

## CLINICAL PHARMACOLOGY REVIEW

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NDA: 20-214 SE-5 / 030	Submission Date(s): 1/10/2008
Brand Name	Zemuron
Generic Name	Rocuronium Bromide Injection
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OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Organon USA Inc.
Relevant IND(s)	32,484
Submission Type; Code	Efficacy Supplement; 1S
Formulation; Strength(s)	Parenteral Injection; 10 mg/mL
Indication	Nondepolarizing neuromuscular blocking agent as an adjunct to general anesthesia to provide skeletal muscle relaxation during surgery or mechanical ventilation.
Proposed Dosage Regimen	Varies with specific procedure. The dosage information is derived from studies based upon units of drug per unit of body weight. It is intended to serve as an initial guide to clinicians familiar with other neuromuscular blocking agents to acquire experience with ZEMURON <sup>®</sup> .

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# 1 Executive Summary

## 1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

## 1.2 Phase IV Commitments

None

## 1.3 Clinical Pharmacology Findings

In the current submission, Organon USA Inc. is responding to the Agency issued Pediatric Written Request (PWR) originally issued on December 31, 2001 and amended on July 3, 2002, June 28, 2004, June 27, 2005, March 27, 2007, June 22, 2007 and January 8, 2008. The basis of this supplement is to qualify for pediatric exclusivity and to incorporate the findings from the pediatric clinical studies in the labeling. This submission consists of the clinical trial reports for the two studies outlined in the PWR.

Clinical studies submitted include the following:

- a) Study # 21-048: An open-label, randomized, phase 3, multicenter trial to evaluate the pharmacodynamic parameters of intubation bolus, and bolus and infusion maintenance doses of Zemuron in pediatric and adolescent subjects. This study 21-048 is referred as study 2 in the PWR.
- b) Study # 21-049: A randomized, assessor-blind, dose-ranging, phase 3, multicenter trial comparing the intubating conditions and time course of block of three different intubating doses (0.45 mg/kg, 0.6 mg/kg, and 1.0 mg/kg) of Zemuron in pediatric and adolescent subjects under general anesthesia. This study is referred as study 1 in the PWR.

*An overview of enrollment, dosing and PK measurement in the clinical studies is as follows:*

Study	Number of PK subjects (planned)	Dosing regimen	PK measurements
021-048	10 neonates (birth to <28 days) 10 infants (28 days to < 3 months) 10 toddlers (>3 months to < 2 years) 10 children (2 years to <11 years) 10 adolescents (11 years to <18 years)	Intubation dose of • 0.6 or 1.0 mg/kg intravenous bolus.  bolus dose maintenance group: • 0.15 mg/kg at each reappearance of T3.  Infusion maintenance group: • at reappearance of T2 initially 10 µg/kg/min, which is adjusted every 2-3 minutes by 2.0-5.0 µg/kg/min to maintain 1-2 twitches.	• Predose  bolus dose maintenance group: • 2 minutes after administration • Just prior to first maintenance bolus dose • 60 or 120 minutes after administration of last bolus dose  Infusion maintenance group: • 2 minutes after administration • Just prior to first maintenance bolus dose • 60 or 120 minutes after • termination of infusion.
021-049	12 neonates (birth to <28 days) 12 infants (28 days to < 3 months) 12 toddlers (>3 months to < 2 years) 16 children (2 years to <11 years) 16 adolescents (11 years to <18 years)	• 1 single intravenous bolus dose • 0.45 mg/kg • 0.6 mg/kg • 1 mg/kg	• Predose • 2 or 4 minutes after dose • 15 or 30 minutes after dose • 60 or 120 minutes after dose

Sevoflurane and nitrous oxide were used for induction of anesthesia until loss of consciousness. Subjects may also have received bolus doses of 1-2 mcg/kg fentanyl, acetaminophen (25-40 mg/kg rectal) or a combination of these agents to provide peri-operative analgesia. Lidocaine, bupivacaine and ropivacaine may have been administered epidurally (including caudal administration).

*Endpoints studied (see Clinical review of Dr. Lester Schulteis for more details):*

Efficacy parameters for study 21-049 included the following:

Primary: total dose of Zemuron® from the reappearance of T3 after last maintenance bolus dose or discontinuation of infusion;

Secondary: duration to recovery of T4/T1 ratio to 70%, 80% and 90% from the reappearance of T3 after last maintenance bolus dose or discontinuation of infusion; and  
Other: time of maximum block and maximum block. T1 - Amplitude of the first response to TOF stimulation, expressed as percentage of control T1. T3 - Amplitude of the third response to TOF stimulation, expressed as percentage of control T3. T4 - Amplitude of the fourth response to TOF stimulation, expressed as percentage of control T4. T4/T1 - Ratio of T4 over T1 (within one TOF stimulus) expressed in decimal form.

Efficacy parameters for Study 2 (21-048) include:

Neuromuscular parameters were evaluated by acceleromyography using the TOF Watch<sup>o</sup> SX (version 1.6) starting after induction of anesthesia, and included the following:

Primary: Time to reappearance of T3 from the end of Zemuron® administration;  
Secondary: Onset time; maximum block; time to reappearance of T1 and T4/T1 ratios of 70%, 80% and 90% from end of Zemuron® administration; and intubation score.

Safety in both studies was evaluated based on the following measures: recording of pre-treatment signs and symptoms, physical examination, recording and monitoring vital signs, cardiovascular assessments (ECG, systolic and diastolic bp) and ventilatory compliance.

Based on sparse blood sampling from the above two studies, population pharmacokinetic analysis was conducted to describe pharmacokinetics of rocuronium and PK-PD analysis of QTc data in pediatric patients. However, the PK-PD analysis was not reviewed due to inadequate strength of the data from various factors including lack of positive control for QT assay sensitivity; lack of time matched placebo controls; administration of concomitantly administered medications including sevoflurane, nitrous oxide, fentanyl.

Pharmacokinetic parameters were determined from assessments of rocuronium plasma concentration from all study participants. Plasma levels of rocuronium were determined by a validated method of liquid chromatography coupled to mass spectrometry (LC-MS) using electrospray ionization in multi reaction monitoring.

Figure below shows the observed rocuronium plasma concentrations and the population predicted rocuronium concentrations for a typical subject (median body weight and age) in each age group for trial 021-049.

# 1 Page(s) Withheld

X Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

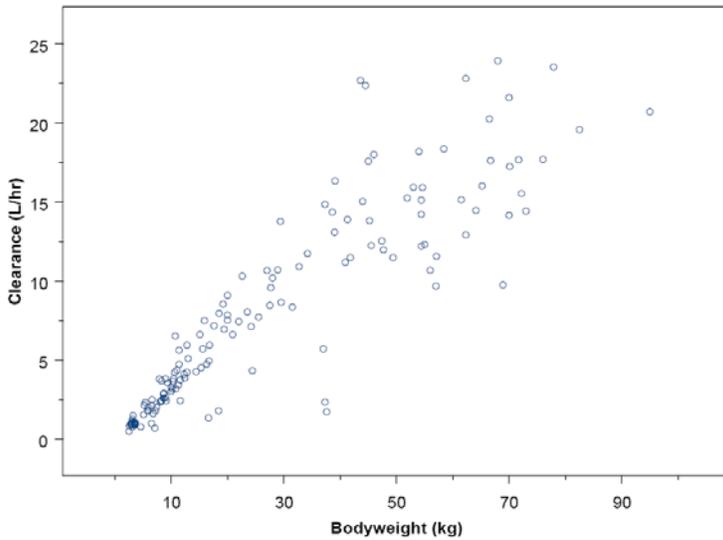
\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

**Rocuronium PK parameters for typical subjects within each age group from studies 21-048 and 21-049.**

Parameter	Neonates (birth to < 28 days)	Infants (28 days to ≤ 3 months)	Toddlers (3 months to ≤ 2 years)	Children (2 years to ≤ 11 years)	Adolescents (11 years to ≤ 17 years)
Median age (years)	0.015	0.22	0.85	5.6	14.9
Median body weight (kg)	3.1	5.8	9.0	19.4	54.4
CL (L/hr)	0.91	1.70	2.64	5.68	15.93
Vc (L)	1.05	1.22	1.33	1.78	4.84
Q (L/hr)	0.47	0.89	1.38	2.97	8.32
V2 (L)	0.26	0.49	0.77	1.65	4.62

Systemic clearance of rocuronium increased with body weight (as shown in the figure below) and this relationship was stronger than with age as concluded in the population PK analysis (see review attached starting page 35). This observation supports the body weight based dosing of Zemuron in pediatric patients.



## 2 Analytical Assay Validation

### 1. OBJECTIVE

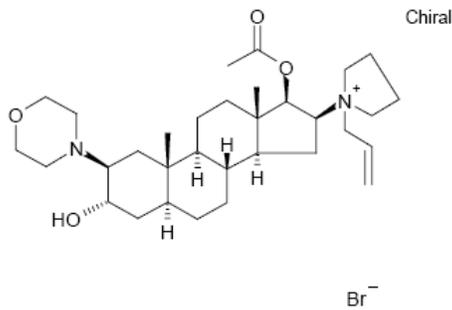
The objective of study MV066 was:

- to validate the LC-MS assay for the determination of Org 9426 in human plasma.

### 2. MATERIALS AND METHODS

#### 2.1 Test- and reference substance

##### 2.1.1 Test Substance



Code : Org 9426  
Batch : AS000009  
Supplier : (b) (4)  
Supplier code :

##### 2.1.2 Reference Substance

(b) (4)

Code : (b) (4)  
Batch :  
Supplier :

Supplier code :

This substance was used as internal standard (IS) in the analysis of Org 9426.

## 2.2 Assay for Org 9426

Org 9426 and its internal standard (b) (4), were isolated from human plasma by solid phase extraction. Liquid chromatography coupled to mass spectrometry (LC-MS) using electrospray ionization in multi reaction monitoring (MRM) mode was performed in order to quantify the concentration of Org 9426 in human plasma samples.

The method described above is presented in Appendix I of this report.

## 2.3 Calculations

The data reduction package (b) (4) was used for all calculations. Several regression methods for the construction of the calibration curve were compared, i.e. linear weighted (1/Y) regression, linear weighted (1/Y<sup>2</sup>) regression and linear weighted (1/Conc<sup>2</sup>) regression. Linear weighted (1/Y) regression was found to be the optimal regression method with respect to the accuracy for the calibration and QC samples (b) (4). From the constructed calibration curves, Org 9426 levels in the calibration and QC samples were calculated. In addition, the overall mean value, standard deviation, precision and accuracy were calculated per concentration for the calibration and QC samples. Quality control (QC) samples, consisting of human plasma spiked with Org 9426 at nominal levels of 0.1 (QC LOQ), 0.3 (low QC), 5 (mid QC), 80 (high QC) and 800 (QC extra) ng/mL, were analyzed.

Accuracy was expressed as a percentage of the nominal concentration and precision as the coefficient of variation according to equation (1) and (2), respectively:

$$Accuracy(\%nom) = \frac{X}{C} \cdot 100\% \quad (1)$$

$$Precision(CV\%) = \frac{SD}{X} \cdot 100\% \quad (2)$$

In which

<i>X</i>	=	Mean calculated Org 9426 concentration in calibration or QC sample
<i>SD</i>	=	Standard deviation
<i>C</i>	=	Nominal concentration
<i>CV%</i>	=	Coefficient of variation in percentage
<i>%nom</i>	=	Percentage of nominal concentration.

## 2.4 Acceptance criteria per series

Series were accepted when:

- The correlation coefficient (*r*) of the calibration curve was greater than or equal to 0.9900
- At least 2/3 of the calibration points were accepted and the accuracy of all accepted calibration points was between (and including limits) 80 and 120% of the nominal concentration
- The accuracy of at least one calibration sample at the lowest and highest concentration was between (and including limits) 80 and 120% of the nominal concentration.
- The accuracy of at least two out of three of the low QC samples (QC A and QC E) was between (and including limits) 80 and 120% and the accuracy of at least two out of three of the other QC samples (QC B, QC C and QC D) was between (and including limits) 85 and 115% of the nominal concentration.

## 2.5 Deviations from protocol

- In contrast to section 2.1.1, the supplier of Org 9426 (b) (4) (b) (4)

Deviations of protocol Appendix I, Method description:

- In contrast to section 1.7.2.1, transfer 250  $\mu\text{L}$  of the working solution (0.001 ng/ $\mu\text{L}$ ) of Org 9426 (1.7.3.5) and 30  $\mu\text{L}$  of the IS working solution (1.7.3.6) into a 1-mL 96 wells collection plate instead of (1.7.3.4) and (1.7.3.5).
- In contrast to section 1.7.3.1, dilute to volume with AB solution (0.1 %) (1.7.2.2) and mix well instead of (4.7.2.2).
- In contrast to section 1.7.3 (last sentence), the solutions mentioned previously (1.7.2.1-1.7.3.6) can be made with other volumes only when the proportions stay the same instead of (1.7.2.1-1.7.3.5).
- In contrast to section 1.8.1 (eighth dash), allow samples to equilibrate at ambient temperature for at least 60 minutes instead of 30 minutes.
- In contrast to section 1.8.1 (twelfth dash), activate the wells with 1 mL methanol and 1 mL 0.5 M NaOH solution (1.7.2.5) instead of Milli-Q water.
- In contrast to section 1.8.1 (nineteenth dash), dissolve the residue of the authentic study samples in AcN:Milli-Q water (20:80 v/v %) (1.7.2.8) depending on the expected concentration instead of AcN:Milli-Q water (80:20 v/v %).
- In contrast to section 1.8.1 (twentieth dash), specify the volume of AcN:Milli-Q water (20:80 v/v %) (1.7.2.8) per series of analysis on Form DM-63 instead of AcN:Milli-Q water (80:20 v/v %).
- In contrast to section 1.8.1 (table),  $\mu\text{L}$  solvent (1.7.2.8) instead of  $\mu\text{L}$  solvent (4.7.2.5).

## 3. VALIDATION

QC B, QC C, QC D and QC E were performed in six validation series, by triplicate analysis in five separate series and six-fold analysis in one series. QC A was performed in five validation series, by triplicate analysis in four separate series and six-fold analysis in two separate series.

### 3.1 Linearity and calibration

The linearity of the assay was evaluated by duplicate analysis of 10 calibration standards (coded STD B up to STD K) containing 0.1, 0.2, 1, 2, 10, 20, 40, 60, 80 and 100 ng Org 9426 per mL human plasma and a fixed amount of 60 ng (b) (4) (IS) per mL human plasma. Furthermore, human plasma not containing test substance (only 60 ng IS per mL human plasma) was analyzed in duplicate (coded STD A) to allow quantification of the blank signal. This was repeated in seven separate calibration series. The regression method linear weighted (1/Y) regression in the data reduction package PhIRSt was used for construction of the calibration curve.

### 3.2 Sensitivity (LOQ)

The lower limit of quantification (LOQ) was assessed for Org 9426 during seven validation series. The LOQ was defined as the lowest concentration of the calibration curve that can be determined in all validation series with an accuracy between (and including limits) 80-120% and a precision (CV%) lower than or equal to 20%. Therefore, the calibration standard at the

LOQ, as well as the QC E (QC at the estimated LOQ) had to have an accuracy between (and including limits) 80-120% and a precision lower than or equal to 20%.

### **3.3 Precision and Accuracy**

Precision (CV%) and accuracy (% nominal) were determined in six separate series by replicate analysis of three QC samples at Org 9426 concentrations of 5, 80 and 800 ng/mL human plasma (coded QC B, QC C and QC D), QC A at Org 9426 concentration of 0.3 ng/mL human plasma was determined in five separate series. Prior to analysis, QC D was processed to a 10-fold dilution with blank human plasma. In addition, in six series of analysis a QC at a Org 9426 concentration of the estimated LOQ (0.1 ng/mL, coded as QC E) was determined.

The QCs were stored at approximately -20 °C.

#### **3.3.1 Inter-assay precision and accuracy**

Inter-assay precision (CV%) and accuracy (% nominal) were assessed for QC B, QC C, QC D and QC E by triplicate analysis in five separate series and six-fold analysis in one series. The inter-assay precision (CV%) and accuracy (% nominal) for QC A was assessed by triplicate analysis in four separate series and six-fold analysis in two separate series. The inter-assay precision of QC A and QC E was not allowed to exceed 20%, whereas the inter-assay precision of QC B, QC C and QC D was not allowed to exceed 15%. The inter-assay accuracy of QC A and QC E had to be between (including limits) 80-120%, while the inter-assay accuracy of QC B, QC C and QC D had to be within (including limits) 85-115%.

#### **3.3.2 Intra-assay precision and accuracy**

Intra-assay precision (CV%) and accuracy (% nominal) were assessed for each QC by six-fold analysis of the QCs in one series.

The intra-assay precision of QC A and QC E was not allowed to exceed 20%, whereas the intra-assay precision of QC B, QC C and QC D was not allowed to exceed 15%. The intra-assay accuracy of QC A and QC E had to be within (including limits) 80-120%, while the intra-assay accuracy of QC B, QC C and QC D had to be within (including limits) 85-115%.

### **3.4 Stability**

#### **3.4.1 Freeze/thaw cycles**

The influence of frequent freezing and thawing was investigated by comparing the mean results of each of the four QCs (QC A -QC D) after one freeze/thaw cycle, with those of two and three times freezing and thawing. Sample preparation was started directly after the samples were thawed, however, the samples which were used for the determination of the stability of two and three freeze/thaw cycles were kept unfrozen for at least 6 hours before the samples were stored in the deep-freezer again.

The mean results of the two and three freeze/thaw cycles compared to one freeze/thaw cycle was not allowed to differ more than 15%.

#### **3.4.2 Short-term room temperature stability**

The short-term room temperature stability was measured over the combined time intervals at which the samples had been at room temperature during cycles two and three.

The mean results of the two and three freeze/thaw cycles compared to one freeze/thaw cycle were not allowed to differ more than 15%.

### 3.4.3 Long-term stability

The QCs containing 0.3, 5, 80 and 800 ng Org 9426 per mL plasma (QC A -QC D) were stored in the deep-freezer at approximately -20°C. In due time, after approximately half a year or in the first clinical trial to come or at any other time point deemed necessary, those samples will be analyzed to assess the long term stability at approximately -20 °C. The results will be reported in an amendment to the validation report.

### 3.4.4 Recovery

The extraction recovery of Org 9426 was assessed at 0.3, 5 and 80 ng/mL by six-fold analysis, IS (b) (4) added after solid phase extraction. Also the extraction recovery of the IS (b) (4) was assessed by sixfold analysis at 60 ng/mL, Org 9426 added after solid phase extraction.

Standard solutions of Org 9426 in solvent, in sixfold per level containing 0.3, 5 and 80 ng/mL and 60 ng/mL IS (b) (4) were injected directly on the LC-MS system. The calculated quotients of the extracted human plasma samples were compared with the quotients of standard solutions at the same levels determined in sixfold analysis.

The ion-suppression of Org 9426 was assessed by the addition Org 9426 at a level of 0.3 ng/mL to the final solution of blank human plasma after complete sample preparation. The ion-suppression of IS (b) (4) was assessed by the addition of IS at a level of 60 ng/mL to the final solution of blank human plasma after complete sample preparation. The ion-suppression effect was determined by comparing the mean response of the extracted samples with the mean response of standard solutions at the same level determined in six-fold analysis.

### 3.5 Selectivity

Blank human plasma samples from ten different donors spiked to the concentration level of STD B and blank water as well were analyzed according to the assay to assess possible endogenous and exogenous interferences. Significant interferences from endogenous and/or exogenous compounds were absent at the retention times of Org 9426 and its internal standard.

In addition, diluted standards of Org 9426 and its internal standard were analyzed separately to assess whether Org 9426 interferes with its internal standard and vice versa. The response of interfering peaks at the retention time of Org 9426 had to be less than 20% of the response of standard B. The response of interfering peaks at the retention time of the internal standard had to be less than 5% of the response of the concentration of the internal standard.

## 4. RESULTS

The validation was performed in 7 analysis series.

The results of the validation experiments are tabulated in Table 1 up to and including Table 7.

### 4.1 Linearity and calibration

For each accepted analysis series the calibration curve parameters, as determined using linear weighted (1/Y) regression, are presented in Table 1. The individual back calculated Org 9426 levels, mean values, precision and accuracy for each calibration standard are presented in Table 2.

## 4.2 Sensitivity (LOQ)

The lowest concentration of the calibration curve that can be determined with an accuracy (expressed as % nominal) between (and including limits) 80-120% and a precision (CV%) less than or equal to 20%, is STD B (0.1 ng/mL) as presented in Table 2. The QC E at a concentration of 0.1 ng/mL had an accuracy (expressed as % nominal) between (and including limits) 80-120% and a precision (CV%) less than or equal to 20%, as presented in Table 3. The LOQ is 0.1 ng/mL.

## 4.3 Precision and Accuracy

### 4.3.1 Inter-assay precision and accuracy

For each QC sample the inter-assay precision (CV%) and accuracy (% nominal) were calculated using the individual levels from all accepted series as presented in Table 3. The inter-assay precision of QC A and QC E did not exceed the 20% while the inter-assay precision of QC B, QC C and QC D did not exceed the 15%. The inter-assay accuracy of the QC A and QC E was within (and including limits) 80-120% while the inter-assay accuracy of QC B, QC C and QC D was within (and including limits) 85-115%.

### 4.3.2 Intra-assay precision and accuracy

Intra-assay precision (CV%) and accuracy (% nominal) were assessed for each QC by six-fold analysis of the QCs in one series as presented in Table 4. QC A and QC E were measured in curve code BAS05, QC B, QC C and QC D were measured in curve code BAS04.

The intra-assay precision of QC A and QC E did not exceed 20%, whereas the intra-assay precision of QC B, QC C and QC D did not exceed 15%. The intra-assay accuracy of QC A and QC E was within (including limits) 80-120%, while the intra-assay accuracy of QC B, QC C and QC D was within (including limits) 85-115%.

## 4.4 Stability

### 4.4.1 Freeze/thaw cycles

The mean results of analysis of the QC samples QC A (BAS07), QC B, QC C and QC D (BAS03) after two and three freeze/thaw cycles compared to one freeze/thaw cycle are shown in Table 5. The mean results of two and three freeze/thaw cycles compared to one freeze/thaw cycle did not differ more than 15%.

The data show that repeated freezing and thawing does not affect the concentration of Org 9426 in human plasma.

### 4.4.2 Short-term room temperature stability

The QCs used for freeze/thaw cycles were used to measure the short-term room temperature stability. As can be read from Table 5, the mean results of the three freeze/thaw cycles compared to one freeze/thaw cycle do not differ more than 15%.

The combined time intervals at which the samples had been at room temperature during freeze/thaw cycles two and three is 12 hours.

## 4.5 Recovery

The extraction recoveries of Org 9426 and (b) (4) are shown in Table 6.

The recoveries for Org 9426 at 0.3, 5 and 80 ng/mL ranged from 47 to 57%. The recovery for the IS was 45% at 60 ng/mL.

The ion-suppression of Org 9426 and (b) (4) are shown in Table 7. There was no ion-suppression of Org 9426 at 0.3 ng/mL and (b) (4) at 60 ng/mL.

#### 4.6 Selectivity

Blank human plasma from ten different donors as well as blank water were analyzed according to the method described in Appendix I. No significant interferences were detected at the retention times of Org 9426 and its IS. In addition diluted standards of Org 9426 and its IS were analyzed separately. Typical chromatograms for selectivity are shown in Appendix II. No significant interferences of Org 9426 at the retention time of its IS and vice versa were detected. Some representative chromatograms are shown in Appendix III.

### 5. CONCLUSION

The LC-MS assay for the determination of Org 9426 in human plasma has been validated.

# 22 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

## 5 Population Pharmacokinetic Analysis

The population PK analysis of plasma sample data from studies 21-048 and 21-049 was performed using the non-linear mixed effects modeling approach. This approach estimated the typical (mean) value of parameters as well as their inter-individual variances. The software package NONMEM version VI (Globomax, 7250 Parkway Drive, Suite 430, Hanover, MD 21076 USA) [1] was used for the analysis. Perl-speaks NONMEM was used for NONMEM execution, bootstrapping and log-likelihood profiling. NONMEM datasets were created using SAS version 9.1. S-PLUS 6.2 (insightful, Seattle, USA) and R were used for model evaluation. In NONMEM the first-order conditional (FOCE) estimation method with interaction was used for all modeling steps. Stability of NONMEM models was assessed on the basis of:

- Successful minimization and covariance step
- Acceptable basic goodness-of-fit plots
- Number of significant digits  $\geq 3$
- Estimates of  $\theta$ 's not close to a boundary
- Condition number (ratio of largest to smallest eigenvalue)  $< 1000$
- Correlation less than 0.95 between any two parameters

Model selection was based on the following criteria:

- Successful minimization with completion of the Covariance step.
- The comparison of full vs. reduced models is based on the Log-Likelihood Criterion: the difference in the minimum value of the objective function between hierarchical models is asymptotically chi-square distributed with degrees of freedom equal to the difference in number of parameters between models.
- Decrease in unexplained variability. Extension of a model by adding independent variables should usually be accompanied by a decrease in random inter- and/or intra individual variability;
- Visual inspection of the fits. Several diagnostic plots were made to examine the goodness-of-fit: e.g. predictions versus observations; residuals versus time. For a model to be accepted, points in the above mentioned plots should be close to and scattered randomly around the line of identity. Systematic patterns should be absent.
- Scientific plausibility of the model

Compartmental analyses of rocuronium reported in literature [4] have indicated a three-compartment model to adequately describe rocuronium plasma concentrations in adults. In pediatrics subjects the pharmacokinetics of rocuronium has been described using a two-compartment model.

### Structural model

Both 2 and 3 compartment models were evaluated during model development.

Allometric scaling based on body weight was included on all pharmacokinetic parameters (CL, Vc, V2 and Q). Parameters were scaled to a mean body weight of 70 kg. Initially the allometric coefficients were fixed to their theoretical values of 0.75 for CL and Q and 1 for Vc and V2. Alternative parameter values for the allometric coefficients were explored either by estimation (assuming coefficients for CL and Q or Vc and V2 to be identical) or fixation to other values.

Goodness-of-fit of the structural model was assessed by diagnostic plots:

- Observations versus population and individual predictions and/or log-log plots
- Population and individual weighted residuals versus time
- Above plots stratified by study

### **Population PK: Random effects model**

Exponential error models were used to describe the inter-individual variability on the model parameters. Additive, proportional and additive + proportional residual error models were explored. Exponential error models were explored for between subject variability in the model parameters. A diagonal  $\Omega$ -structure was employed; the inclusion of off-diagonal elements was to be based on observed correlations in ETA estimates. The goodness-of-fit and appropriateness of the random effects models was assessed by means of diagnostic plots as mentioned above as well as:

- Plots of observations versus time with population and individual fits
- Weighted residuals versus time and individual predictions.
- Above plots stratified by study
- Distribution of WRES by study and age group
- Histograms of ETA estimates
- ETA's versus covariates age, body weight, study and age group
- Box-plots of ETAs versus age group and study
- Correlation between ETA's and included covariates
- (Absolute) individual weighted residuals versus individual predictions
- Mean absolute individual weighted residuals by subject

### **Population PK: Covariate effects**

The effects of age and body weight were tested as covariates on the parameters of the structural pharmacokinetic model were explored graphically. Both linear and non-linear covariate relations were tested for their significance by inclusion in the models. Based on

the log-likelihood criterion a decrease of 3.84 in objective function is significant at the  $p < 0.05$  level.

**Goodness-of-fit:** The goodness-of-fit and appropriateness of the covariate model was assessed by means of diagnostic plots as mentioned above as well as:

- ETA estimates versus covariates, comparison with base model without covariates.

## Results

### *Data*

Six predose samples with Org 9426 plasma concentrations  $>$  LLOQ were removed from the dataset since it was not possible to have Org 9426 plasma concentrations before Zemuron® dosing (Trial 021-048: sample number 1 from subject 111210: 44.5 ng/mL, subject 123402: 255 ng/mL and from subject 129602: 5390 ng/mL. Trial 021-049: sample number 1 from subject 102504: 4770 ng/mL, subject 107601: 2090 ng/mL and from subject 108405: 3.43 ng/mL). Sample number 2 from subject 105409 (trial 021-049, 138000 ng/mL) was excluded from the dataset and considered an outlier since the other rocuronium plasma concentrations ranged from 1340 to 32000 ng/mL in all other samples with sample number 2.

### *Subjects*

All subjects for whom rocuronium PK data were available were included in the dataset for population PK modeling.

The number of subjects with PK samples within each clinical trial by age group is shown below.

Clinical trial	Age group	Number of subjects
021-048	Neonates	8
	Infants	3
	Toddlers	8
	Children	13
	Adolescents	19
021-049	Neonates	6
	Infants	6
	Toddlers	21
	Children	28
	Adolescents	34

The dataset used for population PK modeling included 146 subjects from clinical trials 021-048 and 021-049 of which 14 term neonates (birth to  $<$  28 days), 9 infants (28 days to  $\leq$  3 months), 29 toddlers (3 months to  $\leq$  2 years), 41 children (2 years to  $\leq$  11 years) and 53 adolescents (11 years to  $\leq$  17 years).

### *Model selection*

The rocuronium plasma concentration-time data were best characterized by a two compartment model with a zero order input and first order elimination from the central compartment. The inter-individual variability was assumed to be log normally distributed

on the PK parameters clearance (CL) and central volume of distribution (Vc). No correlation between the parameters describing the inter-individual variability was observed so no off-diagonal elements of the  $\Omega$ -matrix were added to the model.

Allometric scaling based on body weight was included on all pharmacokinetic parameters (CL, Vc, V2 and Q). Initially, the allometric coefficients were fixed to their theoretical values of 0.75 for CL and Q and 1 for Vc and V2. Rocuronium was dosed on body weight, which corresponds to allometric coefficients equal to 1. The effect of fixing the allometric coefficients to 1 was assessed. This resulted in a decrease in the objective function compared to the model with the coefficients on CL and Q fixed to 0.75.

The allometric coefficients were fixed to 1 during development of the covariate model. The allometric coefficients in the final model were re-evaluated by estimating them in a subsequent step. The confidence interval of the obtained estimates included 1 for both allometric coefficients and the objective function did not decrease significantly compared to the final model. Based on observed trends in plots of posthoc parameters, age was tested as a covariate on the central distribution volume (Vc).

**Model building steps are summarized below.**

Model	Parent	structure	Residual error prop	IIV	allometric scaling	covariates	NO. of $\theta$ 's	NO. of $\eta$ 's	OFV	$\Delta$ OFV
1	--	3 compart.	prop	--	CL,Q2,Q3 ~0.75 Vc,V2,V3~1	--	6	0	6040.926	--
2	1	" "	prop + add	--	CL,Q2,Q3 ~0.75 Vc,V2,V3~1	--	6	0	6040.926	0
3*	1	" "	add	--	CL,Q2,Q3 ~0.75 Vc,V2,V3~1	--	6	0	6432.854	391.928
4	--	2 compart.	prop	--	CL,Q~0.75; Vc,V2~1	--	4	0	6055.772	--
5	4	" "	prop + add	--	CL,Q~0.75; Vc,V2~1	--	4	0	6049.98	-5.792
6	4	" "	add	--	CL,Q~0.75; Vc,V2~1	--	4	0	6433.194	377.422
7*	4	" "	prop	CL,Vc,Q2,V2	CL,Q~0.75; Vc,V2~1	--	4	4	5655.238	400.534
8	7	" "	prop	CL,Vc,V2	CL,Q~0.75; Vc,V2~1	--	4	3	5672.259	17.021
9	8	" "	prop	CL, Vc	CL,Q~0.75; Vc,V2~1	--	4	2	5676.536	4.277
10	9	" "	prop	CL, Vc	CL,Q~est; Vc,V2~est	--	6	2	5595.447	-81.089
11	9	" "	prop	CL, Vc	CL,Q~1; Vc,V2~1	--	4	2	5665.506	-11.03
101	11	" "	prop	CL, Vc	CL,Q~1; Vc,V2~1	age_Vc (lin)	5	2	5614.32	-51.186
102	11	" "	prop	CL, Vc	CL,Q~1; Vc,V2~1	age_Vc (exp)	5	2	5628.783	-36.723
103	102	" "	prop	CL, Vc	CL,Q~1; Vc,V2~1	age_Vc (amplitude*exp)	6	2	5579.318	-49.465
104	9	" "	prop	CL, Vc	CL,Q~0.75; Vc,V2~1	age_Vc (amplitude*exp)	6	2	5595.131	-81.405
105	103	" "	prop	CL, Vc	CL,Q~1; Vc,V2~1	age_Vc (amplitude*exp), age_CL (lin)	7	2	5579.121	-0.197
106	10	" "	prop	CL, Vc	CL,Q~est; Vc,V2~est	age_Vc (amplitude*exp)	8	2	5574.869	-20.578

-2LL: -2 times the log likelihood; \* No covariance step; OFV : objective function value;  $\Delta$  OFV: difference in OFV compared to parent run  
IIV: Inter individual Variability; Allometric scaling: Values for allometric coefficients used; structure: model structure; Residual error: Prop: proportional, Add: additional;

Model # 11 was selected as the structural model and model # 103 was selected as the final model

*Final pharmacokinetic model*

The final model was a two compartment model with a zero-order input and first order elimination from the central compartment with log-normally distributed inter-individual variability on clearance and central volume of distribution. The pharmacokinetic parameters of the final model were scaled using allometric scaling based on body weight with the allometric coefficients set to 1. The model included age as a covariate on the

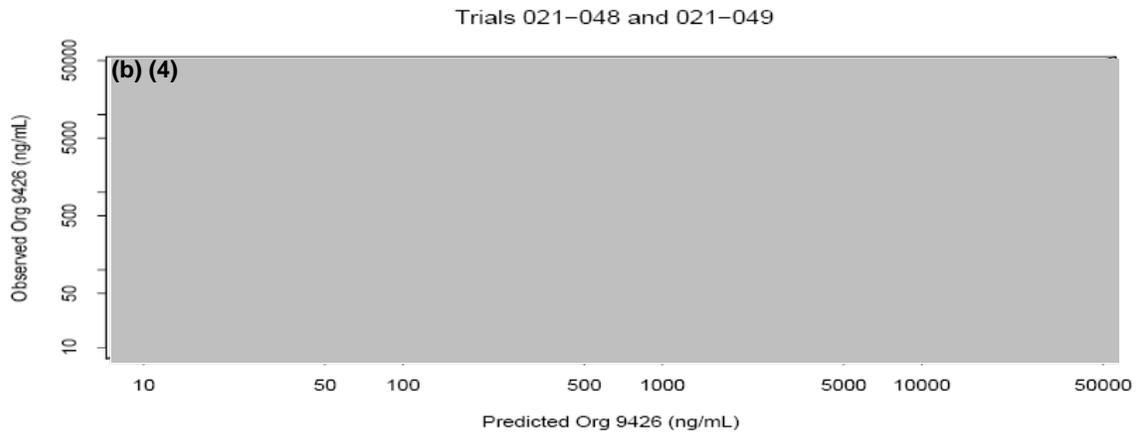
central volume of distribution. The central volume of distribution is given by equation

$$V_c = 6.23 \cdot \left(\frac{bw}{70}\right)^1 + 0.779 \cdot e^{-0.463 \cdot age}$$

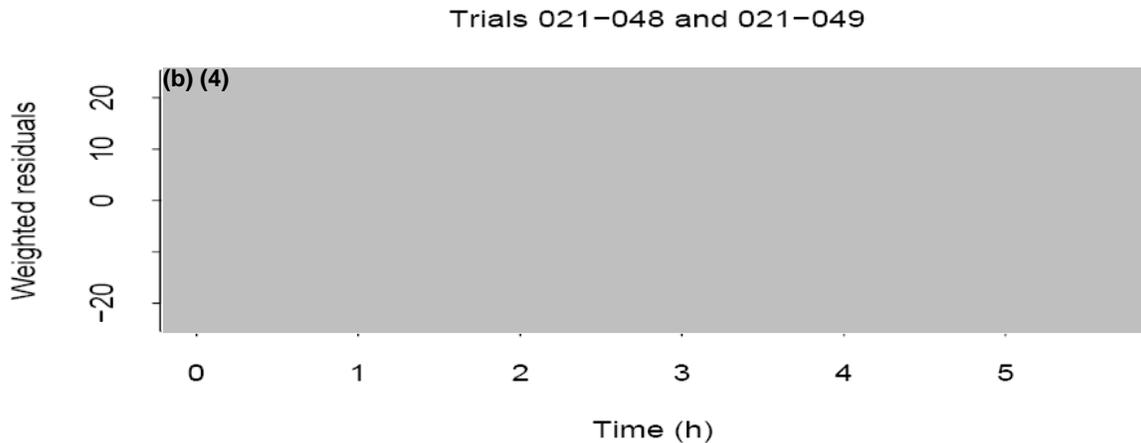
below in the final model.

ETA shrinkage was calculated for the final model. The shrinkage was 8.5 % for ETA1 (CL) and 34.7 % for ETA2 (Vc). In Table 4 the parameter estimates of the final model are given for a hypothetical subject of 70 kg. The estimate and relative standard error (RSE) of the PK parameter was obtained from the NONMEM run of the final model, while the 95% confidence intervals were obtained from a nonparametric bootstrap using the BCa method with 2000 replicates.

**Appropriate goodness-of-fit was achieved with the final PK model for rocuronium, as can be observed below:**

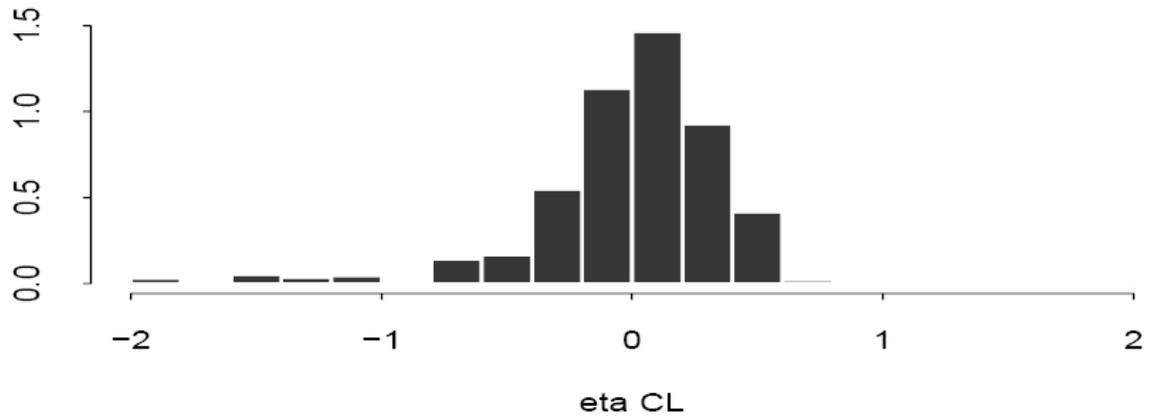


**Weighted residuals Vs time**



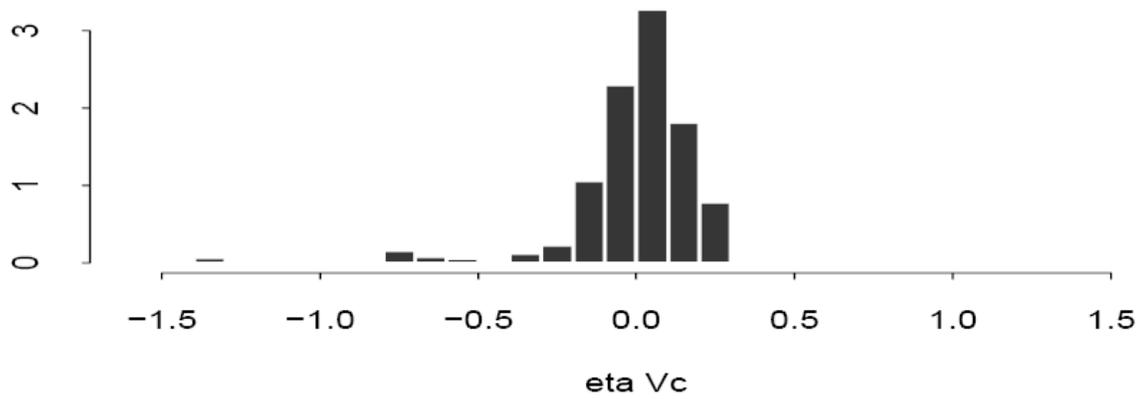
**Distribution of inter individual variability for clearance (Final Pharmacokinetic model Org 9426 by trial)**

### Trials 021-048 and 021-049

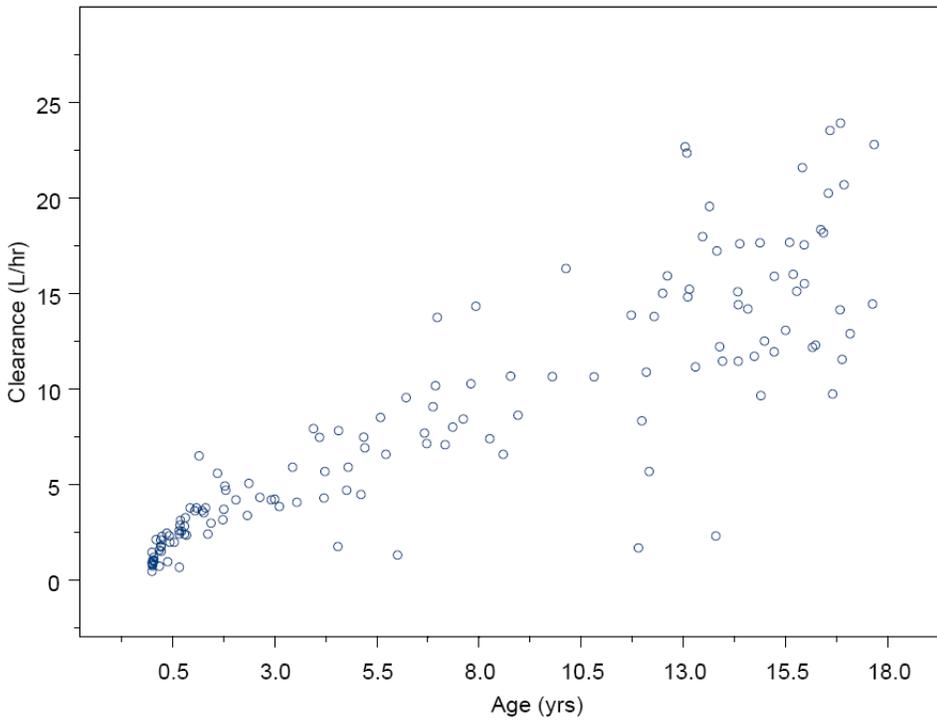


**Distribution of inter individual variability for volume of distribution (Final Pharmacokinetic model Org 9426 by trial)**

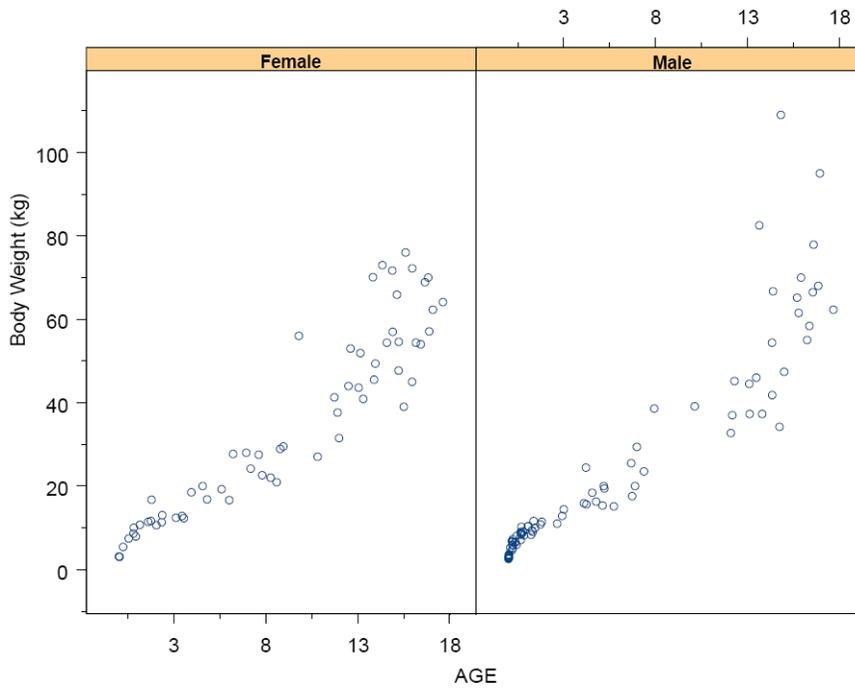
### Trials 021-048 and 021-049



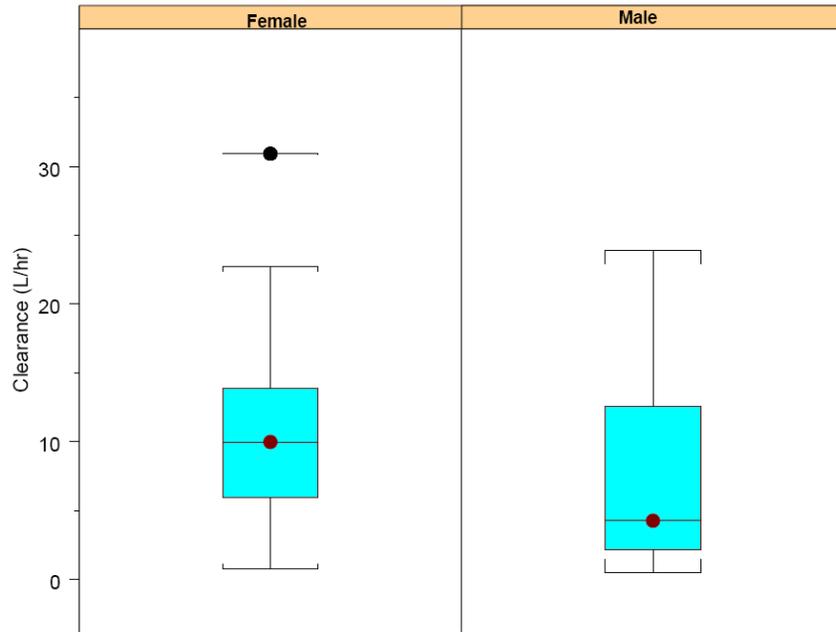
### Relationship between rocuronium clearance and patient age



Based on the above figure age seems to affect rocuronium clearance. However, a curvilinear relationship appears between age and body weight in male or female pediatric patients (see figure below).

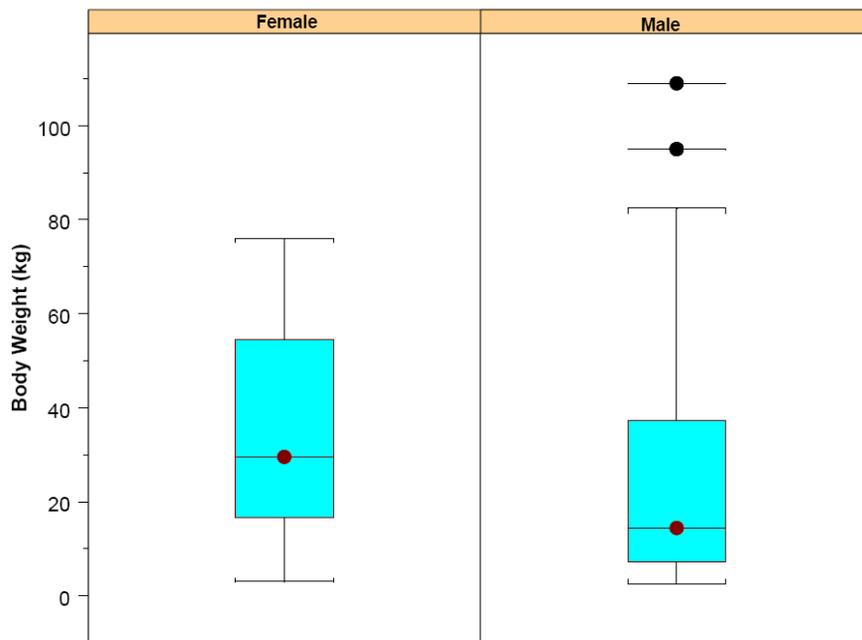


In addition, rocuronium clearance appears to be different in female and male patients seen in the figure below.



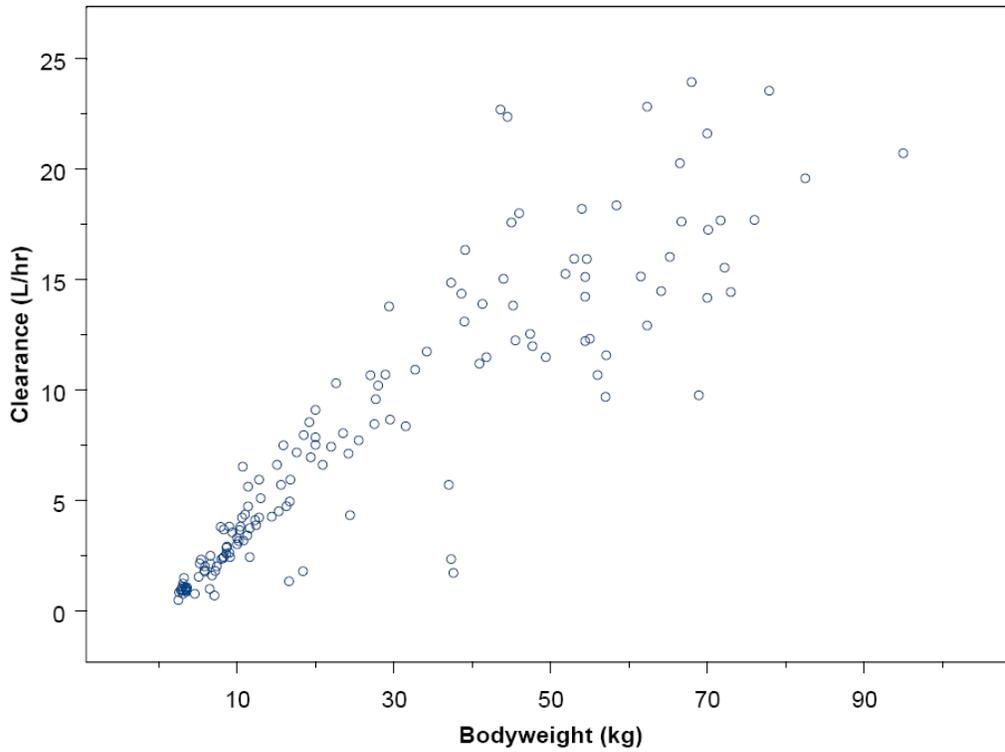
However, this appears to be due to the differences in body weight of female and male patients recruited in the two clinical studies.

### Body weight ranges in male and female patients

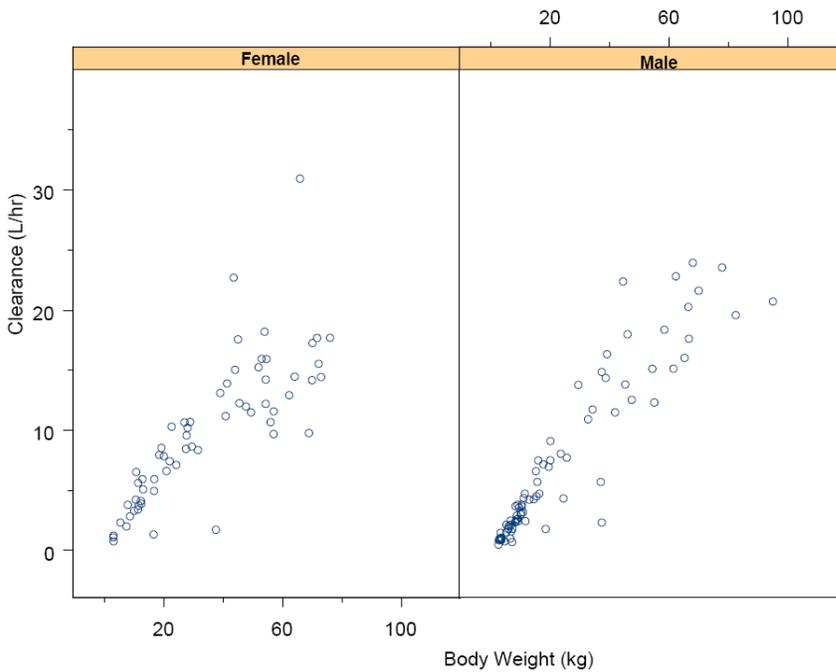


As described in the final PK model and covariate analysis, body weight appears to be the main determinant of rocuronium clearance in male and female pediatric patients.

### Overall relationship of rocuronium clearance to body weight



### Relationship of rocuronium clearance to body weight in male and female pediatric patients



### Summary of rocuronium PK parameters based on final model

Parameter	Units	estimate	RSE (%)	95% confidence interval
CL	L/hr	20.5	4.3	18.9 – 22.4
Vc	L	6.23	7.8	3.51 – 6.89
Q	L/hr	10.7	31.0	7.16 – 39.51
V2	L	5.95	8.1	5.270 – 7.873
A		-0.463	36.5	-2.191 – -0.006
B	L	0.779	16.9	0.614 – 1.02
<b>Inter-individual variability</b>			<b>IIV (%)</b>	
$\omega_1^2$ (Cl)		0.184	42.9	0.103 – 0.280
$\omega_2^2$ (Vc)		0.0982	31.3	0.026 – 0.176
<b>Residual error</b>			<b>CV (%)</b>	
$\sigma_1^2$ (proportional)		0.108	32.8	0.066 – 0.152

### Summary of rocuronium PK parameters by age group

Parameter	Neonates (birth to < 28 days)	Infants (28 days to ≤ 3 months)	Toddlers (3 months to ≤ 2 years)	Children (2 years to ≤ 11 years)	Adolescents (11 years to ≤ 17 years)
Median age (years)	0.015	0.22	0.85	5.6	14.9
Median body weight (kg)	3.1	5.8	9.0	19.4	54.4
CL (L/hr)	0.91	1.70	2.64	5.68	15.93
Vc (L)	1.05	1.22	1.33	1.78	4.84
Q (L/hr)	0.47	0.89	1.38	2.97	8.32
V2 (L)	0.26	0.49	0.77	1.65	4.62

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