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, open-label, prospective bridging, parallel dose-finding trial comparing efficacy and safety of 5 doses of Org 25969 administered at 1-2 PTC after rocuronium or vecuronium in Japanese and Caucasian subjects. Part B: Caucasian subjects.
Clinical Trial Report on Protocol 19.4.209B.

Studied period (years)

October 2005 - May 2006

Clinical phase

Phase II

Objectives

Primary objective:

- To establish the dose-response relation of Org 25969 given as a reversal agent of rocuronium or vecuronium at 1-2 PTCs for Caucasian subjects.

Secondary objectives:

- To show equivalence of recovery of the T_4/T_1 ratio to 0.9 after reversal with Org 25969 administered at 1-2 PTCs between Japanese and Caucasian subjects, for both rocuronium and vecuronium.
- To compare the safety of single doses of Org 25969 administered in subjects of ASA 1 – 3 between Japanese and Caucasian subjects, for both rocuronium and vecuronium.

Methodology

This was a multi-center, randomized, open-label, parallel dose-finding trial.

Number of subjects (total and for each treatment)

In total, 100 subjects were to be randomized. Fifty subject were to receive rocuronium and 50 subjects were to receive vecuronium. The subjects were divided into five dose groups (0.5, 1.0, 2.0, 4.0, and 8.0 $mg.kg^{-1}$ of Org 25969). Eventually, 50 subjects were randomized to receive rocuronium. All of these 50 subjects were treated with Org 25969 and completed the trial. Fifty-two (52) subjects were randomized to receive vecuronium. Of these subjects, 51 subjects were treated with Org 25969 and 50 subjects completed the trial.

Diagnosis and criteria for inclusion

Subjects of ASA class 1 – 3; Subjects at least 20 years but under 65 years of age; Caucasian subjects; Subjects scheduled for elective surgery requiring muscle relaxation in supine position and under sevoflurane anesthesia with an anticipated duration of about 1.5-3 hours; Subjects who had given written informed consent.

Test product, dose and mode of administration.

Org 25969 supplied in 5 mL vials containing 500 mg active entity (i.e., 100 $mg.ml^{-1}$) of Org 25969. Org 25969 was given as an intravenous single bolus dose, which was based on the actual body weight: 0.5, 1.0, 2.0, 4.0, and 8.0 $mg.kg^{-1}$ of Org 25969.
Additional medication
Rocuronium supplied in 5 mL vials containing 50 mg (i.e., 10 $mg.ml^{-1}$) of rocuronium bromide.
Vecuronium supplied in vials containing 10 mg of vecuronium bromide to be dissolved in 5 mL water for injection. Water for injection supplied in 10 mL vials.

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

NA

Criteria for evaluation

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 of the T_4/T_1 ratio to 0.7; Time from start administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.8.
Other efficacy variables: Time from start administration of Org 25969 to reappearance of T_2; Time from start administration of Org 25969 to reappearance of T_3; T_1 at reappearance of T_2; T_1 at reappearance of T_3; Time from start administration of last bolus dose of rocuronium or vecuronium to recovery T_4/T_1 ratio to 0.7; Time from start administration of last bolus dose of rocuronium or vecuronium to recovery T_4/T_1 ratio to 0.8; Time from start administration of last bolus dose of rocuronium or vecuronium to recovery T_4/T_1 ratio to 0.9; Occurrence of recurarization. For subjects with recurarization the time from the start of administration of Org 25969 to the time point of the lowest T_4/T_1 ratio value, the value of the lowest T_4/T_1 ratio and the time from start of administration of Org 25969 to return of the T_4/T_1 ratio to 0.9 were listed by dose group.
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 or vecuronium.

Statistical methods

For all variables appropriate descriptive statistics were calculated. The primary and secondary efficacy variables were analyzed using weighted 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. For safety descriptive statistics are presented.

Summary

Rocuronium group
Fifty (50) subjects who were randomized to receive rocuronium as NMBA were enrolled into the trial and were randomly allocated to one of the five doses of Org 25969. Hence, the ASR group consisted of 50 subjects.
All of these randomized subjects received a dose of Org 25969. Consequently, the AST group consisted of 50 subjects. All subjects in the AST group had at least one efficacy assessment. Therefore, the ITT group consisted of 50 subjects also.
Vecuronium group
Fifty-two (52) subjects who were randomized to receive vecuronium as NMBA were enrolled into the trial and were randomly allocated to one of the five doses of Org 25969. Hence, the ASR group consisted of 52 subjects.
One of these randomized subjects did not receive a dose of Org 25969; the remaining 51 subjects all received a dose of Org 25969. Therefore, the AST group consisted of 51 subjects. All subjects in the AST group had at least one efficacy assessment. Consequently, the ITT group consisted of 51 subjects.

Summary of efficacy
Primary efficacy variable
Rocuronium group *(PP analysis, N=48):*
The mean recovery time of the T_4/T_1 ratio to 0.9 markedly decreased from 79 min:47 sec in the 0.5 $mg.kg^{-1}$ Org 25969 dose group to 1 min:08 sec in the 8.0 $mg.kg^{-1}$ Org 25969 dose group. The estimated fastest achievable time to recovery of the T4/T1 ratio to 0.9 for an average subject was 1 min:14 sec (1.24 min). The dose of interest, i.e., the smallest dose of Org 25969 that resulted in a time to recovery of the T4/T1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9, was 2.50 $mg.kg^{-1}$ Org 25969.
Vecuronium group *(PP analysis, N=47):*
The mean recovery time of the T_4/T_1 ratio to 0.9 markedly decreased from 68 min:24 sec in the 0.5 $mg.kg^{-1}$ Org 25969 dose group to 1 min:39 sec in the 8.0 $mg.kg^{-1}$ Org 25969 dose group. The estimated fastest achievable time to recovery of the T4/T1 ratio to 0.9 for an average subject was 1 min:42 sec (1.70 min). The dose of interest, i.e., the smallest dose of Org 25969 that resulted in a time to recovery of the T4/T1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9, was 4.23 $mg.kg^{-1}$ Org 25969.

Secondary efficacy variables

Rocuronium group *(PP analysis, N=48):*

The mean times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 rapidly decreased from 47 min:43 sec and 57 min, respectively, in the 0.5 mg.kg^{-1} Org 25969 dose group to 56 sec and 59 sec, respectively, in the 8.0 mg.kg^{-1} Org 25969 dose group. The estimated fastest achievable times to recovery of the T_4/T_1 ratio to 0.7 and to 0.8 for an average subject were 58 sec (0.96 min) and 1 min:4 sec (1.07 min), respectively.

Vecuronium group *(PP analysis, N=47):*

The mean times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 rapidly decreased from 30 min:13 sec and 45 min:56 sec, respectively, in the 0.5 mg.kg^{-1} Org 25969 dose group to 1 min:20 sec and 1 min:26 sec, respectively, in the 8.0 mg.kg^{-1} Org 25969 dose group. The estimated fastest achievable times to recovery of the T_4/T_1 ratio to 0.7 and to 0.8 for an average subject were 1 min:23 sec (1.39 min) and 1 min:28 sec (1.47 min), respectively.

Other efficacy variables

Rocuronium group

The mean T_1 values at reappearance of T_2 and T_3 appeared to be increasing with increasing dose of Org 25969, starting from a dose of 1.0 mg.kg^{-1} Org 25969. The mean times from start of administration of Org 25969 to reappearance of T_2 and T_3 showed a decreasing trend with increasing dose of Org 25969.

For four subjects in the PP group recurarization, as defined in the protocol (i.e., a decline in the T_4/T_1 ratio from ≥ 0.9 to < 0.8 in at least three consecutive TOF values), was reported during the period of neuromuscular monitoring (one subject in the 0.5 mg.kg^{-1} Org 25969 dose group and three subjects in the 1.0 mg.kg^{-1} Org 25969 dose group).

Vecuronium group

For all doses groups the mean T_1 values at reappearance of T_2 and T_3 were similar. The mean times from start of administration of Org 25969 to reappearance of T_2 and T_3 shows a decreasing trend with increasing dose of Org 25969, with approximately the same mean values for the 4.0 mg.kg^{-1} and 8.0 mg.kg^{-1} Org 25969 dose groups.

For none of the subjects in the PP group recurarization, as defined in the protocol (i.e., a decline in the T_4/T_1 ratio from ≥ 0.9 to < 0.8 in at least three consecutive TOF values), was reported during the period of neuromuscular monitoring.

Summary of other variables

Rocuronium group

The overall median PTC at which Org 25969 was administered was 1, ranging from 1 to 5. No relevant differences were found between the dose groups.

Vecuronium group

The overall median PTC at which Org 25969 was administered was 2, ranging from 0 to 7. No relevant differences were found between the dose groups.

Summary of safety

Rocuronium group

For 40 out of 50 (80%) subjects at least one AE was reported. For 14 subjects (28.0%) at least one drug-related AE was observed: one AE ('lack of relaxation in relation to medication error') was considered definitely related to Org 25969, two AEs probably related and all other drug-related AEs possibly related to Org 25969 according to the investigator. No dose-response relation was observed for the occurrence of drug-related AEs.

The most frequently reported AEs (incidence at least 10%) were: nausea (34.0%), procedural pain (32.0%), vomiting (16.0%), pain (12.0%), and procedural hypotension (10.0%). Incidences of drug-related AEs were highest for nausea (16.0%). Incidences of all other drug-related AEs were below 5%.

No subjects discontinued from the trial due to an AE. In total three subjects experienced an AE of severe intensity: one subject in the 2.0 mg.kg^{-1} Org 25969 dose group, and two subjects in the 4.0 mg.kg^{-1} Org 25969 dose group. No SPEs and no Medical Device (near) incidents were reported. None of the subjects died during the trial.

SAEs were reported for three subjects who received 0.5 mg.kg^{-1} (wound hemorrhage), 2.0 mg.kg^{-1} (tracheal stenosis; laryngeal edema), and 4.0 mg.kg^{-1} Org 25969 (convulsion; hypoxia; meningitis), respectively. All SAEs were considered either 'not related' or 'unlikely related' to Org 25969 according to the investigator.

Overall, results with regard to hematology, biochemistry, and urinalysis variables were comparable between dose groups.

In total, four subjects had one or more markedly abnormal vital signs values for systolic and/or diastolic blood pressure at 2, 5, 10, and/or 30 minutes post-dose. For one subject, who had a markedly abnormal low diastolic blood pressure value 10 minutes after Org 25969 (2.0 mg.kg^{-1}), this was reported as AE (procedural hypotension). The relationship to IP was considered 'unlikely' according to the investigator. No markedly abnormal values were observed for heart rate.

In general, in all dose groups the systolic and diastolic blood pressure and heart rate under anesthesia were lower as compared to screening. Post-anesthetic systolic and diastolic blood pressure and heart rate values were nearly normalized as compared to pre-trial values.

No clinical evidence of recurarization or residual curarization was observed. However for one subject an AE 'Recurarisation' was reported. The investigator based this AE on the TOF-values. No clinical signs of recurarization were observed for this subject.

Vecuronium group
For 33 out of 51 (64.7%) subjects at least one AE was reported. For nine subjects (17.6%) at least one drug-related AE was observed. All drug-related AEs were considered to be possibly related to Org 25969, according to the investigator (for one AE the relationship to Org 25969 was missing). No dose-response relation was observed for the occurrence of drug-related AEs.
The most frequently reported AEs (incidence at least 10%) were: procedural pain (23.5%), nausea (21.6%), and pain (11.8%). Incidences of drug-related AEs were highest for nausea (5.9%). Incidences of all other drug-related AEs were below 5%.

No subjects discontinued from the trial due to an AE. Six subjects experienced an AE of known severe intensity: two subjects each in the 1.0, 2.0 and 8.0 mg.kg^{-1} Org 25969 dose groups. No SPEs and no Medical Device (near) incidents were reported. None of the subjects died during the trial.
One SAE was reported for one subject who received 8.0 mg.kg^{-1} Org 25969. The SAE (post procedural hemorrhage) was considered 'unlikely' to be drug-related according to the investigator.

Overall, results with regard to hematology, biochemistry, and urinalysis variables were comparable between dose groups.

In total, five subjects had one or more markedly abnormal vital signs values for systolic and/or diastolic blood pressure at 5, 10, and/or 30 minutes post-dose. For one subject (8.0 mg.kg^{-1} Org 25969), who had a markedly abnormal low diastolic and systolic blood pressure value 15 minutes post-dose, a vital signs related AE (procedural hypotension) was reported, starting eight minutes before the assessment of the markedly abnormal vital signs values. The relationship to IP was considered 'unlikely' according to the investigator. For two subjects a markedly abnormal heart rate value was reported, which were both not reported as AE.
In general, in all dose groups the systolic and diastolic blood pressure and heart rate under anesthesia were lower as compared to screening. Post-anesthetic systolic and diastolic blood pressure and heart rate values were nearly normalized as compared to pre-trial values.

No clinical evidence of recurarization or residual curarization was observed.

Conclusions

The trial was conducted in order to establish the dose-response relation of Org 25969 given as a reversal agent of rocuronium or vecuronium at 1-2 PTC for Caucasian subjects.

Administration of Org 25969 after an initial bolus administration of *0.9 mg.kg^{-1} rocuronium* and repeated bolus administration of this NMBA, under propofol (induction) and sevoflurane (maintenance) anesthesia, resulted in a clear dose-response relation between Org 25969 and recovery time.
Similarly, administration of Org 25969 after an initial bolus administration of *0.1 mg.kg^{-1} vecuronium* and repeated bolus administration of this NMBA, under propofol (induction) and sevoflurane (maintenance) anesthesia, resulted in a clear dose-response relation between Org 25969 and recovery time.

In the rocuronium group, the mean recovery time of the T_4/T_1 ratio to 0.9 markedly decreased from 79 min:47 sec in the 0.5 mg.kg^{-1} Org 25969 dose group to 1 min:08 sec in the 8.0 mg.kg^{-1} Org 25969 dose group. The estimated fastest achievable time to recovery of the T4/T1 ratio to 0.9 for an average subject was 1 min:14 sec (1.24 min). The dose of interest, i.e., the smallest dose of Org 25969 that resulted in a time to recovery of the T4/T1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9, was 2.50 mg.kg^{-1} Org 25969.

In the vecuronium group, the mean recovery time of the T_4/T_1 ratio to 0.9 markedly decreased from 68 min:24 sec in the 0.5 mg.kg^{-1} Org 25969 dose group to 1 min:39 sec in the 8.0 mg.kg^{-1} Org 25969 dose group. The estimated fastest achievable time to recovery of the T4/T1 ratio to 0.9 for an average subject was 1 min:42 sec (1.70 min). The dose of interest, i.e., the smallest dose of Org 25969 that resulted in a time to recovery of the T4/T1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9, was 4.23 mg.kg^{-1} Org 25969.

Only in the rocuronium group, recurarization as defined in the protocol (i.e., a decline in the T_4/T_1 ratio from ≥ 0.9 to < 0.8) was reported during the period of neuromuscular monitoring for one subject in the 0.5 mg.kg^{-1} Org 25969 dose group and three subjects in the 1.0 mg.kg^{-1} Org 25969 dose group. These low doses were administered in order to establish a dose-response relationship, and can be considered as suboptimal for reversal of a depth of block investigated in the current study (1-2 PTC, i.e. profound block). No clinical evidence of recurarization or residual curarization was observed.

Overall, the safety data indicate that Org 25969 was well tolerated by the subjects. Results with regard to biochemistry, hematology and urinalysis were comparable between the dose groups. No relevant differences were observed between the dose groups with respect to vital signs. Of the eight SAEs that occurred in this trial, none was considered to be 'related' to Org 25969 according to the investigator.