This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

Name of company NV Organon, part of Schering-Plough Corporation **Name of active substance** Org 28611	**Synopsis / Tabular Format** **referring to**	

Title of the clinical trial

A randomized, double-blind, active and placebo controlled trial to compare the relative analgesic efficacy and safety of a single intravenous dose of Org 28611 3.0 µg/kg, morphine sulfate 0.12 mg/kg, and placebo in patients experiencing moderate to severe pain after dental impaction surgery

Investigator(s)

[redacted]

Clinical trial center(s)

[redacted]

Report/publication (ref)

Not applicable

Studied period (years)

May, 2007
August, 2007

Clinical phase

Phase II

Objectives

The primary objective of this trial was to compare/evaluate the analgesic efficacy of a single IV dose of Org 28611 3.0 µg/kg to placebo in patients experiencing moderate to severe pain after dental impaction surgery. Analgesic efficacy was be defined in terms of overall effect, peak effect, onset and duration of effect, and overall evaluation of the drug as an analgesic. The primary measure of efficacy was total pain relief over the 0 – 4 hour interval ($TOTPAR_{0\text{-}4hr}$).

The secondary objectives of this trial were: (1) to compare the analgesic efficacy of a single IV dose of Org 28611 3.0 µg/kg to morphine sulfate 0.12 mg/kg in patients experiencing acute postoperative pain after dental impaction surgery, (2) to assess the safety and tolerability of Org 28611 3.0 µg/kg compared to morphine 0.12 mg/kg and to placebo, and (3) to characterize the pharmacokinetic (PK) profile of Org 28611 when administered to patients experiencing acute postoperative pain after dental impaction surgery.

Methodology

This trial was to be a single-center, randomized, double-blind, single-dose, 3-arms, parallel-group, active and placebo controlled trial in patients experiencing acute postoperative pain after surgical removal of 1 – 2 impacted third molar teeth, at least one of which had to be a mandibular full or partial bony impaction.

Number of subjects (total and for each treatment)

132 patients were to be allocated to the three treatment groups (44 patients per treatment group). Only 11 subjects completed the trial which was terminated prematurely by the sponsor because the clinical trial site had become insolvent and as result had to be closed.

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Diagnosis and criteria for inclusion

A patient was eligible for participation in the trial if he met the following inclusion criteria:

1. Had at least one mandibular partial or full bony impacted third molar requiring extraction. An ipsilateral maxillary third molar may also be extracted as may any adjacent supernumerary tooth (teeth)
2. Was willing and able to understand and complete the pain evaluations
3. Was male aged 18 to 40 years (inclusive)
4. .A subject, who had sexual partners of child-bearing potential, had agreed to use barrier contraception in addition to having their partner use another method for three months from the time of dosing. Also had agreed to abstain from sexual intercourse with pregnant or lactating women or to use condoms.
5. Had a body mass index (BMI) ≤ 32 kg/m^2 and had a body weight of at least 65 kg
6. Was in generally good health
7. Was able to speak, read, and understand English and provide meaningful written informed consent
8. Was able to remain at the research center for the entire 24-hours trial period
9. Had an initial pain intensity score of at least 45-mm on a 100-mm VAS and moderate or severe pain on a 4-point categorical scale within 6 hours of the end of surgery (VAS as the primary parameter and the categorical as a secondary parameter)
10. Was willing to return to the research center for the post-treatment visit 5 to 9 days after surgery and complete a 30 day SAE telephone call.

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

Patients were to receive a single intravenous (IV) infusion administered over 3 minutes of either Org 28611 3.0 µg/kg, morphine sulfate 0.12 mg/kg, or placebo within 6 hours after dental surgery, when they experienced moderate to severe dental pain.
Org 28611: Batch number used in this trial was [redacted]
Morphine sulfate: obtained by [redacted]
Placebo: Batch number used in this trial was [redacted]

Duration of treatment

Potential patients were asked to present to the research center for a screening visit. On the day of surgery, each patient was to remain at the research center for 24 hours after study drug administration. Each patient was also required to return to the research center for a routine postoperative visit 5 to 9 days after surgery and complete an (S)AE telephone call from the research staff 30 days after surgery.

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

Not applicable.

Criteria for evaluation

Following the surgery, carried out under a standardized local anesthetic technique, patients experiencing moderate to severe dental pain within 6 hours of surgery were to be randomized. Pain Intensity (PI) of 45 to 55–mm on a 100–mm Visual Analog Scale (VAS) was considered moderate and PI of 55–mm or greater was considered severe. Randomized patients were to receive one of the following treatments: Org 28611 3.0 µg/kg, morphine sulfate 0.12 mg/kg, or placebo. Patients will remain seated for about two hours post dosing. Patients were to be evaluated for analgesic efficacy for 8 hours after dosing. PI was to be measured using a standard 4-point categorical scale and a 100-mm VAS. Pain relief (PR) was to be measured using a standard 5-point categorical scale. The primary measure of efficacy is $TOTPAR_{0\text{-}4hr.}$
PI and PR were to be assessed by trained research center staff immediately before dosing and at 5, 10, 15, 30, 45, 60, and 90 minutes after dosing and then hourly from 2 hours through 8 hours. Pain assessments were also to be performed just prior to the rescue medication. . Assessments at 5, 10, 15, and 30 minutes were allowed a deviation up to 2 minutes and assessments done at 45 minutes and beyond were allowed a deviation up to 5 minutes from the specified time.
Patients were to be encouraged to wait at least 60 minutes after dosing to permit maximal evaluation of efficacy. Two stopwatches were to be used to measure the time to onset of first perceptible pain relief and time to onset of meaningful pain relief. Global evaluations of the trial medication and a drug-liking scale were to be performed at 8 hours or immediately prior to rescue medication if taken before 8 hours.

Blood samples for PK analyses were to be collected from all patients at baseline, 1, 3, 12, 17, 32, minutes and at 1:02, 2:02, 4:02, and 8:02 hours post-dose time points. A deviation of the sample collection time was allowed as follows: from dosing up to and including 32 minutes after dosing, 1 minute; from 33 minutes up to and including 4:02 h after dosing, 2 minutes; from 4:03 h up to and including 8:02 h after dosing, 10 minutes.

Vital signs (BP, HR) were to be recorded at screening, baseline (immediately before drug administration), at 6, 13, 20, 35, 65, 95 minutes and 2:05, 4:05, and 8:05 hours post-drug administration. Vital signs were to be obtained at 24 hours discharge and at the 5-9 days follow up visit. SpO_2 was to be recorded at the baseline and continuous pulse oximetry was to be performed for the first 2:05 hours post-drug administration. If SpO_2 fell below 90% saturation, additional O_2 administration was allowed, the onset time and duration was to be recorded. The recording of BP and HR at 6, 13, 20 and 35 minutes was allowed a variation up to 2 minutes and the recording at 65 minutes and beyond was allowed a deviation up to 5 minutes from the specified time. 12-lead ECGs was to be performed prior to surgery, prior to dosing, 22 minutes after the study medication administration, and at 8:08 hours, at 5-9 days follow-up or early termination. Patients were to be prepared for EEG after completion of the surgery and the EEG was to be started as soon as the first signs of pain expressed by the patients. The EEG was to continue recording for a minimum 15 minutes prior to dosing and for 1 hour post dose.

Patients were to remain in the clinical trial unit and were to be followed for safety for 24 hours after dosing regardless of the time to rescue medication. Upon discharge, patients were to undergo a brief physical and dental examination including vital signs (BP and HR) and clinical laboratory testing. All adverse events (AE) and serious adverse event (SAE) observed by trial staff or reported by patients between the screening and first dose and after dosing with trial medication were to be recorded.

Patients were to return to the research center for a follow-up safety evaluation visit 5 to 9 days post-treatment. A physical examination, dental examination and postoperative laboratory tests (biochemistry, hematology, and urinalysis) were to be performed. ECG and vital signs (BP and HR) were to be measured. Patients were to be contacted for 30 day follow up SAEs.

Statistical methods

Analysis Populations: The main emphasis for the primary efficacy analysis was to be on the Intent-to-treat (ITT) population, i.e., all randomized patients who received trial medication and completed at least one post-baseline pain intensity or pain relief assessment according to the treatment to which they were randomized. The Safety population was to consist of all randomized patients who received any trial medication, according to the treatment they actually received.

Primary Efficacy Analysis: For the primary measure of efficacy, $TOTPAR_{0\text{-}4hr}$, analysis of covariance (ANCOVA) was to be performed with treatment and baseline pain intensity score (dichotomous) as factors. The Org 28611 dosage was to be compared to placebo using a 2-sided test derived from this model at an alpha level at the 5%.

Safety Analyses: The safety analysis was on the Safety population. Clinical and statistical interpretation of the standard set of safety measures was to be evaluated: laboratory tests, medical history, vital signs, physical examinations, ECGs, EEGs, and AE data, including serious adverse events.

All AEs, SAEs, and Medical history were to be coded using the latest version of MedDRA at the time of database lock [redacted] Concomitant medications that were to be coded using the World Health Organization (WHO) Drug Dictionary [redacted]

Due to the low number of subjects, it was decided not to use any of the three populations (ITT, PP and safety), but to use the data of all 11 included subjects. The data of these 11 subjects was only to be presented and summarized by means of individual listings and no inferential statistics were to be performed.

Summary

Disposition of patients
Overall 11 subjects were included in the study and received treatment with Org 28611 (n=3), morphine sulfate (n=5) or placebo (n=3).
None of the subjects withdrew consent prior to any treatment. None of the subjects discontinued from this trial. However, 10 subjects used rescue medication (3 subjects in the Org 28611 group, 5 subjects in the morphine group, 2 subjects in the placebo group). One subject in the placebo group did not use any rescue medication.

The screening and dosing of new subjects was stopped, because the clinical trial site had become insolvent and as a result had to close down. The subjects that had been dosed were to be able to attend follow up visits and have data collected in time.

Efficacy

Six subjects, two in the Org 28611 treatment group, three in the placebo treatment group and one in the morphine sulfate treatment group had a little, some, a lot or complete pain relief at any of the planned assessments. One subject in the Org 28611 treatment group had a little relief at the “prior to rescue” assessment.

Out of the 10 subjects who used rescue medication, 9 subjects had no pain relief at the "prior to rescue" assessment.

At the "prior to rescue" assessment, eight subjects had a "severe" pain intensity with corresponding VAS scale value ranging from 78 to 99. At the "prior to rescue" assessment, two subjects had a "moderate" pain intensity with a VAS scale value of 50 and 70, respectively.

Four subjects did not have any perceptible or meaningful pain relief at any timepoint. One subject in the morphine sulfate group had perceptible pain relief at 12 minutes and 28 seconds after study drug administration, but prior to using rescue medication, but no meaningful pain relief. Five subjects (one in the Org 28611 treatment group, two in the placebo treatment group and two in the morphine sulfate treatment group) had perceptible pain relief ranging from 1 minute and 13 seconds to 2 hours, 9 minutes and 9 seconds. Corresponding meaningful pain relief ranged from 9 minutes and 44 seconds to 2 hours, 35 minutes and 9 seconds. Three of these subjects (one in each treatment group) had their perceptible and meaningful pain relief prior to using rescue medication.

One subject in the placebo group had complete pain relief (pain intensity "none", VAS score: 0). For this subject it took 50 minutes and 2 seconds to have perceptible pain relief and 1 hour, 18 minutes and 10 seconds to have meaningful pain relief. This subject did not use rescue medication.

Safety

Adverse events

Nine out of the 11 subjects experienced one or more adverse events (AEs). Nine subjects experienced in total eighteen adverse events which were considered mild. Five subjects experienced in total eight adverse events which were considered moderate. One subject in the placebo treatment group experienced one severe adverse event; i.e., *disturbance in attention.*

Three subjects experienced five AEs that were considered by the investigator to be possibly related to IP. Six subjects experienced seven AEs that were considered by the investigator to be probably related to IP. [redacted] For these related events, the System Organ Classes were: Nervous system disorders (seven events), Investigations (three events), Gastrointestinal disorders (two events) and Vascular disorders (one event).

Two subjects did not recover from their AEs at the end of the trial period. The AEs were *Paraesthesia oral* in the Org 28611 treatment group, SOC: Gastrointestinal disorders and *Nasopharyngitis* in the morphine sulfate treatment group, SOC: Infections and infestations.

The System Organ Classes that were reported are (in order of decreasing occurrence) Nervous system disorders (8 times), Gastrointestinal disorders (6 times), Investigations (3 times), General disorders and administration site conditions (2 times), Infections and infestations (2 times), Injury, poisoning and procedural complications (2 times), Musculoskeletal and connective tissue disorders (2 times), Respiratory, thoracic and mediastinal disorders (once) and Vascular disorders (once).

Deaths, SAEs

None of the subjects died during the study. No other serious adverse events (SAEs) or serious trial procedure related events (SPEs) before or after administration of IP occurred. No other significant adverse events after administration of IP were reported.

For one of the subjects in the placebo group, one AE was considered severe. This subject experienced *Disturbance in attention*. The AE started 23 minutes after placebo administration and lasted 51 minutes. No action on IP was taken. The AE was considered by the investigator to be probably related to investigational product. The subject recovered from this AE.

No other serious adverse events (SAEs) or serious trial procedure related events (SPEs) before or after administration of IP occurred. No other significant adverse events were reported. One other significant Pre-treatment event (pre-existing mild epileptic activity) was reported for one subject in the morphine group and was considered a protocol deviation. During the treatment period the ECG of this subject remained abnormal which was described as epileptiform activity.

Aside from an isolated blood chemistry value, i.e. phosphate, outside the Safety range for one subject in the morphine group at discharge and several subjects with hematology assessments outside the Safety range (monocytes and neutrophils), at discharge, no other laboratory abnormalities were reported. For urinalysis, values outside the Safety range were reported at discharge for erythrocyte count sediment in two subjects in the morphine group and leukocyte count sediment in one subject in the morphine group. No abnormal values were reported as AEs.

One subject in the placebo treatment group and one subject in the morphine treatment group had an abnormal ECG during the treatment period that was considered clinically significant by the investigator (Bazett QT_c in treatment value was 406 ms when compared to baseline value of 360 ms and Bazett QT_c in treatment value was 412 ms when compared to baseline value of 372 ms, respectively). For the placebo-treated subject, the ECG returned to normal at 8hr assessment. For the morphine-treated subject, the ECG did not return to normal values, but was considered clinically insignificant, according to the investigator, at post-treatment.

Three subjects, one in the placebo group, one in the morphine group and one in the Org 28611 group, had an elevated blood pressure starting at 13 minutes, 6 minutes and 6 minutes after IP administration, respectively. The blood pressures returned to normal at the 8 hr assessment. One subject in the morphine treatment group had an elevated blood pressure, which was reported as an AE, and started 6 minutes after IP administration and returned to normal at 8 hr assessment.

PK

After single dose administration, the individual C_{max} values were 3.33, 2.32 and 5.63 ng/ml in plasma. Within a sampling timeframe of 8 hours, the individual overall exposures, expressed by $AUC_{0\text{-}inf}$ were 13.2, 16.0 and 11.2 ng*h/mL, corresponding to a mean exposure of 13.3 ng*h/mL. The mean terminal elimination half-life was 4.45 hr.

Conclusions

No meaningful conclusions can be drawn from the data as only eleven subjects were treated, due to the early termination of this trial, because the clinical trial site had become insolvent and as a result had to close down. Neither can any meaningful conclusion be drawn from the pharmacokinetic results data as only three subjects were treated with Org 28611.

Flow chart of patient assessments

	Screening	Pre-surgery	Pre-dose (Baseline)	Post dosing	Discharge	Post-Treatment (or early termination)	
	Days -28 to -1		0 hour		24 hours	5-9 days	30 days phone call
Informed consent	X						
Inclusion/exclusion criteria[a]	X	X	X				
Demographics	X						
Medical history	X	X					
Physical examination[b]	X	X			X	X	
Vital signs[c] & Dental Exam	X		X	X	X	X	
Pulse oximetry[d]	X		X	X			
Screening EEG[e]	X						
Electrocardiogram[f]	X	X	X	X		X	
Clinical laboratory tests[g]	X				X	X	
Urine drug screen(dipstick)	X	X					
EEG in treatment phase[h]			X	X			
Trial medication			X				
Pain assessments[i]			X	X			
Stopwatches[j]			X	X			
Global evaluation[k]				X			
Drug-liking scale[l]				X			
Pharmacokinetics[m]			X	X			
Concomitant medications	X	X	X	X	X	X	
(S)Adverse events		X	X	X	X	X	X
Diary cards[n]			X	X			
Alcohol breath test		X					

Footnotes for flow chart of Patient Assessments Table

[a] Inclusion/exclusion criteria were to be reviewed at screening, prior to surgery, and prior to administration of study drug.

[b] Physical examination might have to be performed at baseline (prior to surgery) if not performed at screening, at 24 hours discharge and at 5-9 days follow up visit.

[c] Vital signs (blood pressure, heart rate) were to be obtained at screening, baseline (immediately prior to trial drug administration), 6, 13, 20, 35, 65, 95 minutes, 2:05, 4:05, 8:05 and at 24 hours just prior to discharge as well as at the 5-9 days follow up visit.

[d] Pulse oximetry was to be performed at screening, baseline and then continuous pulse oximetry for 2:05 hours and if SpO_2 saturation falls below 90%, additional O2 administration was allowed, the time and duration was to be recorded.

[e] A continuous16-channel EEG was to be recorded at screening.

[f] 12-lead electrocardiograms (ECGs) were to be performed at screening, before surgery, after surgery but before study drug administration, 22 minutes, 8:08 hours after the end of study drug administration, and at 5-9 days follow-up or early termination.

[g] Includes hematology, biochemistry, and urinalysis.

[h] Patients were to be prepared for EEG after completion of the surgery and the EEG was to be started as soon as the first signs of pain expressed by the patients. The EEG was to continue recording for a minimum 15 minutes prior to dosing and for 1 hour post dose.

[i] Pain assessments: pain intensity (categorical scale and VAS) were to be recorded at baseline, 5,10, 15, 30, 45, 60 and 90 minutes and 2 through 8 hours or before rescue medicine and pain relief was to be obtain at 5,10, 15, 30, 45, 60 and 90 minutes and at 2 through 8 hours or before rescue medicine.

[j] Trial personnel were to start two stopwatches (for assessing time to perceptible and meaningful pain relief) for each patient after the trial medication administration.

[k] Global evaluation of trial medication was to be completed by the patient at 8 hours or just prior to rescue medication.

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[l] Drug-liking scale was to be completed by the patient at 8 hours or just prior to rescue medication.

[m] Blood samples for pharmacokinetics were to be collected baseline,1, 3, 12, 17, 32 minutes, and at 1:02, 2:02, 4:02, and 8:02 hours after dosing.

[n] Diary cards were to be provided to the patients before dosing. All of the following measurements of pain were to be assessed and recorded in a diary at each post baseline time point. The diary itself was to be retained at the research center as part of the source documentation. At baseline (0 hour), only PI (categorical scale and VAS) were to be recorded. At 5, 10, 15, 30, 45, 60, 90 minutes after dosing and then hourly from 2 hours through 8 hours post-trial medication administration or just prior to rescue medication, PI (categorical scale and VAS) and PR were to be recorded.

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Authorizations

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