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 group, comparative, active controlled, safety-assessor blinded, phase IIIa, pivotal trial, in adult subjects comparing Org 25969 with neostigmine as reversal agent of a neuromuscular block induced by rocuronium or vecuronium at reappearance of T_2.

Clinical trial center(s)

Multiple sites throughout Austria, Belgium, Germany, Spain, United Kingdom, Italy, and Sweden.

Studied period (years)

November 2005 – March 2006.

Clinical phase

Phase IIIa.

Objectives

Primary objectives:
- To demonstrate faster recovery from a neuromuscular block induced by rocuronium after reversal at reappearance of T_2 by 2.0 $mg.kg^{-1}$ Org 25969 compared to 50 $\mu g.kg^{-1}$ neostigmine.
- To demonstrate faster recovery from a neuromuscular block induced by vecuronium after reversal at reappearance of T_2 by 2.0 $mg.kg^{-1}$ Org 25969 compared to 50 $\mu g.kg^{-1}$ neostigmine.

Secondary objective:
- To evaluate the safety of a single dose of 2.0 $mg.kg^{-1}$ Org 25969 and 50 $\mu g.kg^{-1}$ neostigmine administered in adult subjects.

Methodology

Multi-center, randomized, parallel group, comparative, active controlled safety-assessor blinded, pivotal trial.

Number of subjects (total and for each treatment)

Rocuronium group

In total 98 subjects were randomized, 49 to the Org 25969 group and 49 to the neostigmine group. Of these subjects 96 received the IP: 48 in the Org 25969 group and 48 in the neostigmine group. Two subjects did not complete the trial, one in each treatment group. Hence, 47 subjects in the Org 25969 group and 47 subjects in the neostigmine group completed the trial, i.e. 94 in total. In total 41 females and 55 males were treated with the IP. The mean (range) age of these subjects was 50 (20 - 83) years. The majority (46 out of 48) of these subjects were Caucasian.

Vecuronium group

In total 100 subjects were randomized, 51 to the Org 25969 group and 49 to the neostigmine group. Seven (7) subjects did not receive IP: three in the Org 25969 group and four in the neostigmine group. Of the 93 subjects, who received the IP, two (one in each treatment group) did not complete the trial. Hence 47 subjects in the Org 25969 group and 44 in the neostigmine group completed the trial, i.e. 91 subjects in total. The mean (range) age of these subjects was 51 (18 - 73) years. All subjects in the vecuronium group were Caucasian.

Diagnosis and criteria for inclusion

Subjects of ASA class 1 to 4, above or equal to the age of 18 years; subjects scheduled for surgical procedure with a general anesthesia with the use of rocuronium or vecuronium for endotracheal intubation and maintenance of neuromuscular block; subjects scheduled for surgical procedures in supine position and subjects who had given written informed consent.

Test product, dose and mode of administration

Organon supplied the trial sites with the following trial medication:
- Org 25969, supplied in 5 mL vials containing 500 mg active entity (i.e. 100 $mg.mL^{-1}$) of Org25969.
- Esmeron® (rocuronium bromide), supplied in colorless 10 mL vials containing 100 mg (i.e. 10 $mg.mL^{-1}$) of rocuronium.

- Norcuron® (vecuronium bromide), supplied in colorless 10 mL vials containing 10 mg (i.e. 2 mg.mL^{-1} after dilution with 5 mL water for injection) of vecuronium.
- Water for injection, supplied in 10 mL ampoules.

Duration of treatment

Org 25969 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

- Neostigmine/glycopyrrolate (premix), supplied in 1 mL ampoules (2.5 mg.mL^{-1} neostigmine and 0.5 mg.mL^{-1} glycopyrrolate)

Criteria for evaluation

Primary efficacy variable:
Time from start of administration of Org 25969/neostigmine to recovery of the T_4/T_1 ratio to 0.9.

Secondary efficacy variables:
Time from start of administration of Org 25969/neostigmine to recovery of the T_4/T_1 ratio to 0.7; Time from start of administration of Org 25969/neostigmine to recovery of the T_4/T_1 ratio to 0.8; Assessments clinical signs of recovery, i.e. level of consciousness, 5 seconds head lift, and check for general muscle weakness, prior to the subject's transfer to the recovery room after extubation and prior to discharge from the recovery room.

Other efficacy variables:
Time from start of administration of the last dose of rocuronium/vecuronium to recovery of the T_4/T_1 ratio to 0.7; Time from start of administration of the last dose of rocuronium/vecuronium to recovery of the T_4/T_1 ratio to 0.8; Time from start of administration of the last dose of rocuronium/vecuronium to recovery of the T_4/T_1 ratio to 0.9; Time from start of administration of Org 25969/neostigmine to the time of reappearance of T_3; T_1 at time of reappearance of T_3.

Other neuromuscular variables:
Time from start of administration of the last dose of rocuronium/vecuronium to the time of reappearance of T_2; T_1 at time of reappearance of T_2.

Safety variables:
Pre-treatment events; Serious trial procedure-related events; Vital signs, i.e. heart rate and blood pressure; Central body temperature continuously; Continuous cardiac monitoring of the QT interval changes intra- and postoperatively; TOF-Watch® SX and Armboard related adverse events; (Serious) Adverse events; Physical examination; Laboratory assessments: biochemistry, hematology, urine sediment analysis and urinalysis; Clinical evidence of recurarization or residual curarization, if any; Routine oxygen saturation by pulse oximetry and breathe frequency measurement; Events due to a possible interaction of Org 25969 with endogenous compounds or with exogenous compounds other than steroidal NMBAs, if any.

Other parameters:
For Health Economics, the subject was asked 40 questions of a "Quality of Recovery" questionnaire (QoR-40), which was to be filled out by the safety assessor during the post-anesthetic visit (i.e. twenty-four hours after IP administration, or at discharge (in case the subject was to leave the hospital earlier)) and at the seven day follow-up contact.

Statistical methods

Reporting of the data was done for each of the two NMBAs, rocuronium and vecuronium, separately.
Demographic, baseline, exposure and safety data were summarized by treatment group.
Times from start of administration of IP to recovery of the T_4/T_1 ratio to 0.9, 0.8 and 0.7 were analyzed using a two-way ANOVA model.
The logarithm of the recovery time was taken as response variable, and trial site and treatment group were the factors of the model.
For the ITT population two evaluations were performed: one for which missing recovery times were imputed and one that used only the available recovery times.
Statistical testing for differences between the two treatment groups was done one-sided, at a significance level of 2.5%.

Clinical signs of recovery were summarized by treatment group only.

Summary

Summary of efficacy

Primary efficacy variable

Rocuronium group

The geometric mean time from administration of Org 25969 or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was 1 min:29 sec and 18 min:30 sec, respectively, when missing data were imputed. The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 was estimated to be 12.7 times faster (including imputed data) compared to the time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.9.
Exploratory analysis indicated that reversal of neuromuscular block by Org 25969 did not differ between subjects who received only an intubating dose of rocuronium compared to subjects who received at least one maintenance dose as well.

Vecuronium group

The geometric mean time from administration of Org 25969 or neostigmine to recovery of the T_4/T_1 ratio to 0.9 was 2 min:48 sec and 16 min:48 sec, respectively, when missing data were imputed. The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 was estimated to be 6.7 times faster (including imputed data) compared to the time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.9.
Exploratory analysis indicated that reversal of neuromuscular block by Org 25969 took longer in subjects who received at least one maintenance dose of vecuronium compared to subjects who only received an intubating dose.

Secondary efficacy variables

Rocuronium group

The geometric mean times from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.7 and 0.8 were 1 min:6 sec and 1 min:15 sec, respectively, when missing data were imputed. In the neostigmine group the geometric mean times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 were 7 min:13 sec and 10 min:49 sec, respectively. The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.7 was estimated to be 6.5 times faster compared to the time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.7. The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.8 was estimated to be 8.7 times faster in the Org 25969 group compared to the neostigmine group.
Prior to transfer to the recovery room, the majority of subjects treated with IP were cooperative, except for seven subjects in the Org 25969 group and one in the neostigmine group. Prior to discharge from the recovery room all subjects (except for one subject in the Org 25969 group) were awake and oriented, cooperative, able to perform the head test and did not show muscle weakness.

Vecuronium group

The geometric mean times from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.7 and 0.8 were 1 min:36 sec and 1 min:58 sec, respectively, when missing data were imputed. In the neostigmine group the geometric mean times to recovery of the T_4/T_1 ratio to 0.7 and 0.8 were 6 min:07 sec and 10 min:14 sec, respectively, when missing data were imputed (6 min:25 sec and 10 min:50 sec, respectively, for the complete cases). The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.7 was estimated to be 3.9 times faster compared to the time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.7. The recovery time of the T_4/T_1 ratio to 0.8 was estimated to be 5.4 times faster in the Org 25969 group compared to the neostigmine group.
Prior to transfer to the recovery room, the majority of subjects treated with IP were cooperative, except for seven subjects in both treatment groups. Prior to discharge from the recovery room all subjects (except for one subject in the neostigmine group) were awake and oriented, cooperative, able to perform the head test and did not show muscle weakness.

Summary of other variables

Rocuronium group

The mean time from start of administration of the last bolus dose of rocuronium to the time of reappearance of T_2 was 49 minutes (intubating dose only) and 33 min:03 sec (at least one maintenance dose). The mean T_1 at reappearance of T_2 was about 16%.

Vecuronium group

The mean time from start of administration of the last bolus dose of vecuronium to the time of reappearance of T_2 was 55 min:05 sec (intubating dose only) and 41 min:38 sec (at least one maintenance dose). The mean T_1 at reappearance of T_2 was about 17%.

Summary of safety

Rocuronium group

For a total of 84 out of 96 subjects (87.5%) at least one AE was reported: 41 subjects (85.4%) in the Org 25969 group and 43 subjects (89.6%) in the neostigmine group. Seventeen subjects (17.7%) experienced one or more AEs that were judged to be possibly, probably or definitely related to IP, by the investigator: seven (14.6%) in the

Org 25969 group and 10 (20.8%) in the neostigmine group. The most frequently reported drug-related AEs in the Org 25969 group were: dry mouth (6.3%), nausea (4.2%), vomiting (4.2%) and procedural hypertension (4.2%). In the neostigmine group, the most reported drug-related AEs were: dry mouth (6.3%), nausea (4.2%) and albumin urine present (4.2%).

None of the subjects discontinued from the trial due to an AE. For six (12.5%) subjects in the Org 25969 group and eight (16.7%) in the neostigmine group one or more AEs were reported which were classified as being of severe intensity. Two subjects (one from each treatment group) experienced a severe AE that was judged to be probably related to IP administration. SAEs were reported for five subjects: two subjects (4.2%) in the Org 25969 group and three (6.3%) in the neostigmine group. All SAEs were considered to be 'unlikely' or 'not related' to IP according to the investigator and NV Organon. For none of the subjects an SPE after administration of the IP was reported.

There is no indication that remarkable differences exist in laboratory variables between the Org 25969 group and the neostigmine group.

In total 14 subjects (eight subjects in the Org 25969 and six subjects in the neostigmine group) showed one or more markedly abnormal SBP and/or DBP value. Two of these subjects (one subject from each treatment group) had procedural hypotension reported as an AE after IP administration. The events were considered to be 'not' or 'unlikely' related to the IP. No markedly abnormal values for heart rate were recorded in the Org 25969 group, while two subjects in the neostigmine group showed a low heart rate 30 minutes post-dose (for neither subject this was reported as an AE).

Vecuronium group

For a total of 70 out of 93 subjects (75.3%) at least one AE was reported: 34 subjects (70.8%) in the Org 25969 group and 36 subjects (80.0%) in the neostigmine group. Seventeen subjects (18.3%) experienced one or more AEs that were judged to be possibly, probably or definitely related to Org 25969 or neostigmine, by the investigator: seven (14.6%) in the Org 25969 group and 10 (22.2%) in the neostigmine group. The most frequently reported drug-related AEs in the Org 25969 group were: nausea (4.2%), vomiting (4.2%) chills (4.2%) and procedural hypertension (4.2%). In the neostigmine group, the most reported drug-related AEs were: dry mouth (8.9%), procedural complication (8.9%), nausea (4.4%) and neuromuscular block prolonged (4.4%).

None of the subjects discontinued from the trial due to an AE. For none of the subjects in the Org 25969 group and seven (15.6%) in the neostigmine group one or more AEs were reported which was classified as being of severe intensity. Two subjects experienced a severe AE that was judged to be probably and possibly related to neostigmine administration. No SAEs or SPEs were reported during this trial in the vecuronium group.

There is no indication that remarkable differences exist in laboratory variables between the Org 25969 group and the neostigmine group.

In total 16 subjects (eight subjects in each treatment group) showed one or more markedly abnormal SBP and/or DBP values. For four of these subjects (two subjects from each group) procedural hypertension was reported as an AE after IP administration. Three events were considered to be 'unlikely' related to the IP. One event, which started 30 minutes after Org 25969 administration and lasted 2 hours and 4 minutes, was considered possibly related to IP. No markedly abnormal values for heart rate were recorded in the Org 25969 group, while three subjects in the neostigmine group showed a low heart rate: one subject at 10 minutes and two subjects at 30 minutes post-dose (for none of these subjects this was reported as an AE).

Conclusions

The current trial showed a faster recovery from a neuromuscular blockade induced by rocuronium or vecuronium after reversal at reappearance of T_2 by 2.0 $mg.kg^{-1}$ Org 25969 compared to 50 $\mu g.kg^{-1}$ neostigmine. For subjects treated with rocuronium the time to recovery of the T_4/T_1 ratio to 0.9 was estimated to be almost 13 times faster in the Org 25969 group compared to the neostigmine group: the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was 1 min:29 sec in the Org 25969 group and 18 min:30 sec in the neostigmine group.
For subjects treated with vecuronium the time to recovery of the T_4/T_1 ratio to 0.9 was estimated to be almost 7 times faster in the Org 25969 group compared to the neostigmine group: the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was 2 min:48 sec in the Org 25969 group and 16 min:48 sec in the neostigmine group.

No cases of recurarization or possible interactions occurred in this trial. The safety profile was comparable in both the Org 25969 group and the neostigmine group. Of the five SAEs that occurred during this trial, none was considered to be 'related' to IP according to both the investigator and NV Organon.