# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20984

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-984
NAME: Org 9487 (Rapacuronium Bromide) for Injection
SPONSOR: Organon Inc., #75 Mt. Pleasant Avenue, West Orange, NJ
SUBMISSION TYPE: Response to Approvable Letter
SUBMISSION DATE: June 18, 1999
REVIEWER: Suresh Doddapaneni, Ph.D.

On April 22, 1999, Approvable action was taken on NDA 20-984. On June 18, 1999, the sponsor responded to the items outlined in the Approvable letter. Among other things, sponsor is requesting the Agency that the impurity specification limits for Org 9488 in this product be set at % with a total degradation product specification of % with storage at room temperature. Originally, the Agency recommended specification limits of % for Org 9488 and % for total impurities since clinical trials were conducted using the product stored under refrigerated conditions with low impurities. In justification of the proposed specifications, the sponsor has referred to two pharmacokinetic/pharmacodynamic studies conducted after administration of Org 9488. This review is in response to a consult requested by the chemistry team leader Dr Abi D'Sa to evaluate if the sponsor provided adequate justification.

It should be noted that Org 9488 is not an impurity *per se*. Rather, it is the major and active metabolite of Org 9487 and is metabolically formed immediately upon intravenous administration. Org 9487 undergoes non-specific hydrolysis in the blood to form Org 9488. In addition, non-specific esterases present in the blood are also believed to hydrolyze Org 9487 to generate Org 9488. Org 9488 also appears to be eliminated faster when administered separately and does not seem to have the same prolonged terminal elimination characteristics seen with Org 9487. The sponsor did conduct two PK/PD studies after the administration of Org 9488 to evaluate the pharmacokinetics of Org 9488 as well as to explore PK/PD relationship (Table 1). In study 174206, at a dose of 0.2 mg/kg (this dose approximates the initial plasma concentrations of Org 9488 obtained after the administration of 1.5 mg/kg Org 9487) only one subject out of seven had a meaningful block of 75%. Therefore, it does not appear that plasma levels of Org 9488 obtained after the administration of a 1.5 mg/kg dose of Org 9487 contribute significantly to efficacy. In study 174207, a median dose of 0.68 mg/kg Org 9488 was given. At this dose, maximum blocks of 60-70% were reported in all subjects without any safety problems.

Table 1. PK/PD studies conducted with Org 9488 alone.

| Study | Design | Outcome |
|---|---|---|
| Study 174206 | 0.2 mg/kg Org 9488 was given intravenously to seven healthy volunteers. 0.2 mg/kg dose approximates initial plasma concentrations resulting after the administration of 1.5 mg/kg Org 9487 | 3 out of 7 subjects did not have any block. While, the remaining 4 subjects had a block of 4, 14, 43, and 75%, respectively. No drug related serious adverse events were reported. |
| Study 174207 | A median dose of 0.68 mg/kg Org 9488 was given intravenously to seven healthy volunteers. | Meaningful PK/PD analysis could be done. Org 9488 has a lower onset and a higher potency (about 2 fold) than Org 9487. No drug related serious adverse events reported. |

Therefore, it appears that there is a known safety margin with Org 9488 to doses up to 0.68 mg/kg. Also, it appears that below a dose of 0.2 mg/kg, Org 9488 does not provide meaningful block. From Table 2, it is apparent that the doses of Org 9488 that will be administered at a specification of % are far below the dose of 0.68 mg/kg administered in study 174207 to cause safety concerns. Also, these doses are below the 0.2 mg/kg dose of Org 9488 administered in study 174206, where only a minimum block was seen.

**Table 2.** Doses of Org 9488 at % and % limits of specification for Org 9487.

| Raplon Dose | Agency Proposed specification of % Org 9488 | Sponsor proposed specification of % Org 9488 | Additional Org 9488 at % specification |
|---|---|---|---|
| 1.5 mg/kg | 0.0225 mg/kg | 0.068 mg/kg | 0.0455 mg/kg |
| 2.5 mg/kg | 0.0375 mg/kg | 0.113 mg/kg | 0.0755 mg/kg |

Overall, it does appear that the sponsor's conclusion of safety of Org 9487 at the proposed specification of % for Org 9488 is justified. These issues were discussed in an internal team meeting on July 27, 1999 comprising of Drs Abi D'Sa, Ramana uppoor, Charles Cortinovis, Patricia Hartwell, Susmita Samantha, and Bob Rappaport where there was a general agreement that the sponsor proposed specification is acceptable.

**Recommendation**

From a Clinical Pharmacology and Biopharmaceutics perspective, sponsor provided adequate safety information to justify the proposed specification of % for Org 9488 in Raplon for Injection.

7/28/99

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

FT initialed by Ramana Uppoor, Ph.D. 7/28/99

CC:
NDA 20-984, HFD-170 (Division File, Samantha, Jean), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Barbara Murphy (CDR).

APR 5 1999

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

**NDA:** 20-984 **CODE:** 1S
**NAME:** Org 9487 (Rapacuronium Bromide) for Injection
**SPONSOR:** Organon Inc., #75 Mt. Pleasant Avenue, West Orange, NJ
**SUBMISSION TYPE:** Original NDA
**SUBMISSION DATE:** June 24, 1998, September 3, 1998
**REVIEWER:** Suresh Doddapaneni, Ph.D.

## SYNOPSIS

Organon, Inc., submitted NDA 20-984 seeking marketing approval for the neuromuscular blocking agent, Org 9487 (Rapacuronium Bromide) for Injection. Org 9487 is indicated as an adjunct to general anesthesia for use in outpatients and inpatients to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgical procedures. Currently, it is not marketed in any other country.

Pharmacokinetic data were obtained from 397 subjects in 20 studies. There were six intensive sampling studies and blood samples were obtained for population analysis using sparse sampling technique from fourteen clinical studies.

Mass balance study showed that urine and feces are the main routes of elimination of [$^{14}$C]Org 9487. The mean combined excretion in urine and feces at the end of the continuous collection period of 13 & ½ days was about 56% (range; 50%-64%). Measurable concentrations of radiocarbon were also detected in urine samples collected once a week over four weeks after the end of the continuous collection period of 13 & ½ days. The major metabolic pathway of Org 9487 appears to be hydrolysis of the acetyloxy-ester bond at the 3 position to form the major and active metabolite, Org 9488 (3-hydroxy metabolite). This hydrolysis seems to be spontaneous at physiological pH and temperature. Esterases of unknown identity may also be involved. In addition to Org 9488, there appears to be seven unknown minor metabolites in plasma, urine, and feces. In addition to the hydrolysis metabolic pathway, Org 9487 is also excreted unchanged in urine and feces. Org 9488 that was formed from the hydrolysis of Org 9487 is also excreted in urine and feces without undergoing further biotransformation. The extent of plasma protein binding of Org 9487 varied between 50.2% and 88.3%. This value is unreliable as there were methodological problems in determining the protein binding, partly attributable to Org 9487 undergoing hydrolysis through out the experimental procedure. The specific plasma protein to which the drug binds is unknown. Plasma protein binding of Org 9488 was not determined.

The pharmacokinetics of Org 9487 after I.V. administration were characterized by a mean terminal half-life of about 123 minutes, a mean clearance of about 6.73 mL/kg/minute, and a mean steady state volume of

distribution of 225 mL/kg. The mean cumulative urinary excretion of Org 9487 and Org 9488 were about 6% and 4% respectively at the end of 48 hours.

The pharmacokinetics of Org 9488 after the separate administration of an I.V. dose of Org 9488 were characterized by a mean terminal half-life of about 132 minutes, a mean clearance of about 1.11 mL/kg/minute, and a mean steady state volume of distribution of 175 mL/kg. The mean cumulative urinary excretion of Org 9488 was about 54% at the end of 24 hours (feces was not sampled in this study and presumably some of the dose is also excreted in the feces). Comparison of the pharmacokinetic data of Org 9487 and Org 9488, shows that Org 9488 generated after the administration of Org 9487 is exhibiting formation rate limited kinetics.

The pharmacokinetic-pharmacodynamic relationship of Org 9487 is characterized by a mean $K_{e0}$ of 0.44/minute, a mean $EC_{50}$ of 4.44 μg/mL, and a mean $ED_{90}$ bolus dose of 1.03 mg/kg. For Org 9488, these values were; a mean $K_{e0}$ value of 0.10/minute, a mean $EC_{50}$ value of 2.10 μg/mL, and a mean $ED_{90}$ dose of 0.46 mg/kg. These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487.

The pharmacokinetics of Org 9487 and Org 9488 were altered in patients suffering from end stage renal disease. The mean terminal half-life and clearance values of Org 9487 in ESRD patients were about 83% and 65% of those in normal volunteers. The ratio of Org 9488 (active metabolite) concentration relative to Org 9487 and the plasma concentration time profile clearly show that the pharmacokinetics of Org 9488 were affected in ESRD patients. Pharmacokinetics of Org 9487 were altered after the administration of Org 9487 to a group of mild to moderate hepatic impairment subjects. Contrary to what is generally expected, plasma clearance was greater (about 36%) in hepatic impairment patients compared to patients with normal liver function. Volume of distribution at steady state was also higher (about 85%) in hepatic impairment group. Org 9488 pharmacokinetics did not seem to be affected very much in the hepatic impairment group.

Population pharmacokinetic analysis with age as a covariate showed a negative correlation between age and clearance. Population pharmacokinetic analysis with gender as a covariate showed that there are no gender differences in the pharmacokinetics of Org 9487. Population pharmacokinetic analysis of plasma samples from 65 pediatric subjects (175 observations) ranging in age from 0.025 –12.8 years showed that the steady state volume of distribution is 495 mL/kg, the terminal half-life is 262 minutes, and the clearance was 10.6 mL/kg/minute.

The venous umbilical/maternal concentration ratio data shows that for both Org 9487 (1.8% to 16.1%) and Org 9488 (1.7% to 19.9%), there is only minor placental transfer of the drug from the maternal blood to the fetal blood at delivery.

No specific studies (*in vitro* or *in vivo*) were conducted to examine the pharmacokinetic drug-drug interactions of Org 9487 with any of the usually coadministered drugs as the sponsor felt that metabolic drug-drug interactions would not important for Org 9487 in view of its hydrolytic metabolic pathway (non specific hydrolysis and esterase catalyzed hydrolysis).

**RECOMMENDATION**

New Drug Application 20-984 can be approved from the viewpoint of Office of Clinical Pharmacology and Biopharmaceutics for single dose administration. Additional exposure data from a safety point of view should be submitted addressing the implications of the slow elimination kinetics of the drug when administered by intravenous infusion or by repeated intravenous bolus injections. The sponsor should consult with the Office of Clinical Pharmacology and Biopharmaceutics and Division of Anesthetics, Critical Care, and Drugs of Abuse to discuss the additional Clinical Pharmacology/Clinical studies necessary to address regulatory concerns.

4/5/99

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

RD initialed by Ramana Uppoor, Ph.D. on 3/26/99
FT initialed by Ramana Uppoor, Ph.D. 4/5/99

CC:
NDA 20-984, HFD-170 (Division File, Samantha, Cortinovis, Jean), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), Barbara Murphy (CDR).

TABLE OF CONTENTS

## 1.0. INTRODUCTION

Organon, Inc., submitted NDA 20-984 seeking marketing approval for the neuromuscular blocking agent, Org 9487 (Rapacuronium Bromide) for Injection. Org 9487 is a 16-N-allyl-17-β-propionate analogue of the currently marketed vecuronium and is proposed as the first non-depolarizing alternative to the depolarizing agent, succinyl choline. Org 9487 is indicated as an adjunct to general anesthesia for use in outpatients and inpatients to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgical procedures. Currently, it is not marketed in any other country.

## 2.0. OVERVIEW OF THE NDA

Pharmacokinetic data were obtained from 397 subjects in 24 studies. Six intensive sampling studies were conducted to determine: the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of Org 9487 (174204); the pharmacokinetics and pharmacokinetic/pharmacodynamic relationship of Org 9488 (174206 and 174207); pharmacokinetics of Org 9487 and Org 9488 in end stage renal disease (070003); pharmacokinetics of Org 9487 and Org 9488 in hepatic impairment disease (174309); and mass balance study (174104). A pooled population pharmacokinetic analysis was performed with the NONMEM program to determine the effects of age, gender, renal function, hepatic function, body weight, and other relevant covariates using data from three of the six intensive sampling studies (070003, 174204, and 174309) and from fourteen clinical studies using sparse sampling technique (070001, 070002, 070004, 070005, 070006, 070007, 070008, 070010, 070011, 174208, 174302, 174306, 174307, and 174308). Doses administered in the studies used in the population analysis seem to cover the dosage ranges proposed in the package insert (initial intubation dose of 1.5 mg/kg in adults).

## 3.0. FORMULATION

Org 9487 is a white to off-white cake, yellow orange or pink powder. Its log octanol/phosphate buffer partition coefficient is 1.05. Raplon™ (rapacuronium bromide) for Injection is supplied as a sterile non-pyrogenic lyophilized cake. It is supplied in two different vials (5 mL and 10 mL volumes) with the same strength of 20 mg of Org 9487 per mL to be achieved after reconstitution with sterile water for injection or bacteriostatic water for injection. The composition of the formulations is shown in the table below.

| Ingredient | 100 mg/5 mL vial | 200 mg/10 mL vial |
|---|---|---|
| Org 9487 | | |
| Citric Acid Anhydrous | | |
| Sodium Phosphate Dibasic Anhydrous, USP | | |
| Mannitol | | |
| Sodium Hydroxide, NF-5% w/v solution | | |
| Phosphoric Acid, NF-5% v/v solution | | |
| Water for Injection, USP qs to | | |

## 4.0. MASS BALANCE

This was a phase I, single-center, open-label, single-dose, pharmacokinetic study in six (6) healthy male volunteers who were administered a single I.V. bolus dose of 1.5 mg/kg [$^{14}$C]Org 9487 (**study 174104**). The objectives were to determine: (1) Excretion balance of [$^{14}$C]Org 9487 (2) Pharmacokinetics of radiolabel in blood and plasma, and (3) HPLC profiles of Org 9487 and metabolites in plasma, urine, and feces and to isolate and identify unknown metabolites in urine and feces.

After [$^{14}$C]Org 9487 dosing: blood samples were collected for 24 hours; urine samples were collected continuously for 13.5 days and once a week for the next four weeks; fecal samples were collected for 13 days; and expired air was collected for 24 hours.

**No accurate plasma pharmacokinetic analysis could be performed on the radiocarbon as the last three values obtained after 6, 12, and 24 hours post dosing did not show a single monoexponential pattern.** After 24 hours, the plasma concentrations in the six subjects ranged from 0.05-0.12 µg-eq/gm, above the LOQ of 0.03 µg-eq/gm.

Radioactivity associated with blood cells measured at three time points relative to the amount in whole blood appeared to be very low (mean: 14%; range: 9%-24%).

**Radiocarbon could be measured quantitatively in all urine and fecal samples collected continuously up to 13 & ½ days (324 hours) after injection.** Figure 1 shows the cumulative excretion of radiocarbon in urine and feces after the I.V. administration of 1.5 mg/kg [$^{14}$C]Org 9487. A cumulative mean total of about 28% (range; 22%-33%) of the administered dose was excreted in urine by the end of 13 & ½ days. About 12% of the administered dose was excreted within the first 12 hours following the injection. Thereafter, the excretion rate became much slower. **Measurable concentrations of radiocarbon were also detected in urine samples collected once a week over four weeks after the end of the continuous collection period of 13 & ½ days.** A cumulative mean total of about 28% (range; 22%-35%) of the administered dose was excreted in feces by the end of 13 & ½ days. About 20% of the administered dose was eliminated in feces within 96 hours after injection. Thereafter, the fecal excretion rate became much slower. **The mean combined excretion in urine and feces at the end of the continuous collection period of 13 & ½ days was about 56% (range; 50%-64%).** To put this into perspective with respect to animal data, in rats given 2.5 mg/kg of radiolabeled Org 9487, the overall excretion reached 74% after 7 days.

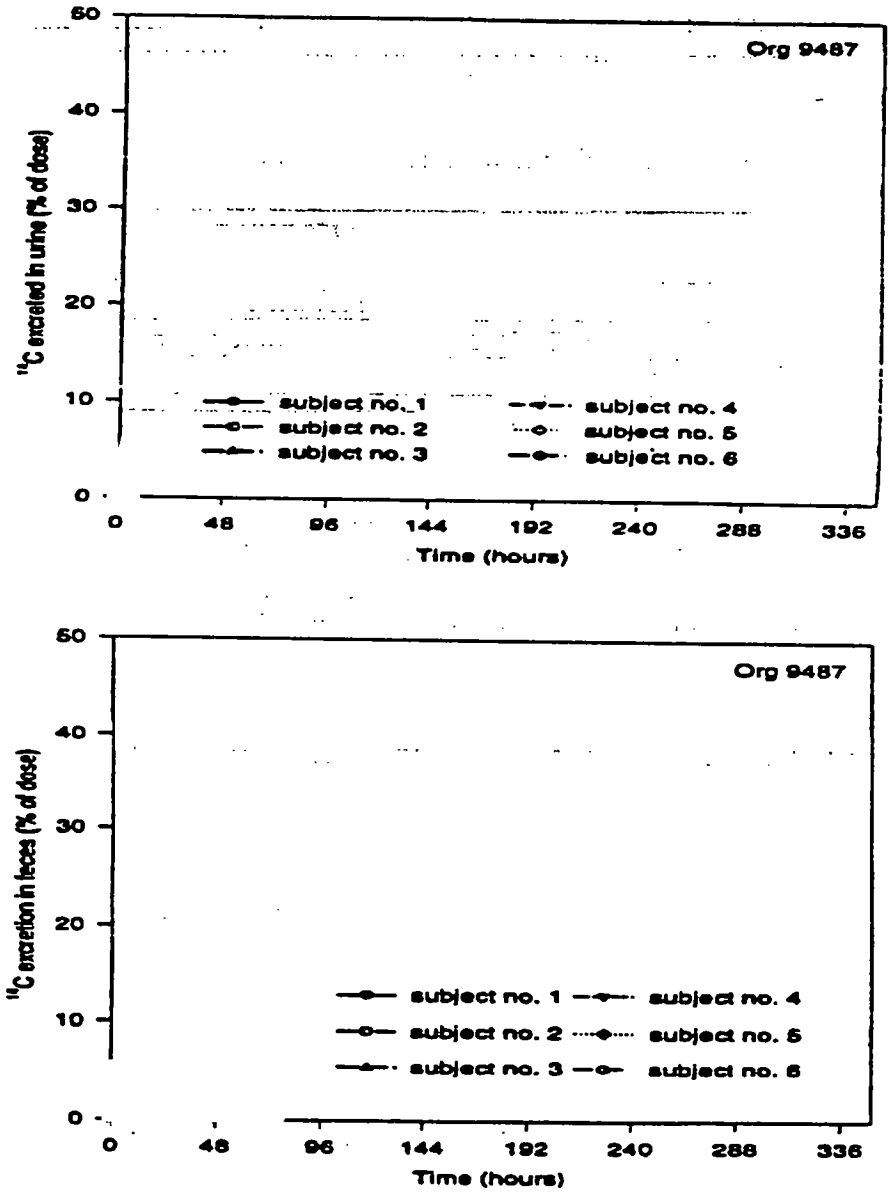



**Figure 1.** Cumulative excretion of radiocarbon in urine (top) and in feces (bottom) after I.V. administration of 1.5 mg/kg [$^{14}$C]Org 9487.

**The approximate cumulative radioactivity in expired air as radioactive carbon dioxide was about 0.6% in 24 hours.** However, this is only a crude estimate as (a) expired air sampling was started two hours post dosing (b) only 7 expired air samples were taken during 24 hours with relatively long intervals between samples (c) the volume of collected $CO_2$ is relatively small and (d) the hourly production of $CO_2$ has not been measured.

A thorough evaluation of the safety aspects of this study was undertaken by the reviewing Medical Officer at the request of this reviewer. It should be noted that the subjects were monitored in-house for routine safety parameters for 13 & ½ days. **The reviewing Medical Officer concurred with the sponsor's statement that all subjects completed the study period without any major problem.** Adverse events such as rhinitis, influenza-like symptoms, upper respiratory tract infection, and dysuria were of mild intensity and were considered as not related to the administered medication. **Therefore, it appears from the safety parameters captured in this study that the subjects did not feel any unusual side effects resulting from the persistence of the drug. However, it cannot be ruled out with absolute certainty that the drug was not causing any other side effects which were not obvious or which were not captured by the safety parameters used in this study.**

The sponsor was requested to explain the mechanism for the slow elimination kinetics of the drug in a letter dated 08/11/98. In a response dated 09/04/98, the sponsor provided explanation for the slow elimination kinetics and why the consequences of the slow elimination are insignificant clinically as follows;

(i) Rapid and extensive distribution into the tissues.

(ii) Possible reversible retention of radioactivity in muscle. In rats, part of the radioactivity not recovered at 336 hours post dosing (about 90% of radioactivity was excreted by this time) was mainly explained by the presence of low concentrations of radioactivity in foreleg muscles (2.38% of the dose), hind leg muscles (1.04% of the dose), and kidneys (0.95% of the dose). Radioactivity was mainly accounted for by the 3-hydroxy metabolite Org 9488.

(iii) No significant toxicity seen in the four-week studies in cats and dogs although high doses up to 18 mg/kg were administered twice a week causing muscle relaxation for several hours. Detailed examinations at termination of the study have not revealed any histopathological sign of organ or tissue damage. The only treatment related effect was increased plasma urea-N, slightly in the high-dose dogs and marked in the high dose cats.

(iv) No changes in the time-course of neuromuscular block in the four-week studies in cats and dogs.

The reviewing pharmacologist concurred with the sponsor's explanation on items ii-iv.

For rocuronium, total excretion in urine and feces of [$^{14}$C]rocuronium ranged from 88% to 94% at the end of nine days (urine, 47%; feces, 43%). About 45-50% of total [$^{14}$C]rocuronium was excreted within 24 hours, while about 70% was excreted by the end of 48 hours.

Metabolite profiles were determined by in plasma, urine, and feces samples at selected time points (plasma) or collection intervals (urine and feces) which ranged from 2 to180 minutes for plasma, 0-12 hours to 297-309 hours intervals for urine, and 0-22 hours to 289-313 hours intervals for feces. Identification of the compounds (Org 9487 and Org 9488) in the metabolite profiles of plasma and urine samples was performed by analysis. The compounds in the metabolite profiles of the feces samples were identified by comparison of the retention times of the metabolites identified in urine and plasma samples. **In all three cases of plasma, urine, and feces, Org 9487 and/or its major and active metabolite Org 9488 formed the majority of the excreted radioactivity at that particular time point for plasma or collection interval for urine and feces.**

The plasma metabolite profile conducted on plasma samples collected at 2, 7, 15, 30, 60, and 180 minutes contained six different compounds overall. Org 9487 and Org 9488 were the main compounds present at all time points. In the metabolite profile of the 3 hour sample, compound P1 comprised a major component (about 50%) of the plasma radioactivity at that time point. However, the total radioactivity concentration at the 3-hour time point is very low (about 60 fold lower than that of the radioactivity at the 2-minute time point). At the 30-minute time point, P1 and two additional components, P3 and P4 were detected. Again, these compounds were present in relatively lower concentrations (13%, 11% and 7% of the radioactivity at that time point). At the 7-minute time point, compound P6 comprising only 3% of the radioactivity at that time point was detected. **Therefore, in addition to Org 9487 and Org 9488, four other compounds of unknown structure, P1, P3, P4, and P6 in very minor concentrations were detected in the plasma.** Compound P1 was also observed in urine of the rat and feces of the female dogs.

**In addition to Org 9487 and Org 9488, three other compounds of unknown structure occurring in very minor concentrations, U1, U2 and U4, were detected in urine.** The concentrations of U1, U2, and U4 did not comprise more than 5.1%, 5.8% and 1.3% of the radioactivity at the respective time intervals. Compound U1 was also observed in urine and feces of female dogs while U2 was also observed in urine and feces of the rats and feces of the dogs.

The main compounds present in the feces samples were Org 9487 and Org 9488. **In addition, four other compounds of unknown structure F1, F2, F3, and F6 were also detected.** Compound F1 was also observed in

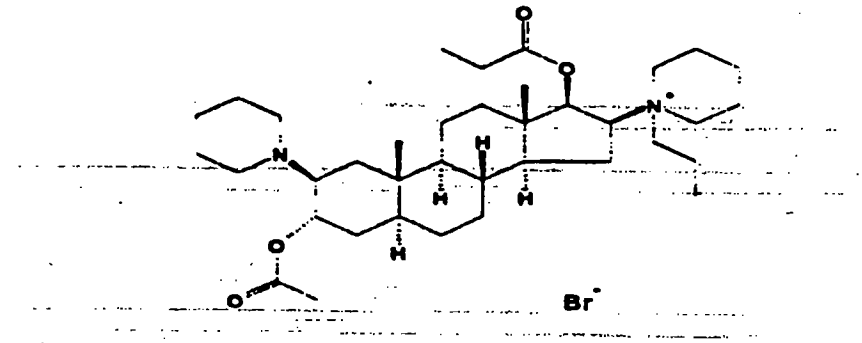
urine of the rat and feces of the female dogs. Compound F2 was observed in urine and feces of the rat. Compound F3 was observed in urine and feces of female dogs.

**Although a total of eleven unknown compounds occurring in minor concentrations were detected in plasma, urine, and feces (P1, P3, P4, and P6 in plasma; U1, U2, and U4 in urine; F1, F2, F3, and F6 in feces), based on the retention times of the metabolites identified in the present study or in the animal studies, it appears that these comprise seven unknown minor metabolites.**

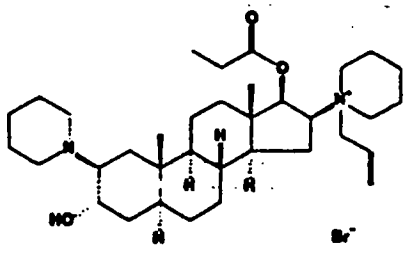
**5.0. METABOLISM**

Investigation with human post mitochondrial liver fractions showed that about 88% of Org 9487 was intact after a time period of 30 minutes. Org 9488 was the main metabolite detected. It was also found that conversion of Org 9487 was independent of NADPH ruling out the role of Cytochrome P450 enzymes in the metabolism of Org 9487. Org 9487 can undergo hydrolysis of the acetyloxy-ester bond at the 3 position to form the 3-hydroxy metabolite (Org 9488), at the 17-position to form 17-hydroxy metabolite (Org 9502), or at the 3 and 17 positions to form 3, 17-dihydroxy metabolite (Org 9504). Figure 2 shows the structures of Org 9487, Org 9488, Org 9502, and Org 9504. It is clear that Org 9488 is a major metabolite of Org 9487. However, in the mass balance study (study 174104), Org 9502 and Org 9504 were not detected in the metabolite profiles of plasma, urine, or feces. Similarly, in the Org 9487 pharmacokinetics /pharmacodynamics study (study 174204) in which plasma and urine samples were screened for Org 9502 and Org 9504, these were not detected. Therefore, unlike in animals where Org 9502 and Org 9504 were detected in minor amounts, it does not appear that *in vivo* hydrolysis occurs in humans at the 17-position and at the 3, 17 positions to form Org 9502 and Org 9504. In a letter dated 08/11/98, the sponsor was requested to provide more information on the hydrolysis pathway, specifically the nature of the hydrolyzing enzyme(s), the sites of hydrolysis, any polymorphism associated with these enzymes, and the metabolic pathways involved in the formation of minor metabolites. In a response dated 09/04/98, the sponsor provided the following information;

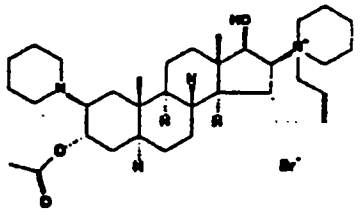
(i) Esterases may be involved in the hydrolysis of Org 9487.
(ii) The exact identity of the hydrolyzing enzymes is unknown.
(iii) Formation of Org 9488 may not be subject to polymorphism as none of the enzymes known to exhibit polymorphism (cytochrome P450, N-acetyltransferase, glutathione S-transferase, and methyltransferase) are involved in the metabolism of Org 9487. Furthermore, clinical pharmacokinetic data does not reveal the presence of subpopulations.
(iv) Spontaneous hydrolysis occurs at physiological temperature and pH.
(v) Org 9488 has been found *in vitro* in plasma (several species) and the liver (rat). It is unknown, if it is formed locally in other tissues.



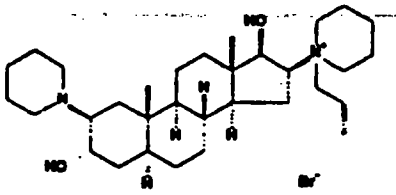
*Org 9487*



*Org 9488*



*Org 9502*



*Org 9504*

**Figure 2.** Structures of the Org 9487, its active and main metabolite Org 9488, and two minor metabolites Org 9502 and Org 9504 (found in animals but not in humans).

From the mass balance study (study 174104), it appears that there may be seven unknown minor metabolites. Neither the structure of these metabolites nor the metabolic pathways involved in the formation of these metabolites is known.

## 6.0. PROTEIN BINDING

Plasma protein binding was determined *in vitro* using the equilibrium dialysis method. The plasma samples were spiked with 0.125-20 µg/mL Org 9487 and the experiment was conducted for two hours at 37° C. **The extent of plasma protein binding of Org 9487 varied between 50.2% and 88.3%. However, these results are not reliable and should be viewed with caution.** The reasons for this are;

(i) Hydrolysis of Org 9487 to its 3-hydroxy metabolite (Org 9488) *in vitro*. Recovery of Org 9487 after equilibrium dialysis varied between 37.0% and 93.8%.

(ii) Concentration of Org 9487 in buffer and plasma occurring below LOQ (LOQ Plasma: 40 ng/mL; LOQ buffer: 100 ng/mL)

(iii) High variability (± 20% of calibration and QC samples) in the HPLC assay used for the analysis of Org 9487 and Org 9488.

**It should also be noted that specific protein to which the drug binds is unknown.** The sponsor was requested to provide information on these aspects in a request dated 08/11/98. In a response dated 09/04/98, the sponsor stated that the low binding of Org 9487 for plasma protein did not warrant identification of the binding plasma protein fraction and also that the hydrolysis of Org 9487 to Org 9488 presents technical problems in identification of the binding protein fraction by gel filtration. **Plasma protein binding of Org 9488 was not determined.**

## 7.0. ORG 9487 PHARMACOKINETICS/PHARMACODYNAMICS

This was an open-label, non-randomized, non comparative study in eleven (11) patients undergoing elective surgery **(study 174204)**. The objectives of this study were to determine the pharmacokinetics and pharmacodynamics of Org 9487.

Org 9487 was administered as a slow infusion at a dose of 0.3 mg/minute/kg over a median time of four minutes and forty seconds (range; 2.5-5.7 minutes). The infusion was discontinued when a neuromuscular block of 70% was reached. A mean dose of 0.93 mg/kg (range; 0.58-1.22 mg/kg) of Org 9487 was administered.

Blood was sampled for 6 hours following the administration of the dose for pharmacokinetic assessments. **The pharmacokinetics of Org 9487 were characterized by a terminal half-life of about 123 minutes, a**

**clearance of about 6.73 mL/kg/minute, and a steady state volume of distribution of 225 mL/kg (Table 1). It should be noted that these parameter values (especially, terminal half-life) might not be entirely accurate since blood sampling was carried out for only 6 hours while a 2-hour half-life value was reported. Also, the fact that Org 9487 was excreted unchanged in urine and feces for several days, reporting a 2-hour half-life is inaccurate.** The mean cumulative urinary excretion of Org 9487 and Org 9488 were about 6% and 4% respectively at the end of 48 hours.

**Table 1.** Pharmacokinetic parameter values of Org 9487 (mean (%CV)).

| Pharmacokinetic parameter | |
|---|---|
| Cl, mL/minute/kg | 6.73 (25) |
| Vdss, mL/kg | 225 (33) |
| $t_{1/2_\gamma}$, minute | 123 (66-283)* |

* Harmonic mean and range

All plasma and urine samples from a group of subjects (4 for plasma and 3 for urine) were screened for the presence of Org 9502 (17-OH metabolite) and Org 9504 (3,17 di-OH metabolite). In both bio fluids, levels of both Org 9502 and Org 9504 were below the LOQ (10.0 ng/mL in plasma, and 100 ng/mL in urine).

The neuromuscular block was measured by mechanomyography of the adductor pollicis, using single twitch stimulation of the ulnar nerve. To describe the concentration-effect relationship of Org 9487 in the effect compartment, the Hill-equation was used;

$$E = E_{max} * C_e^{\gamma} / EC_{50}^{\gamma} + C_e^{\gamma}$$

Where,

E = response (% paralysis)
$E_{max}$ = maximal response (100%)
$C_e$ = concentration in the effect compartment
$EC_{50}$ = concentration in the effect compartment at 50% drug-effect
$\gamma$ = steepness of the concentration-effect relationship

To describe the transport of drug to the effect compartment, the following equation was used;

$$dC_e/dt = K_{eo} * (C_p - C_e)$$

where,

$C_p$ = concentration in plasma
$K_{eo}$ = rate constant of removal from effect compartment

The pharmacokinetic-pharmacodynamic relationship of Org 9487 in this study is characterized by a mean $K_{eo}$ of 0.44/minute, a mean $EC_{50}$ of 4.44 μg/mL, and a mean $ED_{90}$ bolus dose of 1.03 mg/kg (Table 2). For Org 9488, these values obtained from study 174207 were as follows; a mean $K_{eo}$ value of 0.11/minute, a mean $EC_{50}$ value of 1.83 μg/mL, and a mean $ED_{90}$ dose of 0.42 mg/kg. **These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487.** However, when comparing the $ED_{90}$ of Org 9487 (1.03 mg/kg) and Org 9488 (0.42 mg/kg) with the $ED_{90}$ of rocuronium (0.3 mg/kg), vecuronium (0.05 mg/kg) and pancuronium (0.06 mg/kg), **Org 9487 and Org 9488 may be viewed as low potency neuromuscular blocking drugs.**

**Table 2.** Pharmacokinetic/pharmacodynamic modeling parameters of Org 9487 (mean (%CV)).

| Parameter | |
|---|---|
| $K_{eo}$, 1/minute | 0.44 (41) |
| γ | 2.97 (23) |
| $EC_{50}$, mg/liter | 4.44 (33) |
| $ED_{90}$, mg/kg | 1.03 (33) |

## 8.0. ORG 9488 PHARMACOKINETICS/PHARMACODYNAMICS

Animal Pharmacology studies indicated that the potency of Org 9488 is similar to that of Org 9487. Therefore, two studies (174206 & 174207) were conducted to investigate the pharmacokinetics/pharmacodynamics of Org 9488 after the administration of Org 9488.

In **study 174206**, a dose of 0.2 mg/kg of Org 9488 was given so as to approximate the initial plasma concentrations observed immediately after administration of a 1.5 mg/kg dose of Org 9487. This dose resulted in a measurable neuromuscular block in only four of the seven subjects. In these four subjects, maximum block was 4, 14, 43, and 75% respectively. **This suggests that Org 9488 contributes at least to a minimum degree, to the neuromuscular blocking effects observed after administration of the most commonly used dose of 1.5 mg/kg Org 9487.**

Plasma levels were determined for 6 hours after I.V. administration. The mean pharmacokinetic parameter values after the analysis of data using a three compartment model were as follows; terminal half-life of about 150 minutes, clearance of about 1.3 mL/kg/minute, and steady state volume of distribution of about 232 mL/kg. **However, it should be noted that the blood sampling duration of 6 hours is inadequate to report a terminal half-life of 2.5 hours. Therefore, Org 9488 pharmacokinetic parameter values estimated from this study should be**

**viewed as only rough estimates.** The mean cumulative urinary excretion of Org 9488 at the end of 24 hours was 53% (range; 45%-60%).

In **study 174207,** a median dose of 0.68 mg/kg (range; 0.48-0.76) was administered over three to five minutes in a slow running infusion to definitively characterize the pharmacodynamics of Org 9488. The infusion was discontinued when a neuromuscular block of 70% was reached for the first five subjects and for the next two subjects, the infusion was stopped when a neuromuscular block of 60% was reached.

Blood was sampled for 8 hours following the administration of the dose for pharmacokinetic assessments. **The pharmacokinetics of Org 9488 were characterized by a terminal half-life of about 132 minutes, a clearance of about 1.11 mL/kg/minute, and a steady state volume of distribution of 175 mL/kg (Table 3).** Comparing the pharmacokinetics of Org 9488 with those of Org 9487, the elimination half-life of Org 9488 is almost similar (132 minutes versus 121 minutes) and the clearance is lower (1.1 mL/kg/minute versus 7.2 mL/kg/minute). **The mean cumulative urinary excretion of Org 9488 was about 54% at the end of 24 hours (feces was not sampled in this study and presumably some of the dose is also excreted in the feces).** Comparing this data, with the urinary excretion profile of Org 9487 (study 174204), mean amounts of about 10.0% administered dose was excreted in the urine at the end of 24 hours (6% as Org 9487 and 4% as Org 9488). **Looking at this comparative data, it looks as if Org 9488 generated after the administration of Org 9487 is exhibiting formation rate limited kinetics.**

**Table 3.** Pharmacokinetic parameter values of Org 9488 (mean (%CV)).

| Pharmacokinetic parameter | |
|---|---|
| Cl, mL/minute/kg | 1.3 (33) |
| Vdss, mL/kg | 232 (27) |
| $t_{1/2_\beta}$, minute | 150 (123-270)* |

- Harmonic mean and range

To describe the concentration-effect relationship of Org 9488 in the effect compartment, the Hill-equation was used (same model as in study 174204). The pharmacokinetic-pharmacodynamic relationship of Org 9488 is characterized by a mean $K_{e0}$ of 0.10/minute, a mean $EC_{50}$ of 2.1 mg/liter, and a mean $ED_{90}$ bolus dose of 0.46 mg/kg (Table 4). For Org 9487, these values obtained from study 174204 were as follows; a mean $K_{e0}$ value of 0.44/minute, a mean $EC_{50}$ value of 4.44 µg/mL, and a mean $ED_{90}$ dose of 1.03 mg/kg. **These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487.** However, when comparing the $ED_{90}$ of Org 9488

(0.42 mg/kg) with the $ED_{90}$ of rocuronium (0.3 mg/kg), vecuronium (0.05 mg/kg) and pancuronium (0.06 mg/kg), **Org 9488 can be classified as a low potency neuromuscular blocking drug.**

**Table 4.** Pharmacokinetic/pharmacodynamic modeling parameters of Org 9488 (%CV)).

| Parameter | |
|---|---|
| Keo, 1/minute | 0.10 (40) |
| $\gamma$ | 4.83 (44) |
| $EC_{50}$, mg/liter | 2.06 (55) |
| $ED_{90}$, mg/kg | 0.46 (33) |

## 9.0. POPULATION PHARMACOKINETIC ANALYSIS

Plasma samples for a population-based pharmacokinetic analysis were taken, on a limited basis (sparse sampling), from subjects participating in fourteen phase II/III safety and efficacy studies (Table 5). In these studies, a total of 240 adults and 65 pediatric subjects provided three to five blood samples according to a prospectively designed sampling schedule up to 360 minutes after dosing (first sample within 5 minutes of dosing, the second 5-15 minutes after dosing, the third 45-240 minutes after dosing, and if possible a fourth sample 240-360 minutes after dosing). In addition, in three intensive sampling studies, 48 subjects were sampled up to 480 minutes.

Plasma concentration data were analyzed using NONMEM program Version IV Level 2.1 (ADVAN5). Data from the adult subjects and data from the pediatric subjects were analyzed separately. S-PLUS version 3.4 Release 1 was used for graphics. Xpose version 1.15 was used as a diagnostic tool.

The plasma Org 9487 concentration data were described by a three-compartment model that was parameterized in clearances and volumes. The estimates of these parameters were used subsequently to calculate half-lives and steady state volume of distribution. Org 9487 pharmacokinetic parameters were fixed for subsequent modeling of Org 9488. The formation, distribution and elimination of Org 9488 were described by a two-compartment model under the following assumptions: conversion of Org 9487 to Org 9488 occurs in the central compartment and is not reversible; Org 9488 is eliminated from its central compartment and distributed to a peripheral compartment linked bidirectionally to the central compartment. The fraction of the administered dose of Org 9487 metabolized to Org 9488 ($f_m$) cannot be estimated from the available data. However, based on urinary excretion data from Studies 174206 and 174207, an estimate of 0.1 for $f_m$ was deemed reasonable and was therefore used in the pharmacokinetic model. Relationships between covariates and individual parameter estimates obtained with the *posthoc* option of NONMEM were explored. Covariates were tested subsequently for their significance by inclusion in the pharmacokinetic model.

**Table 5.** Overview of studies included in the population-based pharmacokinetic analysis.

| Study Number | Study Type | PK Subjects N | No. Subjects in Subgroups | | | |
|---|---|---|---|---|---|---|
| | | | Dose (mg/kg) | Adults | Pediatric | Geriatric |
| Intensive Sampling Studies | | | | | | |
| 070003 | PK/PD in Renal Failure | 10 renal | 1.5 | 10 | – | – |
| | | 10 normal | 1.5 | 10 | – | – |
| 174204 | Modeling of Org 9487 | 11 | 0.3/min | 11 | – | – |
| 174301 | Org 9487 and Cirrhosis | 0 | 1.5 | – | – | – |
| 174309 | Org 9487 and Cirrhosis II | 9 hepatic | 1.5 | 7 | – | 2 |
| | | 8 normal | 1.5 | 7 | – | 1 |
| Sparse Sampling Studies | | | | | | |
| 070001 | Adult Dose Ranging | 43 | 0-2.5 | 23 | – | 20 |
| 070002 | Potency in Pediatrics | 18 | 0.3-0.9 | – | 18 | – |
| 070004 | Potency in Adults | 6 | 0.3-0.9 | 6 | – | – |
| 070005 | Time Course in Adults | 23 | 1.5-2.5 | 18 | – | 6 |
| 070006 | RSI for Cesarean Section | 17 | 2.5 | 17 | – | – |
| 070007 | Intubation with Org 9487 and Succinylcholine (Propodol) | 56 | 1.5 | 44 | – | 12 |
| 070008 | Time Course in Pediatrics | 18 | 1-3 | – | 18 | – |
| 070010 | Early Reversal | 3 | 1.5 | 3 | – | – |
| 070011 | Histamine Release | 19 | 1-3 | 10 | – | 9 |
| 174208 | Pediatric Dose Ranging | 29 | 0.5-2.5 | – | 29 | – |
| 174302 | Maintenance with Org 9487 or Rocuronium | 26 | 1.5 intub. 0.5-3/min | 26 | – | – |
| 174306 | Early Reversal after Single and Maintenance Doses | 22 | 1.5 | 17 | – | 5 |
| 174307 | Org 9487 in Cardiac Disease | 14 | 1.5 | 2 | – | 2 |
| 174308 | Intubation with Org 9487 and Succinylcholine (thiopental) | 18 | 1.5 | 14 | – | 4 |

**Table 6.** Subjects characteristics (covariates) evaluated in the population pharmacokinetic analysis.

| | Symbol | Model-Development Set median (range) | Model-Validation Set Median (range) |
|---|---|---|---|
| Demographics | | | |
| Age (yr) | AGE | 47 (18-83) | 45 (19-82) |
| Weight (kg) | WT | 74 (33.6-113) | 75 (45-113.5 |
| Height (cm) | HT | 170 (122-210) | 170 (149-195) |
| Body Surface Area (m2) | BSA | 1.84 (1.26-2.37) | 1.87 (1.36-2.42) |
| Lean Body Mass (kg) | LBM | 53.4 (28.7-76.6) | 54.4 (34.7-80.3) |
| Laboratory Parameters | | | |
| Creatinine (µmol/L) | CREA | 71 (18-1353) | 71 (35-1[illegible]9) |
| Albumin (g/L) | ALBU | 39 (16-52) | 39 (21-46) |
| Bilirubin (µmol/L) | BILI | 10 (3-169) | 10 (3-78) |
| ALAT/GPT (IU/L) | GPT | 18 (6-120) | 20 (5-161) |
| ASAT/GOT (IU/L) | GOT | 21 (8-93) | 21 (8-156) |
| Creatinine Clearance (mL/min) | CLCR | 109 (5-198) | 113 (10-227) |
| Other | | | |
| Gender (M/F) | GNDR | 110/96 | 35/28 |
| ASA Class (1/2/3/4) | ASAC | 87/87/31/1 | 29/20/14/0 |
| Dose Group (≤1/>1-≤2/>2-≤3/>3-≤4.9 mg/kg) | DSGR | 32/120/48/6 | 5/45/9/4 |
| Liver Cirrhosis (yes) | CIRR | 8 | 1 |
| End Stage Renal Disease (yes) | ESRD | 7 | 3 |

Model selection was based on visual inspection of the fits, decreases in unexplained variability and Log Likelihood criterion. For each additional parameter added to the model, a decrease of more than 6.6 in -2LL is statistically significant at the $p<0.01$ level.

Seventy-five percent of the subjects were included in a model-development dataset, i.e., this dataset was used to develop the population model. For each study in the population database, every fourth subject (25%) was included in a model-validation dataset, i.e., this dataset was used to test the predictive ability of the population model. The final population model including covariate effects was applied to the model-validation dataset. The differences between observed ($C_{obs}$) and predicted concentration ($C_{pred}$) values were evaluated graphically and by calculating the mean prediction error percentage.

Table 6 lists the subject covariates that were evaluated. The covariates that were examined were; age, weight, height, body surface area; lean body mass, creatinine, albumin, bilirubin, ALT/GPT, AST/GOT, creatinine clearance, gender, ASA class (1/2/3/4), Dose group ($\leq 1 > 1 \leq 2 / > 2 \leq 3 / > 3 \leq 4.9$ mg/kg), liver cirrhosis (yes), End stage renal disease (yes).

In adult subjects the relationships between the pharmacokinetic parameters of the basic three-compartment model and the covariates were investigated by plotting the *posthoc etas* vs. the covariates. A positive correlation was shown between clearance and weight, height, lean body mass, body surface area and creatinine clearance. A negative correlation with age was shown. Clearance seemed lower for female then male subjects, and lower for subjects with ESRD.

Although body surface area, weight, and gender are intercorrelated, inclusion of body surface area improved the most with little further benefit by inclusion of the latter three covariates. Likewise, age and creatinine clearance are intercorrelated with age providing more improvement. The inclusion of creatinine clearance was found to significantly improve the fit for $CL_{slow}$ and V1. No other distinct relationship was found between the pharmacokinetic parameters and the covariates. Thus, the final Org 9487 population model for adult subjects is a three-compartment pharmacokinetic model with clearance changing with body surface area and age and being lower in patients with end stage renal disease, and $Cl_{slow}$ and V1 being higher in patients with liver cirrhosis. Parameter estimates of the final Org 9487 model are presented in Table 7. The steady state volume of distribution was 23110 mL, the clearance was 483 mL/minute, and the terminal half-life was 196 minutes.

Total plasma clearance of Org 9487 in the three intensive sampling studies (174204, 07003, 174309) ranged from 6.1 to 9.9 liter/kg/minute. This value is similar to the clearance value of 483 mL/minute (approximately 6.9 mL/minute for a 70 kg man) found in NONMEM analysis. With respect to half-life, it ranged from 79 to 233 minutes in intensive sampling studies compared

to a value of 180 minutes in the NONMEM analysis. The volume of distribution at steady state was also variable in the intensive sampling studies ranging from 212 mL/kg to 424 mL/kg. In the NONMEM analysis, this value was found to be 23110 mL (approximately 330 mL/kg for a 70 kg man).

**Table 7.** Org 9487 pharmacokinetic parameters for three compartment model with covariates included.

| | | Value | SE | CV% | IIV% |
|---|---|---|---|---|---|
| *Estimated Parameters* | | | | | |
| CL (mL/min) | | *CL = theta1 (theta2 if end stage renal disease) + theta3 * (BSA - 1.84) - theta4 * (AGE - 47)* | | | 22 |
| | theta1 | 483 | 9.26 | 1.9 | |
| | theta2 | 417 | 34.8 | 8.3 | |
| | theta3 | 250 | 38.2 | 15 | |
| | theta4 | 3.34 | 0.586 | 18 | |
| CLrapid (mL/min) | | *Clrapid = theta5* | | | N.D. |
| | theta5 | 185 | 9.50 | 5.1 | |
| CLslow (mL/min) | | *Clslow = theta6 (theta7 if cirrhotic patient)* | | | 56 |
| | theta6 | 44.4 | 4.47 | 10 | |
| | theta7 | 82.5 | 15.1 | 18 | |
| V1 (mL) | | *V1 = theta8 (theta9 if cirrhotic patient)* | | | 24 |
| | theta8 | 5550 | 199 | 3.6 | |
| | theta9 | 7580 | 866 | 11 | |
| V2 (mL) | | *V2 = theta 10* | | | 6.5 |
| | theta1 | 6160 | 524 | 8.5 | |
| V3 (mL) | | *V3 = theta11* | | | 35 |
| | theta1 | 11400 | 1200 | 11 | |
| Residual Variability 21% | | | | | |
| *Derived Parameters* | | | | | |
| Vss (mL) | | 23110 | | | |
| $t_{1/2\alpha}$ (min) | | 5.03 | | | |
| $t_{1/2\alpha}$ (min) | | 33.2 | | | |
| $t_{1/2\beta}$ (min) | | 196 | | | |

Estimated Parameters are estimated by NONMEM.
Value = Typical Value; SE = Standard Error; CV = Coefficient of Variation; IIV = Inter Individual Variability.
ND = not determined.
Derived Parameters are calculated from the estimated parameters for subjects with BSA=1.84m2 and AGE=47 yr not having end-stage renal disease or cirrhosis (SE, CV, IIV not available)
1.84 is median BSA and 47 is median AGE of patient population

The final Org 9487 pharmacokinetic parameters were fixed for subsequent modeling of the metabolite Org 9488. $f_m$, the fraction of Org 9487 metabolized to Org 9488 was assumed to be 0.10. The clearance of Org 9488 decreased with decreasing creatinine clearance. The steady state volume of distribution was found to be 29,400 mL, the clearance was about 133 mL/minute, and the terminal half-life was about 180 minutes.

The plasma Org 9487 concentration data from the pediatric subjects (from 65 pediatric subjects (175 observations) ranging in age from 0.025 –12.8 years) were best described by a three-compartment model in which

all pharmacokinetic parameters were proportional to body weight. An estimate of interindividual variability (IIV) could only be obtained for clearance. Including IIV for the other pharmacokinetic parameters in the model did not improve the fit. The observed age-, and size-related differences in clearance within the pediatric population were accounted for by assuming clearance to be proportional to body weight. No trends were detected between clearance and the remaining covariates. From this analysis, the pharmacokinetic parameter values of Org 9487 were as follows; volume of distribution at steady state was 495 mL/kg, clearance was 10.6 mL/kg/minute, and the terminal half-life was about 180 minutes. It appears as if the clearance in pediatrics is slightly faster compared to adults.

## 10.0. SPECIAL POPULATIONS

### 10.1. Hepatic Impairment

This was an open-label, non-randomized, single-dose study conducted in seven (7) cirrhotic subjects and nine (9) subjects with normal hepatic function scheduled for elective peripheral surgery or endoscopy under general anesthesia. Each subject received a bolus dose of 1.5 mg/kg Org 9487. Blood samples were collected for eight (8) hours post-dosing for Org 9487 and Org 9488 analysis. The efficacy and safety profiles were also characterized in this study.

The cirrhotic group comprised of two (2) completed mild hepatic impairment subjects (Child-Pugh classification A) and four (4) completed moderate hepatic impairment subjects (Child-Pugh classification B). No severe hepatic impairment subjects were recruited into the study. The control group consisted of seven (7) evaluable subjects.

Figures 3 & 4 present the plasma concentration time profiles of Org 9487 and Org 9488 in control subjects and hepatic impairment subjects. The main pharmacokinetic parameters of Org 9487 derived from a two compartment analysis are summarized in Table 8.

The most remarkable finding in this study is the higher clearance of Org 9487 in hepatic impairment group compared to the control group (mean clearance value in hepatic impairment group is about 136% of that in control group). The terminal half-life values were similar between the two groups. This data was substantiated by the fact that recovery from the neuromuscular block was faster in the cirrhotic subjects as compared to the control subjects. These findings are inconsistent with the general expectation of a decreased clearance and a prolonged terminal half-life in the hepatic impairment population (or no change if there are multiple extrahepatic elimination pathways) and the sponsor could not provide a satisfactory explanation for the unexpected findings in this study. However, it has to be noted that hydrolysis of Org 9487 to Org 9488 and renal and fecal excretion of unchanged Org 9487 are the main

elimination pathways for Org 9487. Although, the quantitative contribution of esterases to the overall hydrolysis is not known, the fact that Org 9487 has systemic non specific hydrolysis elimination pathway and renal and fecal elimination of unchanged Org 9487 pathways, it is unlikely that the overall elimination of Org 9487 would be affected in a major way. The mean steady state volume of distribution was higher (185% of that of the control group) in hepatic impairment group.

**Table 8.** Estimates of Org 9487 PK parameters in patients with normal liver function and patients with mild and moderate cirrhosis (mean (SD)).

| PK Parameter | Normal Liver Function (N=7) | Hepatic Impairment (cirrhotic) (N=6) |
|---|---|---|
| $t_{1/2}\beta$, minutes | 84 (4)[a] | 88 (6)[a] |
| Vdss, (mL/kg) | 252 (77) | 465 (82) [b] |
| Cl, mL/kg/minute | 6.6 (1.7) | 9.0 (1.4)[b] |

a= Harmonic mean and standard error of harmonic mean.

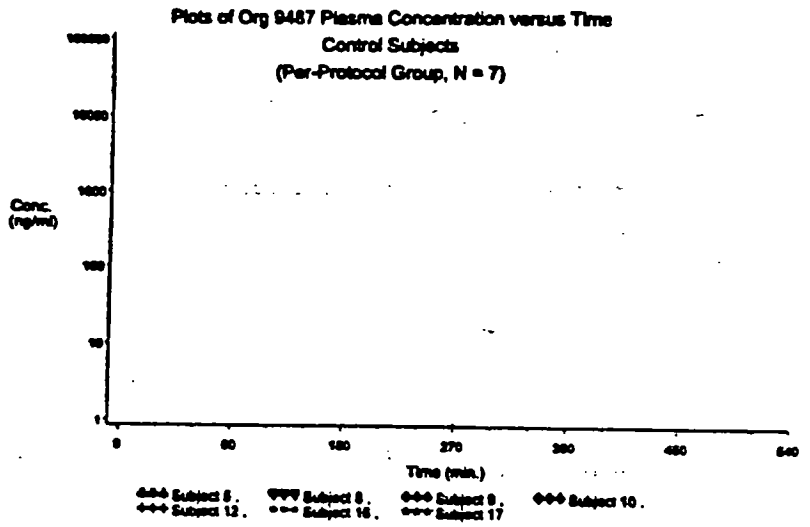
b= $p \leq 0.01$ for comparison with normal patients

**Table 9.** Summary of Org 9488 levels in patients with normal liver function and patients with mild and moderate cirrhosis (median (range)).

| PK Parameter | Normal Liver Function | Hepatic Impairment |
|---|---|---|
| $C_{max}$, ng/mL | 2010 (650-3839) | 1448 (970-2362) |
| Ratio of Org 9488 level over Org 9487 level at last time point | 5.6 (3.9-10.6) | 6.4 (3.3-7.6) |

Table 9 presents plasma levels of Org 9488 in the control and hepatic impairment groups. The median Org 9488 level was higher in the control group (140% of that in hepatic impairment group). The median value of ratio of Org 9488 level over Org 9487 level at last time point was slightly lower in the control group. In general, hepatic impairment does not seem to affect the pharmacokinetics of Org 9488 very much. This may be due to the fact that Org 9488 does not undergo further metabolism but rather it is excreted unchanged in urine and feces.

Regarding the efficacy parameters in this study, the report states that onset and maximum degree of neuromuscular block induced by Org 9487 is similar between cirrhotics and control subjects.



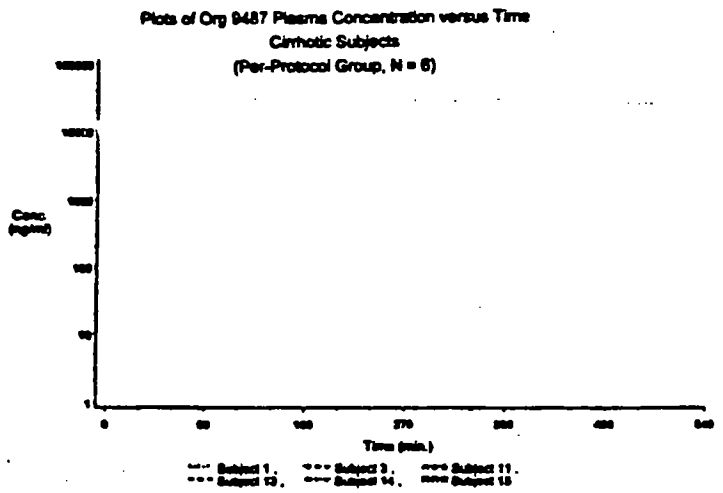
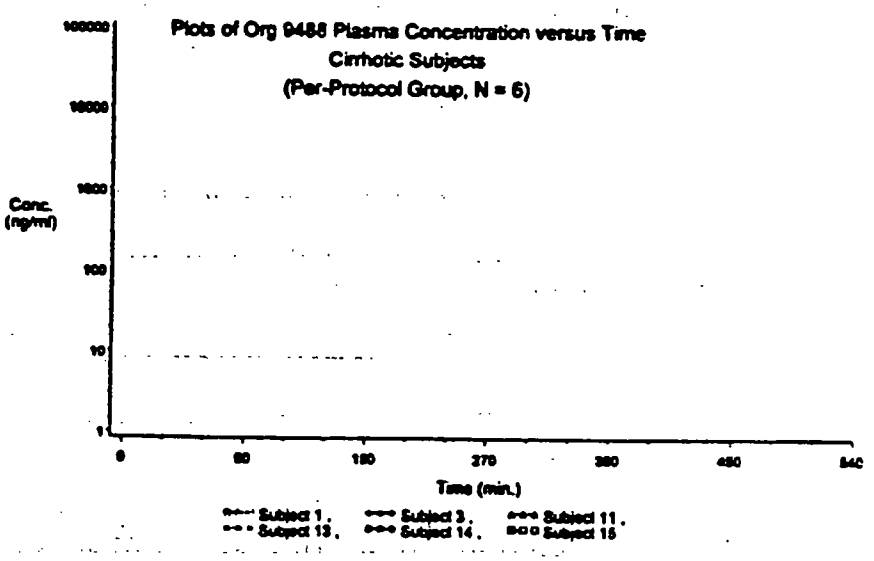




**Figure 3.** Plasma concentration-time profiles of Org 9487 in control subjects and hepatic impairment subjects.



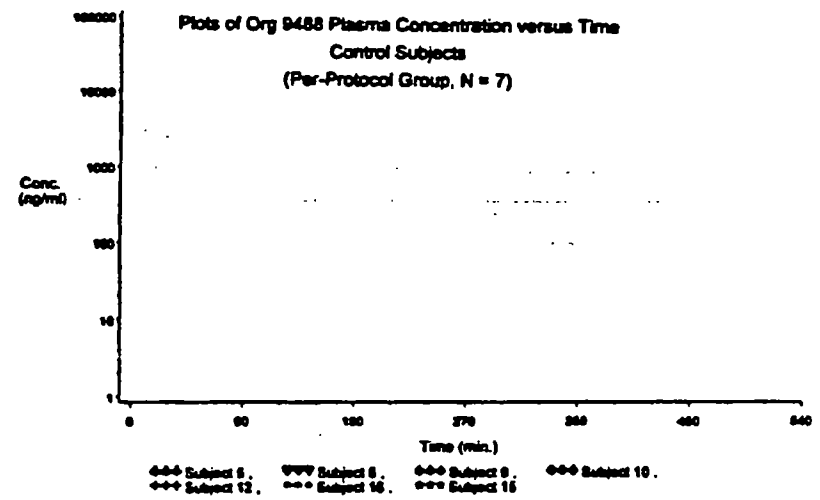




**Figure 4.** Plasma concentration-time profiles of Org 9488 in control subjects and hepatic impairment subjects.

**10.2. End Stage Renal Disease**

This was an open-label, non-randomized, single-dose study conducted in ten (10) volunteers with normal renal function and ten end stage renal disease (ESRD) patients. Each study participant received a bolus dose of 1.5 mg/kg Org 9487. Blood samples were collected for eight (8) hours post-dosing for Org 9487 and Org 9488 analysis. The efficacy and safety profiles were also characterized in this study.

Figure 3 shows the plasma concentration-time profiles of Org 9487 and Org 9488 in subjects with normal renal function and in patients with end stage renal disease. The profiles show that the pharmacokinetics of Org 9487 and Org 9488 were affected in ESRD patients. Particularly, Org 9488 levels show a dramatic difference in that no declining trend was seen at the end of the eight hour sampling duration in contrast to levels in volunteers with normal renal function.

Table 10 lists the main pharmacokinetic parameters of Org 9487 derived from traditional compartment analysis. The pharmacokinetics of Org 9487 were altered in patients suffering from end stage renal disease. The mean terminal half-life and clearance values of Org 9487 in ESRD patients were about 83% and 65% of those in normal volunteers. This signifies the fact that renal elimination of unchanged Org 9487 is a major component of the overall elimination of Org 9487. Although, the mean steady state volume of distribution values were not different in the normal and ESRD patients, the ESRD patients mean value was associated with a high degree of variability (% CV of 78% for ESRD patients versus % CV of 18% for normal subjects).

Table 11 lists the Org 9488 (active metabolite) concentration relative to Org 9487 up to eight hours after Org 9487 administration. In the normal volunteer group, this ratio increases steadily through the 6-hour period but shows a decrease by the 8-hour time period. However, in ESRD patients this ratio showed an increasing trend even at the 8-hour time point. Although, the magnitude of the decrease in clearance of Org 9488 is not apparent from this data, the plasma concentration time profile of Org 9488 (shown in figure 1) shows a dramatic effect. No clear elimination phase could be seen at the end of 8 hours. These results are to be expected since Org 9488 is excreted unchanged in the urine. A prolonged sampling duration to account for the possible decrease in clearance could have helped in quantifying the magnitude of Org 9488 clearance better. Between Org 9487 and Org 9488, the effect of ESRD on Org 9487 pharmacokinetics seems to be less as Org 9487 has additional hydrolytic pathway and biliary excretory pathways contributing to its elimination where as for Org 9488 has additionally only biliary excretory pathway contributing to its elimination.

**Table 10.** Estimates of Org 9487 PK Parameters in Normal Volunteers and Patients With End Stage Renal Disease.

| Parameters | Normal Volunteers[a] | Renal Patients[a] |
|---|---|---|
| $t_{1/2}\beta$, minute | | |
| mean ± SD | 240.0 (96.9) | 197.6 (141.0) |
| median (range) | 233 (138 - 477) | 173 (103 - 561)[b] |
| Vdss, mL/kg | | |
| mean ± SD | 431.7 (77.7) | 440.3 (346.8) |
| median (range) | 424(277 - 568) | 336 (228 - 1349) |
| CL, mL/kg/minute | | |
| mean ± SD | 9.4 (2.2) | 6.1 (1.7) |
| median (range) | 9.9 (6.4 - 13.6) | 5.6 (3.8 - 8.8)[b] |

a= Normal volunteers n=10, renal patients (ESRD) n=9
b= $p \leq 0.05$ for comparison with normal volunteers.

**Table 11.** Ratio of Org 9488/Org 9487 in plasma at different time points (mean (SD)).

| Time (hour) | Normal Renal Function Subjects | ESRD Patients |
|---|---|---|
| 2 | 1.76 (0.54) | 1.08 (0.45) |
| 4 | 3.91 (1.04) | 3.65 (1.45) |
| 6 | 4.90 (0.95) | 6.73 (2.12) |
| 8 | 4.5 (0.83) | 8.08 (1.91) |

With respect to the efficacy and safety parameters, the study report concludes that the (1) efficacy profile is not significantly different between normal and ESRD subjects and that the (2) safety profile is similar except that renal subjects have higher incidence of adverse experiences.

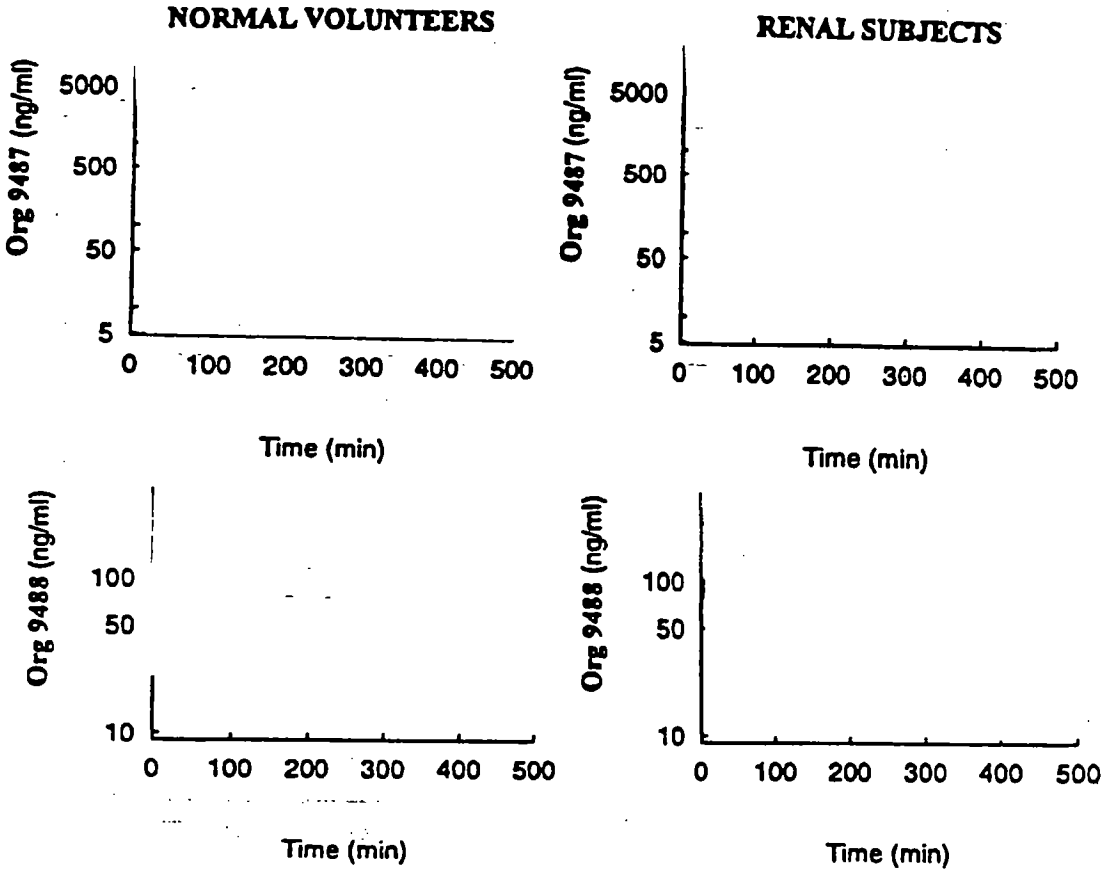



**Figure 3.** Plasma concentration time profiles of Org 9487 and Org 9488 in subjects with normal renal function and patients with end stage renal disease.

**10.3. Elderly**

Population pharmacokinetic analysis with age as a covariate showed a negative correlation between age and clearance. This is to be expected since renal function decreases with age and as such the renal elimination component would be affected.

**10.4. Gender**

Population pharmacokinetic analysis with gender as a covariate showed that there are no gender differences in the pharmacokinetics of Org 9487.

**10.5. Pediatrics**

Population pharmacokinetic analysis of plasma samples from 65 pediatric subjects (175 observations) ranging in age from 0.025 –12.8 years showed that the steady state volume of distribution is 495 mL/kg, the terminal half-life is 262 minutes, and the clearance was 10.6 mL/kg/minute.

**10.6. Maternal/Fetal Ratio**

Maternal plasma and newborn umbilical levels of Org 9487 and metabolites at delivery were determined in study 070006. Study 070006 was designed to compare the neuromuscular parameters, clinical responses and safety of a bolus dose of 2.5 mg/kg of Org 9487 with 1.5 mg/kg of succinyl choline in subjects undergoing Cesarean section surgery with general anesthesia.

A total of forty-three (43) subjects participated in this study and Org 9487/Org 9488 levels were obtained from seventeen (17) of these forty three (43) subjects. The venous umbilical/maternal concentration ratio for Org 9487 ranged from 1.8% to 16.1%. The highest umbilical concentration of Org 9487 (venous sample) in a newborn was 1145.3 ng/mL. In comparison, maternal levels at delivery (a median of 12 minutes after Org 9487 administration) ranged from about 4,900 to 15,400 ng/mL.

The venous umbilical/maternal concentration ratio for Org 9488 ranged from 1.7% to 19.9%. The highest umbilical concentration of Org 9488 (venous sample) in a newborn was 86.7 ng/mL. In comparison, maternal levels at delivery (a median of 12 minutes after Org 9487 administration) ranged from about 400 to 840 ng/mL.

**10.7. Drug-Drug Interactions**

No specific studies (*in vitro* or *in vivo*) were conducted to examine the pharmacokinetic drug-drug interactions of Org 9487 with any of the usually coadministered drugs. This topic came up in the pre-NDA meeting held on 02/24/98 and the sponsor felt that since hydrolysis (non specific hydrolysis as well as that resulting from esterases activity) is the major metabolic pathway, metabolic drug-drug interactions may not be important.

The sponsors above explanation regarding metabolic drug-drug interactions appears to be reasonable.

## 11.0. ANALYTICAL METHODOLOGY

## 12.0. CONCLUSIONS

1) Mass balance study showed that urine and feces are the main routes of elimination of [$^{14}$C]Org 9487. This elimination is very slow. The mean combined excretion in urine and feces at the end of the continuous collection period of 13 & ½ days was about 56% (range; 50%-64%). Measurable concentrations of radiocarbon were also detected in urine samples collected once a week over four weeks after the end of the continuous collection period of 13 & ½ days. If the sponsor proposes to use this drug for situations that may need the use of more than a single bolus dose, then additional data from a safety point of view should be submitted addressing the implications of the slow elimination kinetics of the drug under those administration conditions.

2) The major metabolic pathway of Org 9487 appears to be hydrolysis of the acetyloxy-ester bond at the 3 position to form the 3-hydroxy metabolite

(Org 9488). This hydrolysis seems to be spontaneous at physiological pH and temperature. Esterases of unknown identity may also be involved. Hydrolysis at the 17 position and at the 3 & 17 positions to generate Org 9502 and Org 9504 respectively, does not seem to be occurring in humans. In addition to Org 9487, there appear to be seven unknown minor metabolites in plasma, urine and feces together.

3) In addition to the hydrolysis metabolic pathway, Org 9487 is also excreted unchanged in urine and feces. Org 9488 that was formed from the hydrolysis of Org 9487 is also excreted in urine and feces without undergoing further biotransformation.

4) The extent of plasma protein binding of Org 9487 varied between 50.2% and 88.3%. The specific plasma protein to which the drug binds is unknown. Plasma protein binding of Org 9488 was not determined.

5) The pharmacokinetics of Org 9487 were characterized by a terminal half-life of about 123 minutes, a clearance of about 6.73 mL/kg/minute, and a steady state volume of distribution of 225 mL/kg. The mean cumulative urinary excretion of Org 9487 and Org 9488 were about 6% and 4% respectively at the end of 48 hours.

6) It should be noted that the pharmacokinetic parameter values of Org 9487 reported in this NDA (especially, terminal half-life) might not be entirely accurate since blood sampling was carried out for only 6-8 hours while a 2-hour half-life value was reported. From the mass balance study, it was seen that Org 9487 was excreted unchanged in urine and feces for several days. Therefore, the true terminal half-life of Org 9487 is unknown from the data presented in this NDA.

7) The pharmacokinetics of Org 9488 after the separate administration of an iv dose of Org 9488 were characterized by a terminal half-life of about 132 minutes, a clearance of about 1.11 mL/kg/minute, and a steady state volume of distribution of 175 mL/kg. The mean cumulative urinary excretion of Org 9488 was about 54% at the end of 24 hours (feces was not sampled in this study and presumably some of the dose is also excreted in the feces). Comparison of the pharmacokinetic data of Org 9487 and Org 9488, shows that Org 9488 generated after the administration of Org 9487 is exhibiting formation rate limited kinetics.

8) The pharmacokinetic-pharmacodynamic relationship of Org 9487 is characterized by a mean $K_{eo}$ of 0.44/minute, a mean $EC_{50}$ of 4.44 μg/mL, and a mean $ED_{90}$ bolus dose of 1.03 mg/kg. For Org 9488, these values were; a mean $K_{eo}$ value of 0.10/minute, a mean $EC_{50}$ value of 2.1 μg/mL, and a mean $ED_{90}$ dose of 0.46 mg/kg. These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487.

9) Comparison of the $ED_{90}$ values of Org 9487 (1.03 mg/kg) and Org 9488 (0.42 mg/kg) with those of the currently marketed neuromuscular blocking

agents such as, rocuronium (0.3 mg/kg), vecuronium (0.05 mg/kg) and pancuronium (0.06 mg/kg), Org 9487 and Org 9488 appear to be low potency neuromuscular blocking drugs.

10) Pharmacokinetics of Org 9487 were altered after the administration of Org 9487 to a group of mild to moderate hepatic impairment subjects. Contrary to what is generally expected, plasma clearance was greater (about 36%) in hepatic impairment patients compared to patients with normal liver function. Volume of distribution at steady state was also higher (about 85%) in hepatic impairment group. Org 9488 pharmacokinetics did not seem to be affected very much in the hepatic impairment group.

11) The pharmacokinetics of Org 9487 and Org 9488 were altered in patients suffering from end stage renal disease. The mean terminal half-life and clearance values of Org 9487 in ESRD patients were about 83% and 65% of those in normal volunteers. Although, the mean steady state volume of distribution values were not different in the normal and ESRD patients, the ESRD patients mean value was associated with a high degree of variability (% CV of 78% for ESRD patients versus % CV of 18% for normal subjects). The ratio of Org 9488 (active metabolite) concentration relative to Org 9487 and the plasma concentration time profile clearly show that the pharmacokinetics of Org 9488 are affected in ESRD patients. Although, it was not possible to quantify the magnitude of the decrease in clearance (relatively short blood sampling duration and no urinary excretion data) the available data clearly shows that Org 9488 elimination may be decreased to a much larger extent than that of Org 9487 in ESRD patients.

12) Population pharmacokinetic analysis with age as a covariate showed a negative correlation between age and clearance.

13) Population pharmacokinetic analysis with gender as a covariate showed that there are no gender differences in the pharmacokinetics of Org 9487.

14) Population pharmacokinetic analysis of plasma samples from 65 pediatric subjects (175 observations) ranging in age from 0.025 –12.8 years showed that the steady state volume of distribution is 495 mL/kg, the terminal half-life is 262 minutes, and the clearance was 10.6 mL/kg/minute. It appears as if the clearance is faster in pediatrics compared to adults.

15) The venous umbilical/maternal concentration ratio data shows that for both Org 9487 (1.8% to 16.1%) and Org 9488 (1.7% to 19.9%), there is only minor placental transfer of the drug from the maternal blood to the fetal blood at delivery.

16) No specific studies (*in vitro* or *in vivo*) were conducted to examine the pharmacokinetic drug-drug interactions of Org 9487 with any of the usually coadministered drugs as the sponsor felt that metabolic drug-drug interactions would not be important for Org 9487 in view of its hydrolytic metabolic pathway (non specific hydrolysis and esterase catalyzed hydrolysis).

## 13.0. PROPOSED PACKAGE INSERT

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

## APPENDIX (STUDY SUMMARIES)

## MASS BALANCE

**Study Type**: Mass Balance.

**Study Title**: Compound Recovery Study of $^{14}C$-Labeled Org 9487 in Healthy Volunteers.

**NDA**: 20-984 **Submission Date**: 6/24/98 **Volume**: 1.72 **Protocol**: 174104

**Clinical Investigator:**

**Analytical Investigator:**

**Study Design:**
Single Dose: Yes Other Design: Open-label Fasted: Overnight fast

**Subject Breakdown**
Normal Yes Number = 6 Males = 6
Weight Mean 79 kg Range 70-89 kg
Age Mean 34 yrs Range 28-41 yrs

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| - | 1.5 mg/kg | Sterile solution for Injection | 66.67 mg/mL [$^{14}C$]Org 9487 | 096243 |

**Analytical Methodology**

**Labeling Claims**
None

**Objectives**
(1) Excretion balance of [$^{14}C$]Org 9487.

(2) Pharmacokinetics of radiolabel in blood and plasma.
(3) profiles of Org 9487 and metabolites in plasma, urine, and feces and to isolate and identify unknown metabolites in urine and feces.

**Results and Discussion**

This was a phase I, single-center, open-label, single-dose, pharmacokinetic study in six (6) healthy male volunteers who were administered a single iv bolus dose of 1.5 mg/kg [$^{14}$C]Org 9487. After [$^{14}$C]Org 9487 dosing: blood samples were collected up to 24 hours, urine samples were collected up to 13.5 days, fecal samples were collected up to 13 & ½ days and, expired air was collected up to 24 hours.

Plasma kinetics of radiocarbon

Figure 2 depicts the plasma concentration time profile of radiocarbon in the six individual subjects. No accurate pharmacokinetic analysis could be performed as the last three values obtained after 6, 12, and 24 hours did not show a single monoexponential pattern. Analysis with the available data showed that the mean total body clearance of the radioactivity was 12.2 liters/hour while the mean terminal half-life was about 14.6 hours. After 24 hours, the plasma concentrations in the six subjects ranged from 0.05-0.12 μg-eq/gm, above the LOQ of 0.03 μg-eq/gm.

Radiocarbon in urine

Figure 1 depicts the urinary and fecal excretory profile of the radioactivity. Radiocarbon could be measured in all urine samples collected continuously up to 13 & ½ days (324 hours) after injection. A cumulative mean total of about 28% (range; 22%-33%) was excreted by the end of 13 & ½ days. About 12% of the administered dose was excreted within the first 12 hours following the injection. Thereafter, the excretion rate became much slower. Measurable concentrations of radiocarbon were also detected in urine samples collected over four weeks after the end of the continuous collection period of 13 & ½ days.

Radiocarbon in feces

Radiocarbon could be measured in most feces samples collected continuously up to 13 & ½ days (322 hours) after injection. The cumulative mean total of about 28% (range; 22%-35%) was excreted by the end of 13 & ½days. About 20% of the dose was eliminated within 96 hours after injection. Thereafter, the fecal excretion rate became much slower.

Radiocarbon in expired carbondioxide

The cumulative radioactivity in expired air as radioactive carbon dioxide was about 0.6% in 24 hours. However, this is only a crude estimate as: (i) sampling was started two hours post dosing (ii) only 7 samples were taken during 24 hours with relatively long intervals between samples (iii) the volume

of collected $CO_2$ is relatively small and (iv) the hourly production of $CO_2$ has not been measured.

Total Excretion Balance

The mean combined excretion at the end of the continuous collection period of 13 & ½ days in urine and feces was about 56% (range; 50%-64%).

Metabolite profiles

Metabolite profiles were determined by in plasma, urine, and feces samples at selected time intervals. Identification of the compounds in the metabolite profiles of plasma and urine samples was performed by analysis. The compounds in the metabolite profiles of the feces samples were identified by comparison of the retention times of the metabolites identified in urine and plasma samples. In all three cases of plasma, urine, and feces, Org 9487 and its major metabolite Org 9488 formed the majority of the excreted radioactivity at that particular time point.

Table 1 shows the metabolite profile in human plasma. The plasma metabolite profile conducted on plasma samples collected at 2, 7, 15, 30, 60, and 180 minutes contained six different compounds overall. Org 9487 and Org 9488 were the main compounds present at all time points. In the metabolite profile of the 3 hour sample, compound P1 comprised a major component (about 50%) of the plasma radioactivity at that time point. However, the total radioactivity concentration at the 3-hour time point is very low (about 60 fold lower than that of the radioactivity concentration at the 2-minute time point). At the 30 minute time point, two additional components, P3 and P4 were detected. Again, these compounds were present in relatively lower concentrations (11% and 7% of the radioactivity concentration at that time point). At the 7-minute time point, compound P6 comprising only 3% of the radioactivity at that time point was detected. Therefore, in addition to Org 9487 and Org 9488, four other compounds, P1, P3, P4, and P6 in minor concentrations were detected in the plasma. The structure of these compounds is unknown at this point in time. It should be pointed out that compound P1 was also observed in urine of the rat and feces of the female dogs.

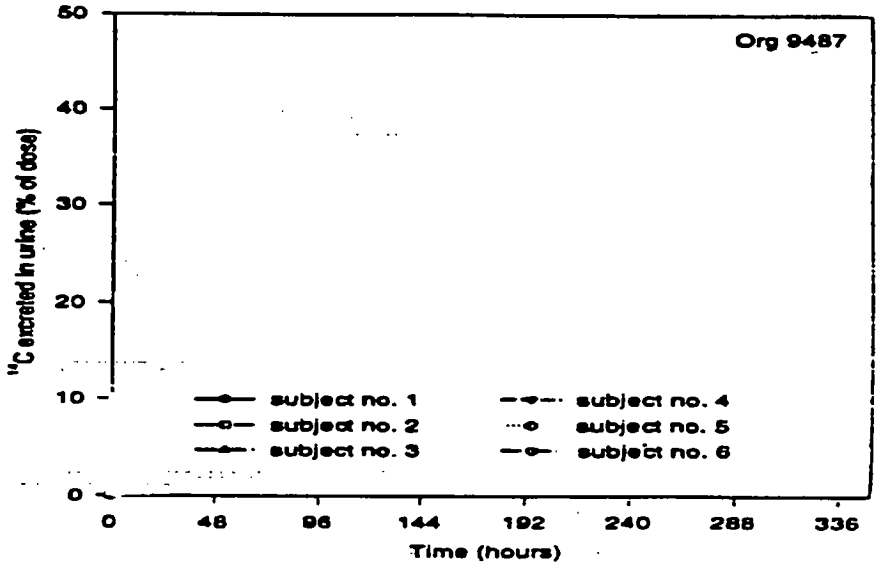
Table 2 shows the metabolite profile in urine samples. In addition to Org 9487 and Org 9488, three other components occurring in low quantities, U1, U2 and U4, were detected. The concentrations of these three unknown compounds relative to the concentrations of Org 9487 and Org 9488 ranged from 1.2% to 4.1% at the respective time points. Compound U1 was observed in urine and feces of female dogs while U2 was detected in urine and feces of the rats and feces of the dogs.

Table 3 shows the metabolite profile in feces samples. The main compounds present in the feces samples were Org 9487 and Org 9488. In addition, four other compounds of unknown structure F1, F2, F3, and F6 were also detected. Compound F1 was also observed in urine of the rat and feces of

the female dogs. Compound F2 was observed in urine and feces of the rat. Compound F3 was observed in urine and feces of female dogs.

Although a total of eleven unknown compounds were detected in plasma, urine, and feces (P1, P3, P4, and P6 in plasma; U1, U2, and U4 in urine; F1, F2, F3, and F6), based on the retention times of the metabolites identified in the present study or in previous studies, it appears that these comprise seven unknown metabolites.

**Figure 1.** Cumulative excretion of radiocarbon in urine (top) and in feces (bottom) after I.V. administration of 1.5 mg/kg [$^{14}$C]Org 9487.



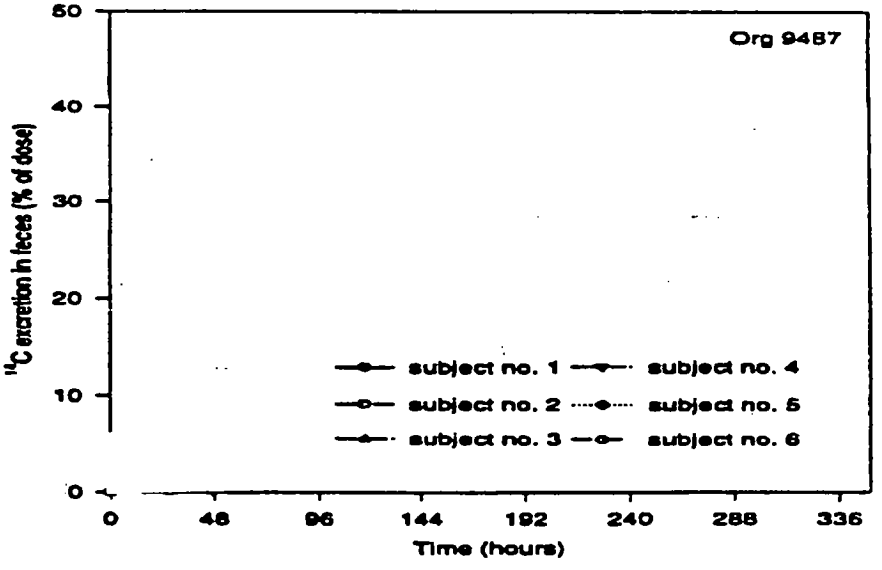



**Figure 2.** Plasma radiocarbon concentration versus time profiles in individual subjects after I.V. administration of 1.5 mg/kg [$^{14}$C]Org 9487.

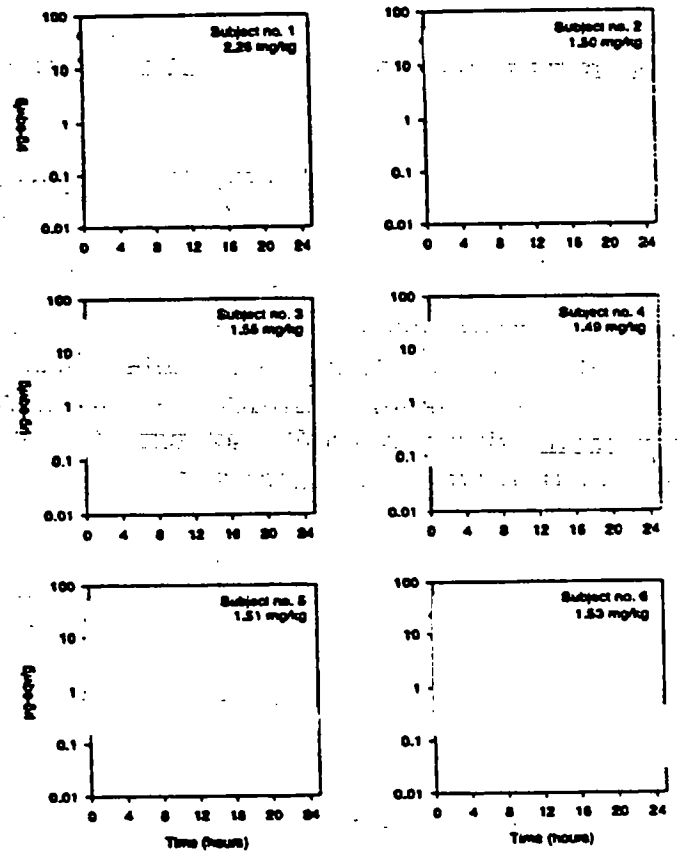


Table 1 metabolite profile of Org 9487 in plasma of human volunteers after a single intravenous injection of [$^{14}$C]-labeled Org 9487.
Data are given as a percentage of total radioactivity in plasma.

| Time (min) | Concentration (Bq/g)* | Compound No | | | | | |
|---|---|---|---|---|---|---|---|
| | | P1 | P2 | P3 | P4 | P5 | P6 |
| 2 | | | | | | | |
| 7 | | | | | | | |
| 15 | | | | | | | |
| 30 | | | | | | | |
| 60 | | | | | | | |
| 180 | | | | | | | |

* Average concentration of the six subjects per time point

\- not detected

ni not interpretable, metabolite profiles noisy

P1, P3, P4 and P6 are unknown.

P2 Org 9488

P5 Org 9487

APPEARS THIS WAY
ON ORIGINAL

**Table 2.** metabolite profiles of Org 9487 in urine of male human volunteers after a single intravenous dose of 1.5 mg/kg [$^{14}$C]Org 9487.

| Subject | Time (h)[a] | % of the dose[b] | U1 | U2 | U3 | U4 | U5 |
|---|---|---|---|---|---|---|---|
| 1 | 11.9 | | | | | | |
| 1 | 108.7 | | | | | | |
| 1 | 203.9 | | | | | | |
| 2 | 11.5 | | | | | | |
| 2 | 71.0 | | | | | | |
| 2 | 251.8 | | | | | | |
| 3 | 11.9 | | | | | | |
| 3 | 119.1 | | | | | | |
| 3 | 287.2 | | | | | | |
| 4 | 11.9 | | | | | | |
| 4 | 94.1 | | | | | | |
| 4 | 226.3 | | | | | | |
| 5 | 11.9 | | | | | | |
| 5 | 48.0 | | | | | | |
| 5 | 165.6 | | | | | | |
| 6 | 11.9 | | | | | | |
| 6 | 128.9 | | | | | | |
| 6 | 308.8 | | | | | | |

[a] Actual time for end of collection of the urine fraction [1]

[b] Percentage of the radioactive dose excreted in each fraction [1].

- = not detected

U1, U2 and U4 are unknown

U3 Org 9488

U5 Org 9487

**Table 3.** metabolite profiles of Org 9487 in feces of male human volunteers after a single intravenous dose of 1.5 mg/kg [$^{14}$C]Org 9487.

| Subject | Time (h)[a] | % of the dose[b] | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|---|
| 1 | 49.0 | | | | | | | |
| 1 | 72.8 | | | | | | | |
| 1 | 97.5 | | | | | | | |
| 1 | 122.0 | | | | | | | |
| 1 | 145.4 | | | | | | | |
| 1 | 169.4 | | | | | | | |
| 1 | 193.0 | | | | | | | |
| 1 | 217.2 | | | | | | | |
| 1 | 240.0 | | | | | | | |
| 1 | 264.7 | | | | | | | |
| 1 | 289.1 | | | | | | | |
| 1 | 313.2 | | | | | | | |
| 1 | 322.3 | | | | | | | |
| 2 | 58.9 | | | | | | | |
| 2 | 77.6 | | | | | | | |
| 2 | 173.5 | | | | | | | |
| 2 | 198.2 | | | | | | | |
| 3 | 80.3 | | | | | | | |
| 3 | 94.8 | | | | | | | |
| 3 | 172.0 | | | | | | | |
| 3 | 191.4 | | | | | | | |
| 4 | 53.3 | | | | | | | |
| 4 | 128.0 | | | | | | | |
| 4 | 286.9 | | | | | | | |
| 5 | 31.4 | | | | | | | |
| 5 | 194.8 | | | | | | | |
| 5 | 238.4 | | | | | | | |
| 6 | 21.6 | | | | | | | |
| 6 | 26.1 | | | | | | | |
| 6 | 141.3 | | | | | | | |
| 6 | 213.1 | | | | | | | |

[a] Actual time for end of collection of the feces fraction [1]
[b] Percentage of the radioactive dose excreted in each fraction [1].
- not detected
ni not interpretable, metabolite profiles noisy
F1, F2, F3 and F6 are unknown
F4 Org 9488
F5 Org 9487

## ORG 9487 PHARMACOKINETICS/PHARMACODYNAMICS

**Study Type**: Pharmacokinetic/Pharmacodynamic Modeling.

**Study Title**: Modeling of The Dose Response Relationship of Org 9487.

**NDA**: 20-984 **Submission Date**: 6/24/98 **Volume**: 1.52 **Protocol**: 174204

**Clinical Investigator:**

**Analytical Investigator:**

**Study design**

Single Dose: Yes Cross-over: No Other Design: non-comparative

**Subject Breakdown**

Patients Yes (scheduled for elective surgery) Number=11 Male=8 Female=3

Subject Type:

Weight Mean 73 kg Range 55-88 kg

Age Mean 46 yrs Range 26-64 yrs

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Org 9487 | 0.3 mg/kg/minute over 5 minutes | Parenteral | 66.67 mg/mL | CP 093090 |

**Analytical Methodology**

**Labeling Claims**
None

**Results and Discussion**
Pharmacokinetics

Org 9487 was administered at a dose of 0.3 mg/minute/kg over a median time of four minutes and forty seconds (range; 2.5-5.7 minutes). The infusion was discontinued when a neuromuscular block of 70% was reached. A mean dose of 0.93 mg/kg (range; 0.58-1.22) of Org 9487 was administered as a slow infusion. Blood was sampled for 6 hours following the administration of the dose for pharmacokinetic assessments.

Figure 1 shows the plasma concentration-time profiles of Org 9487 in individual subjects while Table 1 presents the mean pharmacokinetic parameters of Org 9487 derived from this data. The pharmacokinetics of Org 9487 were characterized by a terminal half-life of about 123 minutes, a clearance of about 6.73 mL/kg/minute, and a steady state volume of distribution of 225 mL/kg. The mean cumulative urinary excretion of Org 9487 and Org 9488 were about 6% and 4% respectively at the end of 48 hours.

All plasma and urine samples from a group of subjects (4 for plasma and 3 for urine) were screened for the presence of Org 9502 (17-OH metabolite) and Org 9504 (3,17 di-OH metabolite). In both bio fluids, levels of both Org 9502 and Org 9504 were below the LOQ (10.0 ng/mL in plasma, and 100 ng/mL in urine).

Pharmacodynamics

The neuromuscular block was measured by mechanomyography of the adductor pollicis, using single twitch stimulation of the ulnar nerve. To describe the concentration-effect relationship of Org 9487 in the effect compartment, the Hill-equation was used;

$$E=E_{max}*C_e^{\gamma}/EC_{50}^{\gamma}+C_e^{\gamma}$$

Where,

E=response (% paralysis)
$E_{max}$= maximal response (100%)
$C_e$=concentration in the effect compartment
$EC_{50}$=concentration in the effect compartment at 50% drug-effect
$\gamma$= steepness of the concentration-effect relationship

To describe the transport of drug to the effect compartment, the following equation was used;

$$dC_e/dt = K_{eo}*(C_p-C_e)$$

where, $C_p$= concentration in plasma
$K_{eo}$= rate constant of removal from effect compartment

Figure 2 presents the individual plots of twitch height versus time while Table 2 presents the mean pharmacodynamic parameters. The pharmacokinetic-pharmacodynamic relationship of Org 9487 in this study is characterized by a mean $K_{eo}$ of 0.44/minute, a mean $EC_{50}$ of 4.44 µg/mL, and a mean $ED_{90}$ bolus dose of 1.03 mg/kg. For Org 9488, these values obtained from study 174207 were as follows; a mean $K_{eo}$ value of 0.11/minute, a mean $EC_{50}$ value of 1.83 µg/mL, and a mean $ED_{90}$ dose of 0.42 mg/kg. These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487. However, when comparing the $ED_{90}$ of Org 9487 (1.03 mg/kg) and Org 9488 (0.42 mg/kg) with the $ED_{90}$ of rocuronium (0.3 mg/kg), vecuronium (0.05 mg/kg) and pancuronium (0.06 mg/kg), Org 9487 and Org 9488 should be classified as a low potency neuromuscular blocking drugs.

**Table 1.** Pharmacokinetic parameter values of Org 9487 (mean (%CV)).

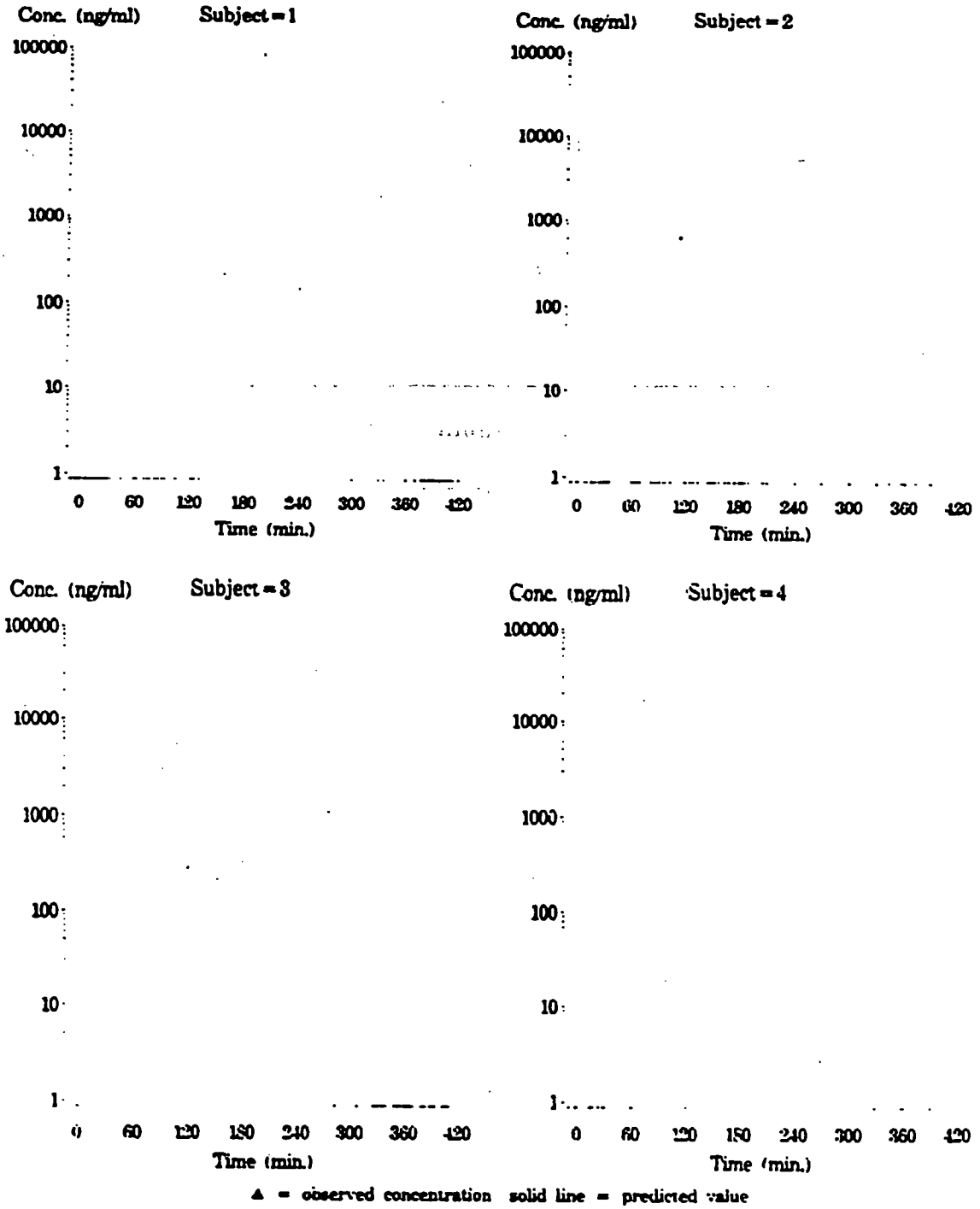
| Pharmacokinetic parameter | |
|---|---|
| Cl, mL/minute/kg | 6.73 (25) |
| Vdss, mL/kg | 225 (33) |
| $t_{1/2\gamma}$, minute | 123 (66-283)* |

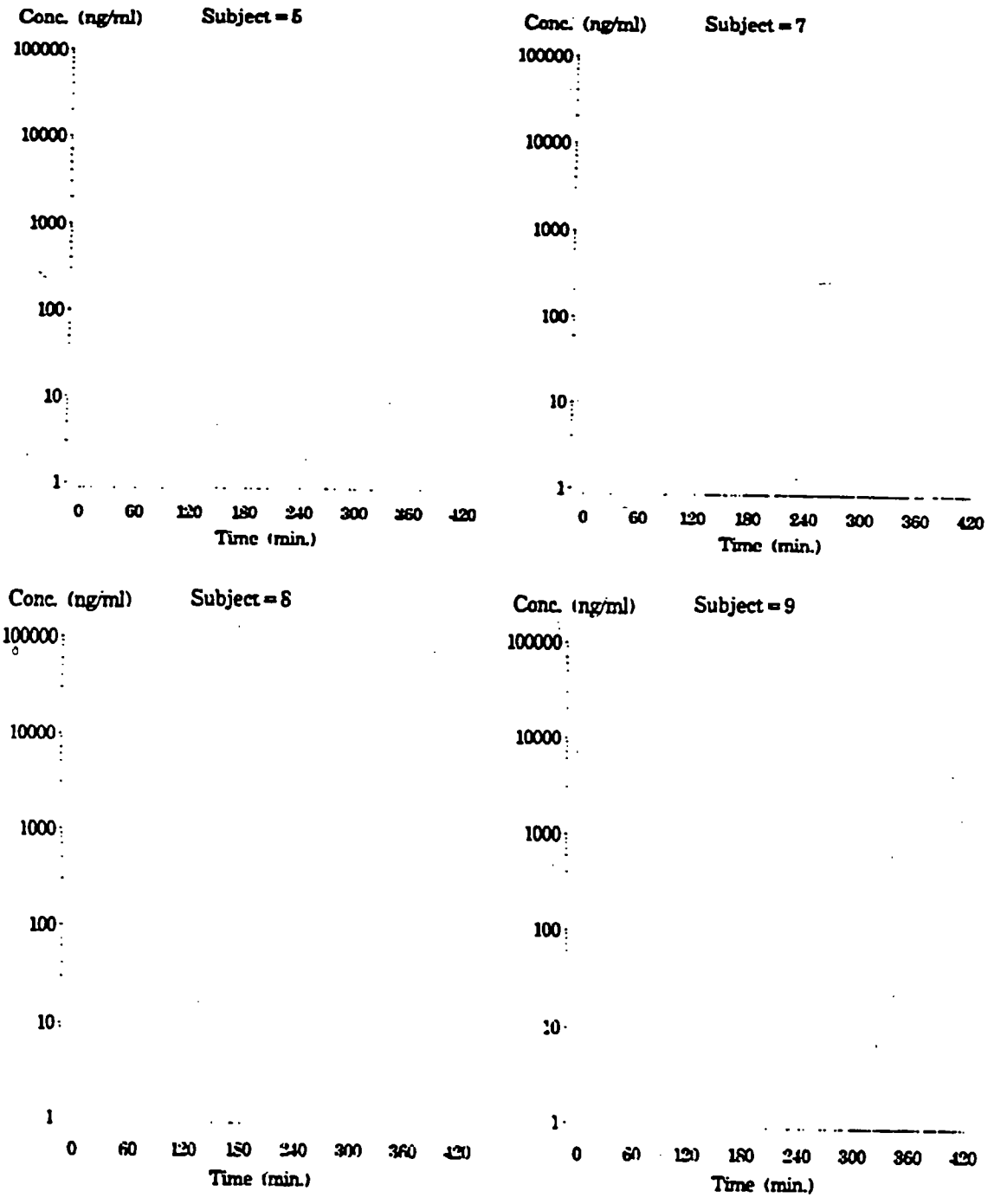
* Harmonic mean and range

**Table 2.** Pharmacokinetic/pharmacodynamic modeling parameters of Org 9487 (mean (%CV)).

| Parameter | |
|---|---|
| Keo, 1/minute | 0.44 (41) |
| $\gamma$ | 2.97 (23) |
| $EC_{50}$, mg/liter | 4.44 (33) |
| $ED_{90}$, mg/kg | 1.03 (33) |

**Figure 1.** Individual plots of Org 9487 plasma concentration versus time.




Conc. (ng/ml)
Subject = 5
100000
10000
1000
100
10
1
0 60 120 180 240 300 360 420
Time (min.)
Conc. (ng/ml)
Subject = 7
100000
10000
1000
100
10
1
0 60 120 180 240 300 360 420
Time (min.)
Conc. (ng/ml)
Subject = 8
100000
10000
1000
100
10
1
0 60 120 150 240 300 360 420
Time (min.)
Conc. (ng/ml)
Subject = 9
100000
10000
1000
100
10
1
0 60 120 180 240 300 360 420
Time (min.)
▲ = observed concentration solid line = predicted value

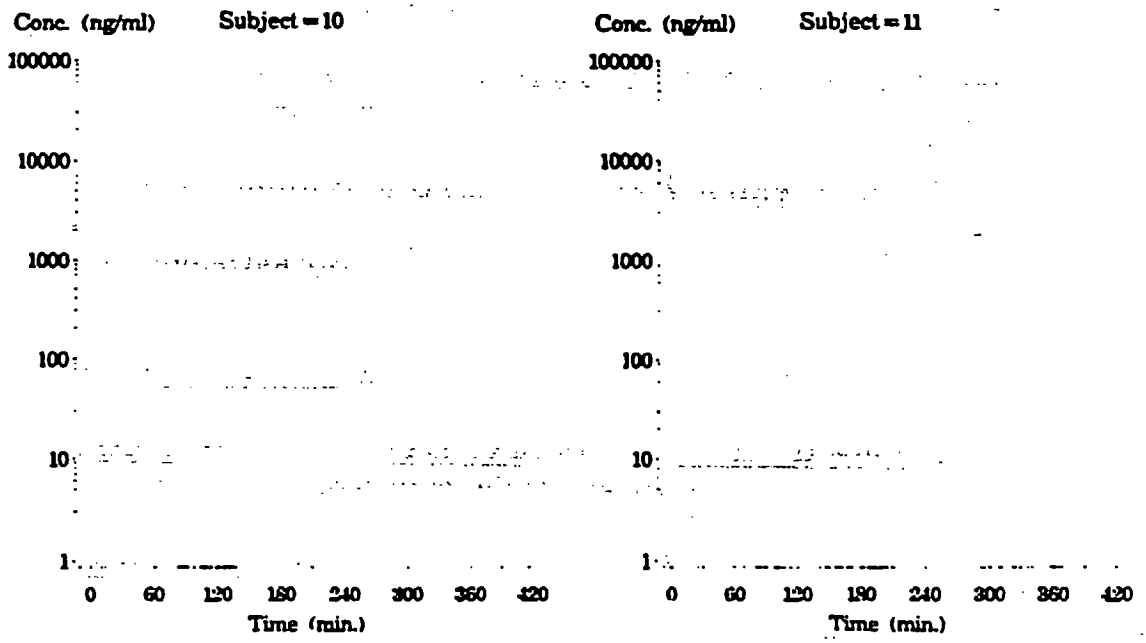
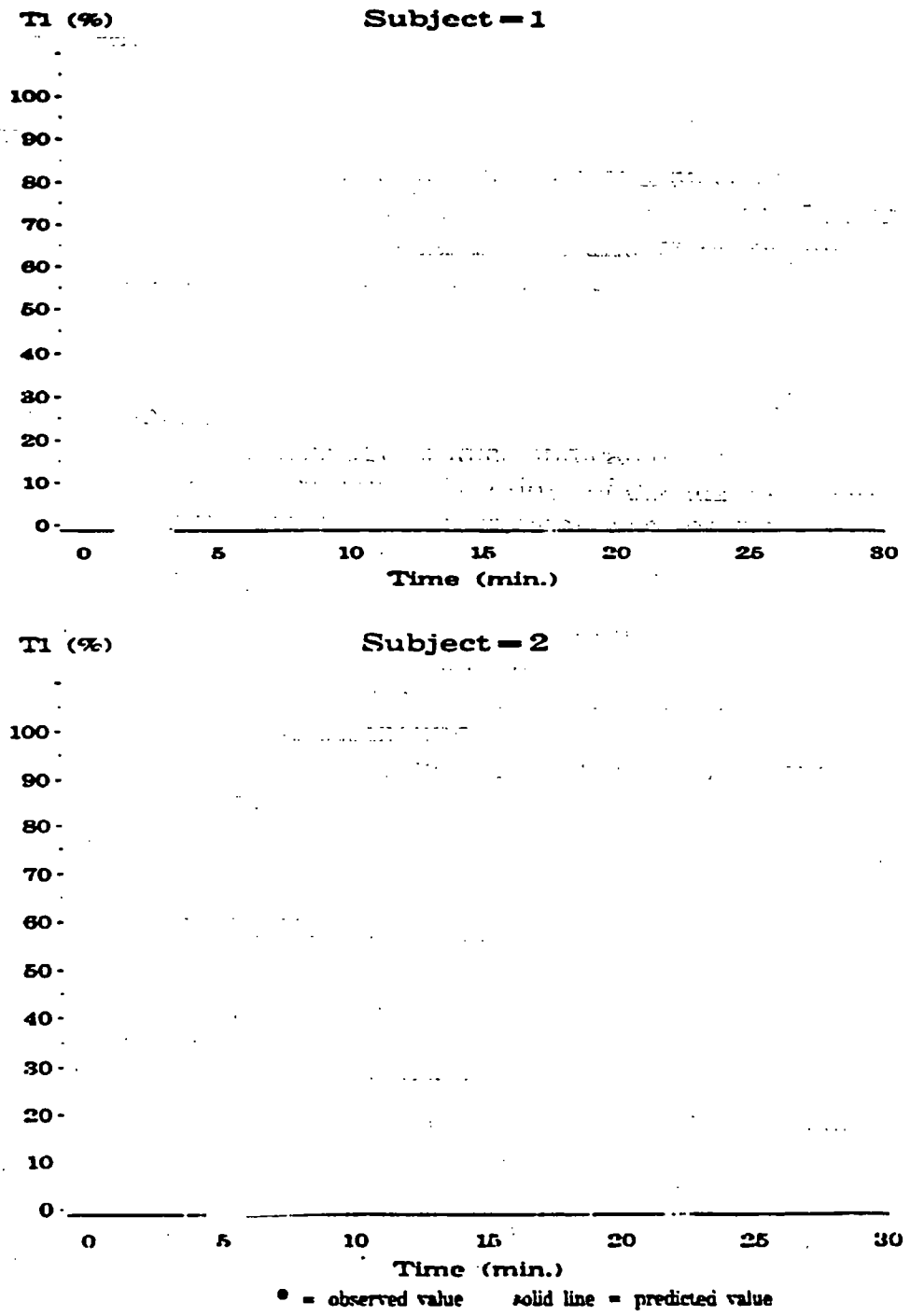
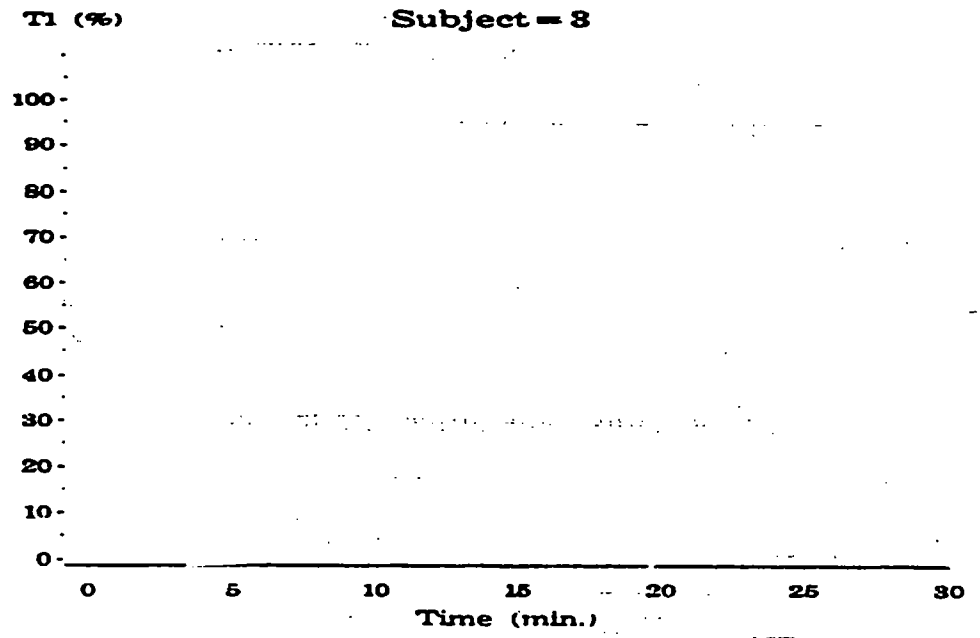
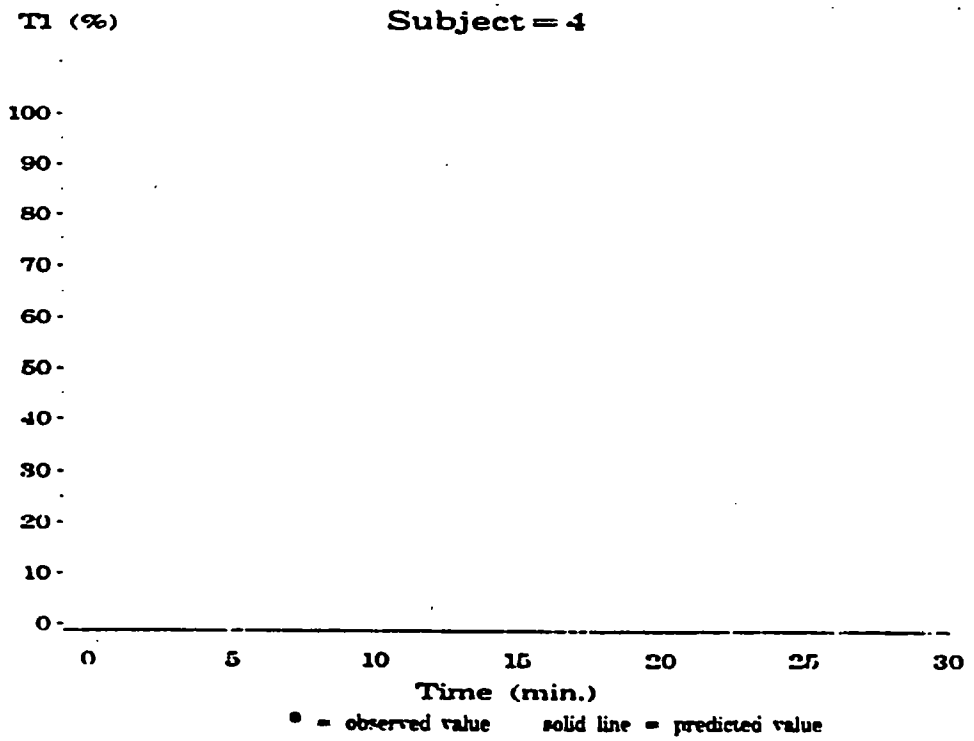
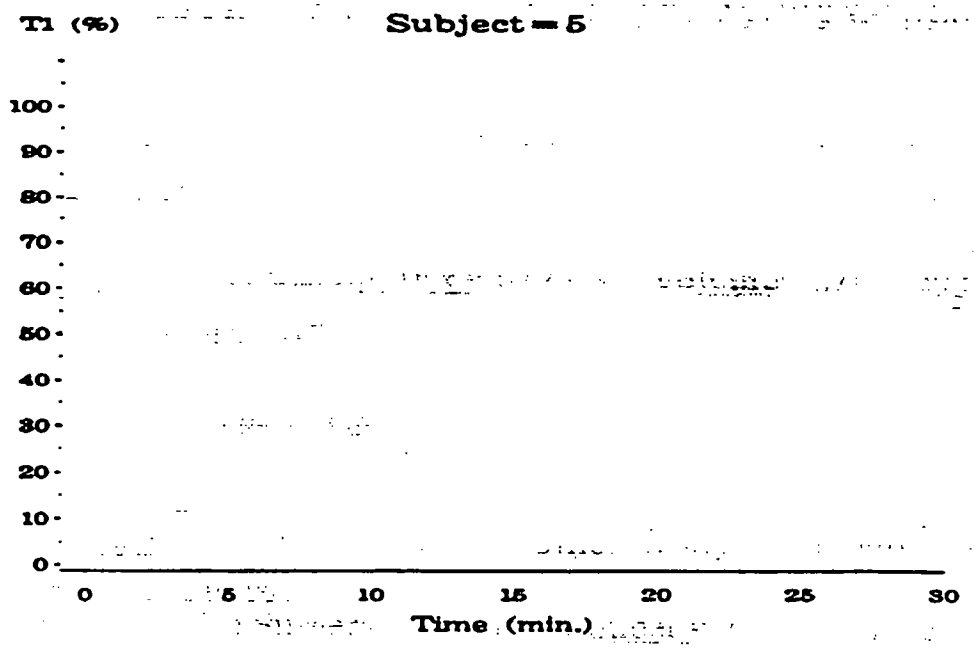

Conc. (ng/ml)
Subject = 10
100000
10000
1000
100
10
1
0
60
120
180
240
300
360
420
Time (min.)
Conc. (ng/ml)
Subject = 11
100000
10000
1000
100
10
1
0
60
120
180
240
300
360
420
Time (min.)

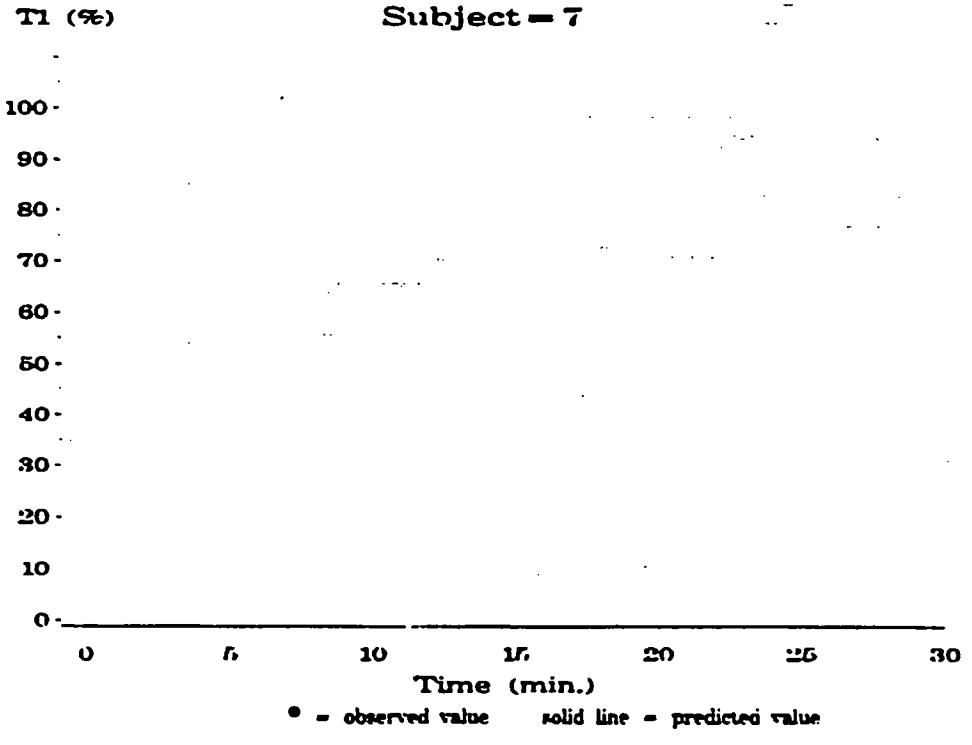
**Figure 2.** Individual plots of twitch height versus time.

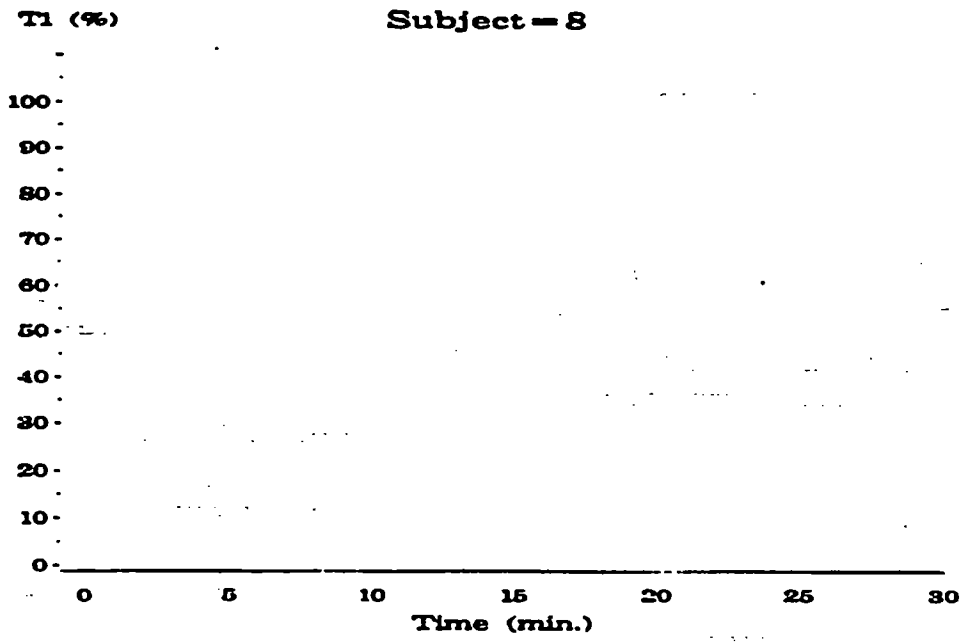


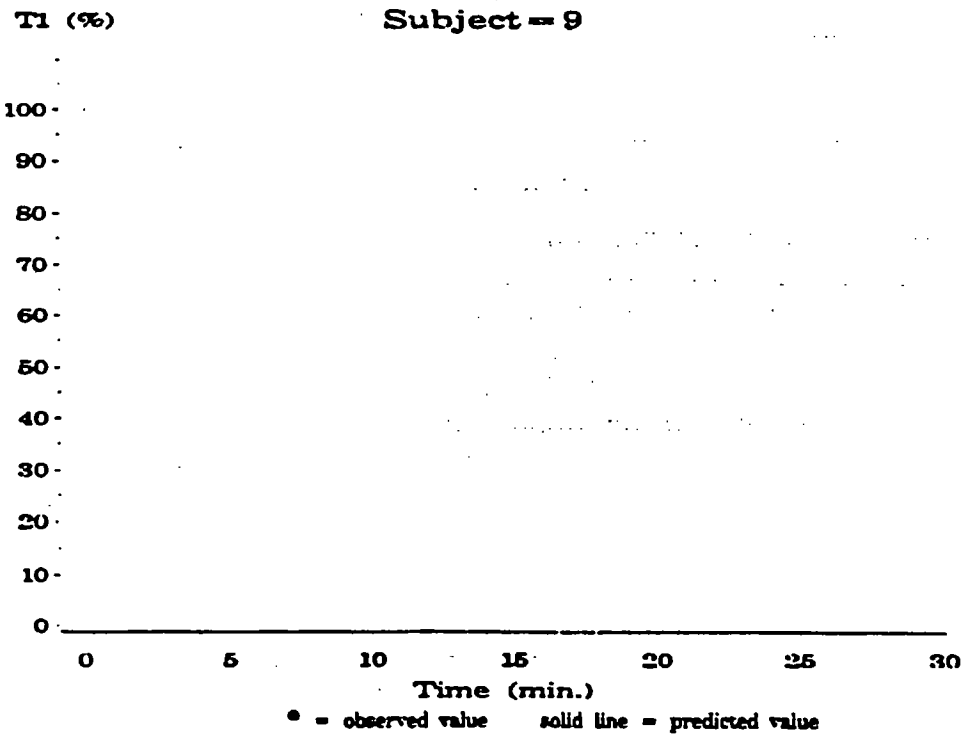

T1 (%)
Subject = 3
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)


T1 (%)
Subject = 4
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)
• = observed value
solid line = predicted value


T1 (%)
Subject = 5
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)


T1 (%)
Subject = 7
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)
• = observed value
solid line = predicted value


T1 (%)
Subject = 8
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)


T1 (%)
Subject = 9
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time (min.)
• = observed value
solid line = predicted value

## Org 9488 PHARMACOKINETICS/PHARMACODYNAMICS (PILOT STUDY)

**Study Type**: Pharmacokinetics and Pharmacodynamics of Org 9488.

**Study Title**: A Study of the Pharmacokinetics and Pharmacodynamics of Org 9488, the 3-OH Metabolite of Org 9487.

**NDA**: 20-984 **Submission Date**: 6/24/98 **Volume**: 1.73 **Protocol**: 174206

**Clinical Investigator**:

**Analytical Investigator**:

**Single Dose**: Yes **Cross-over**: No **Other Design**: Open-label, Non-randomized, non-comparative, Phase IIa study

**Subject Breakdown**

Patients Yes Number = 7 Males = 7

Weight Mean 84 kg Range 68-99 kg

Age Mean 41 yrs Range 19-62 yrs

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Org 9488 | 0.2 mg/kg | Sterile solution for injection | 66.67 mg/mL | CP 094075 |

**Analytical Methodology**

**Labeling Claims**
None

**Objectives**

Primary objective was to study the pharmacokinetics of Org 9488. Secondary objectives were to study the efficacy (onset time, maximum block, Duration 25%, Duration 75%, Duration 90% and recovery time of Org 9488) and safety (cardiovascular data and other adverse events).

**Results and Discussion**

(i) Pharmacodynamics

Animal Pharmacology studies indicated that the potency of Org 9488 is similar to that of Org 9487. At a dose of 0.2 mg/kg of Org 9488 given in this study, the initial plasma concentrations were predicted to approximate those observed immediately after administration of a 1.5 mg/kg dose of Org 9487. This dose resulted in a measurable neuromuscular block in four of the seven subjects. In these four subjects, maximum block was 4, 14, 43, and 75% respectively. This suggests that Org 9488 contributes at least to a minimum degree, to the neuromuscular blocking effects observed after administration of its parent compound. In study 174207, a median dose of 0.68 mg/kg was administered to definitively characterize the pharmacodynamics of Org 9488.

(ii) Pharmacokinetics

(a) Plasma Pharmacokinetics

Plasma levels were determined for 6 hours after drug administration. The mean pharmacokinetic parameter values after the analysis of data using a three compartment model were as follows; terminal half-life of about 150 minutes, clearance of about 1.3 mL/kg/minute, and steady state volume of distribution of about 232 mL/kg. Comparing the pharmacokinetics of Org 9488 with those of Org 9487, the elimination half-life of Org 9488 is longer (143 minutes versus 121 minutes) and the clearance is lower (1.3 mL/kg/minute versus 7.2 mL/kg/minute). However, it should be noted that the blood sampling duration of 6 hours is inadequate to report a terminal half-life of 2.5 hours. Therefore, Org 9488 pharmacokinetic parameter values estimated from this study should be viewed as only rough estimates.

(b) Urine Pharmacokinetics

In five of the seven subjects, urine was collected up to 24 hours. The mean cumulative urinary excretion of Org 9488 at the end of 24 hours

was 53% (range; 45%-60%). A mean cumulative urinary excretion of about 48% was excreted by the end of 12 hours itself. In two of the seven subjects, urine was collected up to 48 hours. In these two subjects, the cumulative urinary excretion of Org 9488 ranged from 56%-61%. Comparing this data, with the urinary excretion profile of Org 9487, median amounts of about 9.0% administered dose was excreted in the urine at the end of 24 hours (6% as Org 9487 and 2.3% as Org 9488).

**Table 1.** Pharmacokinetic parameter values of Org 9488.

| **Pharmacokinetic parameter** | |
|---|---|
| **Cl**, mL/minute/kg | 1.3 (33) |
| **$V_{dss}$**, mL/kg | 232 (27) |
| **$t_{1/2_{\alpha 1}}$**, minute | 150 (123-270)* |

* Harmonic mean and range

APPEARS THIS WAY
ON ORIGINAL

## ORG 9488 PHARMACOKINETICS/PHARMACODYNAMICS (DEFINITIVE STUDY)

**Study Type**: Metabolite Pharmacokinetics & Pharmacodynamics.

**Study Title:** A Modeling Study of the Dose-Concentration-Response Relationship of Org 9488.

**NDA**: 20-984 **Submission Date**: 6/24/98 **Volume**: 1.74 **Protocol**: 174207

**Clinical Investigator:**

**Analytical Investigator:**

**Study Design**

Single Dose: Yes Cross-over: No Other Design: Open-label, Non-randomized

**Subject Breakdown**

Patients Elective Surgery Subjects Number = 7 Males=4 Females=3

Weight Mean 81kg Range 68-100 kg

Age Mean 47yrs Range 21-63 yrs

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Org 9488 | 0.1-0.15 mg/kg/minute infusion over 3-5 minutes | Sterile solution for injection | 66.67 mg/mL Org 9488 | 094075 |

**Analytical Methodology**

**Labeling Claims**
None

**Objectives**

The primary objective was to determine the pharmacokinetics and pharmacodynamics of Org 9488. The secondary objectives were to study the safety profile of Org 9488.

**Results and Discussion**

Pharmacokinetics

Org 9488 was administered over three to five minutes in a slow running infusion. The infusion was discontinued when a neuromuscular block of 70% was reached for the first five subjects and for the next two subjects, the infusion was stopped when a neuromuscular block of 60% was reached. A median dose of 0.68 (range; 0.48-0.76) mg/kg of Org 9488 was administered as a slow infusion. Blood was sampled for 8 hours following the administration of the dose for pharmacokinetic assessments.

Figure 1 shows the plasma concentration-time profiles of Org 9487 in individual subjects while Table 1 presents the mean pharmacokinetic parameters of Org 9487 derived from this data. The pharmacokinetics of Org 9488 were characterized by a terminal half-life of about 132 minutes, a clearance of about 1.11 mL/kg/minute, and a steady state volume of distribution of 175 mL/kg. The mean cumulative urinary excretion of Org 9488 was about 54% at the end of 24 hours.

Pharmacodynamics

The neuromuscular block was measured by mechanomyography of the adductor pollicis, using single twitch stimulation of the ulnar nerve. To describe the concentration-effect relationship of Org 9488 in the effect compartment, the Hill-equation was used;

$$E = E_{max} * C_e^{\gamma}/EC_{50}^{\gamma} + C_e^{\gamma}$$

Where,

E = response (% paralysis)
$E_{max}$ = maximal response (100%)
$C_e$ = concentration in the effect compartment
$EC_{50}$ = concentration in the effect compartment at 50% drug-effect
$\gamma$ = steepness of the concentration-effect relationship

To describe the transport of drug to the effect compartment, the following equation was used;

$$dC_e/dt = K_{eo}*(C_p-C_e)$$

where, $C_p$ = concentration in plasma

$K_{eo}$ = rate constant of removal from effect compartment

Figure 2 presents the individual plots of twitch height versus time while Table 2 presents the mean pharmacodynamic parameters. The pharmacokinetic-pharmacodynamic relationship of Org 9488 in this study is characterized by a mean $K_{eo}$ of 0.10/minute, a mean $EC_{50}$ of 2.06 µg/mL, and a mean $ED_{90}$ bolus dose of 0.46 mg/kg. For Org 9487, these values obtained from study 174204 were as follows; a mean $K_{eo}$ value of 0.44/minute, a mean $EC_{50}$ value of 4.44 µg/mL, and a mean $ED_{90}$ dose of 1.03 mg/kg. These data indicate that Org 9488 has a slower onset and a higher potency than Org 9487. However, when comparing the $ED_{90}$ of Org 9488 (0.42 mg/kg) with the $ED_{90}$ of rocuronium (0.3 mg/kg), vecuronium (0.05 mg/kg) and pancuronium (0.06 mg/kg), Org 9488 should be classified as a low potency neuromuscular blocking drug.

**Table 1.** Pharmacokinetic parameter values of Org 9488 (mean (%CV)).

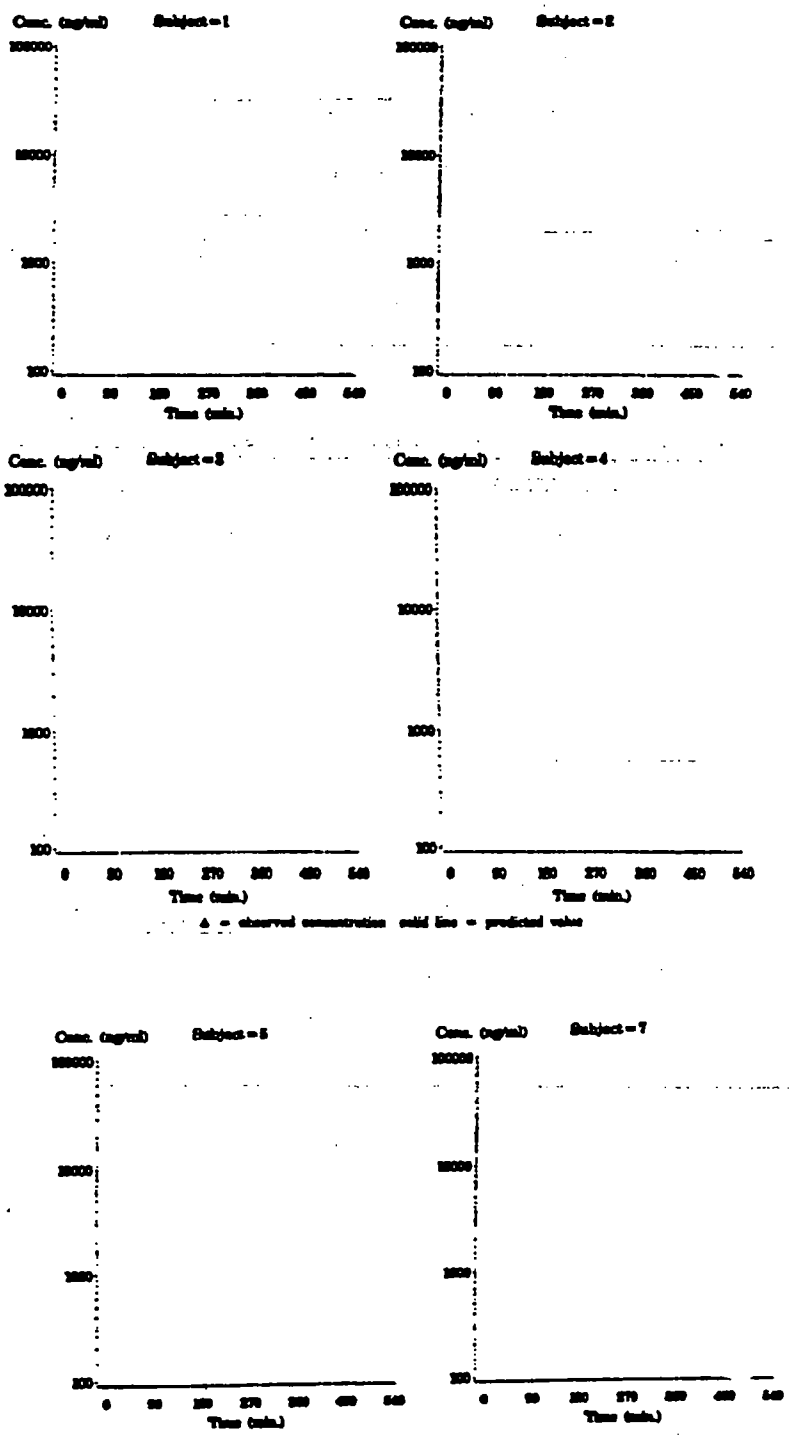
| Pharmacokinetic parameter | |
|---|---|
| Cl, mL/minute/kg | 1.3 (33) |
| Vdss, mL/kg | 232 (27) |
| $T_{1/2}$, minute | 150 (123-270)* |

* Harmonic mean and range

**Table 2.** Pharmacokinetic/pharmacodynamic modeling parameters of Org 9488 (%CV)).

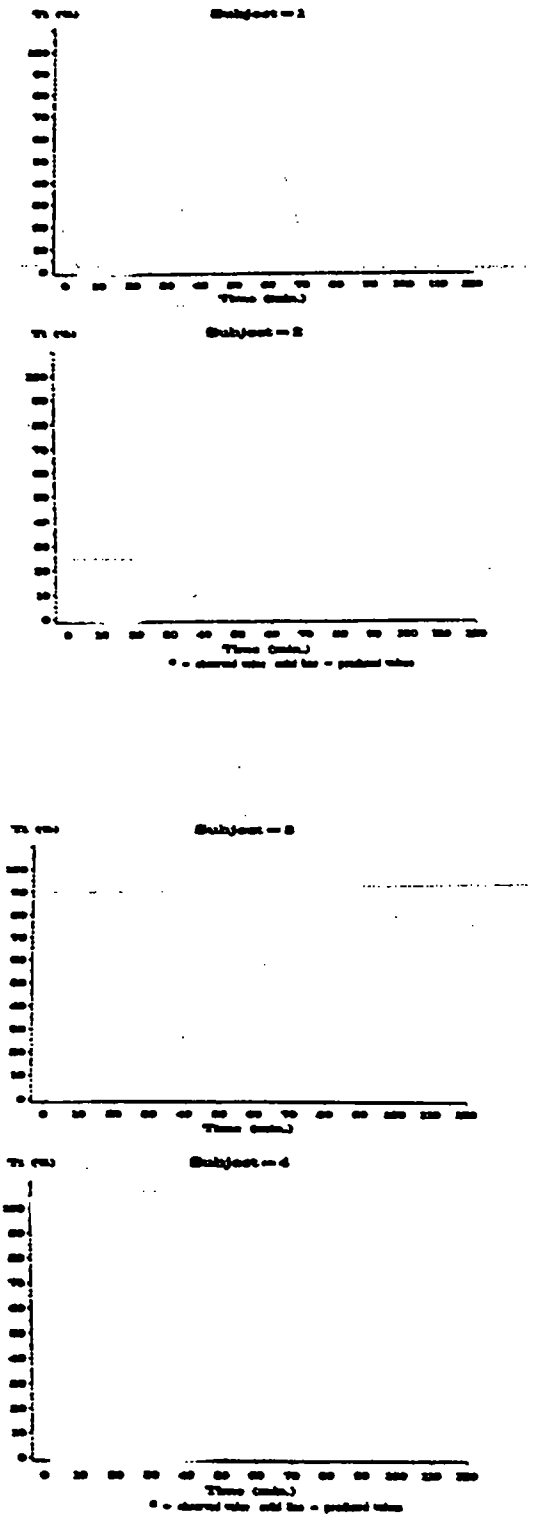
| Parameter | |
|---|---|
| Keo, 1/minute | 0.10 (40) |
| γ | 4.83 (44) |
| $EC_{50}$, mg/liter | 2.06 (55) |
| $ED_{90}$, mg/kg | 0.46 (33) |

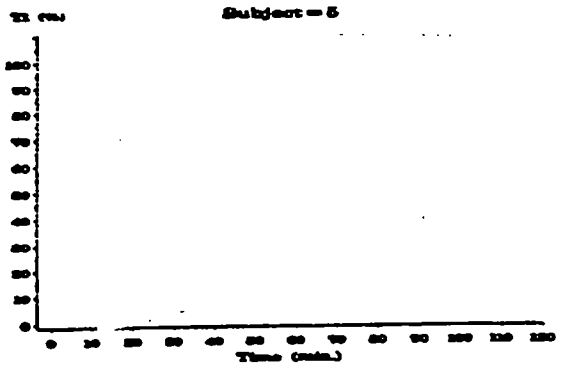
**Figure 1.** Individual plots of Org 9488 plasma concentration versus time.

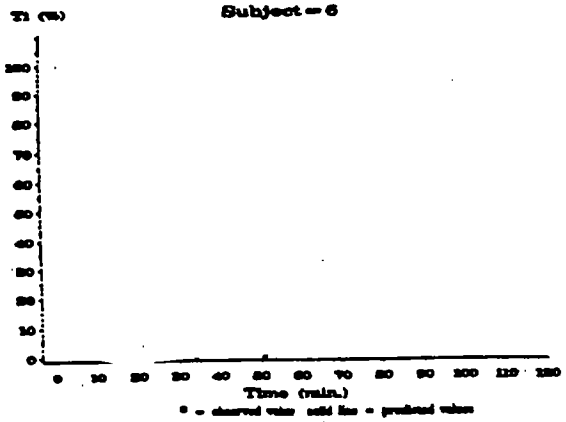


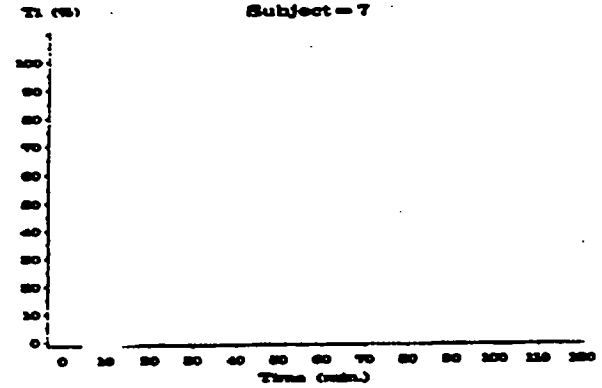
NDA 20-984, Rapacuronium Bromide 62

**Figure 2.** Individual plots of twitch height versus time.




Subject = 5
Time (min.)


Subject = 6
Time (min.)


Subject = 7
Time (min.)

## END STAGE RENAL DISEASE

**Study Type**: Renal Failure.

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

**NDA**: 20-984 **Submission Date**: 6/24/98 **Volume(s)**: 1.42-1.51 **Protocol**: 070003

**Clinical Investigator**:

**Analytical Investigator**:

**Single Dose**: Yes **Cross-over**: No **Other Design**: Open-label, non-randomized

**Subject Breakdown**

Normal Yes (volunteers with normal renal function)

Patients Yes (subjects with end stage renal disease undergoing shunt surgery or cannula insertion)

Number = 20 Male =11 Female = 9

| | Normal (n=10) | Renal Disease (n=10) |
|---|---|---|
| Weight | Mean 70 kg Range 50-85 kg | Mean 63 kg Range 39-103 kg |
| Age | Mean 28 yrs Range 20-42 yrs | Mean 31 yrs Range 18-45 yrs |

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Control | 1.5 mg/kg | Parenteral | 66.67 mg/mL | OA.03.95/B-3 |
| Renal Failure | 1.5 mg/kg | Parenteral | 66.67 mg/mL | OA.03.95/B-3 |

**Analytical Methodology**

**Labeling Claims**

Table 9 summarizes the results of conventional PK analysis from a US study of normal volunteers and patients with end stage renal disease (ESRD) receiving a single bolus dose of 1.5 mg/kg RAPLON™. Patients with renal insufficiency had a 30% reduction in clearance compared with normal adult patients. Volume of distribution is also smaller in renal insufficiency patients.

Table 9. Estimates of PK Parameters in Normal Volunteers and Patients With End Stage Renal Disease

| PK Parameter | Normal Volunteers[a] | Renal Patients[a] |
|---|---|---|
| Elimination Half-Life ($t_{1/2}B$, min) | 233 (138 - 477) | 173 (103 - 561)[b] |
| Volume of Distribution at Steady State (mL/kg) | 424(277 - 568) | 336 (228 - 1349) |
| Plasma Clearance (mL/kg/min) | 9.9 (6.4 - 13.6) | 5.6 (3.8 - 8.8)[b] |

a= Normal volunteers n=10, renal patients (ESRD) n=9, values are median (range)
b= $p \leq 0.05$ for comparison with normal volunteers

**Objectives**

Primary: To determine and compare the pharmacokinetics of subjects with end-stage renal disease and volunteers with normal renal function receiving Org 9487.

Secondary: To determine and compare the neuromuscular responses and safety in subjects with end-stage renal disease and volunteers with normal renal function receiving Org 9487.

**Results and Discussion**

Figure 1 shows the plasma concentration-time profiles of Org 9487 and Org 9488 in subjects with normal renal function and in patients with end stage renal disease. The profiles show that the pharmacokinetics of Org 9487 and Org 9488 were affected in ESRD patients. Particularly, Org 9488 levels show a dramatic difference in that no declining trend was seen at the end of the eight hour sampling duration in contrast to levels in volunteers with normal renal function. Table 1 lists the main pharmacokinetic parameters of Org 9487 derived from traditional compartment analysis. The pharmacokinetics of Org 9487 were altered in patients suffering from end stage renal disease. The mean terminal half-life and clearance values of Org 9487 in ESRD patients were about 83% and 65% of those in normal volunteers. Although, the mean steady state volume of distribution values were not different in the normal and ESRD patients, the ESRD patients mean value was associated with a high degree of variability (% CV of 78% for ESRD patients versus % CV of 18% for normal subjects).

Table 2 lists the Org 9488 (active metabolite) concentration relative to Org 9487 up to eight hours after Org 9487 administration. In the normal volunteer group, this ratio increases steadily through the 6-hour period but shows a decrease by the 8 hour time period. However, in ESRD patients this ratio showed an increasing trend even at the 8-hour time point. Although, urine samples were collected from normal subjects, urine was not collected from ESRD patients (because of the disease state). In normal volunteers, the mean amount of Org 9487 and Org 9488 excreted over 48 hours was 8.1% (%CV of 25%) and 5.0% (%CV of 24%), respectively. These data are consistent with data obtained in healthy volunteers from other studies.

With respect to the safety and efficacy parameters, the study report concludes that the (1) efficacy profile is not significantly different between normal and ESRD subjects and that the (2) safety profile is similar except that renal subjects have higher incidence of adverse experiences.

**Table 1.** Estimates of PK Parameters in Normal Volunteers and Patients With End Stage Renal Disease.

| Parameters | Normal Volunteers[a] | Renal Patients[a] |
|---|---|---|
| $t_{1/2}\beta$, minute | | |
| mean ± SD | 240.0 (96.9) | 197.6 (141.0) |
| median (range) | 233 (138 - 477) | 173 (103 - 561)[b] |
| Vdss, mL/kg | | |
| mean ± SD | 431.7 (77.7) | 440.3 (346.8) |
| median (range) | 424(277 - 568) | 336 (228 - 1349) |
| CL, mL/kg/minute | | |
| mean ± SD | 9.4 (2.2) | 6.1 (1.7) |
| median (range) | 9.9 (6.4 - 13.6) | 5.6 (3.8 - 8.8)[b] |

a= Normal volunteers n=10, renal patients (ESRD) n=9

b= $p \leq 0.05$ for comparison with normal volunteers.

**Table 2.** Ratio of Org 9488/Org 9487 in plasma at different time points (mean (SD)).

| Time (hour) | Normal Renal Function Subjects | ESRD Patients |
|---|---|---|
| 2 | 1.76 (0.54) | 1.08 (0.45) |
| 4 | 3.91 (1.04) | 3.65 (1.45) |
| 6 | 4.90 (0.95) | 6.73 (2.12) |
| 8 | 4.5 (0.83) | 8.08 (1.91) |

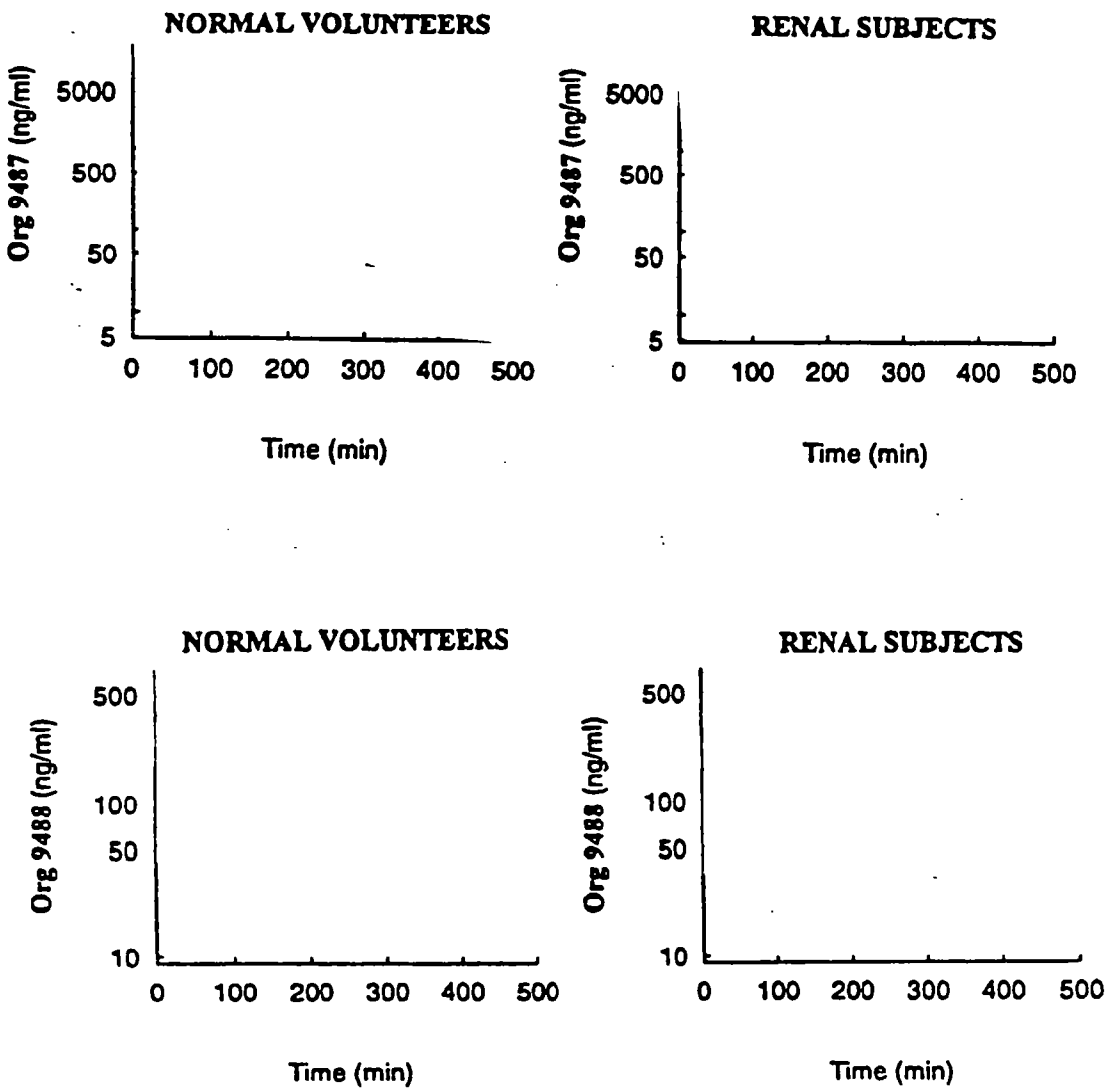



**Figure 1.** Plasma concentration time profiles of Org 9487 and Org 9488 in subjects with normal renal function and patients with end stage renal disease.

## HEPATIC IMPAIRMENT

**Study Type**: Hepatic Impairment.

**Study Title:** Evaluation Of The Neuromuscular Parameters and The Pharmacokinetics of Org 9487 in Patients With Liver Cirrhosis.

**NDA:** 20-984 **Submission Date:** 6/24/98 **Volume:**1.55 **Protocol:** 174309

**Clinical Investigator:**

**Analytical Investigator:**

**Study Design**

Single Dose: Yes Parallel: Yes Other Design: Open-label, non-randomized

**Subject Breakdown**

Patients Yes (Child-Pugh Class A or B cirrhotic subjects or subjects with normal hepatic function scheduled for elective peripheral surgery or endoscopy under general anesthesia)

Number = 17 Males = 14 Females=3

| | Cirrhotic Group | | Control Group | |
|---|---|---|---|---|
| Weight | Mean 76 kg | Range 58-94 kg | Mean 72 kg | Range 59-83 kg |
| Age | Mean 56 yrs | Range 44-74 yrs | Mean 49 yrs | Range 35-68 yrs |

**Formulation**

| Treatment Group | Dose | Dosage Form | Strength | Lot |
|---|---|---|---|---|
| Control<br>Cirrhotic | 1.5 mg/kg<br>1.5 mg/kg | Sterile solution for Injection | 66.67 mg/mL | 096188 |

**Analytical Methodology**

**Labeling Claims**

**The pharmacokinetic parameters for patients with hepatic insufficiency and patients with normal liver function are presented in Table 10. The estimates are based on conventional PK analysis . Plasma clearance and volume of distribution at steady state are greater in cirrhotic patients compared to patients with normal liver function.**

Table 10. Estimates of PK Parameters in Patients With Normal Liver Function and Patients With Cirrhosis

| PK Parameter | Normal Liver Function[a] | Hepatic Insufficiency (cirrhotic)[a] |
|---|---|---|
| Elimination Half-Life ($t_{1/2}\beta$, min) | 79 (75 - 103) | 86 (72 - 122) |
| Volume of Distribution at Steady State (mL/kg) | 261 (155 - 373) | 452 (393 - 596)[b] |
| Plasma Clearance (mL/kg/min) | 6.1 (4.7 - 9.9) | 9.2 (7.2 - 10.4)[b] |

a= Normal liver function n=7, hepatic insufficiency n=6, values are median (range)
b= $p \leq 0.01$ for comparison with normal patients

**Objectives**

Primary objective was to determine and compare the pharmacokinetics and the time course of action and secondary objective was to determine intubation conditions of a single bolus dose of 1.5 mg/kg Org 9487 in cirrhotic subjects Child-Pugh Class A and B, compared with control subjects ASA class 1 and 2.

**Results and Discussion**

The cirrhotic group comprised of two (2) mild hepatic impairment evaluable subjects (Child-Pugh classification A) and four (4) moderate hepatic impairment evaluable subjects (Child-Pugh classification B). No severe hepatic impairment subjects were recruited into the study. The control group consisted of seven (7) evaluable subjects.

Figure 1 presents the plasma concentration time profiles of Org 9487 and Org 9488 in control subjects and hepatic impairment subjects. The main pharmacokinetic parameters of Org 9487 derived from a two compartment analysis are summarized in Table 1.

The most remarkable finding in this study is the higher clearance of Org 9487 in hepatic impairment group compared to the control group (mean clearance value in hepatic impairment group is about 136% of that in control group). The terminal half-life values were similar between the two groups. These findings are inconsistent with the general expectation of a decreased clearance and a prolonged terminal half-life in the hepatic impairment population and the sponsor could not provide a satisfactory explanation for the unexpected findings in this study. The mean steady state volume of

**Figure 1.** Plasma concentration time profiles of Org 9487 and Org 9488 in control subjects and hepatic impairment subjects.