**The study listed may include approved and non-approved uses, formulations, or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this registry, healthcare professionals should consult prescribing information for the product approved in their country.**

**Results presented here may include different data from those shown on http://clinicaltrials.gov/, which specifically identifies data to be disclosed, as mandated by US federal law.**

**Title of the clinical trial**

A multi-center, randomized, parallel dose-finding, safety-assessor blinded trial to explore the efficacy, safety and pharmacokinetics of four doses of Org 25969 and placebo in pediatric and adult subjects.

**Clinical trial center(s)**

Multiple sites in Germany, United Kingdom, Finland, and France.

**Studied period (years)**

May 2005 – May 2006

**Clinical phase**

Phase III

**Objectives**

Primary objective:

- To explore the dose-response relation of Org 25969 given as a reversal agent at reappearance of $T_2$ after 0.6 $mg.kg^{-1}$ rocuronium in pediatric and adult subjects

Secondary objectives:

- To explore the pharmacokinetics of Org 25969 in pediatric and adult subjects
- To evaluate the safety of Org 25969 in pediatric and adult subjects

**Methodology**

This was a multi-center, randomized, parallel dose-finding, safety-assessor blinded trial.

**Number of subjects (total and for each treatment)**

One-hundred twenty subjects were to be enrolled in the trial, six per dose group and per age group. The dose groups were 0.5, 1.0, 2.0, or 4.0 $mg.kg^{-1}$ Org 25969 or placebo, and the age groups were: Infants (28 days - 23 months inclusive), children (2 - 11 years inclusive), adolescents (12 - 17 years inclusive) and adults (18 - 65 years inclusive). In total 94 subjects (8 in the infants group, 26 in the children group, 30 in the adolescents group and 30 in the adults group) were randomized, and 91 subjects (8 in the infants group, 24 in the children group, 31 in the adolescents group and 28 in the adults group) were treated with Org 25969.
A total of 90 subjects completed the trial.

**Diagnosis and criteria for inclusion**

Subjects of ASA class 1 – 2, between the ages of 28 days and 65 years inclusive, but between the ages of 2 and 65 years inclusive for Germany and between the ages of 6 and 65 years inclusive for Finland; Scheduled for general anesthesia with an anticipated duration of anesthesia of at least 60 minutes, without further need for muscle relaxation other than one single dose of 0.6 mg.kg-1 rocuronium; Scheduled for surgical procedures in the supine position; Subjects who, and/or whose parent(s) or legal guardian(s) had given written informed consent [or appropriate assent, if applicable]

**Test product, dose and mode of administration.**

Org 25969 in 5 mL vials containing 500 mg active entity (i.e. 100 $mg.mL^{-1}$) of Org 25969;
Esmeron® (rocuronium bromide) in colorless 10 mL vials containing 100 mg (i.e. 10 $mg.mL^{-1}$) of rocuronium bromide (rocuronium); Dilution for Org 25969 in 10 mL vials containing commercially available NaCl 0.9%

**Duration of treatment**

Org 25969 (investigational product) was given as a single bolus dose. Full recovery from neuromuscular block was expected at the end of anesthesia.

**Reference therapy, dose and mode of administration.**

Placebo in 10 mL vials containing commercially available NaCl 0.9%

**Criteria for evaluation**

Primary efficacy variable: Time from start administration of IP to recovery $T_4/T_1$ ratio to 0.9.

Secondary efficacy variables: Time from start administration of IP to recovery of the $T_4/T_1$ ratio to 0.7; Time from start administration of IP to recovery of the $T_4/T_1$ ratio to 0.8.

Other efficacy variables: Time from start administration of IP to reappearance of $T_3$; $T_1$ at reappearance of $T_3$; Time from start administration of rocuronium to recovery $T_4/T_1$ ratio to 0.7; Time from start administration of rocuronium to recovery $T_4/T_1$ ratio to 0.8; Time from start administration of rocuronium to recovery $T_4/T_1$ ratio to 0.9; Occurrence of recurarization. For subjects with recurarization: time from the start of administration of IP to the time point of the lowest $T_4/T_1$ ratio value; value of the lowest $T_4/T_1$ ratio; and time from start of administration of IP to return of the $T_4/T_1$ ratio to 0.9.

Pharmacokinetic variables: Plasma concentrations of rocuronium and Org 25969

Safety variables: Adverse events (AEs, SAEs, SPEs, MDNIs), laboratory parameters, physical examinations, vital signs (blood pressure and heart rate), clinical evidence of recurarization or residual curarization, clinical assessments of recovery, and events due to interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium.

**Statistical methods**

Reporting of the data was done for each of the age groups separately. For all variables appropriate descriptive statistics were calculated. The primary and secondary efficacy variables were analyzed using weighed non-linear regression analysis to explore the dose response relation between the time to recovery of the $T_4/T_1$ ratios to 0.7, 0.8 and 0.9 and the dose of Org 25969 (including placebo). For safety descriptive statistics are presented. Descriptive statistics for the Org 25969 and rocuronium concentrations in plasma and the pharmacokinetic parameters were calculated.

**Summary**

**Summary of efficacy**

**Infants**

*Primary efficacy variable*

The mean time to recovery of the $T_4/T_1$ ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 20 min:59 sec after placebo to 0 min:40 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. Due to the low number of infants in each of the dose groups, these results should be interpreted with care. Also no dose-response effect could be demonstrated due to the low number of subjects in this age group.

*Secondary efficacy variables*

The mean times to recovery of the $T_4/T_1$ ratio to 0.7 and 0.8 rapidly decreased from 14 min:51 sec and 17 min:51 sec respectively, at spontaneous recovery (placebo), to 0 min:25 sec and 0 min:40 sec after a dose of 4.0 $mg.kg^{-1}$ of Org 25969. Due to the low number of infants in each of the dose groups, these results should be interpreted with care. Also no dose-response effect could be demonstrated due to the low number of subjects in this age group.

*Other efficacy variables*

For none of the infants recurarization was observed during the period of neuromuscular monitoring.

**Children**

*Primary efficacy variable*

The mean time to recovery of the $T_4/T_1$ ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 19 min:34 sec after placebo to 1 min:34 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average child, the fastest achievable time to recovery was 1 min:07 sec. The calculated dose of interest was 1.50 $mg.kg^{-1}$.

*Secondary efficacy variables*

The mean times to recovery of the $T_4/T_1$ ratio to 0.7 and 0.8 rapidly decreased from 12 min:19 sec and 14 min:12 sec respectively, at spontaneous recovery (placebo), to 0 min:34 sec and 0 min:45 sec after a dose of 4.0 $mg.kg^{-1}$ of Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average child, the fastest achievable times for recovery to 0.7 and 0.8 were 36 seconds and 52 seconds, respectively.

*Other efficacy variables*
For none of the children recurarization was observed during the period of neuromuscular monitoring.

**Adolescents**
*Primary efficacy variable*
The mean time to recovery of the $T_4/T_1$ ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 22 min:46 sec after placebo to 1 min:05 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average adolescent, the fastest achievable time to recovery was 1 min:05 sec. The calculated dose of interest was 1.0 $mg.kg^{-1}$.

*Secondary efficacy variables*
The mean times to recovery of the $T_4/T_1$ ratio to 0.7 and 0.8 rapidly decreased from 18 min:37 sec and 21 min:55 sec respectively, at spontaneous recovery (placebo), to 0 min:50 sec and 0 min:52 sec after a dose of 4.0 $mg.kg^{-1}$ of Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average adolescent, the fastest achievable times for recovery to 0.7 and 0.8 were 52 seconds and 53 seconds, respectively.

*Other efficacy variables*
For none of the adolescents recurarization was observed during the period of neuromuscular monitoring.

**Adults**
*Primary efficacy variable*
The mean time to recovery of the $T_4/T_1$ ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 29 min:29 sec after placebo to 1 min:22 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average adult, the fastest achievable time to recovery was 1 min:19 sec. The calculated dose of interest was 0.79 $mg.kg^{-1}$.

*Secondary efficacy variables*
The mean times to recovery of the $T_4/T_1$ ratio to 0.7 and 0.8 rapidly decreased from 19 min:39 sec and 24 min:46 sec respectively, at spontaneous recovery (placebo), to 1 min:07 sec and 1 min:16 sec after a dose of 4.0 $mg.kg^{-1}$ of Org 25969. A dose-response effect was demonstrated, and it was estimated that for an average adult, the fastest achievable times for recovery to 0.7 and 0.8 were exactly 1 minute and 1 min:11 sec, respectively.

*Other efficacy variables*
For none of the adults recurarization was observed during the period of neuromuscular monitoring.

**Summary of other parameters**

*Additional neuromuscular variables*
**Infants**
The results of the infants should be interpreted with care due to the low number of infants in each of the dose groups. For all dose groups combined, the mean $T_1$ value at reappearance of $T_2$ was 9.5%. The mean time from start of administration of rocuronium to reappearance of $T_2$ was 29 min:02 sec.

**Children**
For all dose groups combined, the mean $T_1$ value at reappearance of $T_2$ was 15.5%. The mean time from start of administration of rocuronium to reappearance of $T_2$ was 21 min:48 sec.

**Adolescents**
For all dose groups combined, the mean $T_1$ value at reappearance of $T_2$ was 20.9%. The mean time from start of administration of rocuronium to reappearance of $T_2$ was 26 min:01 sec.

**Adults**
For all dose groups combined, the mean $T_1$ value at reappearance of $T_2$ was 17.1%. The mean time from start of administration of rocuronium to reappearance of $T_2$ was 32 min:52 sec.

*Pharmacokinetics*
Plasma concentrations of Org 25969 were approximately dose proportional over the dose range of 0.5 to 4.0 $mg.kg^{-1}$. Plasma concentrations of rocuronium showed an increase after administration of Org 25969 which was not seen in the placebo group.

**Summary of safety**

**Infants**
For a total of 7 out of 8 infants (87.5%) at least one AE was reported. For one subject one drug-related AE was observed (possibly related to IP according to the investigator).
The most frequently reported AE was vomiting (37.5%).

No infants discontinued the trial due to an AE. None of the infants experienced an AE of severe intensity. No SPEs and no Medical Device (near) incidents were reported in this age group.
One SAE was reported for one subject who received 0.5 mg.kg$^{-1}$ Org 25969. The subject recovered from the SAE and the SAE was not related to IP according to the investigator.
For one subject an AE related to a MAVSV (heart rate) was reported.
For one subject in the infants group an AE related to a markedly abnormal lab value was reported.

**Children**
For a total of 15 out of 24 children (62.5%) at least one AE was reported. For one subject one drug-related AE was observed (possibly related to IP according to the investigator).
The most frequently reported AEs were: vomiting (45.8%) and procedural pain (29.2%).
No children discontinued the trial due to an AE. In total 2 subjects experienced an AE of severe intensity: one subject in the 0.5 mg.kg$^{-1}$ Org 25969 group, and one subject in the 4.0 mg.kg$^{-1}$ Org 25969 dose group.
No SPEs and no Medical Device (near) incidents were reported in this age group. One SAE was reported for one child who received 4.0 mg.kg$^{-1}$ Org 25969. The subject recovered from the SAE, and the SAE was not related to IP according to the investigator.
For none of the children an AE related to a MAVSV was reported.
For none of the subjects in the children group an AE related to a markedly abnormal lab value was reported.

**Adolescents**
For a total of 21 out of 31 adolescents (67.7%) at least one AE was reported. For four subjects one drug-related AE was observed (all were possibly related to IP according to the investigator). No dose-response relation was observed for the occurrence of drug-related AEs.
The most frequently reported AEs were: nausea (19.4%), vomiting (29.0%) and procedural pain (45.2%).
No adolescents discontinued the trial due to an AE. In total 1 subject (placebo group) experienced an AE of severe intensity.
No SPEs and no Medical Device (near) incidents were reported in this age group. No SAEs were reported.
For none of the adolescents an AE related to a MAVSV was reported.
For none of the subjects in the adolescents group an AE related to a markedly abnormal lab value was reported.

**Adults**
For a total of 16 out of 28 adults (57.1%) at least one AE was reported. For one subject one drug-related AE was observed (possibly related to IP according to the investigator).
The most frequently reported AE was procedural pain (21.4%).
No adults discontinued the trial due to an AE. In total 1 subject (placebo group) experienced an AE of severe intensity.
No SPEs and no Medical Device (near) incidents were reported in this age group. No SAEs were reported.
For none of the adults an AE related to a MAVSV was reported.
For one subject in the adults group an AE related to a markedly abnormal lab value was reported.

*All age groups:*
No interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium was reported. No clinical evidence of recurarization or residual curarization was observed. No AEs based on the assessments for clinical recovery were reported.

An independent external cardiologist concluded that this study provides no indication for an association between Org 25969 and QT/QTc prolongation at dose levels of up to 4.0 mg.kg$^{-1}$. However, given the small sample size these results should be interpreted cautiously.

**Conclusions**

The trial was conducted in order to explore the dose-response relation of Org 25969 given as a reversal agent at reappearance of $T_2$ after 0.6 mg.kg$^{-1}$ rocuronium in pediatric and adult subjects, to explore the pharmacokinetics and to evaluate the safety in pediatric and adult subjects.

For children, adolescents and adults a clear dose-response relationship was found. In infants, the mean time to recovery of the $T_4/T_1$ ratio to 0.9 markedly decreased with increasing dose of Org 25969. However no plateau, i.e. no limit of recovery was reached and no dose-response effect could be demonstrated. This was due to the low number of infants (one or two infants in each of the dose groups).

Plasma concentrations of Org 25969 were approximately dose proportional over the dose range of 0.5 to 4.0 mg.kg$^{-1}$ in all age groups. Plasma concentrations of rocuronium showed an increase after administration of Org 25969 which was not seen in the placebo group.

No recurarization was observed during the period of neuromuscular monitoring, and no clinical evidence of recurarization or residual curarization was observed for any of the age groups. No interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium was reported for any of the age groups.

The safety data indicate that Org 25969 was well tolerated by the pediatric and adult subjects. The results of infants should be interpreted with care due to the low number of infants in the trial. Of the two SAEs which occurred in this trial (one in an infant and one in a child), none was considered to be ‘related’ to Org 25969 according to the investigator.