Name of company NV Organon **Name of active substance** Org 4419-2	**Synopsis / Tabular Format** **referring to**	

Title of the clinical trial

A randomized, double-blind, placebo-controlled, multicenter parallel-group dose ranging clinical trial to assess the efficacy and safety of Org 4419-2 in the treatment of obstructive sleep apnea/hypopnea syndrome.
Clinical Trial Report on Protocol 21402

Investigators

PPD

Clinical trial centers

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Report/publication (ref)

Not applicable.

Studied period (years)

September, 2005 – April, 2006

Clinical phase

II

Objectives

The primary objective of this trial was to assess the efficacy of Org 4419-2 in decreasing the Apnea Hypopnea Index (AHI) as compared to placebo.

The secondary objectives of this trial were:
- to explore the efficacy of Org 4419-2 in improving secondary PSG parameters, clinical global impression, MSLT, snoring frequency, daytime sleepiness, functional status and quality of life in OSAHS as compared to placebo;
- to explore a dose-response and/or plasma concentration-response relationship in the efficacy of Org 4419-2;

[1] This site screened one patient, but did not randomize any patients and therefore is not included in his report.

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- to assess the plasma concentration of Org 4419-2, Org 4420, Org 31602 and Org 31603 in OSAHS subjects;
- to assess the safety and tolerability of Org 4419-2, including the key safety aspects of weight gain and sedation;
- to assess whether in vivo conversion of Org 4419 into Org 4420 and/or in vivo conversion of Org 31602 into Org 31603 occurred.

Methodology

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group dose ranging trial. Randomization was stratified for the factor sex (male; female).

Number of subjects (total and for each treatment)

One hundred subjects were to be randomized (25 subjects per treatment group). In total, 141 subjects were screened to participate in the trial, of which 90 fulfilled the in-/exclusion criteria and were randomized: placebo: 23 subjects; 1.5 mg Org 4419-2: 22 subjects; 4.5 mg Org 4419-2: 23 subjects; 13.5 mg Org 4419-2: 22 subjects).

Diagnosis and criteria for inclusion

In order to be included in the trial subjects had to:
1) provide written informed consent after the scope and nature of the investigation had been explained to them, before screening evaluations; 2) be able to speak, read and understand the local language and to possess the ability to respond to questions, follow instructions and complete questionnaires; 3) fulfill AASM (1999) criteria for OSAHS; 4) have an AHI ≥10 (events/h) at the screening PSG; 5) have screening PSG based on ≥ 6 h time in bed and ≥ 4 h total sleep time; 6) be males or females aged 18-65 years; 7) have no current treatment with CPAP or oral appliances (if treated with prior CPAP or oral appliances, this had to have been discontinued ≥3 weeks prior to trial baseline); 8) have no current treatment with modafinil, methylphenidate or other psychostimulant drugs (such prior psychostimulant treatment had to have been discontinued ≥3 weeks prior to trial baseline).

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

Org 4419-2 is the maleic acid salt of Org 4419. Subjects had to take three tablets of trial medication daily, to be taken 30 minutes before anticipated bedtime. Trial medication was Org 4419-2 or placebo. Org 4419-2 tablets contained Org 4419-2, hydroxypropylcellulose, maize starch, lactose monohydrate, colloidal silicon dioxide and magnesium stearate. The Org 4419-2 tablets contained 0.5 mg, 1.5 mg or 4.5 mg of active Org 4419. Medication originated from Batch numbers CZ057 (placebo), CZ056 (4.5 mg strength), CZ055 (1.5 mg strength) and CZ054 (0.5 mg strength), respectively.

Duration of treatment

Subjects were treated for a maximal duration of 28 days.

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

Placebo was provided in a visually identical formulation to ensure double-blindness. Subjects had to take three tablets of trial medication daily, to be taken 30 minutes before anticipated bedtime.

Criteria for evaluation

Efficacy: The primary efficacy variable was the AHI at endpoint in the ITT group. Secondary efficacy parameters were: REM and non-REM AHI; position-specific AHI ([back-AHI and side-AHI]); apnea index (AI): overall AI, REM AI and non-REM AI; hypopnea index (HI): overall HI, REM HI and non-REM HI; number of subjects with post-treatment AHI <5; number of subjects with post-treatment AHI <10; number of subjects with post-treatment decrease in AHI ≥50%;minimum O_2 saturation (throughout a night); number of O_2 desaturations ≥ 4% (per hour of sleep); % of sleep time with O_2 saturation ≤ 90% and ≤ 85%; number of hypopneas accompanied by an arousal/hour; number of EEG arousals and respiratory EEG arousals/hour; snoring index; MSLT; Clinical Global Impression of change (CGI); Epworth Sleepiness Scale (daytime sleepiness); Functional Outcomes of Sleep Questionnaire (daytime functional status); SF-36 (quality of life); total sleep time; sleep efficiency; %REM; % SWS; % time in stage 1/2/3/4 sleep.
Pharmacokinetics: Concentrations of Org 4419 and Org 4420, and their metabolites Org 31602 and Org 31603, were measured in plasma on several time points after dosing. No pharmacokinetic parameters were calculated.
Safety: The following safety parameters were assessed: (S)AEs, vital signs, laboratory parameters, ECG, Lader-Bond self-assessment scale (selected items; VAS) and appetite self assessment scale (VAS).

Statistical methods

Efficacy: The efficacy parameters (log-transformed) were analyzed by means of an analysis of covariance with center, sex and treatment group as explanatory variables. The estimated treatment effects compared to placebo and corresponding two-sided 95% confidence intervals were based on the ANCOVA with explanatory variables center, sex and treatment group.
The dose-response relationship in the frequency of subjects with a ≥ 50% reduction in AHI from baseline at endpoint and the frequency of subjects with AHI < 5 and AHI < 10 at endpoint was investigated through a logistic regression analysis with as explanatory variables center, sex, baseline AHI, baseline BMI and treatment group.
Pharmacokinetics: Descriptive statistics was calculated for demographics and plasma concentrations of Org 4419 and Org 31602.
Safety: The (S)AEs, laboratory parameters, vital signs and body weight and ECG were analyzed descriptively and the special safety considerations, the change from baseline item scores of the Lader Bond Mood Rating Scale and the Appetite Scale were analyzed by means of ANCOVA with center, sex and treatment group as explanatory variables.

Summary

Of the 141 subjects who were screened, 51 subjects were screening failures and 90 subjects were randomized and treated of which 6 subjects discontinued early. The Intent-To-Treat group consisted of 89 subjects (1 subject in the AST group did not have any post-baseline efficacy measurement) and the Per Protocol group consisted of 57 subjects.

Of all subjects treated, 71 subjects (78.9%) were male and 19 subjects (21.1%) were female. The treatment groups were comparable with respect to age, gender, body height, body weight and BMI. The overall mean age, height, body weight and BMI were 49.9 years, 173.8 cm, 95.8 kg and 31.6 kg/m^2, respectively. The majority of the subjects (75.6%) was Caucasian, but also Black, Asian and Other races were reported.

Efficacy:
The primary analysis showed a statistically significant difference in AHI at endpoint between 4.5 mg Org 4419-2 and placebo (ITT: p=0.028; PP: p=0.066). However, this effect was mainly due to an increase in the placebo group and a (very slight) decrease from baseline in the 4.5 mg group. In addition, at endpoint statistically significant differences between 4.5 mg Org 4419-2 and placebo and in a few cases between 1.5 mg Org 4419-2 and placebo were found for other PSG efficacy parameters (apnea index, back AHI, number of O_2-desaturations ≥ 4%, number of hypopneas accompanied by an arousal, number of respiratory EEG arousals, and non-REM AHI). These effects are also the result of an increase in the placebo group and a (very slight) decrease on the respective parameters in the respective Org 4419-2 groups as compared to baseline. Therefore, the observed treatment effects were not considered clinically relevant. The 13.5 mg Org 4419-2 group did not show any consistent effects on the PSG efficacy parameters as compared to placebo. Despite some incidental findings, clinical efficacy could not be established based on secondary efficacy variables, CGI, MSLT, snoring frequency, daytime sleepiness (EES), FOSQ, and SF-36 health and well-being.

Pharmacokinetics:
In this study, plasma concentrations of Org 4419 and Org 31602 were found dose proportional over the dose range of 1.5 mg to 13.5 mg Org 4419-2. The results suggested that in vivo conversion of Org 4419 into Org 4420, and/or in vivo conversion of Org 31602 into Org 31603 did not occur in the investigated dose range.

Safety:
No deaths or SAEs were reported during the trial. Five subjects discontinued from the trial due to an AE. In total, 52 of the 90 treated subjects (placebo: 56.5%; 1.5 mg Org 4419-2: 63.6%; 4.5 mg: 60.9%; 13.5 mg: 50.0%) reported 119 AEs, of which 93 were considered related to the trial medication by the investigator. Most AEs occurred in system organ class 'nervous system disorders' (27 AEs, of which 25 related). AEs with an incidence of more than 10% in one of the treatment groups were: somnolence (Org 4419-2 treatment groups), headache (placebo; 13.5 mg Org 4419-2), fatigue (Org 4419-2 groups), weight increased (placebo; 1.5 mg Org 4419-2), and increased appetite (1.5 mg Org 4419-2). For 'somnolence' and 'fatigue', an increased incidence was observed with Org 4419-2 treatment as compared to placebo.

No notable differences were found between the treatment groups with regard to laboratory variables, vital signs and ECG. In addition, no treatment effect was found for sedation (based on Lader-Bond Mood Rating Scale items) or appetite items.

Conclusions

- The primary analysis showed a statistically significant difference in AHI at endpoint between 4.5 mg Org 4419-2 and placebo (ITT: p=0.028; PP: p=0.066). However, this effect was mainly due to an increase in the placebo

group and a (very slight) decrease from baseline in the 4.5 mg Org 4419-2 group and therefore not considered clinically relevant.

- Treatment with Org 4419-2 in the dose range of 1.5 – 13.5 mg did not lead to a decrease in AHI as compared to placebo and therefore clinical efficacy could not be established.
- Despite some incidental findings, clinical efficacy could not be established based on secondary PSG parameters, clinical global impression, MSLT, snoring frequency, daytime sleepiness, functional status and quality of life in OSAHS.
- In view of the lack of efficacy in this trial, a dose-response and/or plasma concentration-response relationship in the efficacy of Org 4419-2 have not been explored.
- Dosages of 1.5 mg, 4.5 mg and 13.5 mg Org 4419-2 were safe and well tolerated. No SAEs were reported in this trial. For 'somnolence' and 'fatigue' an increased incidence was observed with Org 4419-2 treatment as compared to placebo. No clinically relevant differences as compared to placebo were found on laboratory variables, vital signs and ECG.
- Overall, no indication of weight gain was observed with Org 4419-2 in a dose range of 1.5 mg up to 13.5 mg.
- No consistent treatment effect with Org 4419-2 was observed with regard to sedation (based on LBMRS items) or appetite items.
- Plasma concentrations of Org 4419 and Org 31602 were found to be dose-proportional.