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

Comparison of rocuronium and Org 25969 with cis-atracurium and neostigmine when neuromuscular block is reversed at reappearance of T_2

Clinical trial center(s)

Multiple sites in France, Italy, Spain, and the United Kingdom.

Studied period (years)

November 2005 - May 2006.

Clinical phase

Phase IIIa.

Objectives

Primary objective:
- To show a faster recovery of neuromuscular block with Org 25969 after rocuronium as compared to neostigmine after cisatracurium when administered at reappearance of T_2.

Secondary objectives:
- 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.
- To show a faster onset of neuromuscular block after 0.6 $mg.kg^{-1}$ rocuronium as compared to 0.15 $mg.kg^{-1}$ cisatracurium.

Methodology

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

Number of subjects (total and for each treatment)

In total 84 subjects were randomized, 40 subjects in the roc/Org 25969 group and 44 subjects in the cis/neostigmine group. Of these subjects 73 received the IP: 34 in the roc/Org 25969 group and 39 in the cis/neostigmine group. One subject in the roc/Org 25969 group did not complete the trial. Hence, 33 subjects in the roc/Org 25969 group and 39 subjects in the cis/neostigmine group completed the trial, i.e. 72 subjects in total. In total 36 females and 37 males were treated with the IP. The mean (range) age of these subjects was 45 (22 - 76) years. The majority (72 out of 73) of these subjects 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 under general anesthesia requiring neuromuscular relaxation with the use of rocuronium or cisatracurium; subjects scheduled for surgical procedures in supine position and subjects who had given written informed consent.

Test product, dose and mode of administration.

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

Duration of treatment

Org 25969 was given as a single bolus does. Full recovery from neuromuscular block was expected at the end of anesthesia.

Reference therapy, dose and mode of administration.

- Nimbex® (cisatracurium besilate), supplied in 10 mL ampoules containing 20 mg (i.e. 2 $mg.mL^{-1}$) of cisatracurium;
- 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:
The 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 IP to recovery of the T_4/T_1 ratio to 0.7; Time from start of administration of IP to recovery of the T_4/T_1 ratio to 0.8; Assessments of clinical signs of recovery i.e. time of assessment, level of consciousness, 5 seconds head lift and assessment and rating of general muscle weakness.

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

Other neuromuscular variables:
Onset time; Time from start of administration of the last dose of rocuronium and cisatracurium to the time of reappearance of T_2; T_1 at 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

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
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:2 sec and 8 min:46 sec, respectively, including imputed data. The time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 was estimated to be 4.3 times faster compared to the time from administration of neostigmine to recovery of the T_4/T_1 ratio to 0.9.
Exploratory analyses suggested 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.

Secondary efficacy variables
The geometric mean time from administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.7 and 0.8 was 1 min:23 sec and 1 min:38 sec, respectively, including imputed data. In the neostigmine group the geometric mean time to recovery of the T_4/T_1 ratio to 0.7 and 0.8 was 4 min:52 sec and 6 min:23 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 3.5 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 3.9 times faster in the roc/Org 25969 group compared to the cis/neostigmine group.

Prior to transfer to the recovery room, the majority of subjects treated with IP were cooperative, except for eight subjects in both the roc/Org 25969 and cis/neostigmine group. The majority of cooperative subjects was able to perform the 5 seconds head lift test (25 out of 26 subjects in the roc/Org 25969 group and all subjects in the cis/neostigmine group) and showed no muscle weakness (23 out of 26 subjects in the roc/Org 25969 group and 29 out of 31 subjects in the cis/neostigmine group).
Prior to discharge from the recovery room the clinical signs of recovery were similar in both groups. Except for one subject in the roc/Org 25969 group and two subjects in the cis/neostigmine group, all subjects were awake and oriented. All subjects were cooperative, able to perform the head test and had no muscle weakness.

Summary of other variables
For subjects who only received an intubating dose of NMBA the mean time from last administration of NMBA to reappearance of the T_2 is approximately 10 minutes shorter in the roc/Org 25969 group compared to the cis/neostigmine group. No difference between the treatment groups with regard to T_1 at reappearance of T_2 was observed. For subjects who received an intubating dose of NMBA and an intubating dose and at least one maintenance dose the mean time from last administration of NMBA to reappearance of the T_2 and T_1 at reappearance of T_2 was similar in both treatment groups.
The mean onset of rocuronium was estimated to be 80 seconds faster than the mean onset of cisatracurium. The 95% CI for the estimated difference ranged from 61 to 99 seconds.

Summary of safety
For a total of 55 out of 73 subjects (75.3%) at least one AE was reported: 27 subjects (79.4%) in the roc/Org 25969 group and 28 subjects (71.8%) in the cis/neostigmine group. Five subjects (6.8%) experienced one or more AEs that were judged to be possibly, probably or definitely related to Org 25969 or neostigmine, by the investigator: four (11.8%) in the roc/Org 25969 group and one (2.6%) in the cis/neostigmine group. In the roc/Org 25969 group, one subject experienced 'swelling face' and 'nausea', two subjects experienced 'increased beta-N-acetyl-D-glucosaminidase' and one subject experienced 'chills' and 'tremor', as drug-related AEs. One subject in the cis/neostigmine group experienced 'nausea'.

None of the subjects discontinued from the trial due to an AE, SAE/SPE or medical device (near) incident. For five subjects (14.7%) in the roc/Org 25969 group and five subjects (12.8%) in the cis/neostigmine group an AE was reported which was classified as being of severe intensity. None of these AEs were considered to be related to IP administration. None of the subjects experienced an SAE after IP administration, and for none of the subjects a SPE or a medical device (near) incident was reported.

There is no indication that medically relevant differences exist in laboratory variables between the roc/Org 25969 group and the cis/neostigmine group.

In total 14 subjects (six subjects in the roc/Org 25969 group and eight subjects in the cis/neostigmine group) showed one or more markedly abnormal SBP and/or DBP value. None of these markedly abnormal SBP or DBP values was reported as an AE. For two subjects (one in each treatment group) a markedly abnormal HR value was recorded (for neither subject this was recorded as an AE). The course of the mean SBP over the assessment period was similar in both treatment groups. The mean DBP and the mean HR were higher at 2 to 10 minutes post-dose in the cis/neostigmine group as compared to the roc/Org 25969 group over the studied time period.

Conclusions

This trial showed that the geometric mean time to recovery of the T_4/T_1 ratio to 0.9 was 2 min:02 sec in the roc/Org 25969 group and 8 min:46 sec in the cis/neostigmine group. The time to recovery of the T_4/T_1 ratio to 0.9 was estimated to be over 4 times faster in the roc/Org 25969 group compared to the cis/neostigmine group. The mean onset of rocuronium was estimated to be 80 seconds faster than the mean onset of cisatracurium. In conclusion, the combination of roc/Org 25969 is more efficacious than the combination of cis/neostigmine for control of neuromuscular blockade.

The safety profile was comparable in both the roc/Org 25969 group and the cis/neostigmine group. None of the subjects experienced an SAE after IP administration. No cases of recurarization occurred in this trial.