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, safety and pharmacokinetics of 4 doses of Org 25969 and placebo administered at reappearance of T_2 after rocuronium or vecuronium in Japanese and Caucasian subjects. Part B: Caucasian subjects.

Clinical trial center(s)

Multiple sites throughout Belgium, Germany, Poland, and Sweden.

Studied period (years)

September 2005 - March 2006

Clinical phase

Phase II

Objectives

To establish the dose-response relation of Org 25969 given as a reversal agent of rocuronium or vecuronium at reappearance of T_2 for Caucasian subjects.

Methodology

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

Number of subjects (total and for each treatment)

In total 100 subjects were to be enrolled in the trial. Fifty subjects were to receive rocuronium and 50 subjects were to receive vecuronium. The subjects were divided into five dose groups (placebo or 0.5, 1.0, 2.0, 4.0 $mg.kg^{-1}$ of Org 25969). Eventually, fifty (50) subjects were randomized to receive rocuronium. Of these subjects, 49 subjects were treated with Org 25969/Placebo, and 48 subjects completed the trial.
Fifty (50) subjects were randomized to receive vecuronium. Of these subjects, 49 subjects were treated with Org 25969/Placebo, and 45 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 $mg.kg^{-1}$ of Org 25969.
Additional medication (Neuromuscular blocking agent):
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.

Placebo for Org 25969, consisting of 0.9% NaCl solution supplied in 10 mL vials and given as a single intravenous bolus dose (3 mL).

Criteria for evaluation

Primary efficacy variable: Time from start administration of Org25969/placebo to recovery T_4/T_1 ratio to 0.9.

Secondary efficacy variables: Time from start administration of Org 25969/placebo to recovery of the T_4/T_1 ratio to 0.7; Time from start administration of Org 25969/placebo to recovery of the T_4/T_1 ratio to 0.8.

Other efficacy variables: Time from start administration of Org 25969/placebo to reappearance of T_3; 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/placebo 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/placebo to return of the T_4/T_1 ratio to 0.9 were listed by dose group.

Pharmacokinetic variables: Plasma concentrations of rocuronium, vecuronium 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 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 and were randomly allocated to placebo or one of the four doses of Org 25969. Hence, the ASR group consisted of 50 subjects.
One of these randomized subjects did not receive a dose of Org 25969/Placebo; the remaining 49 subjects received a dose of Org 25969/Placebo. Consequently, the AST group consisted of 49 subjects. All subjects in the AST group had at least one efficacy assessment. Therefore, the ITT group consisted of 49 subjects also.
Major protocol violations were seen in three treated subjects. Hence, the PP group consisted of 46 subjects.

Vecuronium group
Fifty (50) subjects who were randomized to receive vecuronium as NMBA were enrolled and were randomly allocated to placebo or one of the four doses of Org 25969. Hence, the ASR group consisted of 50 subjects.
One of these randomized subjects did not receive a dose of Org 25969/Placebo; the remaining 49 subjects all received a dose of Org 25969/Placebo. Therefore, the AST group consisted of 49 subjects. All subjects in the AST group had at least one efficacy assessment. Consequently, the ITT group consisted of 49 subjects as well.
Major protocol violations were seen in two treated subjects. Hence, the PP group consisted of 47 subjects.

Summary of efficacy
Primary efficacy variable
Rocuronium group *(PP analysis, N=46):*
The mean time to recovery of the T_4/T_1 ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 96 min:18 sec after placebo to 1 min:30 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. The estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 for an average subject was 1 min:27 sec (1.44 min). The dose of interest, i.e. the smallest dose of Org 25969 which resulted in an average recovery time of the T_4/T_1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable recovery time, was 1.53 $mg.kg^{-1}$ Org 25969.

Vecuronium group *(PP analysis, N=47):*
The mean time to recovery of the T_4/T_1 ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 79 min:1 sec after placebo to 3 min:2 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. The estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 for an average subject was 3 min:13 sec (3.21 min). The dose of interest, i.e. the smallest dose of Org 25969 which resulted in an average recovery time of the T_4/T_1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable recovery time, was 1.47 $mg.kg^{-1}$ Org 25969.
Secondary efficacy variables

Rocuronium group
The mean times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 rapidly decreased from 65 min:40 sec and 75 min:51 sec respectively, at spontaneous recovery (placebo), to 1 min:1 sec and 1 min:9 sec after a dose of 4.0 mg.kg^{-1} of Org 25969. The estimated fastest achievable times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 for an average subject were 1 min:2 sec (1.03 min) and 1 min:11 sec (1.19 min), respectively.

Vecuronium group
The mean time to recovery of the T_4/T_1 ratio to 0.7 and 0.8 rapidly decreased from 58 min:7 sec and 64 min:20 sec respectively, at spontaneous recovery (placebo), to 1 min:42 sec and 2 min:7 sec after a dose of 4.0 mg.kg^{-1} of Org 25969. The estimated fastest achievable times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 for an average subject were 1 min:44 sec (1.73 min) and 2 min:6 sec (2.11 min), respectively.

Other efficacy variables
Rocuronium group
The mean T_1 value at reappearance of T_3 appeared to be higher for the higher Org 25969 doses, compared to placebo and the lowest dose of Org 25969. The mean time from start of administration of IP to reappearance of T_3 was clearly higher for placebo compared to the Org 25969 dose groups.
For five 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 (four (4) subjects in the 0.5 mg.kg^{-1} Org 25969 dose group and one (1) subject in the 2.0 mg.kg^{-1} Org 25969 group).

Vecuronium group
For all dose groups the mean T_1 value at reappearance of T_3 was comparable. The mean time from start of administration of IP to reappearance of T_3 was clearly higher for placebo compared to the Org 25969 dose groups.
For two (2) 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 (both in the 0.5 mg.kg^{-1} Org 25969 group).

Summary of other variables
For higher Org 25969 doses, the mean T_1 value at reappearance of T_3 appeared to be higher, compared to placebo and the lowest dose of Org 25969. The mean time from start of administration of IP to reappearance of T_3 was clearly higher for placebo compared to the Org 25969 dose groups.
Plasma concentrations of Org 25969 were approximately dose proportional over the dose range of 0.5 to 4.0 mg.kg^{-1} and independent of the NMBA used. Plasma concentrations of rocuronium and to a lesser extent vecuronium showed an increase after administration of Org 25969 which was not seen in the placebo group.

Summary of safety
Rocuronium group
For a total of 45 out of 49 subjects (91.8%) at least one AE was reported. For nine subjects (18.4%) at least one drug-related AE was observed (possibly related to IP according to the investigator), of which three were in the placebo group and six received a dose of Org 25969. No dose-response relation was observed for these drug-related AEs.
The most frequently reported AEs (incidence above 10%) were: nausea (42.9%), vomiting (20.4%), procedural pain (49.0%), and headache (10.2%). All incidences of drug-related AEs were below 5%.

No subjects discontinued the trial due to an AE. In total 12 subjects experienced an AE of severe intensity: three subjects in the placebo group, and three subjects in each of the 1.0, 2.0 and 4.0 mg.kg^{-1} Org 25969 dose groups. No SPEs and no Medical Device (near) incidents were reported during this trial.

Three SAEs were reported for one subject who received 2.0 mg.kg^{-1} Org 25969. The SAEs included colon injury and procedural complication. The subject eventually died due to a pulmonary embolism (SAE). This SAE started at day 16 (relative to IP administration), and was 'unlikely related' to IP according to the investigator and NV Organon.

In total 10 subjects had one or more markedly abnormal vital signs value for systolic and/or diastolic blood pressure at 2, 5, 10 and/or 30 minutes post-dose. For two subjects who had a markedly abnormal high systolic and diastolic blood pressure value at 30 minutes after Org 25969, this was reported as AE and as such considered clinically significant by the investigator. The relationship to IP was considered 'unlikely' according to the investigator. Furthermore, for one subject who had low systolic and diastolic blood pressure values within the first 10 minutes after IP, an AE (procedural hypotension) was reported (possibly related to IP according to the investigator). In one subject a MAVSV was observed for heart rate at 30 minutes after IP.
In general, in all dose groups including placebo the systolic and diastolic blood pressure and heart rate under anesthesia were much lower as compared to pre-trial. Post-anesthetic systolic- and diastolic blood pressure and heart rate values were nearly normalized as compared to the pre-trial values.

Vecuronium group
For a total of 40 out of 49 subjects (81.6%) at least one AE was reported. For five subjects (10.2%) at least one drug-related AE was observed (one probably, and four possibly related to IP according to the investigator), of which all received a dose of Org 25969. No dose-response relation was observed for these drug-related AEs.
The most frequently reported AEs (incidence above 10%) were: nausea (28.6%), vomiting (16.3%) and procedural pain (32.7%). All incidences of drug-related AEs were below 5%.

No subjects discontinued the trial due to an AE. In total five subjects experienced an AE of severe intensity: two subjects in the placebo group, two subjects in the 0.5 $mg.kg^{-1}$ Org 25969 group and one subject in the 2.0 $mg.kg^{-1}$ Org 25969 group.
No SPEs and no Medical Device (near) incidents were reported during this trial. No subjects died during the trial. SAEs were reported for two subjects in the 0.5 $mg.kg^{-1}$ Org 25969 group. All SAEs were considered 'not related' to IP according to the investigator and NV Organon, and the subjects recovered from the SAEs.

In total eight subjects had one or more markedly abnormal vital signs value for systolic and/or diastolic blood pressure at 2, 5, 10 and/or 30 minutes post-dose. No MAVSVs were observed for heart rate. No AEs related to MAVSVs were reported in the vecuronium group.
In general, in all dose groups including placebo the systolic- and diastolic blood pressure and heart rate under anesthesia were much lower as compared to pre-trial. Post-anesthetic systolic- and diastolic blood pressure and heart rate values were nearly normalized as compared to the pre-trial values.

Conclusions

The trial was conducted in order to explore the dose-response relation of Org 25969 given as a reversal agent of rocuronium or vecuronium at reappearance of T_2 for Caucasian subjects.

For both the rocuronium and the vecuronium group, a clear dose-response relationship was found.
In the rocuronium group, the mean time to recovery of the T_4/T_1 ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 96 min:18 sec after placebo to 1 min:30 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. The estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 for an average subject was 1 min:27 sec (1.44 min). The dose of interest, i.e. the smallest dose of Org 25969 which resulted in an average recovery time of the T_4/T_1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable recovery time, was 1.53 $mg.kg^{-1}$ Org 25969.
In the vecuronium group, the mean time to recovery of the T_4/T_1 ratio to 0.9 markedly decreased with increasing dose of Org 25969, from 79 min:1 sec after placebo to 3 min:2 sec after a dose of 4.0 $mg.kg^{-1}$ Org 25969. The estimated fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 for an average subject was 3 min:13 sec (3.21 min). The dose of interest, i.e. the smallest dose of Org 25969 which resulted in an average recovery time of the T_4/T_1 ratio to 0.9 that was less than a minute slower compared to the estimated fastest achievable recovery time, was 1.47 $mg.kg^{-1}$ Org 25969.

Plasma concentrations of Org 25969 were approximately dose proportional over the dose range of 0.5 to 4.0 $mg.kg^{-1}$ and independent of the NMBA used. Plasma concentrations of rocuronium and to a lesser extent vecuronium showed an increase after administration of Org 25969 which was not seen in the placebo 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 predominantly observed in the 0.5 $mg.kg^{-1}$ Org 25969 group. In only one case this was associated with clinical evidence of recurarization or residual curarization.

The safety data indicate that Org 25969 was well tolerated by the subjects. Of the six SAEs which occurred in this trial, none was considered to be 'related' to Org 25969 according to the investigator.