CONFIDENTIAL I / V 19.4.304

Name of company Organon NV **Name of active substance** Org 25969	**Synopsis / Tabular Format** **referring to**	

Title of the clinical trial

A multi-center, parallel group, comparative trial evaluating the efficacy, pharmacokinetics and safety of Org 25969 in subjects with normal or impaired renal function

Investigator(s)

PPD

Clinical trial center(s)

PPD

Report/publication (ref)

Not applicable

Studied period (years)

June 2005 - April 2006

Clinical phase

Phase IIIa – Special population trial

Objectives

The clinical trial objectives were:
- To show equivalence with respect to the efficacy of Org 25969 in subjects with normal or impaired renal function
- To compare the pharmacokinetics of Org 25969 in subjects with normal or impaired renal function
- To evaluate the safety of Org 25969 in subjects with impaired renal function

Methodology

This was a multi-center, parallel-group, comparative trial in two stages.

Number of subjects (total and for each treatment)

In total 30 subjects were enrolled into the trial; 15 renally impaired subjects and 15 control subjects. None of the subjects discontinued from the trial before administration of Org 25969.
All 30 subjects, 16 females and 14 males, received a dose of Org 25969 and their age ranged from 29 to 81 years (inclusive). Except for two PPD , all subjects were Caucasian. The ethnicity for all subjects was not Hispanic or Latino.

Diagnosis and criteria for inclusion

ASA class 1 – 3 for renally impaired patients, ASA class 1-2 for control group; Age at least 18 years; Scheduled for general anesthesia without further need for muscle relaxation other than one single dose of 0.6 $mg.kg^{-1}$ rocuronium; Scheduled for surgical procedures in the supine position; Written informed consent; Creatinine clearance (CL_{CR}) < 30 mL/min for renally impaired group and CL_{CR} ≥ 80 mL/min for control group.

Test product, dose and mode of administration, batch No.

- Org 25969 (investigational product, IP) supplied in 5-mL vials containing 500 mg active entity (i.e. 100 mg.mL^{-1}) of Org 25969 (Batch numbers: CZ180 and CX203)
- Esmeron® (rocuronium bromide) supplied in colorless 10-mL vials containing 100 mg (i.e. 10 mg.mL^{-1}) of rocuronium bromide (further referred to as rocuronium -> check waar dit voor het eerst al genoemd wordt) (Batch numbers: CZ191 and CX204)

Duration of treatment

Org 25969 was to be given as a single bolus dose. Full recovery from neuromuscular blockade was to be expected at the end of anesthesia.

Reference therapy, dose and mode of administration, batch No.

Not applicable.

Criteria for evaluation

Neuromuscular variables
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 T_4/T_1 ratio to 0.7; Time from start administration of Org 25969 to recovery T_4/T_1 ratio to 0.8.
Other efficacy variables:
Time from start administration of Org 25969 to reappearance of T_3; T_1 at reappearance of T_3; Time from start administration of rocuronium to recovery T_4/T_1 ratio to 0.7; Time from start administration of rocuronium to recovery T_4/T_1 ratio to 0.8; Time from start administration of rocuronium to recovery T_4/T_1 ratio to 0.9; Occurrence of recurarization; Time from start administration of Org 25969 to value of the lowest T_4/T_1 ratio in case of recurarization; Value of the lowest T_4/T_1 ratio in case of recurarization; Time from start administration of Org 25969 to return of T_4/T_1 ratio to 0.9 in case of recurarization.
Other neuromuscular variables:
Time from start administration of rocuronium to reappearance of T_2; T_1 at reappearance of T_2.

Pharmacokinetic assessments
Plasma pharmacokinetic parameters: terminal half-life (t½), effective half-life (t½.effective), (dose-normalized) area-under-the-curve ((dn-)AUC0-tlast and (dn-)AUC0-∞), mean residence time (MRT), (weight-normalized) clearance ((wn-)CL), (weight-normalized) volume of distribution during terminal phase ((wn-)Vz) and (weight-normalized) volume of distribution at steady-state ((wn-)Vss).
Urine pharmacokinetic parameters: (cumulative) amount excreted in urine (Ae(cum,t)) and urinary excretion rate (Ru). In subjects receiving hemodialysis the rates and half-lives of dialysis were calculated.

Safety assessments
Vital signs, i.e. blood pressure (BP) and heart rate (HR); Physical examination; (Serious) adverse events; Laboratory assessments: hematology, biochemistry and urinalysis.
Additional measures of safety
Clinical evidence of recurarization or residual curarization, e.g. respiratory problems; Clinical assessments of recovery, i.e. consciousness, 5 seconds head lift test, presence of diplopia, check of general muscle weakness, tongue depressor test; Signs of poss ble interaction of Org 25969 with endogenous compounds or with exogenous compounds other than rocuronium.

Statistical methods

For all variables appropriate descriptive statistics were calculated. To investigate equivalence, the primary efficacy variable was analyzed using a confidence interval (CI) approach for the subject group difference. Data of the secondary efficacy variables were analyzed in the same way as was done for the primary efficacy variable. For safety descriptive statistics are presented. Descriptive statistics for the Org 25969 and rocuronium concentrations in plasma and the pharmacokinetic parameters were calculated. Analysis of Variance (ANOVA) was used on log-transformed pharmacokinetic parameters with factor group at the 5% level of significance.

Summary

In total 30 subjects were randomized in one of the two subject groups. All subjects received a dose of Org 25969, and hence the AST group consisted of 30 subjects. All subjects who received a dose of Org 25969 also had at least one efficacy assessment and hence the ITT group consisted of 30 subjects. For one subject a major protocol violation was observed and this subject was excluded from the PP group. Consequently, the PP group consisted of 29 subjects.
The ASPE consisted of all subjects from the AST group for whom at least one pharmacokinetic parameter could be calculated according to the protocol and who did not have any protocol violations interfering with PK. This was the case for 26 subjects.

Summary of efficacy
Primary efficacy variable:
Administration of 2.0 mg.kg^{-1} Org 25969 at reappearance of T_2 after an intubating dose of 0.6 mg.kg^{-1} rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 of exactly 2 minutes for the renally impaired subjects, and 1 min:39 sec for the control subjects (PP-group). Based on the pre-specified full ANOVA model, the estimated mean absolute difference in the time from the start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 between the renally impaired and control subjects was +27.3 seconds. The corresponding 95% CI ranged from -10.9 to +65.5 seconds. The CI was not completely within the pre-defined equivalence interval of -60 to +60 seconds and equivalence could not be claimed between the two subject groups.
Based on the additive ANOVA model, the estimated mean absolute difference in the time from the start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 between the renally impaired and control subjects was +20.1 seconds and the corresponding 95% CI ranged from -12.1 to +52.3 seconds. This CI was completely within the pre-defined equivalence interval.

Secondary efficacy variables:
Mean times from start of administration of 2.0 mg.kg^{-1} Org 25969 to recovery of the T_4/T_1 ratios to 0.7 and 0.8 were 1 min:27 sec and 1 min:36 sec, respectively, in the renally impaired group, and 1 min:10 sec and 1 min:19 sec, respectively, for subjects in the control group. Based on the pre-specified full ANOVA model, the estimated mean absolute difference between the renally impaired and control subjects in time from the start of administration of Org 25969 to:

- recovery of the T_4/T_1 ratio to 0.7 was +20.6 seconds, with the corresponding 95% CI ranging from -2.4 to +43.6 seconds; and
- recovery of the T_4/T_1 ratio to 0.8 was +22.5 seconds, with the corresponding 95% CI ranging from -4.9 to +49.9 seconds.

These CIs were completely within the pre-defined equivalence interval of -60 to +60 seconds.
The additive ANOVA model resulted in 95% CIs ranging from -3.8 to +35.2 seconds and –7.3 to +39.2 seconds, respectively.

Other efficacy variables:
The mean time from start of administration of Org 25969 to reappearance of T_3 for the PP group was 1 minute and 2 seconds in the renally impaired group, and 49 seconds in the control group. The mean T_1 at reappearance of T_3 was similar in the two subject groups: 35.0% (renally impaired) and 33.2% (control). Mean times from start of administration of rocuronium to recovery of the T_4/T_1 ratios to 0.7, 0.8 and 0.9 were longer in the renally impaired group than in the control group: 55 min:50 sec, 55 min:59 sec and 56 min:23 sec respectively in the renally impaired group as compared to the mean times 42 min:28 sec, 42 min 37 sec and 42 min 57 sec respectively in the control group. This difference can be explained by the finding that the time from start of administration of rocuronium to reappearance of T_2 is longer in the renally impaired group as compared to the control group. For none of the subjects 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 observed during the time period that neuromuscular monitoring was performed.

Summary of other variables
Pharmacokinetics
In severely renally impaired patients the wn-CL of Org 25969 was reduced approximately 16-fold and terminal $t_{1/2}$ increased 15-fold compared to normal patients. The wn-V_{ss} of Org 25969 was increased 25 % compared to normal patients. This resulted in prolonged exposure and a 17-fold higher dn-$AUC_{0\text{-inf}}$ of Org 25969 in renally impaired patients. However, during the first 60 minutes post administration of Org 25969 only a slight difference in plasma levels could be observed between the two groups. All mentioned PK parameters were statistical significantly different ($p<0.05$).
In severely renally impaired patients wn-CL of rocuronium was reduced approximately 3.7-fold and terminal $t_{1/2}$ increased 2.5-fold compared to normal patients. The wn-V_{ss} of rocuronium was increased with 25% compared to normal patients. This resulted in prolonged exposure and a 4-fold higher dn-$AUC_{0\text{-inf}}$ of rocuronium (bound and unbound) in renally impaired subjects. All mentioned differences were statistically significant ($p<0.05$).

The clearance of Org 25969 and to a lesser extent rocuronium showed a highly significant correlation with creatinine clearance, confirming the importance of renal elimination for the clearance of Org 25969.
The much smaller effect of renal impairment on the $t_{1/2}$ of rocuronium than on that of Org 25969 indicates that a substantial portion of rocuronium was eliminated via the liver, despite the presence of excess binding agent.
Nine renally impaired subjects received hemodialysis within the first 72 h after surgery. The small number of subjects per filter type (2 for high flux and 7 for low flux) and the limited sampling means that results must be interpreted with care. Dialysis half-lives were consistently lower for rocuronium than for Org 25969 for both low and high flux filters. Low flux filters appeared to be almost ineffective for removing Org 25969 from circulation as plasma levels before and after dialysis appeared to be unaffected by dialysis in these seven cases. High flux filters resulted for sugammadex in uncorrected dialysis half-lives of 5 hours and a reduction in plasma concentration of about 40% for the only two subjects dialyzed using the high flux filter.
Urinary excretion of both rocuronium and Org 25969 was much slower in the renally impaired group than in the control group. This suggests that a collection interval of 0-72h is not long enough to determine complete urinary excretion of Org 25969 in renally impaired patients. In the case of rocuronium, a much smaller fraction of the dose was excreted renally in the renally impaired group than in the control group. This can be explained by a relative shift to hepatic elimination of rocuronium in the renally impaired group.

Additional neuromuscular variables
The mean time from start of administration of rocuronium to reappearance of T_2 was longer for the renally impaired subjects (53 min 49 sec) as compared to the control subjects (40 min 38 sec). Mean T_1 values at reappearance of T_2 were 18.0% and 15.7% in the renally impaired and control group, respectively.

Summary of safety
For a total of 20 out of 30 subjects in the AST group (66.7%) at least one AE was reported: 8 subjects in the renally impaired group and 12 subjects in the control group.
For five subjects (16.7%) at least one drug-related AE was observed (possibly, probably or definitely related to IP according to the investigator).
The most frequently (in ≥10% of the subjects) reported AEs were “Nausea” (20.0%), “Procedural pain” (20.0%), “Pain” (10.0%), “Anaesthetic complication” (10.0%) and “Hypocalcaemia” (13.3%)
None of the subjects discontinued from the trial due to an AE. For 2 subjects (one renally impaired and one control subject) adverse events were reported which were classified as being of severe intensity.
No SPEs and no Medical Device (near) incidents were reported during this trial.

SAEs were reported for two subjects. One subject (renally impaired) experienced PPD of which the subject recovered and which had no relationship to IP according to the investigator.
One subject (control) experienced two SAEs: PPD For both SAEs the outcome of the subject on the last assessment was ‘unknown’ and the SAE was unlikely related to IP according to the investigator, but was not related to IP according to NV Organon.

Results with regard to hematology variables were comparable between the two subject groups. For biochemistry variables differences were observed for creatinine and urea nitrogen, which already existed at baseline. Generally results with regard to the urine variables were comparable between the subject groups, except for the parameters that were monitored as sensitive indicators for renal damage. For those parameters values above safety ranges were seen pre-dominantly in the renally impaired group, and generally these high values were already present at the screening assessment.

In total five (5) subjects had markedly abnormal vital signs values post-dose for systolic and/or diastolic blood pressure in comparison to a normal value (within safety ranges) at baseline.
For one subject who had a markedly abnormal low systolic blood pressure value at 10 minutes after Org 25969, this was reported as AE (procedural hypotension) and as such considered clinically significant (not related to IP according to the investigator).
For heart rate no markedly abnormal values were observed.

One event due to a possible interaction of Org 25969 with endogenous or exogenous compounds other than rocuronium was reported in one subject (renally impaired group). The event was PPD , and remifentanil and propofol were reported as compounds.
For one subject (control group) clinical evidence of recurarization or residual curarization was reported, based upon a decrease in oxygen saturation after administration of pethidine.

Conclusions

The trial was conducted in order to show equivalence with respect to the efficacy of Org 25969 in subjects with normal or impaired renal function; to compare the pharmacokinetics of Org 25969 in subjects with normal or impaired renal function; and to evaluate the safety of Org 25969 in subjects with impaired renal function.

- Administration of 2.0 mg.kg^{-1} Org 25969 at reappearance of T_2 after an intubating dose of 0.6 mg.kg^{-1} rocuronium, resulted in a mean time from start of administration of Org 25969 to recovery of the T_4/T_1 ratio to 0.9 of exactly 2 minutes for the renally impaired subjects, and 1 min:39 sec for the control subjects (PP-group).

  Based on the pre-specified full ANOVA model, the calculated CI ranged from -0.9 to +65.5 seconds. This is not completely within the pre-defined interval of -60 to +60 seconds and therefore equivalence between renally impaired and control patients could formally not be claimed. The interaction between trial site and subject group was observed to be not statistically significant (p=0.73) and therefore the additive ANOVA model, excluding the subject group by center interaction, was also applied. This CI was completely within the predefined equivalence interval.

  According to protocol, a stage 2 of the trial should be performed in case no equivalence with respect to recovery from neuromuscular blockade between subjects with normal renal function and those with impaired renal function could be demonstrated. The objective of a stage 2 would be to investigate the optimal dose of Org 25969 in subjects with normal or impaired renal function.
  Stage 1 of the study indicates that a dose of 2 mg.kg^{-1} of Org 25969 is efficacious. The data of the renally impaired subjects show a mean/median time to recovery of the T_4/T_1 ratio to 0.9 of exactly 2 minutes and of 1 min:38 sec, respectively, and given these results a higher dose would not result in a clinically significant decrease in recovery time. Since a similar efficacy would be expected in Stage 2, it was not deemed necessary to continue the trial into Stage 2.

  For none of the subjects 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 observed during the time period that neuromuscular monitoring was performed.

- In severely renally impaired patients plasma clearance of Org 25969 was reduced approximately 16-fold and terminal half-life increased 15-fold compared to normal patients. The volume of distribution of Org 25969 was increased 25 % compared to normal patients. This resulted in prolonged and 17-fold higher exposure to Org 25969 in renally impaired patients. However, during the first 60 minutes post administration of Org 25969 only a slight difference in plasma levels was observed between the two groups.
  In severely renally impaired patients plasma clearance of rocuronium was reduced approximately 3.7-fold and terminal half-life increased 2.5-fold compared to normal patients. The volume of distribution of rocuronium was increased with 25 % compared to normal patients. This resulted in prolonged and 4-fold higher exposure to rocuronium (bound and unbound) in renally impaired subjects.
  The clearance of Org 25969 and to a lesser extent rocuronium showed a highly significant correlation with creatinine clearance, confirming the importance of renal elimination for the clearance of Org 25969.
  Nine renally impaired subjects received hemodialysis within the first 72 h after surgery. The small number of subjects per filter type (2 for high flux and 7 for low flux) and the limited sampling means that results must be interpreted with care. Dialysis half-lives were consistently lower for rocuronium than for Org 25969 for both low and high flux filters. Low flux filters appeared to be almost ineffective for removing Org 25969 from circulation as plasma levels before and after dialysis appeared to be unaffected by dialysis in these seven cases. High flux filters resulted for sugammadex in uncorrected dialysis half-lives of 5 hours and a reduction in plasma concentration of about 40% for the only two subjects dialyzed using the high flux filter
  The urinary excretion of both Org 25969 and especially rocuronium was much slower in renally impaired subjects than in control subjects.

- The safety data indicated that Org 25969 was well tolerated by the subjects. Of the 3 SAEs which occurred in this trial, none were considered to be 'related' to IP according to the investigator. None of the subjects discontinued from the trial due to an AE.
  One event due to a possible interaction of Org 25969 with endogenous or exogenous compounds other than rocuronium was reported in one subject (renally impaired group). The event was PPD and remifentanil and propofol were reported as compounds.
  For one subject (control group) clinical evidence of PPD was reported, based upon a decrease in oxygen saturation after administration of pethidine.

It can be concluded that 2.0 mg.kg^{-1} is efficacious and well tolerated in subjects with severe renal impairment. As expected, in these subjects a different pharmacokinetic profile of both rocuronium and Org 25969 was observed as compared to subjects with normal renal function.