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### **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

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

Treatment Arm	Number in Age Group						Totals
	Neonates	Infants	Toddlers	Child	Adolescents		
<b>Bolus</b>	5	6	18	18	17	64	
<b>Infusion</b>	5	6	19	23	20	73	
<b>Totals</b>	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. The 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 (Rapalox) 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 3<sup>rd</sup> 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 post-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

	<b>Prolonged Block</b>	<b>Reduced Effectiveness</b>	<b>Cardiac Arrest</b>	<b>Anaphylactic Reactions</b>	<b>Blood Pressure Fluctuation</b>	<b>Release of Muscle Proteins</b>
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
<b>Totals</b>	<b>11</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>3</b>	<b>3</b>

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, rhabdomyolysis, 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:

Table 7.1.5-1 Study 021049: Common Adverse Events

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

Dose	Neonates		Infants		Toddlers		Children		Adolescents		Totals
	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)
<i>Vomiting</i>											
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)
<i>Procedural Hypotension</i>											
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)
<i>Nausea</i>											
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:

Table 7.1.5-2 Study 021048: Common Adverse Events

Treatment Group	Neonates		Infants		Toddlers		Children		Adolescents		Totals
	N	n with AE	N	n with AE	N	n with AE	N	n with AE	N	n with AE	n with AE (%)
<i>Procedural Pain</i>											
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)
<i>Vomiting</i>											
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
<i>Hypercapnia</i>											
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)
<i>Nausea</i>											
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 SaO<sub>2</sub> (-16%, -28% and -8%, respectively) due to difficulty with intubation and transesophageal echocardiogram probe pressing on chest. Changes in children included a decrease in FiO<sub>2</sub> levels (-38%) and an increase in ETCO<sub>2</sub> 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						
<b>0.45 mg/kg</b>	5	9	18	16	18	66
<b>0.6 mg/kg</b>	7	6	16	21	16	66
<b>1.0 mg/kg</b>	6	5	15	16	15	57
Race						
<b>White</b>	15	18	42	37	41	153
<b>Black</b>	2	1	5	14	7	29
<b>Asian</b>	1	1	2	2	1	7
Gender						
<b>Male</b>	15	14	35	26	28	118
<b>Female</b>	3	6	14	27	21	71

Table 7.2.1-2 Demographic Distributions in Study 021048

	<b>Neonates</b> n = 10	<b>Infants</b> n = 12	<b>Toddlers</b> n = 37	<b>Children</b> n = 41	<b>Adolescents</b> n = 37	<b>Totals</b> N = 137
<b>Treatment Arm</b>						
<b>Bolus</b>	5	6	18	18	17	64
<b>Infusion</b>	5	6	19	23	20	73
<b>Race</b>						
<b>White</b>	9	11	33	33	34	120
<b>Black</b>	1	0	1	3	2	7
<b>Asian</b>	0	1	3	4	1	9
<b>Pacific Islander</b>	0	0	0	1	37	137
<b>Gender</b>						
<b>Male</b>	6	8	30	22	18	84
<b>Female</b>	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  $\leq$  23 months old),
3. children (2 years to  $\leq$  11 years of age), and
4. adolescents (12 years to  $\leq$  17 years of age)

##### **Inclusion criteria:**

1. Males or non-pregnant (determined by urine or serum HCG test), non-nursing females from birth to  $\leq$  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-trial 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, FiO<sub>2</sub> and ETCO<sub>2</sub> 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 (SaO<sub>2</sub>) in pulse oximetry. The blood pressure cuff should not be on the same arm as the monitor of neuromuscular function. Baseline values of SaO<sub>2</sub>, fraction of inspired oxygen (FiO<sub>2</sub>) and end-tidal carbon dioxide (ETCO<sub>2</sub>) will be recorded on the CRF. Inspired oxygen concentration (FiO<sub>2</sub>) and ETCO<sub>2</sub> will be monitored but only clinically significant changes that require intervention or medication will be recorded including changes in FiO<sub>2</sub> levels to  $\leq 25\%$  and changes in ETCO<sub>2</sub> 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 (SaO<sub>2</sub>) 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 SaO<sub>2</sub> levels that require intervention or medication will be recorded on the CRF including changes in SaO<sub>2</sub> 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<sub>SX</sub> 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 FiO<sub>2</sub>; 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 SAO<sub>2</sub> and ETCO<sub>2</sub>
- 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 SaO<sub>2</sub>
- 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

Summary statistic	Age group and treatment group (Zemuron maintenance)									
	Neonate		Infant		Toddler		Child		Adolescent	
	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

Summary statistic	Age group and treatment group (Zemuron maintenance)									
	Neonate		Infant		Toddler		Child		Adolescent	
	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  $\leq$  23 months old),
3. children (2 years to  $\leq$  11 years of age), and
4. adolescents (12 years to  $\leq$  17 years of age)

#### **Inclusion criteria**

1. Males or non-pregnant (determined by urine or serum HCG test), non-nursing females from birth to  $\leq$  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 SaO<sub>2</sub> 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 Scandinavica* 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, bupivacaine, lidocaine, acetaminophen, or a combination of these agents, to provide perioperative analgesia. Neither lidocaine nor bupivacaine 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 Scandinavica 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 <sup>2</sup>	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, FiO2 and ETCO2 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 <sup>a</sup>			X		X
After intubation dose				X <sup>a</sup>	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		X <sup>b</sup>

**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, FiO<sub>2</sub> 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 (SaO<sub>2</sub>) 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 SaO<sub>2</sub> levels that require intervention or medication will be recorded on the CRF including changes in SaO<sub>2</sub> 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 SaO<sub>2</sub> and ETCO<sub>2</sub>
- 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 SaO<sub>2</sub>
- 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

Summary statistic	Age group and treatment group								
	Neonate			Infant			Toddler		
	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)
<b>Reappearance of T3 (*)</b>									
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
<b>Onset time (*) (a)</b>									
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
<b>Maximum block (%)</b>									
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
<b>Reappearance of T1 (*)</b>									
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)

Summary statistic	Age group and treatment group					
	Child			Adolescent		
	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<sub>2</sub>, 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<sub>max</sub>, CL, and AUC<sub>0-∞</sub>.

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<sub>2</sub>, 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<sub>max</sub>, CL, and AUC<sub>0-∞</sub>.

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<sub>2</sub>O/O<sub>2</sub> 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.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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