle relaxant such as succinylcholine. The mean time to the return of the third twitch for the Org 9487 was 14.1 minute. The adult group had a shorter mean duration (13.3 min) than the geriatric group (17 min).

3. Duration to 70% of T4/T1 (for Org 9487 only)

This parameter was only measured for Org 9487 since this situation does not occur

with depolarizing muscle relaxants. The mean duration was 37 minutes with the adult subjects having a shorter mean duration (34.4 min) when compared to the geriatric subjects (46.9 min). There were no differences in the mean duration to 70% T4/T1 among the centers.

4. Duration to 90% T1

The data are mainly obtained from one center, Site 04. The mean duration to 90% T1 in the succinylcholine group (12.3 min) was shorter than the mean duration in the Org 9487 group (32.9 min). [Call to sponsor by this reviewer 3 Sept 1998 and reply by sponsor 14 Sept 1998 disclose that data was not included for this analysis-by-site if the subjects received another muscle relaxant prior to the recording of the recovery of 90% T1 for Org 9487 or if recovery of 90% T1 for Org 9487 was not recorded for the subject. All sites other than 04 contained only 0-2 subjects as defined by the restrictive criteria].

5. Time to Full Recovery

This parameter was primarily recorded at Site 04. Time to full recovery was longer with the Org 9487 group (mean=46.5 min) when compared with the succinylcholine group (mean=15.1 min).

6. Clinical Signs of Recovery of Neuromuscular Function

Only few subjects had clinical signs of recovery assessed because other muscle relaxants for maintenance (66% in the Org 9487 group and 90% in the succinylcholine group) and reversal agents (62% in the Org 9487 group and 61% in the succinylcholine group) were administered. For Org 9487 the times to head lift, hand squeeze and tongue extension were 82.9 min, 84.5 min and 79.3 min, respectively and for succinylcholine the times to head lift, hand squeeze and tongue extension were 110.7 min, 110.7 min and 112.5 min, respectively. [Call to sponsor by this reviewer 3 Sept 1998 and reply by sponsor 14 Sept 1998 reveals that Clinical Signs of Recovery is actually measuring the clinical signs of recovery from anesthesia and not from the neuromuscular blocking agent].

Table 12
SUMMARY OF RECOVERY

Parameter	Treatment Group	
	Org 9487	SUCCINYLCHOLINE
Time to Return of 3 rd Twitch		
N	94	NA
Mean \pm SD	14.1 (6.2)	
95% CI	12.8-15.3	
Median	13.1	
Range	5.2-32.5	
Duration to 70% T4/T1		
N	77	NA
Mean \pm SD	37 (14.5)	
95% CI	33.7-40.3	
Median	34.2	
Range	13.8-97.3	
Duration to 90% T1		
N	38	27
Mean \pm SD	32.9 (10.6)	12.3 (4.7)
95% CI	29.4-36.4	10.4-14.2
Median	30	11.8
Range	14.7-64.3	4.8-28.2
Time to Full Recovery		
N	34	39
Mean \pm SD	46.5 (17)	15.1 (6.6)
Median	42.3	13.8
Range	23.3-90.2	4-31.7

[Based on Sponsor's Table 22 Vol 92 Page 0070]

SPONSOR'S SUMMARY OF EFFICACY:

The objective of this study was to evaluate the intubating conditions of 1.5 mg/kg of Org 9487 and 1.0 mg/kg of succinylcholine. The percent of acceptable intubation scores was greater for the succinylcholine group (95%) than for the Org 9487 group (87%). The estimated treatment difference in favor of succinylcholine was about 8% with a 95 % CI of [15, 0.1]. The time to the return of the first twitch was considered to be statistically shorter in the succinylcholine group than in the Org 9487 group but not clinically significant. Org 9487 has demonstrated to be a neuromuscular blocking agent with good to excellent intubating conditions.

SECTION 9.2.1.6 REVIEWER'S EFFICACY DISCUSSION

This pivotal trial in adult and geriatric patients evaluated a direct clinical effect rather than a surrogate end point for establishment of efficacy. The primary efficacy variable of this study, sufficient muscle relaxation to permit endotracheal intubation, demonstrates Org 9487 is capable of providing acceptable intubating conditions. However, the 1.5 mg/kg dose of Org 9487 was not shown to be as effective as succinylcholine for the establishment of acceptable intubating conditions. Although this difference was small, it was statistically significant (8 % Difference; 95 % CI [0.1-15]). Of greater clinical concern, succinylcholine was much more effective at establishing excellent intubating conditions than Org 9487.

The secondary objectives of the study, determining the time course of action, provide useful information on the duration of Org 9487. While the secondary efficacy variables are useful for providing information on the duration of action of Org 9487, the subjects were not controlled in a manner that would permit a direct comparison of the clinical duration of action between the two neuromuscular blocking agents.

SECTION 9.3.1 STUDY 174308

SECTION 9.3.1.1 PROTOCOL REVIEW SUMMARY

TITLE: Evaluation of the Intubating Conditions Provided with Org 9487 and Succinylcholine

OBJECTIVES

Primary: To show equivalence in adults of Org 9487 (1.5 mg/kg) to succinylcholine (1.0 mg/kg) in intubation conditions when used in subjects for elective surgery using general anesthesia.

Secondary: 1. To evaluate in a Train of Four Guard calibrated fashion, the time course of action:

- Time to reappearance of the first twitch (both for subjects receiving Org 9487 as well as subjects receiving succinylcholine)
- Time to reappearance of the third twitch (only for subjects receiving Org 9487)
- Time to T4/T1 ratio recovery to 0.7 (only for subjects receiving Org 9487)
- Time to T1 = 90% (both for subjects receiving Org 9487 as well as subjects receiving succinylcholine)
- Time to full recovery from muscle relaxation (both for subjects receiving Org 9487 as well as subjects receiving succinylcholine)

2. To collect sparse samples in a number of subjects for population based pharmacokinetic analysis.

STUDY DESIGN

This study was an assessor blinded, parallel group comparative, randomized, positive-controlled four center phase III study. The study was designed to enroll two hundred and eighty subjects. The subjects were to be stratified for age into two patient groups; 80% aged 18 up to and including 64 years (adults), 20% aged 65 years and over (geriatrics). For each patient group, the subjects were to be equally randomized to one of the two treatment groups (112 adult subjects, and 28 geriatric subjects per group).

STUDY PERIOD:

First Enrollment: September 1996; Last Enrollment: June 1997

SUBJECT SELECTION

280 subjects were to be enrolled. Initially the enrollment was divided as follows: four centers, 56 adult patients and 14 geriatric patients per center. Due to recruitment problems all four investigators were allowed to recruit as many patients as possible. The subjects were randomized to the two treatment groups: group 1 (Org 9487) and group 2 (succinylcholine).

The subjects were enrolled in the study site in Nancy (France) and in the three different study sites in Paris (France).

ENTRANCE CRITERIA:

Subjects were to be enrolled satisfying the following criteria:

1. Criteria for Inclusion

- (a) Male or female patients, > 18 years of age;
- (b) Subjects of ASA class 1, 2, 3 and 4 scheduled for elective surgery not requiring rapid sequence induction;
- (c) Subjects giving written informed consent

2. Criteria for Exclusion

- (a) Subjects not meeting the criteria for inclusion;
- (b) Subjects being pregnant as determined within one day before the study, and/or giving breast-feeding (pregnancy will be excluded by means of medical history and a urinary pregnancy test (HCG-Nostick) in female subjects of childbearing potential);

- (c) Subjects with known significant renal, hepatic or neuromuscular disorders (as determined by physical exam, medical history (including a family history of malignant hyperthermia) renal function tests or elevated liver enzymes);
- (d) Subjects with known allergy to narcotics or other medications used during anesthesia;
- (e) Subjects participating as research subjects in another study not preapproved by Organon Teknika, within 30 days of entering into this study;
- (f) Subjects with known airway abnormalities or airway obstructions that would preclude visualization of the vocal cords or intubation of the trachea;
- (g) Subjects receiving drugs in doses known to modify the action of neuromuscular blocking agents within 48 hours before administration of the Org 9487 or succinylcholine.

A randomization schedule was made by Organon Teknika's biostatistician using the SAS software package for each center and each subject group separately.

Organon Teknika supplied the investigators with the study drugs. Succinylcholine was supplied as Celocurine®. Org 9487 and succinylcholine were dosed on actual body weight. The dose of Org 9487 was 1.5 mg/kg. The dose of succinylcholine was 1.0 mg/kg. The compounds were to be administered as a rapid 5-second bolus into an i.v. line located in the forearm; the line was immediately flushed afterwards.

CONCOMITANT MEDICATIONS:

No particular drugs were forbidden for use during the study except for drugs known to modify the action of neuromuscular blocking agents; these drugs were not allowed during the pre-study period within 48 hour before the administration of the muscle relaxant and during the in-study period until full recovery. [Written clarification 16 October 1998 from sponsor defined the "...drugs known to modify the action of neuromuscular blocking agents..." as aminoglycosides, polypeptides, macrolides and chronically administered anticonvulsants]

DOSING SCHEDULE

Induction and Administration of Muscle Relaxant:

All subjects were to be preoxygenated with 100% oxygen for 3 minutes. Immediately following the start of preoxygenation, anesthesia was to be induced with 2-3 µg/kg of IV fentanyl, to be given over 5 seconds, two to three minutes later followed by 3-6 mg/kg of intravenous thiopental to be given over 10 seconds. Following preoxygenation, induction was to be assisted by inhalation of a gas mixture of nitrous oxide in oxygen at the discretion of the anesthesiologist. Within one minute following administration of thiopental, the muscle relaxant, either Org 9487 1.5 mg/kg or succinylcholine 1.0 mg/kg, was to be given, in accordance with the randomization schedule. Laryngoscopy was to be started at 50 seconds after the end of administration of either Org 9457 or

succinylcholine, followed by intubation by 60 sec or less. If intubation was not possible by 60 sec another attempt was to be made by 90 sec.

PRIMARY OBJECTIVES:

To show equivalence in adults of Org 9487 (1.5mg/kg) to succinylcholine (1.0 mg/kg) in intubation conditions when used in subjects scheduled for elective surgery using general anesthesia.

The intubating conditions were to be evaluated and scored assessor blinded. The assessor could not see the patient (e.g. stayed outside the room in which the study medication was administered) until 45 s after administration of the muscle relaxant. Intubating conditions were to be evaluated and to be scored as proposed by Viby-Mogensen:

Table 13

	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

- * 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 at the first attempt were to be recorded on the case report forms. In case it was not possible to obtain a complete set of subscores from every subject, the investigators were asked whether they considered the overall intubation scores by 60 sec being excellent, good or poor or that an overall score could not be given. In case the overall score by 60 sec was excellent, good or poor according to the investigator, that score was given to that particular subject; in case giving an overall score by 60 S was not possible, two cases were distinguished. If intubation was not possible by 60 sec due to insufficient muscle relaxation, the overall score was recorded as impossible. In case intubation was not possible by 60 sec due to anatomical malformation, the overall score was recorded as impossible due to anatomical malformation.

SECONDARY OBJECTIVES:

For determination of the parameters the following definitions were to be used:
Time to reappearance of the first twitch

The first twitch has reappeared as soon as the response is again and permanently 3% or over ($\geq 3\%$) or permanently over the very low but constant T_1 -value (the horizontal part of the recording).

Time to reappearance of the third twitch

The third twitch has reappeared as soon as the response is again and permanently 3% or over ($\geq 3\%$) or permanently over the very low but constant T_3 value (the horizontal part of the recording)

Time to T_4/T_1 ratio recovery to 0.7

This is the first time point, from a sequence of three time points, that the TOF-ratio is 0.70 or over (all three consecutive TOF determinations must be ≥ 0.70).

Time to $T_1 = 90\%$ (of the final T_1)

This is the first time point, from a sequence of three time points, that the T_1 is 90% of the final T_1 or over (all three consecutive T_1 determinations must be 90% or over 90% of the final T_1). In order to rule out any artifacts, it is important that the TOF-ratio (in case of non-depolarizing muscle relaxants) is also constant or increasing at the time points included in the T_1 90% determination.

Time to full recovery from muscle relaxation

For Org 9487, the time to full recovery from muscle relaxation is indicated by a TOF-ratio over 0.80: this is the first time point, from a sequence of three time points, that the TOF-ratio is 0.80 or over 0.80 (all three consecutive TOF determinations must be over 0.80). The neuromuscular block of succinylcholine cannot be measured by a TOF-ratio; full recovery is indicated by the time after which there is no or very little increase in the height of the twitches for a period of about two minutes: that is when the data indicate that a plateau is reached.

The time of the clinical signs of recovery of the neuromuscular function, i.e. head lift for five seconds, hand squeeze and tongue extension, were to be recorded, but only in the subjects who received only one single dose of Org 9487 or succinylcholine.

During the time-period before the full recovery from muscle relaxation, if possible, no inhalational agents (except for nitrous oxide in oxygen) or muscle relaxants were to be administered. If this was not possible in an individual patient and the use of an inhalational agent or muscle relaxant could not be avoided, the evaluation of the time course of action (secondary objective) was to be (partially) dropped for that particular patient.

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.

The following occurrences were considered major protocol violations:

- Signed informed consent form not available
- Incorrect dose of study medication
- Randomization error; patient received incorrect treatment
- Randomization error; subjects operated before other subjects although they were assigned a higher subject number, i.e. to be enrolled later in the study
- Randomization error; patients received the same subject number
- Patient received Diprivan (propofol) for induction instead of thiopental
- Patient required rapid sequence induction,

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

The following occurrences were considered minor protocol violations:

For intubation:

- Intubation not scored by 60 seconds after administration of the muscle relaxant
- Intubation score impossible, due to anatomical malformation.

For neuromuscular assessments:

- One or more of the neuromuscular parameters could not be determined or were unreliable due to TOF Guard failure and other problems
- Administration of aminoglycoside or macrolide antibiotics during recording of the muscle relaxation
- Inhalational agents were started more than 15 min before recording of some efficacy parameters.

The following occurrences were considered protocol deviations:

- Other drugs than diazepam and lorazepam given as premedication;
- No premedication given;
- No pre-oxygenation;
- Induction doses given too early;
- Doses of induction agents deviating more than 10% from the planned dose (fentanyl 2-3 mg/kg, and thiopental 5-6 mg/kg);
- Administration of thiopental more than 3 min before administration of the muscle relaxant; administration of fentanyl more than 6 min before administration of the muscle relaxant;
- Tube size 7 instead of 8;
- No determinations one or more of the cardiovascular parameters at one or more time points;
- No determination of the clinical signs of recovery from muscle relaxation.
- No pregnancy test done

Blind Broken during Study

Not applicable.

Discontinued Subjects

Subjects who were enrolled in the study, but did not receive study medication were regarded as discontinued subjects.

Subject Data Sets

For evaluation of the data, four subject groups 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 subjects who received the dose of study medication;
- The Intent-To-Treat (IU) group, which includes all subjects who received the dose of study medication and had at least one post baseline efficacy assessment;
- 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.

Discontinued subjects were included only in the all-subjects-randomized group for the evaluation of the data. With respect to the all-subject-treated group, subjects with incorrect randomization (assigned to the incorrect study group) were included under the study group, according to the actual neuromuscular blocking agent received. With respect to the intent-to-treat group, subjects with incorrect randomization (assigned to the incorrect study group) were included under the planned study group as per randomization schedule.

SECTION 9.3.1.2 STATISTICAL ANALYSIS

For statistical evaluation of the intubation conditions the null and alternative hypotheses to be tested were formulated as follows.. $H_0: P_{org} \leq \text{succinylcholine} - \delta$ and $H_1: P_{org} > \text{succinylcholine} - \delta$, where δ is the maximal allowed difference between the two treatment groups that still can be considered to be not clinically relevant ($\delta=10\%$). An estimate for the difference between succinylcholine and Org 9487, with respect to the clinically acceptable intubation conditions, was calculated together with a one-sided 95% CI. The confidence interval was based on the Normal approximation. For testing the above-

mentioned null hypothesis this one-sided 95% CI was used. The null hypothesis will be rejected, in favor of the alternative one, whenever the upper limit of the one-sided 95% CI, for the difference succinylcholine minus Org 9487, does not exceed the value ($\delta = 10\%$). In addition, the percentages of clinically acceptable intubation conditions for Org 9487 and succinylcholine were also analyzed with the Cochran Mantel-Haenszel test, which tests the hypothesis of no difference against the alternative one that the two treatments differ with respect to the percentage of acceptable intubation conditions. The difference between Org 9487 and succinylcholine was calculated together with two-sided 95% confidence intervals. The confidence interval was based on the Normal approximation. A post-hoc evaluation, using log-linear models, was performed to investigate the effect of center, age (adult and geriatric) and treatment on the intubation score by 60 sec (acceptable intubation conditions).

Neuromuscular data were summarized by means of sample size, median, mean, standard deviation, minimum and maximum values. Data were summarized per treatment group, both within and across centers, and within treatment group by age group.

SECTION 9.3.1.3 PROTOCOL AMENDMENTS

Table 14 Amendments

	Date	Contents
1	1/21/97	As there was no Org 9487 that was packed and labeled according to French regulations available in the Organon Teknika central storage, the investigators were resupplied with Org 9487 with a different packaging number
2	1/31/97	As in general enrollment was slower than expected, each study site that had enrolled its 56 adult patients or 14 geriatric patients was allowed to enroll more patients (additional randomization schedules were given).
2a	2/11/97	Two new co-investigators were added
3	10/7/97	A procedure was made for the investigators to evaluate the intubation conditions of subjects with a second intubation attempt, and/or incomplete sets of intubation subscores In addition, the determination of TOF print outs of full recovery from muscle relaxation was adapted.

Modified Sponsor's Table 4 Vol 109 p. 0035

With respect to Amendment 3, Sponsor notes (Addendum D, Vol 109, pp 0352-3) Intubation Conditions were scored on 5 subscores: vocal cords position, vocal cords movements, easiness of laryngoscopy, airway reaction, and movement of the limbs. From these 5 subscores, the intubation score was derived. During the study and subsequent evaluation, it became clear that it was not possible to obtain a complete set of subscores from every subject. Another problem was that some subjects had a complete set of subscores (at 60 sec after administration of the muscle relaxant), but a second attempt to intubate was also performed at 90 sec.

The investigators were contacted in such cases, and the following was done:

1. The investigators were asked whether they considered the overall intubation scores at 60 sec being excellent, good, poor or other
- 2a In case the overall score at 60 sec was excellent, good or poor according to the investigator, that score was given to that particular subject
- 2b In case giving an overall score at 60 sec was not possible, 2 cases were distinguished:
 - 2.b.1. Intubation not possible at 60 sec due to lack of drug effect: overall score "impossible".
 - 2.b.2. Intubation not possible at 60 sec due to anatomical malformation: overall score "not applicable (NA)".

In the statistical analysis and evaluation the following will be done:

1. acceptable intubation conditions are the scores excellent and good (not acceptable intubation conditions are the scores poor, impossible and NA);
2. subjects with the overall score NA will be regarded as minor protocol violators (for the evaluation of the intubation conditions);
3. subjects with the score NA will not be included in the Per Protocol data set;
4. subjects with the score NA will be included in the ITT data set under Not-Acceptable intubation conditions.

SECTION 9.3.1.4 STUDY CONDUCT

DATA SETS:

Table 15 Number of Subjects in Data Sets

	Number of Subjects				
	Treatment Group				Total
	Org 9487	Succinylcholine			
	Adults	Geriatrics	Adults	Geriatrics	
All Subjects Randomized	113	30	112	28	283
Intent to Treat	112	30	112	28	282
Per Protocol	107	26	106	27	266

Modified Sponsor's Table 9, Vol 109 pp 0056

1. One adult subject was enrolled in the study (Org 9487 treatment group) but did not receive study medication. This subject was regarded as a discontinued subject and included in the All Subjects Randomized data set.

143 subjects were assigned to the Org 9487 group (1.5 mg/kg) and 140 were assigned to the succinylcholine group (1.0 mg/kg). Initially the four centers were to enroll 70 patients but due to recruitment problems, the number of subjects per site was no longer restricted as per Amendment 1.

Table 16 Major Protocol Violations

MAJOR PROTOCOL VIOLATIONS	N	
	Org 9487	Succinylcholine
Signed informed consent form not available	1	
Incorrect dose of study medication (dose of muscle relaxant differed more than 10% from planned dose)	2	
Randomized error; subject received Org 9487 while randomized for succinylcholine.		5
Randomization error: subject received succinylcholine while randomized for Org 9487	2	
Randomization error: subjects operated before other subjects although they were assigned a higher subject number, i.e. to be enrolled later in the study	3	
Randomization error: patient 399 was the original subject 310, however this patient did not receive study medication. Therefore the patient who was enrolled as 310 should have been enrolled as 311	1	
Incorrect induction: patient received propofol for induction instead of thiopental		1
Incorrect inclusion: subject required rapid sequence induction		1
TOTAL NUMBER OF SUBJECTS WITH MAJOR PROTOCOL VIOLATIONS:	9	7

Modified from sponsor's Table 6, Vol 109 p.0053

Table 17 Minor Protocol Violations

MINOR PROTOCOL VIOLATION	N	
	Org 9487	Succinylcholine
<u>Reappearance of the First Twitch</u>		
• Reappearance of the first twitch was impossible to determine or unreliable due to TOF unit failure	12	11
• Antibiotics administered before or during neuromuscular assessments	2	1
<u>Reappearance of the Third Twitch</u>		
• Reappearance of the 3 rd twitch was impossible to determine or unreliable due to TOF unit failure	14	1
• Antibiotics administered before or during neuromuscular assessments	5	
<u>Recovery from Muscle Relaxation to TOF > 0.7</u>		
• Recovery from muscle relaxation to TOF > 0.7 was impossible to determine or unreliable due to TOF Guard failure and other problems	15	1
• Antibiotics administered before or during neuromuscular assessments	6	
<u>90% of T1 and Full Recovery From Muscle Relaxation</u>		
• Desflurane was started more than 15 min before full recovery was achieved	1	
• 90% of T1 and full recovery from muscle relaxation was impossible to determine or unreliable due to TOF unit failure	17	20
• Antibiotics administered before or during neuromuscular assessments	3	5

Modified Sponsor's Table 8, Vol 109, p. 0055

Table 18 Subjects Per Center

Center	Org 9487		Succinylcholine		Total
	Adults	Geriatrics	Adults	Geriatrics	
Nancy-Meistelman	17	6	17	5	45
Paris- Desmonts	36	7	35	7	85
Paris-Lienhart	30	8	29	7	74
Paris-Marty	30	9	31	9	79
Total	113	30	112	112	28

Sponsor's Table 5, Vol 109 pp 0052

DEMOGRAPHICS:

Table 19 Demographic Characteristics

		All-Subjects-Treated group (N = 282)					
		Treatment group				Org 9487 (N = 145)	succinylcholine (N = 137)
		Org 9487 (N = 145)		succinylcholine (N = 137)			
		Adult	Geriatrics	Adult	Geriatrics		
Age (yr.)	n	115	30	109	28	145	137
	Mean (SD)	42 (12)	74 (6)	43 (13)	72 (6)	48 (17)	49 (17)
	Median	42	73	43	71	49	48
	Min.-Max.	18 - 64	67 - 90	19 - 64	65 - 88	18 - 90	19 - 88
Weight (kg)	n	115	30	109	28	145	137
	Mean (SD)	70 (12)	70 (16)	71 (13)	65 (12)	70 (13)	70 (13)
	Median	70	70	73	65	70	70
	Min.-Max.	40 - 103	40 - 107	37 - 100	50 - 102	40 - 107	37 - 102
Height (cm)	n	115	30	108*	28	145	136
	Mean (SD)	170 (8)	166 (10)	170 (10)	164 (9)	169 (8)	169 (10)
	Median	170	165	170	162	170	170
	Min.-Max.	150 - 190	149 - 185	142 - 193	150 - 188	149 - 190	142 - 193
Gender (n (%))	Female	46 (40%)	16 (53%)	43 (39%)	13 (46%)	62 (43%)	56 (41%)
	Male	69 (60%)	14 (47%)	66 (61%)	15 (54%)	83 (57%)	81 (59%)
ASA Class (n (%))	1	88 (77%)	6 (20%)	82 (75%)	6 (21%)	94 (65%)	88 (64%)
	2	24 (21%)	18 (60%)	25 (23%)	22 (79%)	42 (29%)	47 (34%)
	3	3 (3%)	6 (20%)	2 (2%)	0	9 (6%)	2 (1%)

* For subject 118, the height was not recorded

Sponsor's Table 10 Vol 109 pp 0057

Table 20 Pre Existing Medical Conditions

Number and percentage of subjects with clinically significant pre-existing medical conditions, All-Subjects-Treated group (N = 282)			
		Treatment group	
		Org 9487 (N = 145)	succinylcholine (N = 137)
Cardiovascular System	Hypertension	18 (12%)	8 (6%)
	Angina, ischemic heart disease, MI, CAD	3 (2%)	
	Valvular disease		
	Arrhythmias		4 (3%)
	Congenital heart disease		
	Miscellaneous conditions	9 (6%)	10 (7%)
Respiratory System	Asthma (history)	2 (1%)	1 (1%)
	COPD		
	Miscellaneous conditions		
Asthma ^a	Childhood only	2 (1%)	2 (1%)
	Recent (< 3 years)	3 (2%)	1 (1%)
Renal failure / insufficiency			
Hepatic dysfunction			
Other ^b	Obesity	1 (1%)	1 (1%)
	Current smoker		1 (1%)
	Miscellaneous conditions	5 (3%)	5 (4%)

Sponsor's Table 11 Vol 109 pp 0058

Although not statistically tested, the summary statistics of demographic characteristics give no indication for relevant differences between the treatment groups, the subject groups and the study sites.

Table 21 Concomitant Medication

Drug Category	Number of subjects exposed	
	Org 9487 (N=145)	Succinylcholine (N=137)
Vasoactive		
Beta Blocker	2	-
Calcium Channel blockers	4	3
Anti-arrhythmics	-	-
Misc antihypertensives	3	1
Cardiac glycosides	1	-
Coronary vasodilators	-	-
Anti-Asthmatics		
Beta agonists inhalants	3	-
Glucocorticoid inhalants	-	-
Other anti-asthma inhalers	-	-
Systemic xanthines,	-	-
Anticonvulsants	1	
Antibiotics		
Aminoglycosides	23	17
Polypeptides	-	-
Macrolides	1	-
Other		
Systemic corticosteroids	7	9
Antihistamines	-	1

Sponsor's Table 15 Vol 109 pp 0062

SECTION 9.3.1.5 SPONSOR'S EFFICACY RESULTS

Table 22 INTUBATION CONDITIONS, PER PROTOCOL GROUP N=266

CENTER	SCORE	TREATMENT GROUP							
		Org 9487				SUCCINYLCHOLINE			
		Adult N=107 (%)		Geriatric N=26 (%)		Adult N=106 (%)		Geriatric N=27 (%)	
Nancy Meistelman	Excellent	1	6.3	2	33.3	3	17.6	1	25
	Good	12	75	4	66.7	10	58.8	3	75
	Poor	2	12.5	0	0	4	23.5	0	0
	Impossible	11	6.3	0	0	0	0	0	0
Paris Desmonts	Excellent	11	30.6	2	33.3	18	54.5	5	71.4
	Good	24	66.7	4	66.7	15	45.5	2	28.6
	Poor	1	2.8	0	0	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0
Paris Lienhart	Excellent	6	26.1	1	20	11	40.7	2	33.3
	Good	13	56.5	0	0	12	44.4	3	50
	Poor	2	8.7	1	20	3	11.1	0	0
	Impossible	2	8.7	3	60	1	3.7	1	16.7
Paris Marty	Excellent	13	46.4	3	37.5	13	52	8	88.9
	Good	10	35.7	4	50	6	24	1	11.1
	Poor	5	17.9	0	0	5	20	0	0
	Impossible	0	0	1	12.5	1	4	0	0
Overall	Excellent	31	30.1	8	32	45	44.1	16	61.5
	Good	59	57.3	12	48	43	42.2	9	34.6
	Poor	10	9.7	1	4	12	11.8	0	0
	Impossible	3	2.9	4	16	2	2	1	3.9
Clinically Acceptable		90	87.4	20	80	88	86.3	25	96.2
Clinically Not Acceptable		13	12.6	5	20	14	13.7	1	3.9

Sponsor's Table 16 Vol 109 p0064

Table 23 INTUBATION SCORES, PER PROTOCOL GROUP N=266

Intubation Score	Treatment Group			
	Org 9487		Succinylcholine	
	N ¹	%	N ²	%
Excellent	39	30.5	61	47.7
Good	71	55.5	52	40.6
Poor	11	8.6	12	9.4
Impossible	7	5.5	3	2.3

Sponsor's Table 17, Vol 109 p 0064

1. Intubation conditions not scored by 60 seconds for 3 Org 9487 patients; these patients are in the PP data set but are not counted in the PP Intubation Scores.
- 2 Org 9487 patients not counted due to intubation impossible due to anatomic malformation.

2. 5 succinylcholine group patients in the PP group were not scored because of impossible intubation due to anatomic malformation.

[Reviewer Note: Reply of Sponsor 16 October 1998 discloses that 22 patients were scored by empirical evaluation rather than the Viby-Mogensen criteria: 12 patients received Org 9487 and 10 patients received succinylcholine.]

The primary objective of this study was to evaluate the intubating conditions provided with Org 9487 and succinylcholine in subjects scheduled for general anesthesia. Therefore the comparison between clinically acceptable intubating conditions (excellent and good) and clinically non-acceptable intubating conditions (poor and impossible) was of interest. Intubating conditions were to be determined by 60 sec after administration of the muscle relaxant. After administration of succinylcholine the percentage of clinically acceptable intubation conditions was 88.3%, with 95% two-sided CI ranging from 81.4% to 93.3%. After administration of Org 9487 the percentage of clinically acceptable intubation conditions was 85.9%, with 95% two-sided CI ranging from 78.7% to 91.4%. The estimated difference in percentage of clinically acceptable intubation conditions between succinylcholine and Org 9487 was 2.3%. The upper limit of the one-sided 95% CI for the difference between the two treatments was 9.2%. When the Cochran Mantel-Haenszel test, adjusted for center and age group, was used, no statistically significant differences were observed between Org 9487 and succinylcholine ($p=0.47$). The two-sided 95% CI for the difference between succinylcholine and Org 9487 ranged from -5.9% to 10.5%.

Table 24 INTUBATION CONDITIONS, INTENT TO TREAT GROUP N=282

CENTER	SCORE	TREATMENT GROUP							
		Org 9487 N=142				SUCCINYLCHOLINE N=140			
		Adult		Geriatric		Adult		Geriatric	
N	(%)	N	(%)	N	(%)	N	(%)		
Nancy Meistelman	Excellent	1	5.9	2	33.3	3	17.6	1	25
	Good	13	76.5	4	66.7	10	58.8	3	75
	Poor	2	11.8	0	0	4	23.5	0	0
	Impossible	1	5.9	0	0	0	0	0	0
Paris Desmonts	Excellent	11	30.6	3	42.9	18	54.5	5	71.4
	Good	24	66.7	4	57.1	15	45.5	2	28.6
	Poor	1	2.8	0	0	0	0	0	0
	Impossible	0	0	0	0	0	0	0	0
Paris Lienhart	Excellent	6	20.7	2	25	11	37.9	2	28.6
	Good	17	58.6	2	25	13	44.8	4	57.1
	Poor	3	10.3	1	12.5	3	10.3	0	0
	Impossible	3	10.3	3	37.5	2	6.9	1	14.3
Paris Marty	Excellent	13	46.4	4	44.4	14	50	8	88.9
	Good	10	35.7	4	44.4	8	28.6	1	11.1
	Poor	5	17.9	0	0	5	17.9	0	0
	Impossible	0	0	1	11.1	1	3.6	0	0
Overall	Excellent	31	28.2	11	36.7	46	43	16	59.3
	Good	64	58.2	14	46.7	46	43	10	37
	Poor	11	10	1	3.3	12	11.2	0	0
	Impossible	4	3.6	4	13.3	3	2.8	1	3.7
Clinically Acceptable		95	86.4	25	83.3	92	86	26	96.3
Clinically Not Acceptable		15	13.6	5	16.7	15	14	1	3.7

Sponsor's Table 19, Vol 109 pp 0065

There is no clear explanation for the low rate of clinically acceptable intubation conditions after treatment with succinylcholine in this study: poor intubation conditions for succinylcholine were found in 3 out of the 4 centers. There is a difference in rate of clinically acceptable intubating conditions between the centers, but the influence of this difference is the same for both muscle relaxants. There is also a rather high incidence of intubations that turned out to be impossible due to anatomical malformations; these cases were also found in 3 out of the 4 study centers.

Table 25 INTUBATION SCORES, INTENT TO TREAT GROUP N=282

Intubation Score	Treatment Group			
	Org 9487		Succinylcholine	
	N ¹	%	N ²	%
Excellent	42	30	62	46.3
Good	78	55.7	56	41.8
Poor	12	8.6	12	9
Impossible	8	5.7	4	3

Sponsor's Table 20 Vol 109, p 0066

1. Intubation impossible due to malformation for 2 Org 9487 subjects
2. Intubation impossible due to anatomical malformation for 5 Succinylcholine subjects.

Table 26 DURATION AND RECOVERY DATA, PER PROTOCOL N=266

		Treatment Group					
		Org 9487		Succinylcholine		Org 9487	Succinylcholine
		Adult	Geriatric	Adult	Geriatric	Pooled	
Time to Reappearance of first twitch (min)	N	61	11	62	15	72	77
	Mean (SD)	7 (2)	10 (7)	5 (2)	7 (4)	7 (4)	5 (2)
	Median	6	7	4	5	6	5
	Min-Max	3-14	5-25	1-11	3-14	3-25	1-14
Time to reappearance of third twitch (Min)	N	84	16	NA	NA	100	NA
	Mean (SD)	10 (4)	11 (6)			10 (4)	
	Median	10	10			10	
	Min-Max	3-22	6-32			3-32	
Duration 0.7 (min)	N	73	16	NA	NA	89	NA
	Mean (SD)	24 (8)	25 (6)			24 (8)	
	Median	24	26			24	
	Min-Max	9-52	14-40			9-52	
Time to 90% of T1 (min)	N	62	13	68	21	75	89
	Mean (SD)	22 (7)	24 (4)	10 (3)	10 (5)	22 (7)	10 (4)
	Median	22	24	10	10	22	10
	Min-Max	8-47	10-34	5-24	5-23	8-47	5-24
Time to Full Recovery (min)	N	62	13	68	21	75	89
	Mean (SD)	27 (9)	29	11 (4)	11 (5)	27 (8)	11 (4)
	Median	27	30	11	10	27	11
	Min-Max	10-57	22-44	5-30	5-26	10-57	5-30

Sponsor's Table 22 Vol 109, p 0067

A secondary objective of the study was the evaluation of the time course of action. Data were recorded with the TOF Guard. The median time to reappearance of the first twitch was 6 min after treatment with Org 9487 and after treatment with succinylcholine it was 5 min. The median time to full recovery was 27 min after Org 9487 and 11 min after succinylcholine. A large number of minor violations with regard to the determination of the neuromuscular data were observed: errors in the recording procedures (no monitoring performed, no calibration or set-up period, inhalational agent started too early, administration of antibiotics, application of single twitch stimulation pattern movement of the arm or hand, or recording stopped because of the start of surgery) and equipment failure.

SECTION 9.3.1.6 REVIEWER'S EFFICACY DISCUSSION:

This pivotal trial in adult and geriatric patients evaluated a direct clinical effect rather than a surrogate end point for establishment of efficacy. The primary objective of this trial was to show equivalence for intubation conditions in adults for Org 9487 1.5mg/kg to succinylcholine 1 mg/kg when used in subjects undergoing general anesthesia for elective surgery. This study demonstrated Org 9487 could provide acceptable intubation conditions. However, this reviewer is not convinced that equivalency to succinylcholine was established. The unusually low rate of acceptable intubating conditions for succinylcholine (88%) is disturbing. Reply by sponsor 16 October 1998 to Agency queries acknowledges this low rate of acceptable conditions for succinylcholine. Sponsor offers some conjectures for this situation but admits there is no clear explanation. Study 174208 in this NDA Application quotes succinylcholine's anticipated rate of excellent or good intubating conditions (e.g. acceptable intubating conditions) at 96% [Vol 87, p 0064]. In addition, a clear difference in Excellent intubating conditions between Org 9487 (30%) and succinylcholine (48%) is noted; Sponsor does not report whether this difference is statistically significant.

The secondary objectives of the study, determining the time course of action, provide useful information on the duration of Org 9487. While the secondary efficacy variables are useful for providing information on the duration of action of Org 9487, the subjects were not controlled in a manner that would permit a direct comparison of the clinical duration of action between the two neuromuscular blocking agents. ✓

SECTION 9.4.1 STUDY 070008**SECTION 9.4.1.1 PROTOCOL REVIEW SUMMARY:**

TITLE: A Time Course Study of Org 9487 in Pediatric Subjects

OBJECTIVE:

Primary: 1. To determine and compare the time course of 2 intubating doses of Org 9487 (1 mg/kg and 2 mg/kg) in children < 2 years of age and to determine and compare the time course of 2 intubating doses of Org 9487 (2mg/kg and 3 mg/kg) to the recommended intubating dose of mivacurium chloride (0.2mg/kg) in children ≥ 2 to <13 years of age.

Secondary: 1. To compare the cardiovascular parameters of Org 9487 and mivacurium chloride during the 10 minutes following administration. 2. Plasma

samples from subjects receiving Org 9487 will be used for a population based pharmacokinetic analysis.

STUDY DESIGN: This was a parallel group, comparative, randomized, Phase IIb, 3 center U.S. study enrolling 120 subjects: 48 subjects from birth to < 2 years of age (of which 16 were to be neonates) and 72 subjects ≥ 2 to < 13 years of age undergoing surgery under halothane anesthesia at a total of 3 sites. Subjects from birth to < 2 years of age were to be randomized to one of 2 Org 9487 doses (1 mg/kg or 2 mg/kg) and subjects ≥ 2 to < 13 years of age were to randomly receive either 2 mg/kg of Org 9487, 3 mg/kg Org 9487 or 0.2 mg/kg mivacurium chloride. Enrollment was to proceed at the sites according to separate randomization schedules for neonates, for subjects ≥ 29 days to < 2 years old and for subjects ≥ 2 to < 13 years. If any site could not enroll a reasonable number of subjects in a timely manner, then, with the written authorization of Organon, more than the scheduled number of subjects were to be enrolled by the other sites. The drugs were to be open label. The dosage groups to which the subject was to be assigned were to be blinded to the investigator prior to the patient enrolling in the study.

SUBJECT SELECTION:

120 ASA Class 1, 2, and 3 subjects (48 subjects from birth to < 2 years of age, 72 subjects ≥ 2 to < 13 years of age) undergoing surgery with halothane anesthesia. 24 subjects were to be enrolled in the 1 mg/kg Org 9487, 3 mg/kg Org 9487 and 0.2 mg/kg mivacurium chloride treatment groups. 48 subjects (24 < 2 years old and 24 ≥ 2 to 13 years old) were to be enrolled in the 2 mg/kg Org 9487 treatment group.

Inclusion Criteria:

- Male or female subjects from full term (gestational age ≥ 37 weeks) neonates (< 29 days old) to 13 years of age.
- Subjects born prematurely whose postconceptual age is ≥ 44 weeks and meet the weight and height criteria.
- Subjects of ASA Class 1, 2, or 3 scheduled for surgery under halothane anesthesia.
- Subjects (excluding neonates) scheduled for surgery with expected minimal blood loss (i.e. < 5% of blood volume)
- Subjects whose weight falls within the 10th to 90th percentile of the National Center for Health Statistics Physical Growth Percentiles Chart.

Exclusion Criteria:

- Subjects ≥ 13 years old or premature neonates (gestational age < 37 weeks)
- Subjects born prematurely whose postconceptual age is < 44 weeks
- Subjects of ASA Class 4 or 5
- Female subjects who are pregnant
- 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 clinically significant cardiovascular disease that requires treatment
- Subjects with known allergy narcotics or other medications used during anesthesia
- Subjects chronically receiving medications (antihistamines, anticonvulsants, aminoglycosides or polypeptide antibodies) in a dosage regimen known to modify the action of neuromuscular blockers
- Subjects with known or suspected airway abnormalities or airway obstructions that would preclude visualization or intubation of the trachea
- Subjects with known lower respiratory disease
- Subjects participating as research subjects in another study not preapproved by Organon
- Subjects for whom written informed consent could not be obtained from a parent or guardian

STUDY FLOW:

The subject's allocation number was to be assigned at the beginning of the in-study period. Subjects were not to be premedicated unless it was clinically required. Those anesthetic practices not designated in the protocol were to be consistent with routine anesthetic practices.

INDUCTION:

Neonates: Atropine was to be administered IV followed by up to 50% nitrous oxide in O₂ and by halothane to achieve an end tidal of 0.5% (or as clinically indicated). After the one minute cardiovascular assessment, nitrous oxide was to be discontinued and 100% O₂ was to be used for intubation. Agents and doses used for induction could be adjusted as necessary in order to provide optimal subject care.

Children ≥ 29 days to < 13 years: Anesthesia was to be induced with 70% nitrous oxide in O₂ and up to 5% inspired halothane until the child was asleep. Halothane was then to be reduced to 2% for stabilization. Atropine and glycopyrrolate were not to be administered until after the 5 minute cardiovascular measurement following the muscle relaxant dose. Ventilation was to be assisted or controlled as necessary to maintain an end tidal CO₂ of 30-40 mm Hg.

ADMINISTRATION OF MUSCLE RELAXANT:

All muscle relaxants were to be administered after stabilization of anesthesia (stable end-tidal halothane concentration for 10 minutes) and hemodynamics (HR and BP < 5 to 10% variation in 5 minutes) and after three stable Train-of-Four responses were attained.

For neonates: The end tidal halothane was to be maintained at a maximum of 0.5% or as clinically indicated (consistent with clinical practice).

For children ≥ 29 days to < 13 years of age: The concentration of inspired halothane was to be decreased to 1.5% at the time the neuromuscular blocker was administered.

For all age groups, the randomly assigned dose of Org 9487 was to be administered as a bolus within 5 seconds into an injection port close to the insertion site of a fast flowing intravenous line. The mivacurium chloride dose was to be administered as clinically indicated.

INTUBATION:

For neonates: Subjects were to be intubated after the two minutes cardiovascular measurements were taken after administration of the muscle relaxant.

For children ≥ 29 days to < 13 years of age: After the three minute cardiovascular measurements were taken following the administration of the muscle relaxant, the subject was to be intubated.

MAINTENANCE OF ANESTHESIA:

For neonates: To maintain adequate depth of anesthesia, nitrous oxide in oxygen was to be adjusted as clinically indicated (up to 70%) and end tidal halothane was to be maintained to a maximum of 0.5%. Agents and doses used for the maintenance of anesthesia were to be adjusted when necessary to provide optimal care.

For children ≥ 29 days to 13 years of age: Adequate depth of anesthesia was to be maintained with 50% nitrous oxide, and from 0.8% to 1.0% end-tidal halothane. As per amendment #2, maintenance was to be with N_2O as clinically indicated and from 0.8% to 1.0% end-tidal. In addition, agents and doses used for the maintenance of anesthesia were to be adjusted when necessary to provide optimal care. For all age groups, oxygen saturation, end-tidal CO_2 , and central or peripheral temperatures were to be continuously monitored.

MAINTENANCE OF MUSCLE RELAXATION:

Whenever possible, spontaneous recovery of T4/T1 to 70% was to be allowed before a maintenance dose of muscle relaxant was administered. Muscle relaxation was to be maintained when clinically indicated with a neuromuscular blocking agent other than Org 9487. No further neuromuscular data was to be recorded after receiving a maintenance dose.

REVERSAL OF NEUROMUSCULAR BLOCKADE:

Subjects were to be allowed, whenever possible, to spontaneously recover from neuromuscular block to 70% T4/T1.

POST-STUDY PERIOD

The post-study period was to start at the transfer of the subject to the recovery room and end when the subject was released from the recovery room.

NEUROMUSCULAR ASSESSMENTS:

Neuromuscular monitoring was to be done using an EMG with train of four (TOF) stimulation. The arm being monitored was to be kept $\geq 32^{\circ} C$ during monitoring.

- The T1 at 60 seconds was to be recorded.

- **Maximum Block (Peak Effect):** was defined and recorded for this study as the value for the first T1 which showed no further decline over three consecutive TOF following the administration of the dose of muscle relaxant.
- **Onset Time:** The time interval between completion of the injection of the muscle relaxant and the time of maximal depression of TOF (peak effect).
- **Clinical Duration:** defined as the time interval between the administration of the dose and the return of T1 to 25% of control.
- **Recovery Rate:** The time to spontaneous recovery from 25% to 75% of control T1 was to be calculated.
- **Duration to 70% T4/T1:** 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.

SECTION 9.4.1.2 PROTOCOL AMENDMENTS

There were 2 amendments to this study:

Amendment #1 changed the concentration of halothane used for induction in neonates and the definition of stabilization of anesthesia. The original procedure for induction stated that after placement of a pulse oximeter, atropine was to be administered i.v followed by up to 50% nitrous oxide and by halothane to achieve an end tidal of 0.5%. The amended procedure states that after placement of a pulse oximeter, induction of anesthesia was to be established by up to 50% nitrous oxide and by halothane to achieve an end tidal of 0.5% or as clinically indicated (consistent with clinical practice). Atropine was to be administered i.v.

The original definition for stabilization of anesthesia stated that all muscle relaxants were to be administered after stabilization of anesthesia (stable end-tidal halothane concentration for 10 minutes) and hemodynamics (Heart Rate and Blood Pressure <5 to 10% variation in 5 minutes) and after three stable Train-of-Four responses were attained. The amended definition states that all muscle relaxants were to be administered after stabilization of anesthesia (stable end tidal halothane concentration for up to 10 minutes) and hemodynamic (Heart Rate and Blood Pressure <5 to 10% variation in 5 minutes) and after three stable Train-of-Four responses were to be attained.

Amendment #2 changed the definition for stabilization of hemodynamics and it also changed the nitrous oxide concentration for maintenance of anesthesia in children ≥ 29 days to <13 years of age. The original definition for stabilization of hemodynamics stated that all muscle relaxants were to be administered after stabilization of anesthesia (stable end-tidal halothane concentration for up to 10 minutes) and hemodynamics (HR and BP <5 to 10% variation in 5 minutes) and after three stable Train-of Four responses were attained. The amended definition states that all muscle relaxants were to be administered after stabilization of anesthesia (stable end-tidal halothane concentration for up to 10 minutes) and hemodynamics (in the investigator's judgment) and after three stable Train-of Four responses were attained. The original procedure for maintenance of anesthesia in this age group was that adequate depth of anesthesia was to be maintained with 50% nitrous oxide and from 0.8% to 1.0% end-tidal halothane. The amended procedure

no more specified

changed this concentration of nitrous oxide to, as clinically indicated and from 0.8% to 1.0% end-tidal halothane.

SECTION 9.4.1.3 STATISTICAL AND ANALYTICAL METHODS

Blind Broken During The Study:

Not applicable to this study (open label)

Protocol Violations:

Major protocol violations lead to the exclusion of all efficacy data for a subject from the Per Protocol analysis. Minor protocol violations result in the exclusion of some 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:

- Subjects not within the 10th to 90th percentile of the NCHS Physical Growth Percentiles Chart
- Subjects who received inhalational anesthetic agent(s) other than halothane or nitrous oxide prior to recording any efficacy parameter.

Minor Protocol Violations:

None

Protocol Deviations:

- Neonates who did not receive atropine during induction
- Children who received atropine or glycopyrrolate before the 5 min cardiovascular assessment

Subject Data Sets:

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. Subjects with incorrect randomization (assigned to wrong age group or treatment group) were included under the actual age/treatment group.

Intent-to-Treat Group: The Intent-to-Treat Group consists of all subjects treated who had at least one post-baseline assessment of at least one of the primary efficacy variables. Subjects with incorrect randomization (assigned to wrong age group or treatment group) were included under the planned age/treatment group as per randomization schedule.

Per - Protocol Group: The Per- Protocol Group consist 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.

Primary Efficacy Parameters:

- T1 at 60 sec
- Clinical Duration: Time interval between drug and return to 25% of control T1

Secondary Efficacy Parameters:

- Onset Time: The time interval between completion of the injection of the muscle relaxant and the time of maximal depression of TOF
- Maximum Block (Peak Effect): Value of the first T1 which shown no further decline over 3 consecutive TOF following administration of relaxant
- Recovery Rate: Recovery of 25% to 75% of control T1.
- Duration to 70% T4/T1: Time from administration of relaxant and return to 70% T4/T1

Statistical Analysis:

Descriptive Statistics (Mean, SD, Median, Minimum, and Maximum) were calculated by age and treatment group. Two-way analysis of variance (ANOVA) was used for comparing subjects (except for neonates) across pairs of treatment groups, using the full model with treatment group and center as the two factors. For children < 2 years of age, the two treatment groups are 1 mg/kg and 2 mg/kg of Org 9487. For children ≥ 2 years of age, the two pairwise contrasts used are 2 mg/kg of Org 9487 vs. Mivacurium Chloride and 3 mg/kg of Org 9487 vs. Mivacurium Chloride. 95% confidence intervals for each of the three pairwise contrasts were calculated using the t-distribution: the estimate of the difference between the two treatment groups, standard error, and the degrees of freedom were based on the additive model of the two-way ANOVA on the untransformed data.

SECTION 9.4.1.4 STUDY CONDUCT

As per study design, 120 subjects were to be enrolled in the study:

16 neonates

32 Children ≥ 29 days to < 2 years

72 Children ≥ 2 years to < 13 years

A total of 113 subjects were enrolled in this study in 3 centers due to insufficient enrollment of neonates at sites 3 and 4.

Table 27 Disposition of Subjects

Data Set	Age/Treatment Group										Total
	Neonates <29 days			Children ≥ 29 days to < 2 years			Children ≥ 2 years to <13 years				
	Org 9487 Mg/kg		Total	Org 9487 9487 Mg/kg		Total	Org 9487 Mg/kg		Mivacurium Mg/kg	Total	
1.0	2.0		1.0	2.0		2.0	3.0	0.2			
ASR	5	4	9	16	17	33	24	24	23	71	113
AST*	5	4	9	16	17	33	24	23	23	70	112
ITT	5	4	9	16	17	33	24	23	23	70	112
PP	5	4	9	14	16	30	23	23	23	69	108

Sponsor's Table 3, Vol 99 p. 0054

ASR: All Subjects Randomized

AST: All Subjects Treated:

*One subject randomized to 3 mg/kg was not treated due to a mechanical error with the EMG

ITT: Intent to Treat

PP : Per Protocol

Protocol Violations/Deviations:

Major: 4 subjects were administered sevoflurane

Minor:

None

Deviations: One neonate did not receive atropine during induction. 4 subjects received atropine before the 5 min cardiovascular assessments.

Table 28 Distribution by Site: All Subjects Treated

Site	Age/Treatment Group									
	Neonates <29 days			Children ≥ 29 days to < 2 years			Children ≥ 2 years to <13 years			
	Org 9487 Mg/kg		Total	Org 9487 Mg/kg		Total	Org 9487 Mg/kg		Mivacurium Mg/kg	Total
1.0	2.0		1.0	2.0		2.0	3.0	0.2		
1	4	4	8	6	6	12	8	8	8	24
2	1	0	1	4	4	8	8	7	8	23
3	0	0	0	6	7	13	8	8	7	23
Total	5	4	9	16	17	33	24	23	23	70

Modified Sponsor's Table Vol99 p 0055

Table 29 Demographic Data: All Subjects Treated Group

Demographic 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 (N=5)	2.0 (N=4)	1.0 (N=16)	2.0 (N=17)	2.0 (N=24)	3.0 (N=23)	0.2 (N=23)
Age ^a							
Mean ± SD	13±8	19±3	10±7	10±6	5±3	8±2	5±3
Median (Min - Max)	8(7-22)	20(14-21)	11(1-20)	11(2-22)	5(2-12)	5(2-10)	4(2-12)
Weight (kg)							
Mean ± SD	3.7±0.3	3.7±0.6	8.9±3.2	9.0±2.6	22.4±10.7	22.9±8.2	19.1±6.4
Median (Min - Max)	3.6(3.4-4.2)	3.6(3.3-4.6)	9.0(4.5-16.0)	10.0(4.4-12.9)	17.8(11.0-50.5)	22.0(13.6-46.0)	19.3(12.6-37.1)
Height (cm)							
Mean ± SD	51.8±1.1	85.0±1.4	88.4±11.1	73.8±11.2	111.7±27.3	113.4±25.5	107.4±22.6
Median (Min - Max)	51.5(50.5-53.0)	55.0(54.0-56.0)	71.0(50.8-82.5)	77.3(53.0-91.4)	114.0(41.7-163.0)	113.5(44.5-157.0)	111.0(89.0-147.0)
Gender n (%)							
Male	1(20)	3(75)	11(69)	13(78)	18(75)	11(48)	17(74)
Female	4(80)	1(25)	5(31)	4(24)	6(25)	12(52)	6(26)
Race n (%)							
Caucasian	4(80)	4(100)	12(75)	10(59)	13(54)	12(52)	11(48)
Asian	0	0	0	0	0	0	0
Black	0	0	4(25)	3(18)	8(33)	7(30)	6(26)
Other	1(20)	0	0	4(24)	3(13)	4(17)	6(26)
ASA Class n (%)							
1	2(40)	2(50)	10(63)	11(65)	17(71)	16(70)	17(74)
2	3(60)	2(50)	6(38)	5(29)	6(25)	7(30)	5(22)
3	0	0	0	1(6)	1(4)	0	1(4)

Sponsor's Table 5 Vol 99 p. 0060

EFFICACY PARAMETERS:

I. Primary

1. T1 at 60 seconds:

Table 30 T1 as Percent of Control: Per Protocol Group

Statistic	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 Mg/kg
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
N	5	4	14	16	23	21 ^a	22 ^b
Mean ± SD % of Control	5.2 ± 9.6	7.6 ± 13.6	9.2 ± 16.9	7.6 ± 21.8	1.0 ± 2.3	5.4 ± 17.5	48.9 ± 40.9
Median % of Control	0	1.3	1.5	0	0	0	52
Min-Max	0-22	0-28	0-56	0-88	0-8	0-80	0-142

Sponsor's Table 10 Vol 99, p. 0069

- a One subject did not have T1 at 60 sec due to an artifact on EMG. Another subject did not have T1 recorded due to a procedural error
- b One subject did not have T1 at 60 sec due to a problem on EMG

The mean T1 at 60 seconds for the children ≥ 2 years 2.0 mg/kg and 3.0mg/kg treatment groups was lower than the 0.2 mg/kg mivacurium treatment group. The results are statistically significant ($p < 0.01$) for both the 2.0 and 3.0 mg/kg groups.

The results for the Intent to Treat analyses were nearly identical to the Per Protocol group.

2. Clinical Duration: defined as the time from end of administration of the intubating dose to return to 25% control T1.

Table 31 Clinical Duration (minutes): Per Protocol Group

Statistic	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 Mg/kg
	1.0	2.0	1.0	2.0	2.0	3.0	0.2
N	4	4	13	16	23	20	23
Mean \pm SD minutes	9.8 \pm 3.1	13.5 \pm 2.8	9.2 \pm 2.6	16.1 \pm 7	13.8 \pm 7.2	17.8 \pm 3.2	10.3 \pm 3
Median minutes	9.7	13.4	9.4	14.7	12.7	17.4	9.5
Min-Max	6-13.7	10.3-16.8	5.5-13	1.7-32.4	8.5- 44.2	11.5- 23.6	4.6-14.9

Sponsor's Table 12 Vol99 p. 0071

Clinical Duration was not measured for one subject in the neonate group, one subject in Children < 2 years group, and three subjects in the Org 9487 Children > 2 years group.

Recovery from neuromuscular block was allowed to occur spontaneously. These findings indicate that both in neonates and children there is an increase in duration of action as the dose of Org 9487 is increased. In comparison to the mivacurium chloride treatment group, both Org 9487 dose groups within the Children (≥ 2 years age group) had a statistically significant ($p < 0.05$) greater duration of action. The results of the Intent to Treat analyses are similar to those of the Per Protocol analyses.

II. Secondary Efficacy Parameters:

Table 32 Secondary Efficacy Parameters: Per Protocol Group