CLINICAL REVIEW

Application Type	20-214
Submission Number	030
Submission Code	SE5
Letter Date	January 10, 2008
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Reviewer Name	Lex Schultheis, M.D., Ph.D.
Review Completion Date	June 11, 2008
Established Name	Rocuronium Bromide
(Proposed) Trade Name	Zemuron
Therapeutic Class	Neuromuscular Blocking Agent
Applicant	Organon USA, Inc.
Priority Designation	P
Formulation	10 mg/mL Injection
Dosing Regimen	0.45 or 0.6 mg/kg intravenous bolus followed by 0.15 mg/kg bolus or 7-10 mcg/kg/min as an infusion.
Indication	To provide skeletal muscle relaxation to facilitate rapid sequence and routine (b) (4) tracheal intubation: as an adjunct to general anesthesia, in either routine inpatient or outpatient settings to provide skeletal muscle relaxation during surgery; to provide skeletal muscle relaxation required for mechanical ventilation.
Intended Population	Pediatric patients

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In an adequate and well-controlled clinical trial (021049), Zemuron was used safely and was effective as a neuromuscular blocking agent given concomitantly with general anesthetics in pediatric patients, including neonates and infants.

The evidence of efficacy in Study 021049 rests primarily upon:

- Compelling pharmacodynamic evidence of neuromuscular blockade demonstrated using quantitative twitch monitor assessments of the Train-of-four (TOF). Quantitative twitch monitor assessment of neuromuscular integrity is an accepted measure of efficacy for neuromuscular blocking drugs. All patients demonstrated a maximum motor blockade in the range of 94% to 100% following administration of 0.45 mg/kg, 0.6 mg/kg or 1.0 mg/kg as a single bolus injection. The onset of maximum blockade ranged from 0.2 minutes to 2.2 minutes.
- A dose-dependent increase in signs of recovery from neuromuscular blockade indicated by reappearance of T3 in the TOF.
- This pharmacodynamic evidence of efficacy is further supported by subjective clinical findings indicating that the clinical conditions of direct laryngoscopy were good or excellent in the majority of cases. Visualization of the glottis is difficult by direct laryngoscopy when skeletal muscle tone is intact.

The evidence of safety of Zemuron in pediatric patients, including neonates and infants, is based primarily upon data from Study 021049 and a randomized, open-label comparison (Study 021048) of Zemuron maintenance dosing as either repeated boluses or a continuous infusion in patients undergoing surgery:

- An absence of mortality among patients who received Zemuron in Study 021049 and 021048.
- An absence of serious adverse events that were caused by Zemuron.
- An absence of dose-dependent changes to vital signs, in each age group.
- An absence of a dose-dependent decrease ventilatory compliance.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

No additional Phase 4 requests are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two studies were submitted in response to a Pediatric Written Request (PWR). The PWR underwent multiple amendments between the initial (December 21, 2001) and final (January 8, 2008) versions. The final revision to the PWR was made after review of summary data of the studies in this submission was provided under the IND 32, 484. These data illustrated that there was considerable interpatient variability in response to Zemuron, especially among neonates and infants so that additional data to improve the estimate measures of central tendency would not have been clinically meaningful. Following consultation with the Pediatric Review Committee, the PWR was amended.

Study 021049 entitled "A randomized, assessor-blind, dose-ranging, phase IIIB, 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" also underwent multiple amendments. A total of 207 patients were enrolled with 201 enrolled after major amendments to the protocol. An additional 16 patients were discontinued before receiving Zemuron. Therefore, 185 patients in the ITT study population were evaluated for efficacy. In this study, patients were recruited in the following age groups: term neonates (birth to <28 days old), infants (28 days to ≤3 months), toddlers (>3 months to ≤2 years old), children (>2 to ≤11 years of age) and adolescents (>11 to ≤17 years of age). These patients underwent a variety of surgical procedures under general anesthesia. In order to limit possible confounding effects of concomitant medication on assessment of neuromuscular blockade, the general anesthetic agents used and their doses were stipulated in the protocol. Furthermore, the use of certain antibiotics and intravenous local anesthetics were also excluded to avoid their possible effect on neuromuscular blockade. Clinical assessment of motor weakness was primarily based upon quantified thumb twitch response to a Train-of-four

transcutaneous stimulus of the ulnar nerve. The amplitude of thumb acceleration as an indication of force was measured for T2, T3 and T4 as a percentage of T1.

After these responses were abolished following administration of Zemuron, the time to reappearance of T3 served as the primary efficacy endpoint for each of the doses in the comparison, evaluated using descriptive statistics. Also included were secondary endpoints such as the maximum block, assessed as a percentage T1 before Zemuron administration to the minimum T1 observed after Zemuron administration. The time to maximum block, the time to reappearance of T1 and the time to T4/T1 expressed as 70%, 80% and 90% were also assessed. Furthermore, anesthesiologist investigators evaluated conditions of direct laryngoscopy on a subjective categorical scale.

A second Study 021048, in a pediatric population of the same age distribution as Study 021049, provided a randomized open-label comparison of repeated bolus to continuous infusion supplementary dosing of Zemuron. As in Study 021049, the anesthetic regimens were standardized and intravenous local anesthetics and antibiotics were specifically excluded. The use of caudal local anesthetics was permitted because systemic absorption from the caudal space occurs slowly and the procedure did not interfere with TOF assessments. The bolus (0.15mg/kg) and continuous infusion (2 to 5 mcg/kg/min) were begun at time of reappearance of T3 in the TOF. The total dose of Zemuron was the primary parameter evaluated in this comparison. The study was not blinded so that the statistical description of the findings cannot be used to provide evidence of efficacy. Additional evaluations included the time to spontaneous recovery of 70%, 80%, and 90% of the T4/T1 ratio. The onset time of blockade following a 0.6 mg/kg bolus dose of Zemuron was also evaluated.

1.3.2 Efficacy

Study 021049 was randomized, blinded and provided a dose-comparison to evaluate efficacy of Zemuron. After induction of general anesthesia and calibration of the TOF monitor, Zemuron was administered. Following administration of Zemuron, the time to reappearance of T3 after these responses was abolished served as the primary efficacy endpoint, evaluated using descriptive statistics, for each of the doses in the comparison. For each of the doses in the comparison, secondary endpoints were also included such as the maximum block, assessed as a percentage of the T1 present before Zemuron administration to the minimum T1 observed after Zemuron administration. The time to maximum block, the time to reappearance of T1 and the time to T4/T1 expressed as 70%, 80% and 90% were also assessed. Furthermore, anesthesiologist investigators evaluated conditions of direct laryngoscopy on a subjective categorical scale.

1.3.3 Safety

Safety of Zemuron was evaluated in the 338 patients exposed to Zemuron in Studies 021049 and 021048. An analysis of adverse events indicated that there were no deaths or serious adverse events attributable to Zemuron. Common adverse events were consistent with the product labeling.

A review of the AERS database revealed 41 reports for 38 unique pediatric patients including four neonates and three infants as defined by the age groupings used in Studies 021048 and 021049. Among these reports, the most common event was prolonged neuromuscular block (11 patients). Other findings were associated with bradycardia and/or cardiac arrest (6 patients), anaphylactic or anaphylactoid reactions (7 patients) drug tolerance and/or reduced effectiveness (5 patients), blood pressure changes (3 patients) or syndromes associated with plasma elevations of muscle proteins (3 patients).

1.3.4 Dosing Regimen and Administration

When given as a bolus to facilitate intubation, there was a dose-related trend toward increasing duration of action of Zemuron. The practical significance of this trend was minimal because individual variability at each dose was greater than the trend among each age group.

There was a trend toward faster recovery and a lower total dose for infusions among the child and adolescent age groups, but not for toddlers, infants or neonates, in the open-label study comparing bolus to continuous infusion maintenance dosing regimens. The small number of neonates and infants studied made comparisons difficult.

A dose relationship between common adverse events coded as procedural pain and as vomiting was based upon small numbers of patients having these events. Procedural pain included complications associated with injection such as infiltration that are unlikely to be related to Zemuron. Post-operative vomiting has multiple etiologies and the trend associated with increasing Zemuron dose was small. Therefore, there were no compelling dose-related safety signals identified in the data from the submitted studies.

1.3.5 Drug-Drug Interactions

No drug-drug interactions were evaluated.

1.3.6 Special Populations

The submitted studies were conducted in pediatric patients ranging in aged from neonate through adolescence. Patients categorized on the ASA physical classification scale as 1 through 3 were included, but no analysis for specific comorbidities was performed. No other special population analyses were performed.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zemuron (rocuronium bromide) is a neuromuscular blocking agent administered intravenously that binds noncompetitively with acetylcholine at the motor endplate of skeletal muscle. It is indicated as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery and mechanical ventilation. The applicant's submission is intended to extend the database in the pediatric population and specifically to include dosing information in neonates and infants below the age of 3 months.

- Route of administration: IV
- Initial Dosage 0.45, 0.6 or 1.0 mg/kg
- Maintenance Regimen: Bolus 0.15 or infusion 2 to 5 mcg/kg/min or 1 to 3 mg/kg/hr
- Formulation: Zemuron 10 mg/mL in 5 or 10 mL multiple dose vial (Marketed Product)

2.2 Currently Available Treatment for Indications

There are multiple alternative neuromuscular blocking agents approved for use in the United States. These include pancuronium bromide (NDA 072058, 072060, 072059, 072320 and 072321), vecuronium bromide (NDA 075218, 075549, 075164, 075558, 074688 and074334), atricurium besylate (NDA 074768, 074753, 074901, 074900, 074741, 074740, 074945, 07494, and 074784) and cisatricurium besylate (NDA 020551). However, none of the other products include specific dosing information based upon controlled clinical study data in neonates and infants.

2.3 Availability of Proposed Active Ingredient in the United States

Zemuron is available in the United States and holds a large market share of among the available nondepolarizing neuromuscular blocking agents.

2.4 Important Issues With Pharmacologically Related Products

Raplon (rapcuronium bromide, NDA 020984, approved August 1999) was withdrawn from the market approximately nineteen months after approval because of a high incidence of severe bronchospasm associated with its use in the pediatric population.

2.5 Presubmission Regulatory Activity

The study reports 021049 and 021048 were submitted to address the requirements of Studies 1 and 2 described in a Pediatric Written Request, (PWR). The PWR was amended as summarized in the following table.

Table 2.5-1 Regulatory History of the Pediatric Written Request for Zemuron

Date	Version of Written Request
December 31, 2001	Original submission
June 28, 2004	Amendment to anesthetic regimens: change maintenance anesthetic from sevoflurane to isoflurane
June 27, 2005	Amendment to change format of patient demographics in reports to be submitted
March 27, 2007	Amendment to extend deadline for submission of reports
June 22, 2007	Amendment to anesthetic regimen: eliminate minimum concentration of inhaled anesthetic, deadline extension for report submission
January 8, 2008	Amendment to change wording in Number of Patients section from "divided" to "randomized" and the number of patients in the birth to less than three month age group in Study 2 from 20 to 10.

The Sponsor had difficulty meeting recruitment targets in the neonatal and infant populations stipulated by the Pediatric Written Request (PWR) of December 31, 2001. Some, but not all of the Sponsor's earlier requests to amend the PWR in order to facilitate recruitment were previously accepted Agency on July 2, 2002, June 28, 2004, June 27, 2005 and March 27, 2007. In a teleconference held on September 4, 2007, the Sponsor clarified that a significant limitation of their studies was that few data were available to establish the end of neuromuscular blockade in the neonatal and infant populations.

To enable the Agency to determine whether amendment to the Pediatric Written Request was warranted, summary data from Studies 021049 and 0210048 were submitted to the IND 32, 484 in November 26, 2007. These data demonstrated a high level of interpatient variability especially among neonates and infants despite a highly selected study population and careful quantitative monitoring. Therefore, assessments of the data based upon statistical measures of central tendency would not be clinically useful for management of patients with Zemuron. Instead, each patient would require individualized monitoring and assessment to use Zemuron safely. Because study of additional patients was not necessary, and a conscientious effort had been made to a sufficient clinical population, the Pediatric Written Request was amended on January 8, 2008 following consultation with the Pediatric and Maternal Health Staff.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

No new information was presented in this submission.

3.2 Animal Pharmacology/Toxicology

No new information was presented in this submission.

3.3 Clinical Pharmacology

Pharmacokinetic data were collected from the two clinical studies whose clinical data are reviewed here. In Study 021048 patients received an intubation bolus dose followed by either bolus or maintenance doses of Zemuron. In Study 021049 subjects received a single intubation dose of Zemuron.

A derived dataset for the population PK analysis was generated, and consisted of the observed rocuronium plasma concentrations. A population pharmacokinetic model was developed describing the rocuronium plasma concentration versus time profiles in a pediatric population. Allometric scaling based on bodyweight was used on all pharmacokinetic parameters. Models were validated using a non-parametric bootstrap and log-likelihood profiling.

Pharmacokinetic data were collected as follows:

Table 3.3-1 Pharmacokinetic Measurements in Studies 021049 and 021048

Study 021049	Study 021048
• Predose	• Prior to administration of peri-operative medications (at least 1 baseline)
• 2 or 4 minutes after dose	• After induction of anesthesia
• 15 or 30 minutes after dose	• At 2,10 and 30 minutes after the intubation dose.
• 60 or 120 minutes after dose	

Table 3.3-2 Pharmacokinetic parameters for patients according to age derived from data applied to a population kinetics model.

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
Derived PK parameters					
CL(L/hr/kg)	0.293	0.293	0.293	0.293	0.293
Vc (L/kg)	0.339	0.210	0.147	0.092	0.089
Q (L/hr/kg)	0.153	0.153	0.153	0.153	0.153
V2 (L/kg)	0.085	0.085	0.085	0.085	0.085
Vss (L/kg)	0.424	0.295	0.232	0.177	0.174
$t_{1/2\beta}$ (hr)	1.1	0.9	0.8	0.7	0.7
0.45 mg/kg					
AUC0-∞ (mg·hr/L)	1.54	1.54	1.54	1.54	1.54
Cmax (ng/mL)	1329	2139.2	3053	4891	5055
0.6 mg/kg					
AUC0-∞ (mg·hr/L)	2.05	2.05	2.05	2.05	2.05
Cmax (ng/mL)	1772	2852.3	4070	6521	6741
1.0 mg/kg					
AUC0-∞ (mg·hr/L)	3.41	3.41	3.41	3.41	3.41
Cmax (ng/mL)	2954	4753.8	6783	10868	11234

From Sponsor's Study Report Table 6, Page 15.

The pharmacokinetics of rocuronium were best described with 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.
All pharmacokinetic parameters were proportional to body weight. As a result the derived pharmacokinetic parameters CL, Q and V2 were equal in each age group. As a consequence of the additional effect of age comma the central volume of distribution (Vc) decreased with age. Volume of distribution at steady state and the terminal half-life both decreased with age.

A pharmacokinetic – pharmacodynamic assessment was also performed comparing concentration of rocuronium to QTc (Bassett's correction). However, this analysis did not conform to the requirements for a thorough QT study (http://www.fda.gov/cder/guidance/6922fnl.htm, accessed May 9, 2008) and therefore the concomitant administration of general anesthetic agents confounded interpretation of the results.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data reviewed in the Sponsor's submission was the SAS transport compatible data tables provided electronically by the Sponsor. The AERS database was also reviewed for additional safety information regarding adverse events associated with Zemuron in pediatric patients. Additional safety information from the medical literature, provided by the Sponsor, was reviewed to evaluate the prolonged weakness in pediatric patients who are not pharmacologically reversed after treatment with Zemuron. This weakness is due to steroid-induced myopathy and residual paralysis in patients.

4.2 Tables of Clinical Studies

Study	Refers to PWR	Study Type	Number of Patients Enrolled	Provides: Safety/Efficacy/Pharmacokinetic Data	Dosing Regimen
021049	Study 1	Randomized Blinded, Dose-comparison	207	Safety, efficacy based primarily on pharmacodynamic data, pharmacokinetic data	Single bolus, initial dose
021048	Study 2	Randomized, Open-label	149	Safety, pharmacodynamic comparison of dosing regimens, pharmacokinetic data	Maintenance bolus vs infusion

4.3 Review Strategy

Evaluation of efficacy was based primarily upon Study 021049 because the study design was blinded and randomized. Therefore, it was expected to yield the information regarding the relative differential duration of neuromuscular blockade associated with various Zemuron doses in the age groups studied.

The Sponsor defined the ITT population as having had at least one efficacy assessment in patients who received at least one dose of Zemuron. Efficacy was also evaluated in the per protocol (PP) population, the patient population without a major protocol violation. Patients in the per protocol population with minor protocol violations had the relevant efficacy assessment affected by the violation deleted from the analysis. In this review, the most clinically important analyses are the incidence of neuromuscular blockade and the duration of action of the initial dose of Zemuron.

4.4 Data Quality and Integrity

The primary data contained in this submission was found by this reviewer to be internally consistent and appeared to be of good quality.

An inspection by the Division of Scientific Investigations (DSI) was conducted at 5 study sites to further evaluate study practices and integrity of data collection procedures. A report from the DSI investigators has indicated that there were significant administrative errors in the informed consent process in one study site (Site 107). Original informed consent documents were missing and copies of these documents were completed by a research coordinator employed by the Principal Investigator in an effort to provide complete documentation. Signature blocks on the consent forms that were to have been completed by the parents or guardians of the patients involved were in fact completed by the research coordinator. The Principal Investigator notified the FDA (OHRP) in a letter dated March 21, 2008 in advance of the DSI investigation as soon as he discovered this noncompliance with the protocol. The research coordinator involved in these procedural errors is no longer working at the institution that served as Site 107.

Other findings by the DSI investigators identified the following irregularities in the data collected at the same study site:

- Drug dilution information was not entered onto the CRF and the volumetric infusion rate was not calculated correctly. Instead, the study coordinator entered the amount of drug administered per kg per minute. Documentation of dilution and/or infusion rate to verify this information was not recorded according to the protocol. Documentation of the dose administered to the patients was consistent with the investigator's pattern of practice and was verified by the DSI team.

- There are also brief gaps in the infusion timebase between dose changes that were not captured. These gaps are brief (30 seconds) compared to the overall duration of Zemuron administration.

At the time of this review, the DSI evaluation was completed and the protocol violations including errors in data documentation were determined to have not affected the conclusions of this review.

4.5 Compliance with Good Clinical Practices

The Sponsor has indicated that the two clinical trials whose reports are included in this submission were conducted in compliance with 21 CFR 314.50 (d)(3)(i) and 21 CFR 314.50 (d)(5)(ix). Clinical study sites in the US were conducted under IND no. 32, 484. Investigators agreed to comply with Part 50 (protection of Human patients) and Part 56 (Institutional Review Boards of Title 21, code of Federal Regulations. Approvals for each protocol, protocol amendment and informed consent form were given by an IRB/local ethics committee associated with each study location. Informed consent was required prior to participation in clinical trials.

The Agency DSI review team has reported that an exception occurred at Study site 107 as described in Section 4.4 (Data Quality and Integrity) of this review.

For the six study sites in Belgium, Germany and Argentina, the protocol and amendments likely to affect the safety, scope of investigation, or quality of the study, and consent forms were approved by local ethics committees. An informed consent process addressing the elements of the Declaration of Helsinki and/or local requirements, whichever afforded greater protection of the subject, was conducted at these sites.

4.6 Financial Disclosures

All participating principal investigators certified that they had not entered into any financial arrangement with the Sponsor whereby the compensation to the investigator could be affected by the outcome of the study a defined in 21 CFR 54.2 (a). Clinical investigators further stipulated that they did not hold proprietary interests in Zemuron or significant equity in the Sponsor as defined in 21 CFR 54.2 (b). No Investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

A pharmacokinetic analysis was developed by the Sponsor based upon data collected in Studies 021049 and 021048. These data are useful to determine whether or not accumulation of Zemuron occurred in patients with immature hepatic and renal function at the dosing proposed by the Sponsor. Tissue redistribution accounts for most of the initial rocuronium administered. Rocuronium is not metabolized by circulating plasma cholinesterases. Zemuron is approximately 30% bound to circulating proteins and eliminated by the liver. Therefore, on theoretical ground hepatic immaturity may be expected to prolong the duration of effect of rocuronium. The rocuronium analog 17-deacetyl-rocuronium, a metabolite is rarely detected in urine. Therefore, renal immaturity is not expected to alter rocuronium dosing.

Dr. Srikanth Nallani has reviewed the Sponsor's pharmacokinetic findings and is in agreement with the Sponsor's analysis.

5.2 Pharmacodynamics

Evaluation of efficacy was largely based upon analysis of pharmacodynamic endpoints such as onset time and recovery from neuromuscular blockade suing a twitch monitor. These findings are discussed in Section 6.

5.3 Exposure-Response Relationships

The dose relationship to pharmacodynamic findings was used to evaluate efficacy associated with Zemuron and is reviewed under Efficacy Findings in Section 6.1.4.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The current indication for ZEMURON is: a nondepolarizing neuromuscular blocking agent indicated as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

No changes are proposed to be made to the indication. The current submission is to enable additional dosing information to be included for the pediatric population. In particular, new data about neonates and infants who are below the age of three months is reported. The pediatric database is extended by additional information provided about pediatric patients older than three months of age through adolescence.

6.1.1 Methods

Evaluation of efficacy in the submitted study data is based upon a quantitative analysis of patient pharmacodynamic motor responses to sequential transcutaneous electrical stimulation of the ulnar nerve associated with administration of Zemuron. The electrical stimulator, called a twitch monitor, delivers a sequence of four constant current pulses called a train-of-four or TOF. The resultant muscle contraction causes opposition of the thumb and is measured quantitatively as acceleration. The ratio of acceleration resulting from the first to last twitch stimulus is expressed as a percentage. A patient without neuromuscular blockade exhibits a baseline TOF of 100%. A thorough discussion of methods of analysis of neuromuscular blockade is beyond the scope of this review, but may be found in any comprehensive text of anesthesiology. Assessment of neuromuscular blockade using quantitative assessment of a twitch monitor has been used for approval of all nondepolarizing neuromuscular blocking agents. Approval of earlier product submissions was based upon the use of mechanomyography for twitch monitor assessment. However, to address the requirements of the Pediatric Written Request, the Division accepted the Sponsor's proposed use of acceleromyography during development of the study protocols because this technology is approved and mechanomyographic devices were not sufficiently available to conduct the studies proposed by the PWR. Additional definitions of specific measures used for analysis of neuromuscular blockade based upon the TOF are found in the Appendix of this review.

Study 021049 was a randomized, blinded dose-ranging study intended to evaluate the effect of a single bolus dose of Zemuron on the duration of neuromuscular blockade, the latency of onset, and the quality of neuromuscular blockade. This study was intended to address the requirements of Study 1 described in the Pediatric Written Request. This study is a well-controlled trial, but the enrolled population is small because it was not intended to discriminate outcomes based upon inferential statistical testing. Instead, a descriptive statistical analysis was performed to enable the identification of trends in pharmacodynamic outcomes associated with increasing dose.

Study 021048 was an open-label randomized study intended to evaluate the cumulative dose requirements of Zemuron administered as either supplementary bolus doses of as a continuous infusion for maintenance of neuromuscular blockade. This Study was intended to address the requirements of Study 2 described in the Pediatric Written Request. The analysis of pharmacodynamic data was intended to be descriptive rather than to discriminate clinical benefits between study arms.

6.1.2 General Discussion of Endpoints

In Study 021049, Zemuron was administered as a single bolus to facilitate endotracheal intubation. Patients were randomized to one of three Zemuron double-blinded dose groups: 0.45 mg/kg, 0.6 mg/kg or 1.0 mg/kg. The intention of the Study was to permit spontaneous resolution of neuromuscular blockade to reach a nearly complete recovery as evidenced by a T4/T1 ratio of 90%. In practice this was not always practical, so that for many patients the T4/T1 ratio had spontaneously recovered to 80% before pharmacological reversal of neuromuscular blockade was required. The primary analysis made regarding the time to reappearance of T3 from end of administration of Zemuron intubating dose. Since reappearance of T3 is often used as the point for supplemental dosing of a neuromuscular blocking agent for maintenance of muscle relaxation during surgery, this was a clinically relevant endpoint. It is also a marker of recovery when pharmacologic reversal of neuromuscular blockade may be safely attempted. When efforts to pharmacologically reverse neuromuscular blockade are attempted before T3 reappears, some patients may experience recurarization after a period of apparent full recovery of muscle strength. Some investigators conducting pharmacodynamic studies of nondepolarizing neuromuscular blocking agents have also proposed that reappearance of T3 corresponds to approximately 75% occupancy of skeletal motor endplates by the study drug.

Other stated objectives were to evaluate the time course of action (onset time, maximum block, reappearance of T1, and recovery to 70%, 80% and 90% T4/T1) following one of the three intubating doses of Zemuron studied. The clinical relevance of studying onset time is an obligatory delay in placement of an endotracheal tube in a patient who is apneic and may be difficult to ventilate by mask. Maximum block is an indicator of the degree of neuromuscular blockade associated with study drug administration. The ratio of T4/T1 as a function of time enables clinical prediction of the timing of recovery from neuromuscular blockade. In addition, a subjective assessment of the intubating conditions was recorded for each patient. This type of assessment is most useful as an indicator of poor conditions and efficacy failure. However, in some cases when muscle relaxation is good, the intubating conditions may be considered poor if unexpected anatomical obstacles to laryngoscopic visualization are encountered.

In open-label Study 021048, patients were randomized to receive either bolus doses (0.15 mg/kg) or a continuous infusion (2-5 mcg/kg/min; 0.1 to 0.3 mg/kg/hr) of Zemuron as maintenance neuromuscular blockade. Maintenance neuromuscular blockade was defined as the dose needed to maintain one or two twitches following recovery to reappearance of T3 after 0.6 mg/kg of Zemuron (or 1.0 mg for patients having a rapid sequence induction) as an initial dose administered to facilitate intubation. The total dose of Zemuron administered as maintenance was used for the primary analysis. This endpoint is clinically relevant as an estimate of the rate

at which Zemuron will be needed to provide an adequate level of relaxation for surgery. Additional analyses included the time to recovery of T4/T1 ratio to 70%, 80% and 90% after the end of the Zemuron maintenance regimen, the maximum block and the onset time to maximum block.

6.1.3 Study Design

The two study reports submitted were intended to fulfill a Pediatric Written Request to provide additional data in pediatric/adolescent patients receiving Zemuron.

Study 1. (021049) A randomized, assessor-blinded, dose-ranging, multicenter trial evaluating three different intubating doses of Zemuron (0.45 mg/kg, 0.6 mg/kg or 1.0 mg/kg) on the intubating conditions and time course of block in pediatric and adolescent patients scheduled to undergo surgery under general anesthesia.

The anesthetic regimen was standardized to control the possible synergy between Zemuron and general anesthetics in causing neuromuscular blockade. Sevoflurane 2.0 – 2.5 MAC to up to 7%-8% inspired concentration in 0%-70% nitrous oxide was used for induction of anesthesia until loss of consciousness. At loss of consciousness, nitrous oxide at 0%-70% and sevoflurane of only up to 5% end tidal concentration was administered. Sevoflurane was to be continued until the endotracheal tube was placed. In term neonates only, anesthesia was induced with propofol if rapid sequence intubation was clinically indicated. Depth of anesthesia was to be sustained with inhalation of isoflurane (1.0+0.2% expired end tidal concentration) in 0%-70% nitrous oxide.

Patients were enrolled from the following age groups: term neonates (birth to <28 days old), infants (28 days to ≤3 months), toddlers (>3 months to ≤2 years old), children (>2 to ≤11 years of age) and adolescents (>11 to ≤17 years of age). Of the 207 patients enrolled, 201 were enrolled after major amendments to the protocol, and an additional sixteen patients were discontinued before receiving Zemuron.

The ITT analysis was conducted on 185 patients according to the following distribution by age and dose:

Table 6.1.3-1 ITT Analysis Population: Patients Who Received Zemuron and at Least One Efficacy Assessment

	Number in Age Group					
Dose (mg/kg)	**Neonates**	**Infants**	**Toddlers**	**Children**	**Adolescents**	**Totals**
0.45	5	9	17	14	18	63
0.6	7	6	16	21	16	66
1.0	6	5	15	16	14	56
Totals	18	20	48	51	48	185

In the ITT population, five adolescents exceeded the stipulated maximum age requirement ranging from 17.1 to 17.7 years.

The primary endpoint was: Time to reappearance of T3 (time from end-administration of Zemuron to reappearance of the third twitch of TOF stimulation).

Other endpoints were:

• Onset time (time to maximum block);
• Maximum block (descriptive only; twitch height of three consecutive T1 values with no further decrease);
• Time to reappearance of T1 (time from end-administration of Zemuron to reappearance of the first twitch of a TOF stimulation).
• Recovery to TOF 0.7 (time from end-administration of Zemuron until recovery of T4/T1 ratio = 70%);
• Recovery to TOF 0.8 (time from end-administration of Zemuron until recovery of T4/T1 ratio = 80%);
• Recovery to TOF 0.9 (time from end-administration of Zemuron until recovery of T4/T1 ratio = 90%);
• Intubation score (descriptive only), which was to be based on the Viby-Mogensen Scale, a subjective scale previously utilized for labeling descriptions of intubating conditions.

Study 2. (021048) An open-label, randomized, multicenter trial evaluating maintenance Zemuron dose requirements in pediatric patients scheduled to undergo surgery under general anesthesia. As defined for Study 021049, eligible patients ranging in age from neonate to adolescent were randomized to one of the two Zemuron maintenance treatment groups: continuous infusion or supplemental bolus doses. The maintenance Zemuron regimen began at the reappearance of T3 following an initial 0.6 mg/kg bolus dose of Zemuron administered to all patients to facilitate intubation. At the reappearance of T2, subjects in each age group randomized to receive a continuous infusion, were administered Zemuron at an initial rate of 10 mcg/kg/min (0.6 mg/kg/hr) and then adjusted approximately to 2-5 mcg/kg/min (0.1-0.3 mg/kg/hr) every three minutes until one or two twitches were maintained. At the reappearance of T3, patients randomized to maintenance bolus dosing received 0.15 mg/kg bolus doses of Zemuron.

The anesthetic regimen was identical to that used for Study 1 (021049) except that caudal analgesia with a local anesthetic was also specifically permitted. Caudal anesthesia does not interfere with assessment of neuromuscular blockade assessed on the upper limbs and blood levels of local anesthetic remain low with this technique.

The ITT analysis was conducted on 137 patients according to the following distribution according to treatment group and patient age.

Table 6.1.3-2 ITT Analysis Population: Patients Who Received Zemuron and at Least One Efficacy Assessment

		Number in Age Group					
Treatment Arm		**Neonates**	**Infants**	**Toddlers**	**Child**	**Adolescents**	**Totals**
Bolus		5	6	18	18	17	64
Infusion		5	6	19	23	20	73
Totals		10	12	37	41	37	137

In the ITT population, two adolescents exceeded the stipulated maximum age requirement ranging from 17.7 to 17.9 years.

The primary endpoint was: The total dose of Zemuron from the reappearance of T3 after last maintenance bolus dose or discontinuation of infusion.

Other endpoints were:

- 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
- time of maximum block
- maximum block

6.1.4 Efficacy Findings

The findings from the ITT population in Study 021049, found in the Appendix of this review, demonstrated wide interpatient variability in the time to reappearance of T3. Similar interpatient variability in the time to reappearance of T1 was noted. The effect of increasing dose was to increase the maximum latency to T1 and T3, particularly among neonates and infants. The data for T4/T1 ratios equal to 70, 80 and 90% were incomplete. However, the same trends noted for recovery of T3 was noted for these parameters in the data that was available. The longest recovery times were observed in neonates and infants. The fastest recovery was observed in children. The onset time of neuromuscular blockade ranged from under a minute to more than two minutes among neonates and sometimes exceeded one minute in infants at the lowest dose (0.45 mg/kg). Nearly all patients achieved a maximum block of 100% and among those that did not reach 100%, the maximum block was only deficient by a few percent. These results indicate that Zemuron was efficacious as a neuromuscular blocking agent in all age groups. The subjective evaluation of intubating conditions did not indicate that increasing the dose also improved intubating conditions.

The findings from the ITT population in Study 021048, found in the Appendix of this review, indicate the range of maintenance dosing from the intubating dose to the time to reappearance of T3. The cumulative dose of Zemuron and the rate of Zemuron administration were similar for infants and neonates and between bolus and infusion regimens for these age groups. Across age groups, the total dose and rate of Zemuron administration was lowest in neonates and infants and highest in children. Among children and adolescents, the total dose and rate of Zemuron administration was slightly lower for continuous infusions than for bolus administration.

Data to evaluate secondary endpoints were limited especially among neonates and infants because of the small numbers of patients who were allowed to spontaneously recover from neuromuscular blockade. Among the child and adolescent study groups, recovery from a maintenance infusion was more expedient than for bolus dosing.

6.1.5 Clinical Microbiology

No clinical microbiology information was included in this submission.

6.1.6 Efficacy Conclusions

Zemuron is efficacious as a neuromuscular blocking agent in the pediatric population, including neonates and infants below the age of three months. All patients studied developed strong pharmacodynamic evidence of profound blockade as evidenced by achievement of a maximum block of nearly 100% in all patients. This degree of pharmacodynamic response is an unequivocal indicator of meaningful clinical paralysis when induced as an adjunct to general anesthesia and is more profound relaxation than is needed for mechanical ventilation.

Among parameters indicating dose-related increase in duration of an initial bolus dose of Zemuron, the variability between patients is more striking than the dose-related trend. This wide individual variability in duration of paralysis, as shown by the time to recovery of T3, is important clinical information especially in neonates and infants. These findings indicate that each patient must be individually monitored and assessed for residual paralysis. The duration of paralysis cannot be accurately predicted for pediatric patients based upon the duration of elapsed time after a dose of Zemuron. This means that the timing of supplemental doses and the amount of Zemuron likely to be required to complete a procedure must be individualized. It also indicates that careful consideration must be given to administering a pharmacological reversal agent for Zemuron to be certain that patients will not experience weakness in the immediate post-operative period that may impair spontaneous ventilation.

Following a bolus dose of Zemuron administered to facilitate intubation, the time of onset of paralysis varied from less than one minute to more than one minute among all age groups at all doses with the exception of infants administered 1.0 mg/kg. This suggests that Zemuron may not be reliable for a rapid sequence induction technique in the pediatric population. However, the risk-benefit relationship for this use will depend on each individual patient's comorbid conditions.

Among the child and adolescent groups studied with maintenance doses of Zemuron, there was a trend toward lower doses and faster recover with a continuous infusion compared to supplemental doses administered as boluses. However the trend is modest and individual variability was more pronounced than the trend related to the maintenance dosing regimen.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Sponsor's analysis of safety included an analysis of adverse events in each study (021049 and 021048) with stratification by age and other demographic groups. They Sponsor also pooled the adverse event data from these two studies and evaluated the incidence of adverse events according to the total dose of Zemuron administered. These data were further integrated with the adverse event data from 15 legacy trials conducted worldwide. The combined dataset was analyzed according to the subsets of pediatric patients who were in intensive care during treatment.

The Sponsor's analysis of 021049 and 021048 included an analysis of changes in vital signs such as heart rate and blood pressure with boundary conditions for adverse event reporting that were specified in the protocol. Changes to the electrocardiogram were also reported, with particular attention to the QTc interval. However, all patients studied were also exposed to concomitant medications, such as halogenated inhalational anesthetics, that are believed to increase the QTc.

The Sponsor also specifically evaluated ventilatory compliance in Studies 021049 and 021048 for changes associated with Zemuron because other nondepolarizing neuromuscular blocking agents (Rapalon) are associated with increased airways resistance.

An analysis of safety of neostigmine was conducted by the Sponsor because neuromuscular blockade was pharmacologically reversed with neostigmine in many patients participating in Studies 021049 and 021048.

This reviewer's analysis focused on adverse events reported among patients in Studies 021049 and 021048 in comparison to adverse events previously reported in the product label and in the AERS database. Common changes in vital signs and ventilatory compliance were also evaluated. A detailed analysis of the Sponsor's QTc findings was not conducted because the studies were not adequately designed to enable the findings to be related to Zemuron. The studies were also not intended to evaluate safety of neostigmine and there were insufficient data to evaluate safety of this product.

7.1.1 Deaths

There were no deaths among the patients studied in 021049 or 021048.

7.1.2 Other Serious Adverse Events

In Study 021049, there were three serious adverse events during the trial period where administration of Zemuron was intended to result in neuromuscular blockade.

1. Infant, 0.45 mg/kg: Patient 120301 had a cardiac arrest, associated with a cardiac catheterization for a ventricular septal defect. The patient was resuscitated.

2. Toddler, 0.45 mg/kg: Patient 102406 was diagnosed with post-procedural hemorrhage approximately 8 hours after administration of the intubating dose of Zemuron, or 4 hours after surgery for cleft lip and nose repair. The patient recovered 2 hours later.

3. Child, 0.6 mg/kg: Patient 105503 had 2 SAEs: cerebrospinal fistula and lymphocele. Both SAEs were diagnosed during the surgical procedure for excision and debulking of right orbital mass. The patient recovered 3 days later.

This reviewer's evaluation of the case reports for these reported SAEs is that the events were not related to Zemuron.

In the Study 021049 post-trial period, when neuromuscular blockade associated with Zemuron had resolved, there were four additional SAEs.

1. Neonate, 0.45 mg/kg: Patient 115206 had a diagnosis of ventricular septal defect and 3rd degree atrioventricular block. The patient recovered with sequelae.

2. Neonate, 0.6 mg/kg: Patient 108403 developed signs of dyspnea on post procedure day 2 and recovered the following day.

3. Toddler, 0.6 mg/kg: Patient 122606 had pneumonia. The patient recovered.

4. Adolescent 0.45 mg/kg: Patient 122201, 3 SAEs Abscess in the surgical incision, E. coli sepsis and suspected cholangitis. The patient recovered.

This reviewer evaluation is that the reported events were not related to Zemuron.

In Study 021048, there were no serious adverse events during the trial period where administration of Zemuron was intended to result in neuromuscular blockade.

One patient had a serious adverse event in the post-trial period. Patient 430001, a toddler who received bolus doses of Zemuron developed a pot-operative wound infection beginning 5 days after surgery for a cleft lip. The patient recovered. This reviewer's evaluation is that the reported event was unrelated to Zemuron.

7.1.3 Dropouts and Other Significant Adverse Events

One patient (104503, a child treated with 0.45 mg/kg) was discontinued from Study 021049 because of "bucking" on the endotracheal tube approximately 38 minutes after administration of Zemuron. Maximum block (100%) was achieved approximately 37 minutes prior to the onset of

the adverse event. This reviewer's evaluation is that the event was unrelated to administration of Zemuron.

No patient was discontinued from Study 021048 because of an adverse event.

7.1.4 Other Search Strategies

Review of the AERS database revealed 41 reports from 38 unique patients. The highest incidence of reported adverse events was patients with prolonged block. The following table indicates the incidence of adverse events grouped according to the age distributions used in Studies 021048 and 021049.

Table 7.1.4-1 Incidence of Adverse Events Associated with Zemuron Reported in AERS

	Prolonged Block	**Reduced Effectiveness**	**Cardiac Arrest**	**Anaphylactic Reactions**	**Blood Pressure Fluctuation**	**Release of Muscle Proteins**
Neonates	3	0	1	0	0	0
Infants	2	0	1	0	0	0
Toddlers	0	0	1	0	1	0
Children	2	4	3	2	0	2
Adolescents	4	1	0	5	2	1
Totals	**11**	**5**	**6**	**7**	**3**	**3**

Events such as paralysis, dyspnea or prolonged blockade were listed together as "Prolonged Block" because the events are likely to be related to prolonged neuromuscular blockade. "Reduced Effectiveness" includes events such as drug tolerance. The patients listed under "Cardiac Arrest" included cases of circulatory collapse and bradycardia requiring chest compressions. It was not always possible to differentiate anaphylactic from anaphylactoid reactions from the case narratives. Therefore, all cases of similar presentation were grouped together as "Anaphylactic Reactions". "Blood Pressure Fluctuations" were more commonly hypertensive episodes rather than events of hypotension. Cases with reported elevations in creatine phosphokinase, rhabdomiolysis, or a putative diagnosis of malignant hyperthermia are listed in the column "Release of Muscle Proteins".

7.1.5 Common Adverse Events

In Study 021049 the adverse events occurring in at least 5% of patients were:

Table7.1.5-1 Study 021049: Common Adverse Events

	Neonates		**Infants**		**Toddlers**		**Children**		**Adolescents**		**Totals**
Dose	**N**	**n with AE**	**N**	**n with AE**	**N**	**n with AE**	**N**	**n with AE**	**N**	**n with AE**	**n with AE (%)**
Procedural Pain											
0.45 mg/kg	**5**	0	**9**	0	**18**	3	**16**	2	**18**	4	9 (14)

	Neonates		Infants		Toddlers		Children		Adolescents		Totals
Dose	N	n with AE	N	n with AE	N	n with AE	N	n with AE	N	n with AE	n with AE (%)
0.6 mg/kg	**7**	1	**6**	1	**16**	2	**21**	3	**16**	4	11 (17)
1.0 mg/kg	**6**	1	**5**	1	**15**	2	**16**	3	**15**	3	10 (18)
Vomiting											
0.45 mg/kg	**5**	0	**9**	0	**18**	1	**16**	1	**18**	2	4 (6)
0.6 mg/kg	**7**	1	**6**	0	**16**	0	**21**	2	**16**	2	5 (8)
1.0 mg/kg	**6**	0	**5**	0	**15**	2	**16**	2	**15**	3	7 (12)
Procedural Hypotension											
0.45 mg/kg	**5**	3	**9**	0	**18**	0	**16**	0	**18**	0	3 (5)
0.6 mg/kg	**7**	3	**6**	0	**16**	0	**21**	0	**16**	0	3 (5)
1.0 mg/kg	**6**	2	**5**	0	**15**	0	**16**	0	**15**	0	2 (4)
Nausea											
0.45 mg/kg	**5**	0	**9**	0	**18**	0	**16**	0	**18**	0	0
0.6 mg/kg	**7**	0	**6**	0	**16**	1	**21**	1	**16**	1	3 (5)
1.0 mg/kg	**6**	0	**5**	0	**15**	0	**16**	0	**15**	2	2 (4)

Adapted from the Sponsor's Study Report Table 8.1.3-A.1, page 1129. The percentage noted in the"Totals" column is the number of adverse events reported within each dosage group.

The small number of patients in each category makes it difficult to establish any type of dose-related relationship.

In Study 021048 the common adverse events reported were as follows:

Table7.1.5-2 Study 021048: Common Adverse Events

	Neonates		Infants		Toddlers		Children		Adolescents		Totals
Treatment Group	N	n with AE	N	n with AE	N	n with AE	N	n with AE	N	n with AE	n with AE (%)
Procedural Pain											
Bolus	**5**	0	**6**	0	**18**	3	**18**	3	**17**	3	9 (14)
Infusion	**5**	0	**6**	0	**19**	2	**23**	2	**20**	5	9 (12)
Vomiting											
Bolus	**5**	0	**6**	0	**18**	0	**18**	2	**17**	0	2 (3)
Infusion	**5**	0	**6**	0	**19**	0	**23**	0	**20**	0	0
Hypercapnia											
Bolus	**5**	0	**6**	0	**18**	0	**18**	0	**17**	0	0
Infusion	**5**	0	**6**	0	**19**	0	**23**	0	**20**	2	2 (3)
Nausea											
Bolus	**5**	0	**6**	0	**18**	0	**18**	0	**17**	0	0
Infusion	**5**	0	**6**	0	**19**	0	**23**	0	**20**	2	2 (3)

Adapted from the Sponsor's Study Report Table 8.1.3-A.1, page 1246. The percentage noted in the"Totals" column is the number of adverse events reported within each dosage group.

In these studies, any procedural complication associated with injection of Zemuron may have been encoded as Procedural Pain. This includes I.V. infiltration.

The overall assessment of the safety data in this submission was that the safety profile was consistent with the current label, that there were no serious adverse events attributable to Zemuron, and that the common adverse events observed did not demonstrate an exposure-response relationship.

7.1.6 Less Common Adverse Events

In Study 021048, an adolescent (infusion maintenance, patient 117603) had tachycardia (cardiac disorders) and hypertension (vascular disorders) beginning 2 minutes and 4 minutes, respectively, after the dose of Zemuron (0.6 mg/kg) given to facilitate intubation. The investigator attributed this adverse event to Zemuron.

7.1.7 Laboratory Findings

Laboratory parameters were not assessed.

7.1.8 Vital Signs

Ventilatory Compliance
Clinically significant abnormal changes: A total of 5 subjects had a clinically significant change in ventilatory setting during the in-trial period, including 3 neonates (0.6 mg/kg, 1 subject; 1.0 mg/kg, 2 subjects) and 2 children (0.6 mg/kg, both subjects). All 3 neonates had a decrease in SaO2 (-16%, -28% and -8%, respectively) due to difficulty with intubation and transesophageal echocardiogram probe pressing on chest. Changes in children included a decrease in FiO2 levels (-38%) and an increase in ETCO2 levels (change 33 mmHg), due to "subject breathing on own" and hypoventilation, respectively.

Total ventilatory compliance: Within each age group, mean total ventilatory compliance values were generally comparable across post-intubation assessments. No dose-dependent relationship between Zemuron intubating dose and mean total ventilatory compliance was seen. Across age groups, mean total ventilatory compliance values increased with age at each of the time points assessed.

Age-dependent differences were seen in blood pressure and heart rate. Mean systolic and diastolic blood pressure values were generally higher in older age groups, while mean heart rate values were lower in children and adolescents.

Blood pressure: Overall, the percentage of subjects across age groups with clinically significant abnormal blood pressure values was small. No consistent pattern of mean change from baseline in blood pressure values was seen 1-30 minutes post intubating dose of Zemuron. There was no dose-dependent relationship between Zemuron intubating dose and blood pressure.

Heart rate: Few neonates and infants showed clinically significant abnormal high heart rate; whereas clinically significant abnormal high heart rate values across treatment groups were seen

in 22%-40% of toddlers, 19%-48% of children and 33%-56% of adolescents. One patient exhibited a clinically significant abnormally low heart rate.

- Neonates: In the 0.45 mg/kg or 0.6 mg/kg groups, no clinically meaningful change from baseline was seen from 1 to 30 minutes post-intubating dose of Zemuron. In the 1.0 mg/kg group, an increase in median change from baseline was seen with the largest change at 2 minutes post intubation (19 bpm).
- Infants: In the 0.45 mg/kg group, no clear effect on heart rate was seen. Generally, in the 0.6 mg/kg and 1.0 mg/kg groups, an increase in median change from baseline was seen at 3 minutes post-intubating dose (16.5 bpm and 17 bpm, respectively).
- Toddlers, children and adolescents: In each age group, no dose-dependent relationship between Zemuron intubating dose and heart rate was seen. There was a trend for median change from baseline values to increase over time, with the greatest median change seen approximately 3-5 minutes post-intubating dose of Zemuron (range across intubating dose: toddlers, 14-24 bpm; children, 15-24 bpm; adolescents, 21-30 bpm).

7.1.9 Electrocardiograms (ECGs)

An analysis of the effects of Zemuron on ECG measurements was conducted in Studies 021049 and 021048. Results suggest that increased QTc occurs with concomitant anesthesia and Zemuron, at bolus doses of 0.45 mg/kg, 0.6 mg/kg and 1.0 mg/kg, followed by maintenance treatment. Anesthesia was administered simultaneously with Zemuron, both the anesthetics and their doses were changed during Zemuron treatment and ECGs were not performed immediately upon Zemuron administration. A PK-PD analysis based on combined data from 021048 and 021049 indicated that QTc prolongation following Zemuron® administration was unrelated to rocuronium plasma concentrations.

7.1.10 Immunogenicity

No new studies of immunogenicity were submitted.

7.1.11 Human Carcinogenicity

No new studies of human carcinogenicity were submitted.

7.1.12 Special Safety Studies

No new studies of special safety studies were submitted.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No new studies of withdrawal or abuse potential were submitted.

7.1.14 Human Reproduction and Pregnancy Data

No new studies of human reproduction or pregnancy were submitted.

7.1.15 Assessment of Effect on Growth

No new studies of effect on growth were submitted.

7.1.16 Overdose Experience

In studies 020148 and 021049, 1 child (Trial 021048, bolus maintenance, Subject 119505) had an overdose of the bolus maintenance dose of Zemuron. This subject received a 1.5 mg/kg bolus maintenance dose of Zemuron® at the reappearance of T3, instead of the protocol recommended 0.15 mg/kg dose, which was reported as an AE. Maximum intensity was mild and the subject recovered without any action taken. No other AEs except this overdose were reported for this subject.

7.1.17 Postmarketing Experience

This reviewer evaluated pediatric reports in the AERs database with findings as described in Section 7.1.4.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The distribution of patients by demographic group for Studies 021049 and 021048 are listed in the following tables.

Table 7.2.1-1 Demographic Distributions in Study 021049

	Neonates n = 18	**Infants** n = 20	**Toddlers** n = 49	**Children** n = 53	**Adolescents** n = 49	**Totals** N= 189
Dose						
0.45 mg/kg	5	9	18	16	18	66
0.6 mg/kg	7	6	16	21	16	66
1.0 mg/kg	6	5	15	16	15	57
Race						
White	15	18	42	37	41	153
Black	2	1	5	14	7	29
Asian	1	1	2	2	1	7
Gender						
Male	15	14	35	26	28	118
Female	3	6	14	27	21	71

Table 7.2.1-2 Demographic Distributions in Study 021048

	Neonates n = 10	**Infants** n = 12	**Toddlers** n = 37	**Children** n = 41	**Adolescents** n = 37	**Totals** N = 137
Treatment Arm						
Bolus	5	6	18	18	17	64
Infusion	5	6	19	23	20	73
Race						
White	9	11	33	33	34	120
Black	1	0	1	3	2	7
Asian	0	1	3	4	1	9
Pacific Islander	0	0	0	1	37	137
Gender						
Male	6	8	30	22	18	84
Female	4	4	7	19	19	53

The racial demographic distribution was biased toward patients identified as white and included a predominance of male patients in the neonatal, infant and toddler age groups. The gender bias is consistent with the general surgical population because of the higher incidence of urological procedures performed.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

This reviewer evaluated pediatric reports in the AERs database with findings as described in Section 7.1.4. The AERs database consisted of 41 reports from 38 unique pediatric patients from September 19, 1994 through January 10, 2007.

7.2.3 Adequacy of Overall Clinical Experience

The extent of exposure indicated in the studies submitted in terms of the number of patients studied and their distribution according to dose, age, race and gender is adequate for a safety evaluation of Zemuron administration in the pediatric population.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal or in vitro testing was performed.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of patients in Studies 021049 and 021048 was adequate to define the safety profile associated with Zemuron administration to pediatric patients.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Analysis of pharmacokinetic data collected in Studies 021048 and 021049 were analyzed using 2 and 3 compartment population pharmacokinetic models. A single pharmacokinetic model could describe the pharmacokinetics of Zemuron in pediatric patients. All model parameters were proportional to body weight. An additional age effect on central volume of distribution was found. The observed QTc prolongation following Zemuron administration was unrelated to rocuronium plasma concentrations.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The evaluation of safety of Zemuron was adequate for the new pediatric populations studied (neonates and infants below the age of 3 months).

7.2.8 Assessment of Quality and Completeness of Data

The general quality and completeness was acceptable. Site inspection by the Division of Scientific Investigations indicated that protocol violations did not affect the conclusions drawn from the Sponsor's data.

7.2.9 Additional Submissions, Including Safety Update

No additional material was submitted.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The population studied was generally representative of the pediatric population expected to be exposed in practice. The adverse event profile for Zemuron in the studied pediatric population was consistent with the label. In these studies there were no serious adverse event attributed to Zemuron and common events did not demonstrate dose-relationship. It is also noteworthy that a quantitative analysis performed to evaluate a possible effect of Zemuron on ventilatory compliance did not reveal an adverse effect associated with the drug. In summary, although the number of neonatal and infants studied is small, it is expected to be sufficient to detect a major safety signal. Therefore, based upon the available data this reviewer concludes that Zemuron is safe for administration to pediatric patients including neonates and infants.

7.4 General Methodology

The most severe adverse events associated with administration of nondepolarizing neuromuscular blocking drugs are typically related to changes in heart rate, signs of increased airway resistance and hypotension associated with anaphylaxis. Therefore, this reviewer

specifically focused evaluation of the adverse event database on these areas. Studies 021049 and 021048 were evaluated separately because the extent of exposure differed in each study. Furthermore, the patient populations were somewhat different because patients enrolled in Study 021048 tended to have longer procedures than the patients in Study 021049.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Because of differences in study protocol that may have been expected to change adverse event reporting, safety data was evaluated for each study. For example, repeat bolus injection or a continuous infusion maybe expected to have an increase incidence of venous irritation compared to symptoms following a single bolus. A dose-related comparison was possible only for Study 012049 because of the blinded study design. Evaluation of serious adverse events was based upon pooled data for both studies and trends in common adverse events were compared between studies.

7.4.2 Explorations for Predictive Factors

In general, the few adverse events limited the meaningfulness of explorations for dose dependency, time dependency, drug disease interactions or drug-drug interactions. Study 021049 enabled an analysis of dose dependency of adverse events because of the dose-ranging study design. However, the small number of adverse events in each dosing category indicates that an apparent finding of dose dependency for adverse events of procedural pain, vomiting or procedural hypotension may also be influenced by surgical events unrelated to Zemuron that contribute to apparent trend.

7.4.3 Causality Determination

No dose-relationship to an incidence in adverse events was established. Trends in certain events that are common to the surgical procedure or route of administration could not be established because of the few patients who experienced these adverse events i.e., procedural pain and vomiting.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

All proposed doses for single bolus administration were effective. Individual variability in response to Zemuron necessitates individualized monitoring and assessment. Higher doses were associated with a higher duration of action among the patients having the longest duration of action in each age group. Efficacy was not established for maintenance dosing regimens because of the nature of the study design. However, maintenance dosing of Zemuron appeared to be safe in appropriately monitored patients and resulted in persistent pharmacodynamic signs of neuromuscular blockade.

8.2 Drug-Drug Interactions

No drug-drug interactions were evaluated or identified.

8.3 Special Populations

No special populations besides the pediatric population were studied.

8.4 Pediatrics

The submitted studies were of pediatric patients only.

8.5 Advisory Committee Meeting

No Scientific Advisory Committee review of this submission was conducted.

8.6 Literature Review

A general review of the medial literature indicated that the proposed dosing is consistent with current clinical practice.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan was proposed by the Sponsor.

8.8 Other Relevant Materials

No other materials were reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data contained in this submission indicates that Zemuron is safe and effective at the dosing proposed by the Sponsor.

9.2 Recommendation on Regulatory Action

The product labeling should be revised to include dosing information for the neonatal and infant patient populations.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are recommended.

9.4 Labeling Review

The changes to the label proposed by the Sponsor in this submission include changes to the following sections:

Dosage and Administration (2.5)
Use in Specific Populations (8.4)
Clinical Pharmacology (12.2) (12.3)
Clinical Studies (14.3)
Pediatric patients
Warnings and Precautions (5.1) (5.5)

Proposed revisions to Warning s and Precautions Sections relate to cases of residual paralysis and myopathies described in reports published in the medical literature and are not a consequence of findings of the studies conducted in response to the Pediatric Written Request.

Reviewer's comment: The Sponsor's proposals are, in general, acceptable. However, the proposed statements regarding the effect of Zemuron on the QT interval should be modified as an exception. The study of Zemuron on the EKG did not conform to the requirements for a thorough QT study and included concomitant anesthetic agents that are believed to prolong the QT interval. The pharmacokinetic-ECG pharmacodynamic analysis suggesting that Zemuron was not responsible for observed QT prolongation should not be used as evidence of safety in the product label.

10 APPENDICES

10.1 Review of Individual Study Reports

Study Protocol 021048: Sponsor's Response to Pediatric Written Request Study 2

Title: An open-label, randomized, phase IIIB, multicenter trial to evaluate the pharmacodynamic parameters of intubation bolus, and bolus and infusion maintenance doses of Zemuron in pediatric and adolescent patients.

Clinical Trial Objectives:

Primary objective:
To determine the dose requirements of Zemuron, when administered as a bolus dose for intubation and when administered by either continuous infusion or bolus doses for maintenance.

Secondary objectives:
1. To evaluate the spontaneous recovery time to 70%, 80%, and 90% of T4/T, ratio from the reappearance of T3 after the termination of Zemuron infusion or after the last maintenance bolus dose in term neonates, infants and toddlers, children, and adolescent patients.
2. To determine the onset times of a bolus intubating dose of Zemuron in term neonates, infants and toddlers, children, and adolescent patients.
3. To collect sparse samples for population pharmacokinetic analysis.
4. To evaluate safety data of intubation and maintenance doses of Zemuron".

Study Design: randomized, open-label, uncontrolled

Population: N=120
Age group: not fewer than 20 nor more than 30 patients each:
1. term neonates (birth to < 28 days old),
2. infants and toddlers (28 days to ≤ 23 months old),
3. children (2 years to ≤ 11 years of age), and
4. adolescents (12 years to s 17 years of age)

Inclusion criteria:
1. Males or non-pregnant (determined by urine or serum HCG test), non-nursing females from birth to ≤ 17 years of age; and
2. Patients of ASA Class 1, 2, or 3 scheduled for surgery with an anticipated duration of anesthesia of about 2 hours or more requiring a maintenance muscle relaxation dose(s).

Exclusion criteria:

1. Age > 17 years or preterm neonates (< 37 weeks gestational age at birth);
2. Congenital anomalies or airway obstructions that would preclude visualization or intubation of the trachea;
3. Known significant renal or hepatic disorders determined by medical history, physical examination, or laboratory tests;
4. Known or suspected of having neuromuscular disorders;
5. Known or suspected of having personal or family history of malignant hyperthermia;
6. Known or suspected of having allergy to narcotic analgesics, hypnotics, neuromuscular blocking agents, or other medications used during general anesthesia;
7. Pre-trail medications (systemic corticosteroids, anticonvulsants, aminoglycosides, macrolides or polypeptide antibiotic) or in-trial (systemic corticosteroids, anticonvulsants, aminoglycosides, macrolides or polypeptide antibiotic) during the in-trial period in a dose regimen known to modify the action of neuromuscular blocking agents;
8. Pneumatic tourniquet during the surgical procedure;
9. Participation in another clinical trial not preapproved by Organon within 30 days before this trial;
10. Patients who have already participated in this trial; or
11. Patients whose parent(s) or legal guardian(s) are not willing to give written consent and where applicable, the subject has not given appropriate assent to participate in accordance with the current revision of the Declaration of Helsinki, the ICH
12. Guidelines for Good Clinical Practice and current FDA regulations.

Trial medication, dose schedule, and mode of administration:

• Zemuron (rocuronium bromide) Injection supplied in colorless 10 mL vials containing 100 mg (10 mg/mL) of rocuronium bromide.

• Each patient is be randomized to receive either infusion maintenance or bolus maintenance dose(s) of Zemuron. After a bolus intubating dose of 0.60 mg/kg or 1.0 mg/kg of Zemuron (for neonatal rapid sequence intubation only), maintenance Zemuron doses are to be administered by either intravenous continuous infusion starting at a rate of 10 pg/kg/min or by bolus doses of 0.15 mg/kg.

• The bolus dose of Zemuron will be administered within 5 seconds into a fast running venous infusion. The amount of Zemuron administered would be based on the actual body weight.

Schematic:

Preanesthetic preparation:

Patients may receive pre-operative medications prior to induction if clinically

necessary.

Induction of general anesthesia:
• Inhalation: Anesthesia will then be induced with sevoflurane, 2.0 - 2.5 MAC (up to 7% - 8% inspired concentration), and 0% - 70% nitrous oxide until loss of consciousness, at which time sevoflurane will be reduced (down to 5% end-tidal concentration). Sevoflurane will be continued only until the endotracheal tube has been in place.

Or

• Intravenous: The term neonate group may also be induced with propofol (1 - 3 mg/kg) if clinically indicated for rapid sequence intubation. Fentanyl, 1 - 3 pg/kg, may also be administered if clinically necessary.

Maintenance anesthesia:
Following induction with sevoflurane, patients are to receive a single intravenous bolus dose of Zemuron, 0.60 mg/kg, for intubation. However, those patients who received propofol for induction will be administered a single intravenous bolus dose of Zemuron, 1.0 mg/kg, for intubation. When the endotracheal tube is in place, sevoflurane and propofol will be discontinued and a mixture of isoflurane with 0% - 70% nitrous oxide will be started to achieve 0.8 - 1.2% expired end-tidal concentration of isoflurane. At the investigator's discretion, propofol may also be administered at 50 - 200 pg/kg/min in addition to isoflurane.

Efficacy Assessment:
Patients in each of the age groups randomized to continuous infusion maintenance will receive Zemuron at the reappearance of T2 at an initial rate of 10 pg/kg/min for maintenance of neuromuscular blockade. The infusion will be adjusted to approximately 2.0 - 5.0 pg/kg/min every three minutes until one or two twitches are maintained. Patients in each of the age groups randomized to bolus dose maintenance will receive 0.15 mg/kg bolus dose of Zemuron at the reappearance of T3. Subsequent maintenance bolus dose(s) will be administered at the reappearance of T3 after the administration of the previous bolus dose.

Neuromuscular parameters will be evaluated by monitoring acceleromyographic (AMG) responses to TOF stimulation using the TOF-Watch SX. Neuromuscular monitoring will start after induction of anesthesia, but before the administration of Zemuron and will continue until there is a spontaneous stable neuromuscular recovery (up to 90% T4/T1 ratio). Pharmacodynamic parameters to be recorded are the following:

- maximum block
- time of maximum block;
- time of reappearance of T2 after the intubating dose, for patients randomized to the continuous infusion maintenance group;
- time of reappearance of T3 after the intubating dose, for patients randomized to the

bolus dose maintenance group;
- time of spontaneous reappearance of T3 after the last maintenance bolus dose of Zemuron or discontinuation of Zemuron infusion; and
- time from spontaneous reappearance of T3 after the last maintenance bolus dose of Zemuron or discontinuation of Zemuron infusion to 70%, 80%, and 90% recovery of T4/T1 ratio.

(Onset time is defined as the elapsed time from the end of the administration of Zemuron until the maximum block is achieved.)

Primary Efficacy Endpoint:

The total dose from administration of intubating dose to the time of reappearance of T3 after the last maintenance bolus dose of Zemuron, or discontinuation of Zemuron infusion.

Secondary Efficacy Endpoints:

Time from spontaneous reappearance of T3 after the last maintenance bolus dose of Zemuron or discontinuation of Zemuron infusion to:
- 70%, recovery of T4/T1 ratio
- 80%, recovery of T4/T1 ratio
- 90% recovery of T4/T1 ratio

Safety Assessment:

Physical examination including vital signs determinations will be performed prior to surgery. ECG, vital signs, pulse oximetry, Fi02 and ETC02 are to be monitored continuously. The incidence of pre-treatment signs and symptoms and adverse events will be assessed.

Cardiovascular assessments will be performed and recorded using routine anesthetic monitoring of the subject's heart rate (HR), systolic blood pressure, diastolic blood pressure, and arterial oxygen percent saturation (Sa02) in pulse oximetry. The blood pressure cuff should not be on the same arm as the monitor of neuromuscular function. Baseline values of Sa02, fraction of inspired oxygen (Fi02) and end-tidal carbon dioxide (ETC02) will be recorded on the CRF. Inspired oxygen concentration(Fi02) and ETC02 will be monitored but only clinically significant changes that require intervention or medication will be recorded including changes in Fi02 levels to $\leq 25\%$ and changes in ETC02 levels to $\leq 25\%$ or $\geq 50\%$. Electrocardiographic (ECG) assessments will be performed at specific time points. Adverse events will also be recorded throughout the trial period.

Heart rate (HR), systolic and diastolic blood pressures (SBP/DBP), and arterial oxygen percent saturation (Sa02) will be monitored and recorded at the following time points:

- prior to induction of anesthesia;
- just prior to administration of intubating dose;
- at 1, 2, 3, 4, 5, 10, 15, 20, 25, and 30 minutes after the administration of the intubating dose; and
- every 15 minutes thereafter until 2 hours after the last maintenance bolus dose or until 2 hours after discontinuation of maintenance infusion.

HR and SBP/DBP values obtained just prior to administration of intubating dose (post-induction) of Zemuron will be considered baseline values and clinically significant changes that require intervention or medication will be monitored and recorded on the CRF. In order to be identified as clinically significant change, a HR, SBP or DBP value during the clinical trial would need to meet absolute criterion value and also represent a relative change of at least the magnitude noted in the change column (Sponsor's Table 12.6, pp. 85 of their protocol) of the age-specific criteria for clinically significant abnormal values.

Clinically significant changes in Sa02 levels that require intervention or medication will be recorded on the CRF including changes in Sa02 levels to less than 87% in neonates and to < 90% in infants and toddlers, children, and adolescents. Twelve-lead electrocardiographic assessments (investigator may use six-lead ECG when the physical requirements demand) will be performed at the following time points:

- prior to administration of pre-operative medications (at least one baseline assessment is required and, if possible, a total of three baseline assessments, about five minutes apart);
- after induction of anesthesia.
- at 2, 10, and 30 minutes after the intubating dose.
- For patients randomized to the bolus dose maintenance group, an ECG assessment will be performed at 2, 10, and 30 minutes after every maintenance dose of Zemuron and at 60 and 120 minutes after the last maintenance bolus dose of Zemuron.
- For patients randomized to the continuous infusion maintenance group, an ECG assessment will be performed at 2, 10, and 30 minutes after the start of the Zemuron infusion, every 30 minutes during the Zemuron infusion and at 60 and 120 minutes after discontinuation of the Zemuron infusion.

Telephone calls will be made by the investigator's staff to each parent or legal guardian no earlier than the seventh day after surgery to determine if SAEs have occurred and to determine the status of AEs that were still present at the end of the in-trial period.

Pharmacokinetic Assessment:

Sparse blood samples will be collected for determination of rocuronium pharmacokinetics in the pediatric/adolescent population. The investigators were instructed to obtain, a total of four blood

samples from 40 selected patients (10 term neonates, 10 infants/toddlers, 10 children, and 10 adolescents). Each sample will have at least 0.5 mL for term neonates and 1.0 mL for all other age groups. For patients randomized to the continuous infusion maintenance group, sample #1 will be taken prior to the intubating dose, sample #2 will be taken two minutes after administration of the intubating dose, sample #3 will be taken just prior to administration of the continuous maintenance infusion, and sample #4 will be taken at 60 minutes or 120 minutes after termination of the continuous maintenance infusion. For patients randomized to the bolus dose maintenance group, sample #1 will be taken prior to the intubating dose, sample #2 will be taken two minutes after the administration of the intubating dose, sample #3 will be taken just prior to administration of the first maintenance bolus dose, and sample #4 will be taken at 60 minutes or 120 minutes after the last maintenance bolus dose. The pharmacokinetic data obtained will contribute to a population pharmacokinetic analysis.

Statistics: Sample size is based upon clinical considerations rather than statistical calculations. Statistical analysis will be descriptive rather than inferential, although the Sponsor plans to examine the effect of age on treatment effect of Zemuron and examine changes in electrocardiographic QT interval using statistical methods.

Duration of treatment: Peri-operative.

Amendments:

1. *February, 2004*

The protocol was modified:

- To determine onset times of an intubating bolus dose of Zemuron in term neonates, infants and toddlers, children, and adolescents and to schedule and evaluate electrocardiographic assessments at specified time points during the trial,
- To revise Sections 3 and 4, Clinical Trial Design, to accommodate the necessary study design changes as indicated in the PWR;
- To revise Section 6, Statistical and Analytical Methods, to accommodate the necessary changes for the statistical analyses as consistent with the PWR;
- To revise the list of investigators and centers;
- To revise the exclusion criteria and the list of Organon study personnel and;
- To include any administrative changes (addition of CRO name/address, addition of CRA fax numbers, etc.).

2. *April, 2004*

The protocol was modified:

- To revise Section 4.8, Hazards and precautions, to include indications and possible complications of rapid sequence intubation;
- To transfer and file the Neuromuscular Transmission Monitoring Guidelines for Protocol 021048 with the TOF-Watch_ SX and TOFMON program from the protocol to the Trial Documentation File (TDF) so that all current versions of the guidelines are included in the TDF;
- To update the list of references;

- To revise the clinical trial start and completion;
- To revise the case report forms by standardizing the pages for the project;
- To include any administrative changes (e.g., replacing the term newborn(s) with neonate(s), revising the list of Organon personnel, correcting misspelled drug names); and
- To accommodate requests by IRBs for a Clinical Trial Protocol with Amendments 1 and 2 Inclusive whereby changes laid down in Amendment 1 (dated February 2004) and Amendment 2 (dated April 2004) were incorporated into the protocol.

3. June, 2004

The protocol was modified:

- To revise the exclusion criteria by incorporating suggestions of participating investigators;
- To standardize the start time of administration of the intubating dose of the neuromuscular blocking agent for the project;
- To revise the clinical trial start and completion;
- To revise the list of investigators and external committees by indicating the replacement of one investigational site with another new site;
- To standardize the collection times of sparse samples for population pharmacokinetic analysis for the project;
- To revise the list of Organon personnel;
- To revise the case report forms by incorporating changes in the exclusion criteria and blood sampling and standardizing the reporting of FiO2; and
- To accommodate requests by IRBs for a final copy of the Clinical Trial Protocol 021048 with Amendments 1, 2 and 3 Inclusive whereby changes laid down in Amendment 1 (February, 2004), Amendment 2 (April, 2004) and Amendment 3 (June, 2004) were incorporated to the Clinical Trial Protocol (October, 2003).

4. August, 2004

The protocol was modified:

- To revise the case report form in compliance with the new US Food and Drug Administration (FDA) directive regarding the collection and recording of race and ethnicity data in clinical trials;
- To revise the clinical trial start and completion;
- To revise the list of Organon personnel; and
- To accommodate requests by IRBs for a final copy of the Clinical Trial Protocol with Amendments 1, 2, 3, and 4 Inclusive whereby changes laid down in
- Amendment 1 (February, 2004), Amendment 2 (April, 2004), Amendment 3 (June, 2004), and Amendment 4 (August, 2004) were incorporated to the Clinical
- Trial Protocol (October, 2003).

5. July, 2005

The protocol was modified:

- To exclude the use of intravenous lidocaine and glycopyrrolate, and specifically predefine the use of fentanyl for induction and maintenance of

anesthesia
- To redefine the age groups for patients included in this clinical trial
- To permit the direct measurements of the ventilatory parameters, which will allow to calculate and evaluate the ventilatory compliance
- To include the measurement of the central body temperature
- To revise the directions in the protocol for induction with sevoflurane and the description of boundary conditions for SAO2 and ETCO2
- To clarify the description of the reduction of sevoflurane after intubation
- To remove from the protocol the list of investigators and centers
- To revise the procedures and the fax numbers for reporting SAEs
- To revise the blood sampling schedules
- To revise the clinical trial start and completion dates

6. September, 2005

The protocol was modified:
- To include reporting of Medical Device Reporting (MDR) reportable events

7. November, 2005

The protocol was modified:
- To specifically predefine the use of local anesthetics as a component of the pre-medication regimen and during the In-trial period
- To define the duration of the induction of anesthesia
- To revise the direction for the administration of Zemuron for intubation
- To revise the directions for obtaining measurements of the ventilatory parameters
- To revise the description of boundary conditions for SaO2
- To include a recommendation for establishing a dedicated I.V. line to be used for obtaining pharmacokinetic blood sampling
- To include a requirement for obtaining the acceptable practice neuromuscular recordings before neuromuscular transmission evaluation in trial patients
- To revise the clinical trial completion date
- To revise contact phone number the pharmacokinetic samples receiving officer
- To revise the address for shipment of the pharmacokinetic samples
- To revise and specify that the newest versions of the TOF-Watch SX and the Neuromuscular Transmission Monitoring Guideline for Clinical Studies to be used in the study

8. January, 2006

The protocol was modified:
- To indicate that non-US centers would not be conducting trial 021048 under the IND
- To pre-specify criteria for defining perturbation in vital signs and ECG as adverse events
- To revise the clinical trial completion date

9. September, 2006

The protocol was modified:

- To indicate that the sites from Argentina will be involved in clinical trial 021048, and to update the information on the number of sites participating in the study;
- To add the use of epidural/caudal anesthesia to general anesthesia;
- To revise the clinical trial completion date.
- To revise the Cardiovascular Assessments Case Report Form to make it agree with the revised protocol.

10. September, 2007

The protocol was modified:

As a result of a meeting on September 4th with FDA regarding the Pediatric Written Request (PWR), FDA asked for additional data regarding recovery from muscle paralysis after administration of Zemuron, which was not collected as part of the case report forms designed for this study but should be available on the anesthesia records of the participating patients. Specifically, FDA requested extubation times of each of the participants in trial 021048.

Conduct of the Trial:

Major revisions to the protocol were introduced in Protocol Amendments 5, 6 and 7, which substantially altered trial conditions and assessment parameters. The trial was temporarily suspended during this period, and re-initiated after Protocol Amendment 8 to enroll the number of patients originally recommended by the FDA in the PWR (N=120).

After Amendment 5 (July 2005)

A total of 131 patients were enrolled and randomized in the trial after Amendment 5, including 63 patients in the bolus maintenance group and 68 patients in the infusion maintenance group. By age group, 12 neonates (5, bolus; 7 infusion), 13 infants (8, bolus; 5, infusion), 32 toddlers (15, bolus; 17, infusion), 39 children (18, bolus; 21, infusion) and 35 adolescents (17, bolus; 18, infusion) were randomized.

A total of 120 patients were treated with Zemuron, including 57 patients in the bolus maintenance group and 63 patients in the infusion maintenance group; of the randomized patients, 11 discontinued prior to treatment with Zemuron. By age group, 10 neonates (5, bolus; 5 infusion), 11 infants (6, bolus; 5, infusion), 31 toddlers (15, bolus; 16, infusion), 35 children (16, bolus; 19, infusion) and 33 adolescents (15, bolus; 18, infusion) were treated.

A total of 116 patients enrolled after Amendment 5 completed the trial. Four patients discontinued the trial after treatment with Zemuron.

Before Amendment 5 (July 2005)

A total of 18 patients were randomized in the trial prior to Amendment 5, including 8 patients in the bolus maintenance group and 10 patients in the infusion maintenance group. By age group, 1 infant (infusion), 6 toddlers (3, bolus; 3, infusion), 7 children (3, bolus; 4 infusion) and 4 adolescents (2, bolus; 2, infusion) were randomized. Of the 18 randomized patients, 17 received Zemuron; one subject (child, bolus maintenance [440001]) was discontinued from the trial before receiving Zemuron.

Key findings are tabulated below:

Table 6.1.4-2 Summary of the Total Zemuron Maintenance Dose from ITT Population in Study 021048

	Age group and treatment group(Zemuron maintenance)									
	Neonate		Infant		Toddler		Child		Adolescent	
Summary statistic	Bolus (N=3)	Infusion (N=5)	Bolus (N=5)	Infusion (N=2)	Bolus (N=14)	Infusion (N=15)	Bolus (N=16)	Infusion (N=19)	Bolus (N=15)	Infusion (N=16)
Total dose(mg)										
n	3	5	5	2	14	15	16	19	15	16
Mean(SD)	2.74(0.64)	3.08(1.18)	4.14(1.01)	4.80(2.24)	7.88(2.05)	8.36(2.93)	16.07(7.85)	28.60(30.13)	52.44(18.08	56.07(28.63)
Median	2.70	3.10	4.40	4.80	7.50	7.97	15.13	21.23	47.50	47.90
Min-max	2.12-3.40	1.87-4.87	2.80-5.40	3.21-6.38	5.25-12.80	4.36-16.25	9.20-42.00	7.14-145.5	28.40-99.75	26.74-121.5
Total dose(mg/kg)										
n	3	5	5	2	14	15	16	19	15	16
Mean(SD)	0.91(0.17)	1.01(0.37)	0.78(0.07)	0.85(0.17)	0.87(0.17)	0.91(0.13)	0.89(0.33)	1.15(0.77)	0.96(0.16)	1.05(0.46)
Median	0.87	0.91	0.75	0.85	0.82	0.92	0.75	0.99	0.91	0.92
Min-max	0.76-1.10	0.71-1.62	0.74-0.90	0.73-0.97	0.72-1.35	0.70-1.14	0.75-2.10	0.63-4.10	0.75-1.35	0.66-2.23
Total dose(mg/kg/hr)*										
n	3	3	4	1	11	12	15	17	13	14
Mean(SD)	0.34(0.09)	0.35(0.13)	0.53(0.13)	0.37(0.00)	0.58(0.15)	0.55(0.29)	0.84(0.27)	0.69(0.25)	0.57(0.15)	0.57(0.12)
Median	0.30	0.34	0.47	0.37	0.55	0.45	0.86	0.67	0.57	0.57
Min-max	0.28-0.45	0.22-0.48	0.44-0.71	0.37-0.37	0.42-0.87	0.17-1.23	0.45-1.30	0.23-1.15	0.30-0.84	0.39-0.76
Total maintenance dose(mg)										
n	3	5	5	2	14	15	16	19	15	16
Mean(SD)	0.94(0.54)	1.26(1.11)	0.98(0.40)	1.50(1.25)	2.41(1.58)	2.87(1.54)	5.43(6.80)	15.11(27.45)	19.33(9.54)	24.03(25.96)
Median	0.90	1.10	0.90	1.50	1.75	2.65	3.50	7.88	20.00	14.00
Min-max	0.42-1.50	0.37-3.07	0.60-1.60	0.61-2.38	1.05-7.10	0.93-6.25	1.80-30.00	0.34-124.2	7.00-42.75	3.93-88.50

From Sponsor's Study Report Table 6.1.A, page 1104

Table 6.1.4-3 Summary of Time to Recovery T4/T1 Ratio (70%, 80%, 90%) Data in ITT Population in Study 021048

	Age group and treatment group(Zemuron maintenance)									
	Neonate		Infant		Toddler		Child		Adolescent	
Summary statistic	Bolus (N=3)	Infusion (N=5)	Bolus (N=5)	Infusion (N=3)	Bolus (N=17)	Infusion (N=18)	Bolus (N=18)	Infusion (N=23)	Bolus (N=17)	Infusion (N=18)
Recovery to TOF 0.7										
n	2	3	4	2	13	12	17	19	13	15
Mean(SD)	29.62(13.60	43.42(1.53)	33.25(16.17)	35.75(3.54)	24.48(8.00)	25.71(13.02)	18.11(7.16)	18.21(11.55)	27.17(12.54)	28.35(14.03)
Median	29.62	43.75	26.75	35.75	24.50	24.62	15.25	15.00	27.23	23.00
Min-max	20.00-39.23	41.75-44.75	22.50-56.98	33.25-38.25	8.50-38.00	10.50-49.50	8.50-34.50	7.00-54.25	12.75-55.25	13.00-56.50
Recovery to TOF 0.8										
n	2	3	3	1	12	12	15	19	13	12
Mean(SD)	36.62(17.14	57.83(12.33)	43.58(21.47)	44.75(0.00)	35.44(15.26)	32.60(16.19)	22.73(9.52)	21.79(13.36)	34.69(18.23)	33.71(17.32)
Median	36.62	53.50	33.50	44.75	34.13	33.38	20.75	18.28	32.23	31.13
Min-max	24.50-48.73	48.25-71.75	29.00-68.23	44.75-44.75	10.75-69.00	12.25-59.50	9.75-46.00	9.25-61.50	16.25-77.00	14.50-71.00
Recovery to TOF 0.9										
n	1	1	3	1	11	12	11	17	9	11
Mean(SD)	28.25(0.00)	52.25(0.00)	53.66(14.58)	50.75(0.00)	49.62(21.41)	41.35(18.64)	25.48(10.44)	27.68(19.01)	46.47(28.66)	37.44(15.81)
Median	28.25	52.25	45.75	50.75	48.00	43.87	22.25	21.25	36.00	35.50
Min-max	28.25-28.25	52.25-52.25	44.75-70.48	50.75-50.75	13.25-95.00	14.25-71.00	11.00-47.75	11.75-76.75	21.00-98.48	21.25-69.48

From Sponsor's Study Report Table 6.1.2.A.3, page 1108.

Study Protocol 021049: Sponsor's Response to Pediatric Written Request Study 1

Title: A randomized, assessor-blind, dose-ranging, phase IIIB, 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 patients under general anesthesia.

Clinical Trial Objectives:

Primary objective:
To evaluate the time interval between the end of administration of the Zemuron intubating dose and the reappearance of T3 following one of three intubating doses of Zemuron (0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg) in term neonates, infants and toddlers , children, and adolescents .

Secondary objectives:
1. To evaluate the time course of action (onset time, maximum block, reappearance of T1, and recovery to 70%, 80% and 90% T4/T1,) following one of three intubating doses of Zemuron (0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg) in term neonates, infants and toddlers, children, and adolescent patients.
2. To evaluate the intubating conditions following one of three intubating doses of Zemuron (0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg) in term neonates, infants and toddlers, children, and adolescent patients.
3. To collect sparse samples for population pharmacokinetic analysis.
4. To evaluate safety data of three different intubating doses of Zemuron (0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg).

Study Design: randomized, controlled, assessor blinded

Population: N=180
Definition of each age group:
1. term neonates (birth to < 28 days old),
2. infants and toddlers (28 days to ≤ 23 months old),
3. children (2 years to ≤ 11 years of age), and
4. adolescents (12 years to ≤ 17 years of age)

Inclusion criteria

1. Males or non-pregnant (determined by urine or serum HCG test), non-nursing females from birth to ≤ 17 years of age; and
2. Patients of ASA Class 1, 2, or 3 scheduled for surgery under general anesthesia.

Exclusion criteria

1. Age > 17 years or preterm neonates (< 37 weeks gestational age at birth);
2. Congenital anomalies or airway obstructions that would preclude visualization or intubation of the trachea;
3. Known significant renal or hepatic disorders determined by medical history, physical examination, or laboratory tests;
4. Known or suspected of having neuromuscular disorders;
5. Known or suspected of having personal or family history of malignant hyperthermia;
6. Known or suspected of having allergy to narcotic analgesics, hypnotics, neuromuscular blocking agents or other medications used during general anesthesia;
7. Pre-trial medications (systemic corticosteroids, anticonvulsants,
8. Aminoglycosides, macrolides or polypeptide antibiotic) or in-trial medications (systemic corticosteroids, anticonvulsants, aminoglycosides, macrolides or polypeptide antibiotic) dose regimen known to modify the action of neuromuscular blocking agents;
9. Pneumatic tourniquet during the surgical procedure;
10. Participating as research patients in another clinical trial not preapproved by Organon within 30 days before this trial;
11. Patients who have already participated in this trial; or Patients whose parent(s) or legal guardian(s) are not willing to give written consent and where applicable, the subject has not given appropriate assent to participate in accordance with the current revision of the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice and current FDA regulations.

Trial medication, dose schedule, and mode of administration:
Zemuron (rocuronium bromide) Injection 10 mg/mL (in 10 mL vials containing 100 mg rocuronium) without benzyl alcohol will be supplied. A single IV Zemuron bolus dose of 0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg is to be administered to each subject.

Schematic:
The trial will consist of a pre-trial period, an in-trial period, and a post-trial period. Medications administered during the clinical trial other than those required for anesthesia will be recorded as concomitant medications on the CRF.

Pre-trial period (Preanesthetic preparation):
Medications taken within 24 hours prior to surgery will be recorded as pre-trial medications on the Medication CRF. Patients may be premedicated (e.g., atropine or glycopyrrolate) before induction of anesthesia, if clinically indicated. Fentanyl at 1-3 mg/kg may be administered to provide analgesia if clinically necessary. Lidocaine may be administered for prevention of pain on injection. Lidocaine should not be administered epidurally.

In-trial Period:
Induction of general anesthesia:
The in-trial period starts at the time of induction and ends when there is a stable neuromuscular recovery (up to T4/T1 ratio of 90%), at the administration of another muscle relaxant, or a reversal agent, whichever occurs first in patients providing only efficacy and safety data. For those in the PK evaluation, it ends at the collection of the

last blood sample and a stable neuromuscular recovery (T4/T1 ratio of 80%) has been obtained. ECG assessment will be performed, blood sample for pharmacokinetic analysis will be drawn, and HR, SBP/DBP and Sa02 will be determined during the in-trial period.

• Inhalation: The baseline neuromuscular exam will include three responses to TOF stimulation that vary from the first by a target of <10% during a stable end-tidal % of sevoflurane. Zemuron is to be administered within a target window of 5-10 minutes after loss of consciousness. The randomized dose of Zemuron (0.45 mg/kg, 0.6 mg/kg, or 1.0 mg/kg) is to be administered as an I.V. bolus over 5 sec close to the vein into a fast flowing infusion line. Start and end times of Zemuron administration will be recorded on the CRF. Intubation will be attempted by 90 sec following the administration of Zemuron. If intubation is not possible by 90 sec, a second attempt will be made by 150 sec following administration.

Or

• Intravenous: In term neonates only, anesthesia may also be induced with propofol (1-3 mg/kg), if clinically indicated (rapid sequence intubation for patients who are at risk of aspiration of gastric contents). Lidocaine may be administered for prevention of pain on injection. Intubation should be attempted at 60 sec following administration of Zemuron. If intubation is not possible at 60 sec, a second attempt will be made at 90 sec following administration.

Intubation conditions will be assessed as described by Viby-Mogensen et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anesthesiologica Scaninavica 40:59-74, 1996. described in Table 1. below.

Maintenance anesthesia:
Following intubation, maintenance of anesthesia may be initiated. Depth of anesthesia will be sustained with inhalation of isoflurane (1.0±0.2% expired end-tidal concentration) in 0-70% nitrous oxide. Anesthetic concentrations will be maintained for the entire duration of time that pharmacodynamic parameters are measured. The initially set expired end-tidal concentration of isoflurane should be maintained in a range not exceeding ± 0.2%. If clinically indicated, however, the expired end-tidal concentration of isoflurane may be adjusted outside of this range. If clinically indicated, patients may also receive propofol in addition to isoflurane. Patients may also receive any opioid, bupivicaine, lidocaine, acetaminophen, or a combination of these agents, to provide perioperative analgesia. Neither lidocaine nor bupivicaine should be administered epidurally during the entire period that pharmacodynamic parameters are measured.

Maintenance of muscle relaxation and recovery:
Patients are to be allowed to recover to 80% T4/T, and, if possible, 90% T4/T, after receiving Zemuron before any maintenance dose of another muscle relaxant or any reversal agent is administered. The neuromuscular data is to be recorded on the CRF.

No further neuromuscular data will be recorded after receiving a maintenance dose of a muscle relaxant or reversal agent.

Post-trial period:
The post-trial period starts when there is a stable neuromuscular recovery (up to 90% of T4/T, ratio), or at the administration of a maintenance dose of a muscle relaxant, or at the administration of a reversal agent, whichever occurs first, in patients providing only efficacy and safety data and ends after the seventh post-operative day follow-up. For those in the pharmacokinetic evaluation, the post-trial period starts at the collection of the last blood sample and a stable neuromuscular recovery of T4/T, ratio of 80% has been obtained and ends after the seventh post-operative day follow-up

Efficacy Assessment:

Neuromuscular parameters will be evaluated by monitoring acceleromyographic (AMG) responses of the adductor pollicis to TOF stimulation using the TOF-Watch SX. Neuromuscular monitoring will start after induction of anesthesia, but before the administration of Zemuron and will continue until there is a spontaneous stable neuromuscular recovery (up to 90% T4/T, ratio). A temperature sensor will be affixed on the palm of the hand for recording of the temperature.

Primary Efficacy Endpoint:

- Time to reappearance of T3 (time from end-administration of Zemuron to reappearance of the third twitch of a TOF stimulation).

Secondary Efficacy Endpoints:

- Onset time (time to maximum block);
- Maximum block (descriptive only; twitch height of three consecutive T1 values with no further decrease);
- Time to reappearance of T, (time from end-administration of Zemuron to reappearance of the first twitch of a TOF stimulation).
- Recovery to TOF 0.7 (time from end-administration of Zemuron until recovery of T4/T1 ratio = 70%);
- Recovery to TOF 0.8 (time from end-administration of Zemuron until recovery of T4/T1 ratio = 80%);
- Recovery to TOF 0.9 (time from end-administration of Zemuron until recovery of T4/T1 (ratio = 90%);
- Intubation score (descriptive only), which is to be based on the Viby-Mogensen scale. (From Viby-Mogensen, J. et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anesthesiologica Scaninavica 40:59-74, 1996.)

Table 1. Viby-Mogensen Intubation Assessment Scale

	CLINICALLY ACCEPTABLE		UNACCEPTABLE
	EXCELLENT	GOOD	POOR
VOCAL CORD POSITION	Abducted	Intermediate	Closed
VOCAL CORD MOVEMENT	None	Moving	Closing
EASE OF LARYNGOSCOPY[2]	Easy	Fair	Difficult
AIRWAY	None	Diaphragm	Sustained>10 sec
LIMB	None	Slight	Vigorous

Intubation conditions
Excellent: All qualities rated excellent
Good: All qualities rated either excellent or good
Poor: The presence of a single quality rated as poor.

Laryngoscopy
Easy: Jaw relaxed, no resistance to blade in the course of laryngoscopy
Fair: Jaw not fully relaxed, slight resistance to blade
Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy

- Pharmacokinetic assessments:
  Blood samples for determination of rocuronium are to be taken from 60 selected patients (10 at each study site).

Number of patients in each age group for pharmacokinetic sampling
1. 12 patients, term neonates (birth to < 28 days old),
2. 12 patients, infants and toddlers (28 days to ≤23 months old),
3. 18 patients, children (2 years to ≤11 years of age), and
4. 18 patients, adolescents (12 years to ≤17 years of age)
Each subject will be assigned to one of the eight sampling schemes presented in Table 2.

Table 2. Time points of pharmacokinetic blood sampling

Target time points for blood sampling (time in minutes relative to Zemuron® administration)				
newborn	pre-dose	2	15	120
	pre-dose	4	30	60
Infant/toddler	pre-dose	2	30	120
	pre-dose	4	15	60
child	pre-dose	2	15	60
	pre-dose	4	30	120
adolescent	pre-dose	2	30	120
	pre-dose	4	30	120
	pre-dose	4	30	120
Sample no.	1	2	3	4

A maximum of four blood samples is to be obtained from each of the patients selected for pharmacokinetic blood sampling. The first sample will be taken prior to administration (pre-dose sample) and three subsequent samples will be drawn at specified target points post administration of the intubation dose of Zemuron□.

- Physical examination including vital signs determinations will be performed prior to surgery. ECG, vital signs, pulse oximetry, Fi02 and ETC02 are to be monitored continuously.

Table 3. Assessments

Time of Assessment	Medical History	Physical Exam	CV Measurements	TOF	Intubation Scores	Ventilatory Compliance	AEs SAES	ECG	PK Sampling
Pre-surgery	X	X	X					X	
Before muscle relaxant			X	X[a]			X		X
After intubation dose				X[a]	X	X	X	X	
1,2, 3, 4,5, 10, 15, 20, 25, 30 min post intubation dosing			X				X		
2, 10, and 30 minutes after the intubating dose							X	X	
Selected times post intubation dose							X		Xb

a Train-of-Four is recorded continually throughout the protocol. Baseline measurements (three stable Train-of-Four responses) are made prior to giving Zemuron".
b PK sampling is to be done in 50 selected patients at specified times

- Unsuccessful (clinically unacceptable) intubation, either first or second attempt, should be reported to Organon Pharmaceuticals USA Inc. on the same day. After two incidences of failed intubations within one of the age categories, all relevant data from each site should be evaluated. Based on this evaluation, the decision may be made to discontinue a treatment arm (e.g., by restricting a dose up to a certain age, or by restricting a dose if used in combination with a specific anesthetic) in that age category.

- Respiratory events that require pharmacological or nonpharmacological intervention, including altering anesthesia depth, Fi02 or altering ventilation mode or settings will be documented. Ventilatory noncompliance is to be measured as any significant changes to the ventilator mode or settings apart from the initial settings.

- Cardiovascular assessments will be performed and recorded using routine anesthetic monitoring of the subject's heart rate (HR), systolic blood pressure, diastolic blood pressure, and arterial oxygen percent saturation (Sa02) in pulse oximetry. HR and SBP/DBP values obtained just prior to administration of intubating dose (post-induction) of Zemuron will be considered baseline values and clinically significant changes that require intervention or medication will be monitored and recorded on the CRF. In order to be identified as clinically significant change, a HR, SBP or DBP value during the clinical trial would need to meet absolute criterion value and also represent a relative change of at least the magnitude noted in age-specific criteria for clinically significant abnormal values.

- Clinically significant changes in Sa02 levels that require intervention or medication will be recorded on the CRF including changes in Sa02 levels to less than 87% in neonates and to < 90% in infants and toddlers, children, and adolescents.

- Twelve-lead electrocardiographic assessments (investigator may use six-lead ECG when the physical requirements demand) will be performed at the following time points:

    • prior to administration of pre-operative medications (at least one baseline assessment is required and, if possible, a total of three baseline assessments, about five minutes apart);
    • after induction of anesthesia.
    • at 2, 10, and 30 minutes after the intubating dose of Zemuron

  QT correction will be performed using Bazett's correction for heart rate as the primary measurement and Fridericia's correction as the secondary measurement. Telephone calls will be made by the investigator's staff to each parent or legal guardian no earlier than the seventh day after surgery to determine if SAEs have occurred and to determine the status of AEs that were still present at the end of the in-trial period. Statistics: HR and QTc interval data will be analyzed statistically using two-sided testing with p-values less than or equal to 0.05 being considered statistically significant. P-values will be interpreted in an exploratory sense. Regression analysis will be used to assess HR and QTc recorded at the pre-dose point and at 2 minutes

post-intubation as a function of the plasma concentration.

Duration of treatment: Peri-operative.

Amendments:

1. September, 2004

The protocol was modified:
This protocol amendment modifies the list of investigators and study centers to reflect the change of the Principal Investigator at Site 6.

2. August , 2005

The protocol was modified:

- To exclude the use of intravenous lidocaine and glycopyrrolate, and specifically predefine the use of fentanyl for induction and maintenance of anesthesia
- To redefine the age groups for patients included in this clinical trial
- To permit the direct measurements of the ventilatory parameters, which will allow calculation and evaluation of the ventilatory compliance
- To include the measurement of the central body temperature
- To revise the directions for induction with sevoflurane and the description of boundary conditions for SaO2 and ETCO2
- To clarify the description of the reduction of sevoflurane after intubation
- To remove from the protocol the list of investigators and centers
- To revise the procedures and the fax numbers for reporting SAEs
- To revise the blood sampling schedules
- To revise the clinical trial start and completion dates
- To include reporting of Medical Device Reporting (MDR) reportable events

3. November, 2005

The protocol was modified:

- To specifically predefine the use of local anesthetics as a component of the pre-medication regimen and during the In-trial period
- To define the duration of the induction of anesthesia
- To revise the direction for the administration of Zemuron for intubation
- To revise the directions for obtaining measurements of the ventilatory parameters
- To revise the description of boundary conditions for SaO2
- To include a recommendation for establishing a dedicated I.V. line to be used for obtaining pharmacokinetic blood sampling
- To include a requirement for obtaining the acceptable practice neuromuscular recordings before neuromuscular transmission evaluation in trial patients
- To revise the clinical trial completion date
- To revise and specify that the newest versions of the TOF-Watch SX and the Neuromuscular Transmission Monitoring Guideline for Clinical Studies to be

used in the study

4. January, 2006

The protocol was modified:

- To indicate that non-US centers would not be conducting trial 021049 under the IND
- To include the assessment of appropriateness to initiate laryngoscopy at 60 seconds after administration of Zemuron
- To pre-specify criteria for defining perturbation in vital signs and ECGs as adverse events
- To specify that any signs of histamine release should be captured as adverse events
- To clarify how the assessor of intubation conditions should be blinded
- To revise the age-specific criteria for clinically significant abnormal values for cardiovascular parameters
- To revise the clinical trial completion date

5. September , 2006

The protocol was modified:

- To add the use of epidural/caudal anesthesia to general anesthesia;
- To revise the clinical trial completion date.
- To update the information on the number of sites participating in the study
- To revise the Cardiovascular Assessments Case Report Form to make it agree with revisions to of the protocol.

6. September, 2007

The protocol for the Germany-specific sites was modified:

As a result of a meeting on September 4th with FDA regarding the Pediatric Written Request (PWR), FDA asked for additional data regarding recovery from muscle paralysis after administration of Zemuron, which was not collected as part of the case report forms designed for this study but should be available on the anesthesia records of the participating patients. Specifically, FDA requested extubation times of each of the participants in trial 021049.

7. September, 2007

The protocol for the Belgium-specific sites was modified:

As a result of a meeting on September 4th with FDA regarding the Pediatric Written Request (PWR), FDA asked for additional data regarding recovery from muscle paralysis after administration of Zemuron, which was not collected as part of the case report forms designed for this study but should be available on the anesthesia records of the participating patients. Specifically, FDA requested extubation times of each of the participants in trial 021049.

Disposition of patients:

A total of 207 patients were enrolled.

A total of 201 patients were enrolled after amendment 2.

A total of 189 patients were treated with Zemuron.

Neonates	Infants	Toddlers	Children	Adolescents	Totals
18	20	49	53	49	189

The ITT population enrolled after protocol amendment 2 was used for efficacy analysis by this reviewer..

Neonates	Infants	Toddlers	Children	Adolescents	Totals
18	20	48	51	48	185

The per protocol population enrolled after amendment 2 was used by the Sponsor for their primary efficacy analysis. These patients had at least one major protocol violation. The protocol violations included receiving a dose of Zemuron outside the prespecified limits, use of concomitant medication prohibited by the protocol, use of isoflurane instead of sevoflurane for induction of anesthesia, use of isoflurane outside the prespecified range, and randomization schedule violations.

Neonates	Infants	Toddlers	Children	Adolescents	Totals
16	20	45	49	46	176

Key Findings:

Table 6.1.4-1 Summary of Pharmacodynamic Findings Supporting Efficacy From ITT Population in Study 021049

	Age group and treatment group								
	Neonate			Infant			Toddler		
Summary statistic	0.45mg/kg (N=5)	0.60mg/kg (N=7)	1.0mg/kg (N=6)	0.45mg/kg (N=9)	0.60mg/kg (N=6)	1.0mg/kg (N=5)	0.45mg/kg (N=17)	0.60mg/kg (N=16)	1.0mg/kg (N=15)
Reappearance of T3(*)									
n	5	6	2	8	6	3	16	15	13
Mean(SD)	46.11(12.65)	55.68(32.31)	114.43(30.91)	46.44(23.07)	62.34(20.36)	116.48(34.23)	35.66(10.98)	41.64(11.19)	73.00(25.13)
Median	40.27	50.37	114.43	49.08	57.87	103.30	39.15	41.42	71.95
Min-max	32.45-62.58	20.15-111.73	92.57-136.28	13.47-79.85	32.28-87.77	90.80-155.35	16.92-59.38	18.88-59.33	36.18-128.20
Onset time(*)(a)									
n	5	7	6	9	6	5	17	15	15
Mean(SD)	1.21(0.58)	1.10(0.67)	0.80(0.56)	0.69(0.35)	0.52(0.21)	0.41(0.19)	0.80(0.47)	0.67(0.30)	0.60(0.32)
Median	1.10	1.15	0.57	0.53	0.53	0.32	0.75	0.65	0.50
Min-max	0.58-2.17	0.32-2.07	0.33-1.82	0.35-1.25	0.23-0.82	0.23-0.70	0.32-1.92	0.27-1.55	0.23-1.52
Maximum block(%)									
n	5	7	6	9	6	5	17	16	15
Mean(SD)	99.00(2.24)	97.86(2.73)	100.00(0.00)	100.00(0.00)	99.50(1.22)	100.00(0.00)	100.00(0.00)	100.00(0.00)	100.00(0.00)
Median	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Min-max	95.00-100.00	94.00-100.00	100.00-100.00	100.00-100.00	97.00-100.00	100.00-100.00	100.00-100.00	100.00-100.00	100.00-100.00
Reappearance of T1(*)									
n	5	6	5	9	6	3	17	15	13
Mean(SD)	35.21(11.26)	40.80(23.70)	112.09(43.14)	37.55(19.97)	49.01(14.01)	94.08(16.54)	29.84(9.74)	35.36(9.60)	63.73(23.87)
Median	34.27	38.00	106.07	36.95	51.64	85.55	31.32	35.17	64.73
Min-max	20.67-47.08	14.40-83.98	71.32-180.65	8.97-69.35	24.53-67.52	83.55-113.15	15.83-54.38	16.13-50.23	29.43-118.45

From Sponsor's Study Report Table 6.1.1.A.1, page 941

Table 6.1.4-1 Summary of Pharmacodynamic Findings Supporting Efficacy from ITT Population in Study 021049 (Continued)

	Age group and treatment group					
	Child			Adolescent		
Summary statistic	0.45mg/kg (N=14)	0.60mg/kg (N=21)	1.0mg/kg (N=16)	0.45mg/kg (N=18)	0.60mg/kg (N=16)	1.0mg/kg (N=14)
Reappearance of T3(*)						
n	13	21	14	17	16	12
Mean(SD)	24.66(6.36)	38.25(11.28)	53.46(16.13)	38.22(13.96)	41.78(15.22)	62.59(18.84)
Median	21.45	38.20	53.09	37.48	41.66	67.09
Min-max	17.45-37.98	21.65-65.85	31.22-89.90	18.27-65.67	16.30-81.85	25.57-93.75
Onset time(*)(a)						
n	14	21	16	18	16	14
Mean(SD)	0.90(0.40)	0.86(0.33)	0.67(0.21)	1.12(0.37)	1.08(0.47)	0.76(0.21)
Median	0.88	0.85	0.69	1.03	1.06	0.72
Min-max	0.40-1.92	0.32-1.70	0.38-1.17	0.53-1.67	0.18-2.08	0.53-1.23
Maximum block(%)						
n	14	21	16	18	16	14
Mean(SD)	100.00(0.00)	100.00(0.00)	100.00(0.00)	100.00(0.00)	99.69(1.25)	100.00(0.00)
Median	100.00	100.00	100.00	100.00	100.00	100.00
Min-max	100.00-100.00	100.00-100.00	100.00-100.00	100.00-100.00	95.00-100.00	100.00-100.00
Reappearance of T1(*)						
n	13	21	16	17	16	14
Mean(SD)	20.35(5.24)	31.57(9.10)	48.00(14.70)	29.50(12.32)	33.09(12.93)	57.25(22.29)
Median	17.45	30.75	43.94	28.20	33.52	54.03
Min-max	14.95-30.23	17.90-54.60	28.47-78.15	13.77-58.42	12.55-67.35	20.82-100.82

From Sponsor's Study Report Table 6.1.1.A.1, page 942

Pediatric Written Request-Final

Type of studies:

Two or more studies to examine the efficacy, safety, dose response, and pharmacokinetics of rocuronium bromide in pediatric patients undergoing general anesthesia. General anesthesia will be induced with sevoflurane, and anesthesia maintenance will utilize isoflurane as the primary agent. Neonates (birth to less than 1 month of age) for whom rapid sequence induction is indicated may have general anesthesia induced with propofol. The onset, duration, and recovery profiles of intubation, maintenance bolus, and maintenance infusion doses other than those recommended currently in the approved package insert should be studied to provide guidance for the use of rocuronium bromide as a neuromuscular blocking agent in pediatric patients.

Study 1: A randomized, assessor-blind, dose-ranging, multicenter trial comparing the intubating conditions and time course of block for three different intubating doses (0.45 mg/mg, 0.6 mg/kg, and 1 mg/kg) of rocuronium bromide in pediatric (including adolescent) patients under general anesthesia.

Study 2: An open label, randomized, multicenter trial to evaluate the pharmacodynamic parameters of intubation bolus, and bolus and infusion maintenance doses of rocuronium bromide in pediatric and adolescent patients under general anesthesia.

Objectives:

The general objectives of these investigations are to:

- Evaluate the safety and effectiveness of rocuronium bromide in pediatric patients when using sevoflurane for induction and isoflurane for maintenance of general anesthesia. In neonates requiring a rapid sequence technique, propofol may be used for induction of general anesthesia.
- Evaluate the pharmacokinetics and dose response of rocuronium bromide in pediatric patients including those of less than 3 months of age.
- Evaluate maintenance dose requirements for rocuronium bromide by intravenous infusion and by intermittent intravenous bolus.
- Evaluate time course of action of rocuronium bromide after bolus maintenance doses and after the termination of maintenance infusions.

Age group in which stud(ies) should be performed:

All studies: ASA I-III pediatric patients from birth to 17 years of age.

Number of patients:

Study 1: 180 total, approximately equally randomized among the three dosage groups, with at least 25 total patients in the birth to less than 3 months age group, also approximately equally divided among the dosage groups. At least 3 neonates (birth to less than 1 month of age) will be randomized to each dosage group. A minimum of 15 neonates are to complete the study. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study 2: 120 total, approximately equally randomized between the two treatment arms, at least 10 total patients in the birth to less than 3 months age group, approximately equally divided between the treatment arms to include at least 3 neonates per treatment arm. The minimum number of patients required for each of the efficacy endpoints will be guided by a concurrent analysis of interpatient response variability.

Study Endpoints

Study 1:

Efficacy: Maximum block, onset time, reappearance of T1 and T3, spontaneous recovery to 70%, 80%, and 90% T4/T1, assessment of appropriateness to initiate laryngoscopy at 60 seconds (based upon twitch and clinical criteria, unless intubation is accomplished earlier than 60 seconds), time to intubation based on pre-specified standardized twitch and clinical criteria, intubating conditions

Safety: ECG, heart rate, blood pressure, pulse oximetry, clinical assessments of histamine release following drug administration, adverse events. Significant changes

in cardiovascular parameters during the study period or in ventilatory compliance during the study period should be recorded. "Significant changes" should be pre-defined and include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events will be monitored and recorded at least through discharge from the post-anesthetic care unit. Criteria for defining perturbations in vital signs and ECG as adverse events should be pre-specified.

Pharmacokinetics: Blood samples should be taken from patients in all age groups, including at least 10 patients less than 3 months of age. A minimum of 6 neonates will undergo blood sampling. At least 2 samples per subject should be taken: one immediately after drug administration and one just before administration of the dose to determine C_{max}, CL, and $AUC_{0-\infty}$.

Study 2:

Efficacy: Maintenance dose requirements, maximum block, time course of recovery (reappearance of T3, spontaneous recovery to 70%, 80%, and 90% T4/T1) after bolus doses or termination of infusion of rocuronium bromide.

Safety: ECG, heart rate, blood pressure, pulse oximetry, adverse events. Clinically significant changes in cardiovascular parameters (pre-defined) or ventilatory compliance during or following drug administration should be recorded. Significant events should include hemodynamic or respiratory events that require pharmacologic or non-pharmacologic intervention, including altering anesthesia depth, FIO_2, or altering ventilation mode or settings. Adverse events should be monitored and recorded at least through discharge from the post-anesthetic care unit.

Criteria for defining perturbations in vital signs and ECG as adverse events should be pre-specified.

Pharmacokinetics: Samples should be taken from patients in all age groups, including at least 10 patients less than 3 months of age. A minimum of 6 neonates will undergo blood sampling. At least 2 samples per subject should be taken: one immediately after drug administration and one just before administration of the next dose to determine C_{max}, CL, and $AUC_{0-\infty}$.

Drug information :

Dosage form: Rocuronium bromide 10 mg/mL (marketed product),

Dose: 0.45, 0.6, or 1 mg/kg

Route of administration: IV

Regimen:

Study 1:

After induction of anesthesia with N_2O/O_2 and sevoflurane (in neonates requiring rapid sequence induction, propofol may be used for induction instead of sevoflurane/nitrous oxide), isoflurane and nitrous oxide concentrations should be stabilized within a prespecified range of concentrations that will be standardized for all patients. Anesthetic concentrations should be maintained in this range for the duration of time that pharmacodynamic parameters are measured. This range should not exceed a span of greater than +0.2% end tidal isoflurane. Following stabilization, the device for assessment of the degree of neuromuscular blockade should be calibrated, and the assigned intubating dose of rocuronium bromide will be administered as a rapid bolus.

Study 2:

After induction of anesthesia, isoflurane and nitrous oxide concentrations should be stabilized within a prespecified range of concentrations that will be standardized for all patients. Anesthetic concentrations will be maintained in this range for the entire duration of time that pharmacodynamic parameters are measured. This range should not exceed a span of greater than +0.2% end tidal isoflurane. Following stabilization, the device for assessment of the degree of neuromuscular blockade will be calibrated, and a standard dose of rocuronium bromide should be administered as a rapid bolus. Adjunctive anesthetics (e.g., propofol, narcotics, thiopental, and benzodiazepines) may be given within pre-specified dose ranges as appropriate to provide optimal care.

Patients randomized to the bolus group will receive standardized rocuronium bromide bolus doses at the reappearance of T3. Patients randomized to the continuous infusion group will have the rocuronium bromide infusion begun at reappearance of T2 and titrated to maintain one or two twitches according to a pre-specified protocol. The protocol would call for assessment of neuromuscular blockage at fixed time intervals, with mandatory adjustments of the infusion rate in pre-specified increments according to the assessment result.

Statistical information, including power of study and statistical assessments:

Descriptive statistics will be presented by age and dose.

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

FORMAT OF REPORTS TO BE SUBMITTED:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. This report should conform with the *Guideline for Format and Content of Clinical and Statistical Sections of New Drug Applications* (July 1988) and ICH E3, *Structure and Content of Clinical Study Reports* (July 1996).

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDY(IES):

Reports of the above studies must be submitted to the Agency on or before January 13, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please keep in mind that pediatric exclusivity attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Errata: The report was to be in the following format as stated in amendment 3 to the Pediatric Written Request as requested in a letter from the Agency on June 25, 2008.

Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African America, Native Hawaiian, or other Pacific Islander or White. For ethnicity, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Lester Schultheis
7/17/2008 08:05:38 AM
MEDICAL OFFICER

Rigoberto Roca
7/17/2008 06:25:21 PM
MEDICAL OFFICER