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 Study: A multi-center, randomized, parallel group, safety assessor-blinded trial comparing efficacy and safety of 4.0 $mg.kg^{-1}$ Org 25969, administered at T_1 3-10% after continuous infusion of rocuronium, and pharmacokinetics of rocuronium, between subjects receiving maintenance anesthesia using propofol and subjects receiving maintenance anesthesia using sevoflurane

Studied Period: December 2006 – March 2007

Clinical Phase: Phase IIIa

Objective(s): The clinical trial objectives were:

- To show equivalence in recovery from neuromuscular block after a single dose of 4.0 $mg.kg^{-1}$ Org 25969, administered at T_1 3-10% after continuous infusion of rocuronium, between subjects receiving maintenance anesthesia using propofol and subjects receiving sevoflurane.
- To investigate the safety of a single dose of 4.0 $mg.kg^{-1}$ Org 25969, administered at T_1 3-10% after continuous infusion of rocuronium, under either propofol or sevoflurane anesthesia.

To compare the plasma levels of rocuronium in subjects after continuous infusion of rocuronium and before the administration of Org 25969, under either propofol or sevoflurane anesthesia

Methodology: This was a multi-center, randomized, parallel-group comparative, safety assessor-blinded trial

Number of Subjects: In total 50 subjects were to be included in the trial; 25 were to receive propofol anesthesia and 25 were to receive sevoflurane anesthesia.

In total 52 subjects were randomized to either sevoflurane (n=26) or propofol (n=26) and 51 subjects were treated with Org 25969: 26 sevoflurane and 25 propofol. These 51 subjects completed the trial

Diagnosis and Criteria for Inclusion: Subjects of at least 20 years but under 65 years of age; Of ASA class 1 – 3; Scheduled for a surgical procedure under general anesthesia requiring neuromuscular relaxation with use of a NMBA, with an anticipated duration of surgery between 2 and 5 hours; Scheduled for a surgical procedure in the supine position; who had given written informed consent

Test Product, Dose, Mode of Administration: Org 25969 (investigational product, IP) supplied in 5 mL vials containing 500 mg active entity (i.e. 100 $mg.mL^{-1}$) of Org 25969; Esmeron® (rocuronium bromide) supplied in colorless 5 mL vials containing 50 mg (i.e. 10 $mg.mL^{-1}$) of rocuronium bromide

Duration of Treatment: Org 25969 was to be given as a single bolus dose. Full recovery from neuromuscular blockade was to be expected at the end of anesthesia

Reference Therapy, Dose, Mode of Administration: Not applicable

Criteria for Evaluation: *Neuromuscular variables*

Primary efficacy variable:

Time from start administration of Org 25969 to recovery T_4/T_1 ratio to 0.9.

Secondary efficacy variables:

Time from start administration of Org 25969 to recovery T_4/T_1 ratio to 0.7;

Time from start administration of Org 25969 to recovery T_4/T_1 ratio to 0.8.

Other variables:

Twitch height of T_1 at the start of administration of Org 25969.

Pharmacokinetic assessments

Plasma concentrations of rocuronium

Safety assessments

Vital signs, i.e. blood pressure (BP) and heart rate (HR); Physical examination; (Serious) adverse events; Laboratory assessments: hematology, biochemistry and urinalysis.

Additional measures of safety

Clinically relevant events due to recurarization or residual curarization; Signs of possible interaction of Org 25969 with endogenous compounds or with exogenous compounds other than rocuronium

Statistical Methods: For all variables appropriate descriptive statistics were calculated. To investigate equivalence, the primary efficacy variable was analyzed using a confidence interval (CI) approach for the subject group difference. The equivalence margins were pre-defined. Data of the secondary efficacy variables were analyzed in the same way as was done for the primary efficacy variable. For safety descriptive statistics are presented. Descriptive statistics for the rocuronium concentrations in plasma were calculated

SUMMARY-CONCLUSIONS:

RESULTS:

Efficacy: *Primary efficacy variable*

The median recovery time from administration of 4.0 $mg.kg^{-1}$ Org 25969, after continuous infusion of rocuronium, to recovery of the T_4/T_1 ratio to 0.9 during sevoflurane anesthesia, was 1 min:20 sec. The median recovery time from administration of 4.0 $mg.kg^{-1}$ Org 25969 after continuous infusion of rocuronium, to recovery of the T_4/T_1 ratio to 0.9 during propofol anesthesia, was 1 min:11 sec. The trial shows no differences between trial sites with respect to recovery times and no interaction between trial site and treatment group was found.

The statistical evaluation of the time to recovery of the T_4/T_1 ratio to 0.9 showed that the estimated treatment difference in recovery time was 9 seconds with corresponding 95% CI ranging from -6 seconds to + 20 seconds.

Since this 95% CI lies entirely within the pre-defined equivalence interval, which ranges from -60 to +60 seconds, equivalence can be claimed. Thus, the time from administration of 4.0 $mg.kg^{-1}$ Org 25969 after continuous infusion of rocuronium, to recovery of the T_4/T_1 ratio to 0.9 is independent from the anesthetic technique used for maintenance.

Secondary efficacy variables

Subjects who received sevoflurane for maintenance of anesthesia had a median time to recovery of the T_4/T_1 ratio to 0.7 and 0.8 of 1 min:3 sec and 1 min:12 sec, respectively. Median time to recovery of the T_4/T_1 ratio to 0.7 and 0.8 in subjects who received propofol for maintenance of anesthesia was 56 sec. and 1 min:3 sec, respectively. The estimated difference between the two groups was 6 seconds for both recovery variables and that their corresponding 95% CI ranged from -3 seconds to + 13 seconds for recovery of the T_4/T_1 ratio to 0.7 and ranged from -2 to 16 seconds for recovery of the T_4/T_1 ratio to 0.8. Thus, as was found for the time to recovery of the T_4/T_1 ratio to 0.9, the current trial shows that the times to recovery of the T_4/T_1 ratio to 0.8 and to 0.7 are independent from the anesthetic technique used for maintenance.

Safety: For a total of 46 out of 51 subjects (90.2%) at least one AE was reported: 24 subjects in the sevoflurane group and 22 subjects in the propofol group. The most reported AEs (≥ 20%) were:

- in the sevoflurane group: procedural pain (n=14, 53.8%), constipation (n=12, 46.2%), nausea (n=9, 34.6%) and insomnia (n=7, 26.9%); and
- in the propofol group: procedural pain (n=19, 76.0%), nausea (n=5, 20.0%), constipation (n=5, 20.0%) and flatulence (n=5, 20.0%).

One subject (sevoflurane) experienced an AE that was judged to be probably related to Org 25969 (procedural hypotension). For one (3.8%) subject in the sevoflurane group and three (12.0%) subjects in the propofol group an AE was reported, which was classified as being of severe intensity. None of the subjects discontinued from the trial due to an AE.

None of the subjects died during the trial, and no SAEs, SPEs or medical device (near) incidences were reported following administration of a dose of 4.0 $mg.kg^{-1}$ Org 25969.

For the laboratory values (hematology and biochemistry) there was no indication of a clinically relevant difference between the two treatment groups. Results with regard to hematology variables were generally comparable between the two treatment groups (<10% difference between the two

groups in the number (%) of subjects with markedly abnormal values at baseline and at the post-anesthetic visit (except for hematocrit at baseline) and <10% difference between the two treatment groups in the percentage of subjects showing notable shifts. The number (%) of subjects with markedly abnormal biochemistry values at baseline and at the post-anesthetic visit were comparable between the two treatment groups. A difference in percentage (>10%) of notable shifts between the treatment groups of 10% or more was observed for ALAT, albumin, alkaline phosphatase, chloride, glucose fasting, protein total and urea nitrogen. There was little difference between treatment groups in mean and median values of the biochemistry values with the exception of gamma GT, the mean gamma GT was higher in sevoflurane subjects.

For the vital signs (blood pressure and heart rate) there was no indication of a clinically relevant difference between the two treatment groups. The mean systolic blood pressure was similar in both treatment groups, with the exception of the assessment done before rocuronium and at 10 minutes and 30 minutes after Org 25969, at which time points the SBP was slightly higher in sevoflurane subjects. The mean diastolic blood pressure was similar in both treatment groups except for the assessments done before rocuronium and at 2 minutes and 30 minutes after Org 25969. Before rocuronium and 30 minutes after Org 25969 the DBP was slightly higher in sevoflurane subjects, but at 2 minutes after Org 25969 it was slightly higher in propofol subjects. The mean heart rate was similar in both treatment groups, with the exception of the assessment done before rocuronium, where the mean HR was slightly lower in sevoflurane subjects.

There were no reports of recurarization based on neuromuscular monitoring data for any of the subjects. No interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium was reported. None of the subjects showed clinical signs of recurarization or residual curarization.

CONCLUSIONS: The trial was conducted: 1) to show equivalence in recovery from neuromuscular block after a single dose of 4.0 mg.kg^{-1} Org 25969 administered at T_1 3-10% after continuous infusion of rocuronium, between subjects receiving maintenance anesthesia using propofol and subjects receiving maintenance anesthesia using sevoflurane, 2) to investigate the safety Org 25969 in these subjects, and 3) to compare the plasma levels of rocuronium before the administration of Org 25969.

The median recovery time from administration of 4.0 mg.kg^{-1} Org 25969, after continuous infusion of rocuronium, to recovery of the T_4/T_1 ratio to 0.9 during sevoflurane anesthesia, was 1 min:20 sec., and during propofol anesthesia it was 1 min:11 sec. The statistical evaluation of the time to recovery of the T_4/T_1 ratio to 0.9 showed that the estimated treatment difference in recovery time was 9 seconds with corresponding 95% CI ranging from -6 seconds to + 20 seconds. Since this 95% CI lies entirely within the pre-defined equivalence interval, which ranges from -60 to +60 seconds, equivalence can be claimed. In other words, the time from administration of 4.0 mg.kg^{-1} Org 25969 after continuous infusion of rocuronium, to recovery of the T_4/T_1 ratio to 0.9 is independent from the anesthetic technique used for maintenance.

Plasma concentrations of rocuronium just before administration of Org 25969 at T_1 being 3-10%, were 33% lower during maintenance anesthesia with sevoflurane than with protocol. The variability was similar in both groups (30% for sevoflurane and 31% for propofol).

The safety data indicate that a dose of 4.0 mg.kg^{-1} Org 25969 was well tolerated when administered after continuous infusion with rocuronium. No SAEs were reported following administration of a dose of 4.0 mg.kg^{-1} Org 25969. For the laboratory values (hematology and biochemistry) and vital signs (blood pressure and heart rate) there was no indication of a clinically relevant difference between the two treatment groups. There were no reports of recurarization based on neuromuscular monitoring data for any of the subjects and no clinical evidence of recurarization or residual curarization was observed. No interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium was reported.

It can be concluded that 4.0 mg.kg^{-1} Org 25969 after continuous infusion with rocuronium is equally efficacious during maintenance anesthesia with propofol or sevoflurane, and Org 25969 is well tolerated under these circumstances. As expected, rocuronium concentrations just before administration of Org 25969 were lower during maintenance anesthesia using sevoflurane as compared to maintenance anesthesia using propofol.