SYNOPSIS

NAME OF SPONSOR/COMPANY:	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Janssen-Cilag EMEA, a division of Janssen Pharmaceutica NV, Beerse, Belgium NAME OF FINISHED PRODUCT: OROS® Hydromorphone (AP-77) NAME OF ACTIVE INGREDIENT(S): Hydromorphone Hydrochloride	Volume: Page:	

Protocol No: OROS-ANA-3001

Title of Study: Randomized, open-label, comparative parallel group study to assess efficacy and safety of flexible dosages of OROS® hydromorphone once-daily compared to sustained release (SR) oxycodone twice-daily in subjects with chronic non-malignant pain severe enough to require continuous opioid therapy.

Coordinating Investigator: Associate Professor Rainer Sabatowski MD, Universitäts-SchmerzCentrum, Universitätsklinikum Carl Gustav Carus, Dresden, Germany.

Study Centers: 64 study centers in 11 European countries: Czech Republic, Denmark, France, Germany, Italy, Norway, Poland, Slovakia, Slovenia, Sweden and Switzerland.

A total of 20 study centers in 4 European countries (Czech Republic, Germany, Poland, and Slovakia) participated in the Extension phase.

Publication (Reference): Not applicable.

The Preliminary CSR (dated 19 June 2008) is provided in Appendix 1.8.

Please note that for the Preliminary CSR, results of subjects from one centre could only be included in the Safety population and thus results given in this Final CSR (including data from this centre) may vary. For further details see 'Preamble' on page 18.

Studied Period (years): 1 year **Phase of Development:** Phase 3b
Core phase (Weeks 0-24): 4 weeks titration phase followed by 20 weeks maintenance phase
Extension phase (Weeks 24-52): 28 weeks

First Subject First Visit: 15 March 2006

Last Subject Last Visit (Core Phase): 13 September 2007

Last Subject Last Visit (Extension Phase): 30 April 2008

Objectives:

Primary Objective: to demonstrate non-inferiority of OROS® hydromorphone compared to SR oxycodone with regard to pain control and to determine the equi-analgesic dosage of OROS® hydromorphone once-daily and SR oxycodone twice-daily.

Secondary Objectives:

- Compare OROS® hydromorphone to SR oxycodone with regard to different pain parameters.
- Compare the side-effect profiles of OROS® hydromorphone and SR oxycodone.
- Evaluate the impact of OROS® hydromorphone and SR oxycodone on well-being and functionality in daily living.

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- Compare possible increase in dosages over time.
- Assess and compare resource utilization of pain management with OROS® hydromorphone and SR oxycodone.
- Assess subject satisfaction on mode and convenience of drug intake.

Methodology: Randomized, open label, comparative parallel group study. The ratio of subjects allocated to each treatment arm was 1:1.

Number of Subjects (planned and analyzed): Planned: 504 subjects; Analyzed: 504 subjects (Safety population), 504 subjects (Intent-to-Treat [ITT] population), 223 subjects (Per Protocol [PP] population).

277/504 subjects completed the Core phase (Weeks 0 to 24).

97/112 subjects completed the Extension phase (Weeks 24 to 52).

Diagnosis and Main Criteria for Inclusion:

- Subjects with chronic non-malignant pain, severe enough to require continuous opioid therapy, such as:
    - chronic low back pain,
    - musculoskeletal pain such as osteoarthritis, rheumatoid arthritis,
    - neuropathic pain like post-herpetic neuralgia, diabetic polyneuropathia,
    - other chronic pain conditions usually responsive to opioid treatment like peripheral arterial occlusion disease, phantom limb pain or chronic pancreatitis,
    - Subjects who were at that time treated with non-opioids or with weak opioids such as codeine, dihydrocodeine or tramadol, or subjects treated with a daily oral dose of up to 60 mg morphine or an equivalent dose of another oral strong opioid and subjects using fentanyl TTS 25 µg/h or buprenorphine TTS 35 µg/h.
- Subjects with rheumatoid arthritis, who were on a stable dosage of disease modifying anti-rheumatic drug (DMARDs).
- Subjects with chronic pain from which they had been suffering for more than 3 months for at least 20 days per month.
- Subjects who experienced at that time insufficient pain control, with a baseline score of 5 or more on item “pain right now” on an 11 point numeric rating scale.

Test Product, Dose and Mode of Administration, Batch No.:

OROS® hydromorphone, oral administration once daily, initial dose: 8 mg, maximal daily dosage:

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32 mg.

- 8 mg tablets: batch no. 0524291 (Core and Extension Phases until Oct 2007); batch no. 0710014 (Extension Phase from Oct 2007).
- 16 mg tablets: batch no. 0524310 (Core and Extension Phases until Oct 2007); batch no. 0707807 (Extension Phase from Oct 2007).
- 32 mg tablets: batch no. 0524312 (Core and Extension Phases until Oct 2007); batch no. 0707808 (Extension Phase from Oct 2007).

Duration of Treatment: 24 weeks (Core phase only); 52 weeks (if subject entered the Extension phase); plus 4 weeks follow-up after either core or extension phase.

Reference Therapy, Dose and Mode of Administration, Batch No.:

SR oxycodone, (commercial goods of Oxycontin® 10, 20, and 40 mg tablets), oral administration: twice daily, initial dose: 10 mg twice daily, maximal daily dosage: 80 mg.

- 10 mg tablets: batch no. 127196 (expiry date: Jul 2008).
- 20 mg tablets: batch no. 125739 (expiry date: May 2008).
- 40 mg tablets: batch no. 126791 (expiry date July 2008).

Note: In Poland, further to re-labeling, batch numbers were amended (see Appendix 1.6).

Criteria for Evaluation:

Efficacy: Brief pain inventory (BPI) short form, subject diary on pain assessment, SF-36 Questionnaire, Medical Outcomes Study (MOS) sleep subscale, global assessment on mode and convenience of drug intake, Clinical global assessment of efficacy.

Primary endpoints:

- Pain control, defined as change in BPI pain severity sub-score "pain right now" (BPI item 6) from baseline to endpoint of the first study phase.
- Equi-analgesic dosage of OROS® hydromorphone once-daily and SR oxycodone twice-daily with regard to pain control, defined as average dose used at endpoint of first study phase (core phase) under the condition that non-inferiority with respect to pain control has been established.

Secondary endpoints:

Main secondary endpoints in hierarchical order:

1. Change in BPI pain severity sub-score "pain at its worst" (BPI item 3) from baseline to endpoint

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of core phase.

2. Change in sleep quality, i.e. MOS sleep scale index 1, from baseline to endpoint of core phase.

3. Change in subject diary evening mean pain score "pain right now" from baseline to endpoint of core phase.

4. Change in subject diary morning mean pain score "pain right now" from baseline to endpoint of core phase.

5. Proportion of subjects with dose escalation, i.e. dose increase in study medication from Week 4 (end of titration phase) to Week 24.

There were several other secondary efficacy endpoints (see Section 3.9.3.2).

Safety: The safety endpoints were incidence and type of treatment-emergent adverse events (AEs) during the treatment period, change in vital signs from baseline to endpoint, physical examination by body system and clinical global assessment of tolerability.

Statistical Methods:

Efficacy:

Testing for non-inferiority of OROS® hydromorphone as compared to SR oxycodone with respect to the primary endpoint pain control, as defined by the change in BPI pain severity sub-score "pain right now" (BPI item 6) from baseline to endpoint of core phase (Week 24 or endpoint of first phase), was done in a confirmatory sense. For this test the 95% confidence intervals were computed. The statistical significance level used for this test was 0.025 one-sided (i.e. 0.05 two-sided). If non-inferiority of pain control could be demonstrated, the co-primary endpoint equi-analgesic dose was to be determined descriptively.

Analysis of the primary endpoint was carried out on both the ITT and PP populations, with the PP population being the population of primary interest. In addition, an analysis of the observed cases in the ITT population was conducted.

The following hypotheses were tested (Δ denotes the change from baseline):

H_0: ΔOROS® hydromorphone – ΔSR oxycodone ≥ 1

H_1: ΔOROS® hydromorphone – ΔSR oxycodone < 1

For testing these hypotheses the two-sided 95% confidence interval of the treatment difference based on the least square (LS) means and error terms obtained from ANCOVA with baseline as covariate and country, previous pain treatment, underlying disease and treatment as factors were computed. In addition, the p-value obtained from ANCOVA for testing these hypotheses was presented. If the right side of confidence interval was less than 1, then the H_0 was rejected in favor of the H_1, and non-inferiority of OROS® hydromorphone as compared to SR oxycodone with respect to pain control was

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confirmed.

If non-inferiority of the primary endpoint pain control was established, also confirmatory two-sided testing of the main secondary endpoints for a statistically significant difference between OROS® hydromorphone and SR oxycodone was to be conducted to evaluate those main secondary endpoints for superiority of OROS® hydromorphone as compared to SR oxycodone. The statistical significance level to be used for these tests was 0.05 two-sided and a closed hierarchical testing approach was to be used to control the overall Type I error.

The following hypotheses were tested (Δ denotes the change from baseline):

H0: ΔOROS® hydromorphone – ΔSR oxycodone = 0

H1: ΔOROS® hydromorphone – ΔSR oxycodone ≠ 0

Thus, only if the test for the first main secondary endpoint was significant at the 0.05 level, the next secondary endpoint was assessed and so on. Once the first test failed to demonstrate significance at the 0.05 level, the hierarchical procedure was stopped. Conclusions were only to be drawn with respect to the last significant test.

All other statistical tests were only explorative in nature and therefore no α error adjustment was conducted for those tests. Consequently, corresponding p values only represent the comparison-wise α error probabilities.

Safety:

All safety parameters were analyzed descriptively for the Safety population. Summary statistics were presented for treatment groups and the total number of subjects.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary Efficacy Analysis

After 24 weeks of treatment, both treatment groups showed an improvement in pain control. In the PP population, the decrease in BPI pain severity sub score "pain right now" was -2.8 for OROS® hydromorphone and -3.2 for SR oxycodone. In the ITT population, it was -2.1 for both treatments.

Non-inferiority of OROS® hydromorphone compared to SR oxycodone with respect to pain control was demonstrated both for the PP population ($p=0.011$) and the ITT population ($p<0.001$). The treatment difference with respect to change in BPI pain severity sub-score "pain right now" was 0.29 [95% CI: 0.27; 0.84] for the PP population and -0.12 [95% CI: -0.53; 0.29] for the ITT population.

At Week 24, mean equi-analgesic doses per day were determined as 18.9 mg OROS® hydromorphone (59.1% of the allowed maximum daily dose) and 48.3 mg SR oxycodone (60.4% of the allowed maximum daily dose) in the PP population. For the ITT population, mean equi-analgesic doses per day were 18.4 mg OROS® hydromorphone and 43.8 mg SR oxycodone. The median equi-analgesic

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doses were 16 mg for OROS® hydromorphone and 40 mg for SR oxycodone. The mean equi-analgesic dose at steady state (i.e. during the maintenance phase) was 18.95 mg and 47.82 mg (PP population) for the OROS® hydromorphone and SR oxycodone groups, respectively. Similar values were shown for the ITT population.

Secondary Efficacy Analysis

For the main secondary efficacy endpoints, both treatment groups showed improvements in BPI pain severity sub-score "pain at its worst", sleep quality, subject diary evening mean pain score "pain right now", and subject diary morning mean pain score "pain right now". However, there were no statistically significant differences between OROS® hydromorphone and SR oxycodone for these endpoints.

In the maintenance phase (Week 4 to 24), the proportion of subjects with dose escalation was slightly higher in the SR oxycodone group (13.6%) in comparison to the OROS® hydromorphone group (10.6%), however, this treatment difference was not statistically significant (p=0.249).

With regard to the improvements in the other secondary efficacy endpoints (analyzed for exploratory purposes only), other pain scores (BPI pain severity, pain relief, pain interference, subject pain diary), sleep quality (MOS sleep scale indices 1 and 2), and quality of life (SF-36 questionnaire) all generally improved in both treatment groups. At the end of the titration phase (Week 4), the change in sleep quantity was statistically significantly different between the treatment groups at the end of Week 4 (p=0.044 [ITT population]) in favor of OROS® hydromorphone, however, there was no difference between the treatment groups at the end of the core phase (p=0.880 [ITT population]). No statistical differences were shown between the treatment groups during the core phase, with the exception of the MOS sleep subscale score for somnolence (p=0.020 [ITT population]) and the SF 36 domain score for physical functioning (p=0.010 [ITT population]) which were shown to be significantly different between treatments groups in favor of the OROS® hydromorphone group.

Changes in the secondary efficacy endpoints from baseline to Week 38 and to the endpoint of the extension phase (Week 52) were generally comparable to the changes from baseline to the endpoint of the core phase and in general indicate that the achieved efficacy was maintained during the studied time period for both treatments.

In the majority of subjects, and for a slightly higher percentage of subjects in the OROS® hydromorphone group (67.7% vs. 57.6% [SR oxycodone]), there was no net change in dose of study treatment during the maintenance period (Week 4 to 24). The majority of subjects who entered the extension phase (treatment phase II) did not change dose of study medication (56/60 subjects [OROS® hydromorphone]; 50/52 subjects [SR oxycodone]).

The proportion of drop-outs due to inefficacy at maximal dosage was generally low in both treatment groups (6.7% [OROS® hydromorphone] vs. 4.8% [SR oxycodone]).

During the core phase, the median total amount of add-on paracetamol (38.50 g [OROS® hydromorphone] vs. 32.75 g [SR oxycodone]) and the mean number of days with add-on paracetamol (68.2 days [OROS® hydromorphone] vs. 66.1 days [SR oxycodone]) was comparable between the

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treatment groups.

In the global assessments of efficacy, after 24 weeks, the investigators rated the efficacy of OROS® hydromorphone as "very good" or "good" in 54.7% of subjects, and as "very good" or "good" in 53.6% of subjects treated with SR oxycodone. After 52 weeks, the global assessments of efficacy was rated as "very good" or "good" in the majority of subjects who entered the extension phase. This included 55/60 subjects (91.7%) in the OROS® hydromorphone group and 45/52 subjects (86.5%) in the SR oxycodone group.

At Week 24, a slightly higher percentage of subjects (24.8%) in the OROS® hydromorphone group compared to 21.2% of subjects in the SR oxycodone group assessed their mode of drug intake as "very convenient". No statistically significant difference was shown between the treatment groups (p=0.843). For subjects who entered the extension phase, more subjects assessed their mode of drug intake as "very convenient" in the OROS® hydromorphone group (21/60 subjects [35.0%]) than in the SR oxycodone group (11/52 subjects [21.2%]).

In terms of resource utilization, the mean number of additional visits during the overall treatment phase was comparable between the treatment groups (2.1 visits [OROS® hydromorphone] vs. 1.9 visits [SR oxycodone]).

Overall, OROS® hydromorphone (administered once daily) was found to be as efficacious as SR oxycodone (administered twice daily).

SAFETY RESULTS:

The majority of SAEs (55/71 SAEs) were assessed by the investigator as being unrelated to the study medication. The incidences of SAEs, together with no fatal events, indicated no safety concerns.

In the OROS® hydromorphone group, there was one Suspected Unexpected Serious Adverse Reaction (SUSAR) assessed as related to study medication (i.e. drug withdrawal syndrome due to diarrhea and constipation). Among the related SAEs in the SR oxycodone group, there were single incidences of rectocele, cholecystitis and benign prostatic hyperplasia that were unexpected according to the known product characteristics of SR oxycodone.

Both groups had a similar number of subjects with AEs related to study medication: 171 (67.3%) OROS® hydromorphone vs. 174 (69.9%) SR oxycodone. Overall, the most frequent related AEs were constipation (167 AEs), nausea (162 AEs), vomiting (78 AEs), and fatigue (66 AEs).

The most frequent AEs that led to withdrawal were nausea (15 AEs [OROS® hydromorphone] vs. 20 AEs [SR oxycodone]), vomiting (9 vs. 14 AEs) and dizziness (5 vs. 8 AEs), which are known side effects of the study medications (as well as for other opioids).

Vital signs assessments showed a slight decrease in median systolic blood pressure, which is consistent with the known pharmacologic properties of the study medications. Median diastolic blood pressure and heart rate remained stable throughout the study.

Physical examination results did not raise any safety concerns and revealed no notable differences

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between treatment groups.

At Week 24, the investigators rated the global tolerability as "very good" or "good" in 64.3% of subjects in the OROS® hydromorphone group and in 58.3% of subjects in the SR oxycodone group. Tolerability at Week 4 (end of the titration phase) and at Week 52 (end of the extension phase) also showed a good tolerability of both treatments.

CONCLUSION:

- OROS® hydromorphone proved to be non-inferior to SR oxycodone with respect to the change in BPI pain severity sub-score "pain right now" after 24 weeks of treatment.
- At 24 weeks, the mean equi-analgesic doses per day were 18.9 mg OROS® hydromorphone (59.1% of the allowed maximum daily dose) and 48.3 mg SR oxycodone (60.4% of the allowed maximum daily dose) for the PP population.
- OROS® hydromorphone was also similar to SR oxycodone with respect to improvements in the other pain scores (BPI, subject pain diary), and quality of life (SF-36 questionnaire). The OROS® hydromorphone group showed a statistically significantly greater decrease in MOS sleep subscale score for somnolence and increase in SF-36 domain score for physical functioning during the core phase i.e. better improvements in comparison to SR oxycodone.
- Changes in the secondary efficacy endpoints from baseline to Week 38 and to the endpoint of the extension phase (Week 52) were generally comparable to the changes from baseline to the endpoint of the core phase and in general indicate that the achieved efficacy was maintained during the studied time period for both treatments.
- OROS® hydromorphone was comparable to SR oxycodone with respect to the total amount of add-on paracetamol and the mean number of additional visits.
- OROS® hydromorphone was comparable to SR oxycodone with respect to the investigators' global assessments of efficacy and the subjects' assessments of mode and convenience of drug intake. However, the investigator's assessment of tolerability slightly favored the OROS® hydromorphone group during the core phase. In the present study, OROS® hydromorphone was as safe and well tolerated as SR oxycodone.
- None of the safety results in this study necessitate revising the risk/benefit ratio of OROS® hydromorphone.

Date of the report: 08 August 2008 (Final Version)

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