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, placebo-controlled, safety-assessor blinded trial, evaluating the safety and efficacy of Org 25969 in cardiac patients

Studied period (years)

November 2005 – August 2006

Clinical phase

Phase IIIa

Objectives

Primary objective:

To evaluate the safety of 2.0 and 4.0 $mg.kg^{-1}$ Org 25969 in cardiac patients compared to placebo.

Secondary objective:

To evaluate the time to recovery from a neuromuscular blockade induced by rocuronium after reversal at reappearance of T_2 by 2.0 and 4.0 $mg.kg^{-1}$ Org 25969 in cardiac patients.

Methodology

This was a multi-center, randomized, parallel-group, placebo-controlled, safety-assessor blinded trial.

Number of subjects (total and for each treatment)

In total, 120 patients were planned to be included, 40 in each of the three treatment groups, i.e. placebo, 2.0 $mg.kg^{-1}$ Org 25969, and 4.0 $mg.kg^{-1}$ Org 25969.
In total 121 subjects were randomized and 116 subjects were treated with IP: 38 subjects with 2.0 $mg.kg^{-1}$ Org 25969, 38 subjects with 4.0 $mg.kg^{-1}$ Org 25969 and 40 with placebo. In total 116 subjects completed the trial.

Diagnosis and criteria for inclusion

Cardiac patients (i.e. patients with ischemic heart disease, chronic heart failure or arrhythmia), of NYHA Class II to III; ASA class maximally 4 (class 4 only because of NYHA class III); Age at least 18 years; Scheduled for elective, non-cardiac surgery under general anesthesia with propofol in the supine position, with planned muscle relaxation using rocuronium and allowing for 12-lead ECG assessment during surgery; 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;
- Esmeron® (rocuronium bromide), supplied in colorless 10 mL vials containing 100 mg (i.e. 10 $mg.mL^{-1}$) of rocuronium

Duration of treatment

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

Reference therapy, dose and mode of administration

- Placebo, supplied in 10 mL miniplasco's containing commercially available NaCl 0.9%

Criteria for evaluation

Safety variables: Adverse events (AEs, SAEs, SPEs, MDNIs), laboratory parameters, physical examinations, vital signs (blood pressure and heart rate), ECGs, clinical evidence of recurarization or residual curarization, and events due to interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium.
Efficacy variables: Time from start administration of IP to recovery T_4/T_1 ratio to 0.9, to 0.8 and to 0.7; time from start administration of the last dose of rocuronium to recovery T_4/T_1 ratio to 0.9, to 0.8 and to 0.7; time from start administration of IP to reappearance of T_3; T_1 at reappearance of T_3; clinical signs of recovery.

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

Statistical methods

For all variables including efficacy parameters appropriate descriptive summary statistics were calculated including frequency tables for events and categorical results. The safety parameters blood pressure, heart rate and corrected QT intervals derived from ECG were compared between treatment groups using an ANCOVA with factor treatment (and gender for ECG) with baseline value as covariate, presenting pairwise contrasts between each dose group of Org 25969 and placebo with two-sided 95% confidence intervals. Assumptions of the ANCOVA were checked and in case of marked deviation an ANOVA on changes from baseline was performed, in addition. For vital signs and ECG data descriptive summary statistics are also presented, including statistics on changes from baseline and frequency tables with shifts from baseline.

Summary

Summary of safety

For a total of 89 out of 116 subjects (76.7%) at least one AE was reported: 27 subjects (71.1%) in the 2.0 $mg.kg^{-1}$ Org 25969 group, 32 subjects (84.2%) in the 4.0 $mg.kg^{-1}$ Org 25969 group and 30 subjects (75.0%) in the placebo group.

In total 18 subjects (15.5%) experienced one or more AEs that were judged to be (possibly) related to Org 25969 or placebo by the investigator: 5 (13.2%) subjects in the 2.0 $mg.kg^{-1}$ Org 25969 group, 6 (15.8%) subjects in the 4.0 $mg.kg^{-1}$ Org 25969 group and 7 (17.5%) in the placebo group.

The most frequently reported AEs were procedural pain (for 40- 47% of subjects of each treatment group), nausea (placebo: 22.5%, 2.0 $mg.kg^{-1}$ Org 25969 group: 13.2%, 4.0 $mg.kg^{-1}$ Org 25969 group: 23.7%), and pharyngo-laryngeal pain (placebo: 7.5%, 2.0 $mg.kg^{-1}$ Org 25969 group: 13.2%, 4.0 $mg.kg^{-1}$ Org 25969 group: 15.8%).

The most frequently reported (possibly) drug-related (according to the investigator) AEs were “Beta 2 microglobulin (urine) increased” in 5 cases and “Electrocardiogram QT (corrected interval) prolonged” in 3 cases.

None of the subjects discontinued from the trial due to an AE.

For 9 (23.7%) subjects in the 2.0 $mg.kg^{-1}$ Org 25969 group, 6 (15.8%) subjects in the 4.0 $mg.kg^{-1}$ Org 25969 group and 9 (22.5%) in the placebo group an adverse event was reported which was classified as being of severe intensity.

For none of the subjects an SPE or a medical device related (near) incident was reported after administration of IP.

One subject in the placebo group died during the trial, 11 days after the surgery.

SAEs starting after IP administration were reported for 16 subjects: 5 subjects in the 2.0 $mg.kg^{-1}$ Org 25969 group, 6 subjects in the 4.0 $mg.kg^{-1}$ Org 25969 group and 5 subjects in the placebo group. The 3 SAEs that were assessed to be (possibly) related to study drug, were 3 cases of ‘Electrocardiogram QT (corrected) interval prolongation’, one in each treatment group.

For none of the subjects a markedly abnormal hematology value was reported as a drug-related AE. For 1 subject in the placebo group two markedly abnormal values for biochemistry were reported as (possibly) related AEs: “Alanine aminotransferase increased” and “Aspartate aminotransferase increased”.

For 5 subjects (two in the placebo group and three in the Org 25969 groups) markedly abnormal urinary results post-anesthesia were reported as possibly related AE: five (5) cases of “Beta 2 microglobulin (urine) increased”; and one case of “Albumin urine present”.

A significant difference between treatment groups in both systolic and diastolic blood pressure was seen at 30 min post-IP, when both dose groups of Org 25969 had markedly higher values than placebo, i.e. returning to normal levels. A difference between treatment groups in heart rate was seen in change from baseline at 2, 5 and 10 min post-IP, when both dose groups of Org 25969 showed greater decrease from baseline than placebo. This trend reversed at 30 min post-IP. The most probable reason for these differences at 30 minutes was that for a considerable number of subjects in the two dose groups of Org 25969 anesthetic medication was stopped before the 30 minutes assessment, in contrast to the placebo group.

Interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium (i.e. atracurium) was reported for one subject. No events due to recurarization or residual curarization were reported.

Referring to the ECG report, the majority of the point estimates for the difference in QTc (Fridericia) between the active and placebo groups were negative; only one estimate (at 5 minutes in the 4.0 $mg.kg^{-1}$ Org 25969 group) showed a positive point estimate, but none of these differences was statistically significant. These data therefore gave no indication of a possible prolongation effect of Org 25969 on QTcF.

The number of subjects with abnormal QTcF interval was at all timepoints post-IP higher or at least as high in the placebo group as in each of the two dose groups of Org 25969, and higher for placebo especially at 10 and 30 min post-IP.

The incidence of T-wave abnormalities was similar across all treatment groups at all timepoints. Pathological U-waves not yet present at baseline were seen in 5 subjects (4 in the 4.0 $mg.kg^{-1}$ Org 25969 group, 1 in the 2.0 $mg.kg^{-1}$ Org 25969 group, and none in placebo). No other treatment related ECG morphology or diagnostic abnormalities of clinical relevance were reported.

Summary of efficacy

The mean times from the start of the administration of IP to recovery of the T_4/T_1 ratio to 0.9 were 36 min:52 sec in the placebo group and 1 min:57 sec and 1 min:26 sec respectively in the 2.0 and 4.0 $mg.kg^{-1}$ Org 25969 dose groups. Furthermore the 4.0 $mg.kg^{-1}$ Org 25969 group had a faster mean recovery than the 2.0 $mg.kg^{-1}$ Org 25969 group according to the point estimates (difference in geometric means of 23 seconds).

The mean times from the start of the administration of IP to recovery of the T_4/T_1 ratio to 0.7 were 27 min:12 sec in the placebo group and 1 min:23 sec and 1 min:07 sec respectively in the 2.0 and 4.0 mg.kg^{-1} Org 25969 dose groups. The mean times from the start of the administration of IP to recovery of the T_4/T_1 ratio to 0.8 were 31 min:38 sec in the placebo group and 1 min:33 sec and 1 min:13 sec respectively in the 2.0 and 4.0 mg.kg^{-1} Org 25969 dose groups.
Although there was a difference between treatment groups in performing the 5-sec head lift test prior to transfer to the recovery room, the majority of subjects in each treatment group were awake and oriented, cooperative, and able to do the head lift with no general muscle weakness. Also, this number increased from assessment 1 to assessment 2.
Summary of other variables
The mean time from the start of administration of the last bolus dose of rocuronium to the time of reappearance of T_2 was 41 min:39 sec in case only an intubating dose was administered and 29 min:21 sec in case one or more maintenance doses of rocuronium were administered. The mean T_1 at reappearance of T_2 for the two groups was 20.6% or 18.4%, respectively.
The QoR-40 results will be presented in a separate Health Economics report for the Org 25969 program.

Conclusions

This trial was conducted in order to evaluate the safety of 2.0 and 4.0 mg.kg^{-1} Org 25969 in cardiac patients compared to placebo, and to evaluate the time to recovery from a neuromuscular blockade induced by rocuronium after reversal at reappearance of T_2 by 2.0 and 4.0 mg.kg^{-1} Org 25969.
The safety data indicated that Org 25969 at dose levels of up to 4.0 mg.kg^{-1} can be used safely in cardiac patients. Interaction of Org 25969 with an endogenous or exogenous compound other than rocuronium was reported for one subject who had a report of fast recovery after application of 15 mg of atracurium, administered 12 minutes after IP. Recurarization as defined in the protocol (i.e. a decline in the T_4/T_1 ratio from ≥ 0.9 to <0.8) was not observed in this trial, nor were there any cases of clinical evidence of recurarization or residual curarization reported.
This trial showed that for cardiac patients treated with rocuronium the mean time to recovery of the T_4/T_1 ratio from IP administration to 0.9 was 36 min:52 sec in the placebo group and 1 min:57 sec and 1 min:26 sec respectively in the 2.0 and 4.0 mg.kg^{-1} Org 25969 dose groups. This indicates that Org 25969 at dose levels of 2.0 and 4.0 mg.kg^{-1} is effective in cardiac patients.
According to the independent cardiologist from Covance, this study provides no indication for an association between Org 25969 and QT/QTc prolongation or other morphologic or diagnostic ECG abnormalities at dose levels of up to 4.0 mg.kg^{-1} in cardiac patients.