SYNOPSIS CR012601

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Name of Sponsor/Company	Janssen-Cilag International N.V.
Name of Finished Product	AP-77, OROS® Hydromorphone hydrochloride
Name of Active Ingredient(s)	Hydromorphone hydrochloride

Protocol No.: CR012601, HOP Trial

Title of Study: Randomised, double-blind, placebo-controlled, parallel-group trial to investigate the analgesic effect of OROS hydromorphone hydrochloride in comparison with placebo in subjects with moderate to severe pain induced by osteoarthritis of the hip or the knee.

EudraCT Number: 2006-006911-60

Coordinating Investigator: Prof. Richard M Langford, LRCP; MRCS, MB BS, FRCA

Publication (Reference): None

Study Period: 05 October 2007 – 24 November 2008

Four countries participated in the study (Czech Republic, Romania, Slovakia and the UK) and 18 centres recruited subjects.

Phase of Development: IIIb

Objectives: The primary objective was to compare the analgesic effect of flexibly titrated OROS hydromorphone hydrochloride and placebo in subjects with moderate to severe pain induced by osteoarthritis (OA) of the hip or knee which had not been adequately controlled by previous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol. This was assessed by the Brief Pain Inventory (BPI) item 5 "pain on average".

The secondary objectives of the study were as follows:

- To assess the drop-out rate due to adverse events (AEs)
- To assess the effect of treatment on subjects' functionality using the total score of the Western Ontario and McMaster Universities (WOMAC) OA index
- To assess the effect of treatment on pain using the pain subscales of the WOMAC OA index and the health-related quality of life (HRQoL) instrument short form-36 (SF-36) and pain-related items 3, 4 and 6 of the BPI
- To assess the overall safety and tolerability of the drug.

The following secondary objectives were analysed on an exploratory basis:

- To compare the drop-out rate due to AEs in the active group with drop-out rates observed in other trials that have used a higher starting dose
- To assess the effect of treatment on subjects' HRQoL, which was assessed using all subscales, except pain, of the instrument SF-36
- To assess the effect of treatment on subjects' functional impairment and stiffness using these subscales of the WOMAC OA index
- To assess the effect of treatment on subjects' quality of sleep using a medical outcome study (MOS) sleep subscale score
- Assessment of the drop-out rate due to inefficacy

- Assessment of the time until drop-out/withdrawal.

Methods: This was a phase IIIB, multi-centre, randomised, parallel-group, placebo-controlled, double-blind study in subjects with moderate to severe pain induced by OA of the hip or knee, which had not been adequately controlled by previous treatment with NSAIDs or paracetamol. Subjects were randomised to receive either oral OROS hydromorphone hydrochloride 4 mg once daily or matched placebo. In the event of unsatisfactory pain control, subjects had their dose titrated 3–4 days after randomisation until week 4 of the study with intervals of at least 3–4 days between dose increments. Possible doses were 4 mg, 8 mg, 12 mg, 16 mg, 24 mg and a maximum daily dose of 32 mg. There followed a 12-week maintenance phase on as stable a dose as possible. If a dose of 32 mg did not provide sufficient analgesia, subjects were withdrawn owing to lack of efficacy, and had their dose tapered off by reducing their dose in specified increments every 2 days.

Subjects returned to the clinic at 1, 2, 3, 4, 8, 12, and 16 weeks for scheduled assessments and were contacted by telephone call between visits. At the end of the double-blind treatment phase, subjects had their dose tapered off to allow safe discontinuation of the study drug. This tapering off phase also applied if subjects discontinued prematurely.

Number of Subjects (planned and analyzed):

Planned: 270 subjects (135 per group)
Analyzed: 288 subjects randomised, 287 subjects included in the intent-to-treat (ITT) population and 191 subjects included in the per-protocol (PP) population.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 40 years or over with moderate to severe pain induced by OA (as defined by the American College of Rheumatology) of the hip or knee defined as a mean weekly score of ≥ 5 on a scale of 0–10 in the BPI item 5 "pain on average", which had not been adequately controlled by previous treatment with NSAIDs or paracetamol. Subjects should have been taking NSAIDs or paracetamol for the month before the beginning of the study. Subjects included suffered from chronic pain for more than 3 months treated with daily analgesic for the month before beginning the study.

Test Product, Dose and Mode of Administration, Batch No.: Oral OROS hydromorphone hydrochloride at a starting dose of 4 mg once daily. In the event of unsatisfactory pain control, the dose could be increased in increments to 8 mg, 12 mg, 16 mg, 24 mg or 32 mg with intervals of at least 3-4 days between dose increments.

OROS hydromorphone 4 mg and 8 mg tablets were derived from batch numbers indicated in the table below. For the 4 mg tablets, 2 different batches were used for first and second shipment due to the expiration dates. "Pink 4 mg tablets" were dispensed to subjects enrolled before 20 March 2008, and "Beige 4 mg tablets" were dispensed to subjects randomised either before or after 20 March 2008. For the 8 mg tablets, both shipments were derived from the same batch.

Batch Numbers of Test Product and Reference Therapy

	4 mg	Matching placebo	8 mg	Matching placebo
First shipment (US to Europe):	0601265[1]	0601064	0706049	0601067
Second shipment (US to Europe)	0706048[2]	0701475	0706049	0601067

[1] "Pink 4 mg tablets".
[2] "Beige 4 mg tablets".
US = United States.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo to the OROS hydromorphone hydrochloride 4 mg and 8 mg tablets were derived from batch numbers indicated in the table above.

Duration of Treatment: 16 weeks (4-week titration phase and 12-week maintenance phase).

Criteria for Evaluation:

Primary Efficacy Variable: Mean score in the BPI item 5 "pain on average" recorded at each study visit.

Secondary Efficacy Variables: Drop-out rate due to TEAEs; total score, and pain, functional impairment and stiffness subscales of the WOMAC OA index (visits 1, 5, 6, 7, and 8); all subscales and pain subscales of the HRQoL instrument SF-36 (visits 1, 5, 6, 7, and 8); items 3, 4, and 6 of the BPI (visits 1, 2, 3, 4, 5, 6, 7, and 8)*; MOS sleep subscale (visits 1 and 8); percentage of subjects responding to treatment; Subject and Physician Global Assessments (visits 5 and 8); drop-out rate due to inefficacy; and time until drop-out/withdrawal.

* Only BPI items 3, 4 and 6 were part of the secondary objectives which were evaluated with the Mixed Model for Repeated Measures. Other BPIs were displayed descriptively. Item 9 was also included in additional analyses for the change from baseline comparison with the WOMAC functional impairment score.

Post-hoc concomitant medication analyses were performed to assess the impact of concomitant medication in the effectiveness of OROS hydromorphone hydrochloride and placebo treatments.

Comparison of normalised WOMAC-OA indices subscale and overall scores were performed between the current study and 2 other placebo-controlled studies, M03-644-05 and FEN-EMA-1

Safety Variables: TEAEs, dropouts due to TEAE, vital signs and physical examination.

Statistical Methods: It was assumed that 3 baseline and 7 post-baseline measures had to be collected. Calculating the sample size using the "sampsi" command in Stata Version 8.2 for repeated measures, 81 subjects were required per group to detect a difference of 1 point in the BPI measure with 90% power at a significance level of 5%. To allow for a drop-out rate of approximately 40%, the study planned to recruit 135 subjects per group. A reassessment of the sample size was done, without breaking the blind, when 50% of subjects were randomised and approximately 40% of subjects had either completed the study or dropped out. This analysis confirmed the assumptions of the sample size calculation.

The primary efficacy variable was the BPI item 5 "pain on average". This was analyzed using a mixed-model regression analysis, which took account of the correlation among repeated measures within individual subjects and allowed subjects with incomplete data as a result of early drop-out to contribute their existing data to the analysis. The model included terms for treatment, timepoint, most affected joint, and baseline BPI as fixed effects and subject as a random effect. Data from clinic visits only were used for the primary efficacy analyses. Similar methods were used for analysis of the secondary outcome measures. In addition, the percentage of subjects responding to treatment in each treatment group was assessed. A subject was classified as a responder to treatment when the last post-baseline assessments (Visit 8) of the BPI item 5 showed a 30% improvement compared to the baseline value. Subjects with a reduction of BPI item 5 from baseline to last visit by 3 points were counted as responders.

As a sensitivity analysis to examine the effect of missing data due to drop-outs on the conclusions of the primary analysis, appropriate imputation methods were used on the dataset. The methods are defined in detail in the statistical analysis plan, dated 19 December 2008.

The safety population was defined as all randomised subjects who received at least one dose of study drug and was the primary population used for safety analyses. The ITT population was defined as a subgroup of the safety population, excluding subjects who had no post-baseline efficacy data and was the primary population for efficacy analyses. The PP population was defined as a subgroup of the ITT population, excluding subjects who discontinued early and all major protocol violators. This population was used for supportive evidence for the efficacy analyses.

Safety data, including TEAEs, dropouts due to TEAE, vital signs and physical examination, were presented descriptively for each treatment group. TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.0. The percentage of subjects with specific TEAEs was

summarised for each treatment group. Descriptive statistics were provided to evaluate the changes at each scheduled time point for physical examinations and vital signs.

Post- hoc analyses (i.e., not specified in the protocol or statistical analysis plan) were performed to examine the effect of concomitant analgesic medication on the primary efficacy variable. A WOMAC comparison with other placebo-controlled studies was also performed. Confirmatory subgroup analyses were performed to assess the primary efficacy variable in various subgroups (baseline pain severity and dose at the end of the titration phase).

RESULTS:

EFFICACY RESULTS:

The primary objective was to compare the analgesic effect of OROS hydromorphone hydrochloride and placebo by BPI item 5 "pain on average" which was recorded at each study visit and analysed using a Mixed-Model for Repeated Measures (MMRM). In the ITT population, both treatment groups showed a mean decrease (improvement) in BPI Item 5 score from baseline at all study visits. At the end of the titration period (Visit 5), mean (SD) decrease from baseline in pain score was -2.8 (1.98) and -2.6 (1.89), for OROS hydromorphone hydrochloride and placebo, respectively. Corresponding changes at the end of the maintenance period (Visit 8) were -2.4 (2.11) and -2.6 (2.30), respectively. No statistically significant difference was observed between treatment groups (point estimate –0.24; 95% confidence interval [CI]: -0.54, 0.06). Similar results were observed in the PP population (point estimate –0.26; 95% CI: -0.63, 0.11).

Both groups also showed an improvement compared to baseline for secondary variables WOMAC OA index (total score and subscales), SF-36 (pain and other subscales), BPI Items 3, 4 and 6, MOS sleep subscales. Similar to the primary variable, these secondary efficacy analyses failed to show any statistically significant difference between OROS hydromorphone hydrochloride and placebo (WOMAC total score point estimate 0.10; 95% CI: -1.01, 1.21; WOMAC pain subscale point estimate 0.05; 95% CI: -0.72, 0.81; SF-36 pain subscale point estimate –1.06; 95% CI: -5.02, 2.89; BPI Item 3 point estimate –0.31, 95% CI: -0.61, 0.00; BPI Item 4 point estimate –0.23, 95% CI: -0.53, 0.07; BPI Item 6 point estimate –0.26; 95% CI: -0.64, 0.11). Similar results were observed in the PP population.

Treatment response was comparable between treatment groups in the ITT population: 51% and 56% for the OROS hydromorphone hydrochloride and placebo, respectively. A higher treatment response was observed for both treatment groups in the PP population, with no notable differences between OROS hydromorphone hydrochloride (73%) and placebo (72%).

Global assessment by subject was higher in the placebo group compared to OROS hydromorphone hydrochloride group. At Visit 8, subjects rated their current dose regimen as very convenient or convenient (27% and 42% respectively in OROS hydromorphone hydrochloride group, 34% and 48% in the placebo group). Most were happy to stay on their current dose regimen (72% and 78% for OROS hydromorphone hydrochloride and placebo, respectively) and preferred a once daily regimen for future pain treatment (72% and 77% for OROS hydromorphone hydrochloride and placebo, respectively). Similar results were reported in the PP population.

Global assessment by physician was also comparable between treatment groups of the ITT population. At Visit 8, the physician's global assessment of efficacy was rated as very good (28% and 33%), good (29% and 27%) and moderate (25% and 17%) for OROS hydromorphone hydrochloride and placebo, respectively. Global assessment of tolerability was very good (26% and 53%), good (28% and 30%) or moderate (20% and 10%) for OROS hydromorphone hydrochloride and placebo, respectively.

The drop-out rate due to TEAEs (26% and 5% for OROS hydromorphone hydrochloride and placebo, respectively) was comparable to those observed in previous clinical studies with OROS hydromorphone hydrochloride (studies M03-644-05 and OROS-ANA-3001). The drop-out rate due to inefficacy (4% and 11% OROS hydromorphone hydrochloride and placebo, respectively) was comparable to those observed in other studies with OROS hydromorphone hydrochloride and other opioid analgesics (e.g., 9% for the OROS hydromorphone hydrochloride group in study OROS-ANA-3001. The overall drop-out rate was 40% for OROS hydromorphone hydrochloride and 22% for placebo. Similar dropout rates were observed in studies OROS-ANA-3001 and FEN-EMA-1.

Similarly to the primary and secondary efficacy analyses, subgroup analyses by average baseline pain severity, age, number of dose titration steps, reached maintenance dose, amount of rescue medication taken on average during one week, body mass index (BMI) or reached dose per visit or period showed changes from baseline in both treatment groups. Variable trends were observed, but no subgroup analyses demonstrated significant differences between treatment groups.

Post-hoc concomitant medication analyses showed that in a subgroup of subjects taking NSAIDs, pain scores were similar with OROS hydromorphone and placebo. In a subgroup of subjects not taking NSAIDs, pain scores were lower with OROS hydromorphone compared with placebo. In a subgroup of subjects using concomitant paracetamol, pain scores appeared be lower with OROS hydromorphone compared with placebo. In subjects using rescue paracetamol at doses between 1001 and 1500 mg, the pain score was lower with OROS hydromorphone compared with placebo. This is consistent with OROS hydromorphone being more effective in subjects suffering more severe pain than in subjects in less pain.

For the confirmatory subgroup analyses, subjects were divided according to whether they reached a dose of at least 16 mg by the end of the study (low dose, < 16 mg; high dose, ≥ 16 mg). More placebo group subjects were taking high doses of study medication by the end of the titration phase, whereas more OROS hydromorphone hydrochloride group subjects were taking low doses. There was a greater difference between the two treatments in subjects who took low doses of study medication compared to high doses, which argues against the theory that the doses used in this study were too low.

The comparison of WOMAC scores between studies FEN-EMA-1, M03-644-05, and the current study suggested that subjects in the FEN-EMA-1 study may have been in more pain, experienced more impairment of physical functioning, and experienced more stiffness than those subjects in studies M03-644-05 and the current study. Subjects in study M03-644-05 may have experienced more stiffness and a higher overall WOMAC score than subjects in the current study.

SAFETY RESULTS:

183 subjects (64%) in the Safety population experienced 537 TEAEs: 115 subjects (83%) in the OROS hydromorphone hydrochloride group experienced 397 TEAEs, and 68 subjects (46%) in the placebo group experienced 140 TEAEs.

One subject in the placebo group died during the study due to an SAE of myocardial infarction. However, this death occurred 131 days after starting study treatment and the SAE was classified as not related to study drug. A total of 11 subjects (4%) experienced 19 SAEs (4 subjects [3%] in the OROS hydromorphone hydrochloride group experienced 10 SAEs, and 7 [5%] subjects in the placebo group experienced 9 SAEs).

A higher proportion of subjects in the OROS hydromorphone hydrochloride group (27%) experienced TEAEs that led to discontinuation from the study (5% in the placebo group). Similarly, over twice the proportion of subjects in the OROS hydromorphone hydrochloride group (78%) reported TEAEs that were possibly, probably, or very likely related to study drug, compared to placebo (37%). TEAEs of clinical interest namely fall, contusion, depression, oliguria were only reported in the OROS hydromorphone hydrochloride group (4%).

The body systems most commonly affected in both treatment groups were the gastrointestinal system (70% for OROS hydromorphone hydrochloride and 22% for placebo), with the most frequently reported preferred terms being constipation, nausea, dry mouth, vomiting and diarrhoea; and the nervous system (45% for OROS hydromorphone hydrochloride and 21% for placebo), with the most frequently reported preferred terms being somnolence, dizziness and headache.

In the OROS hydromorphone group, drug-related TEAEs were also most frequently reported in the gastrointestinal body system (69%, in particular constipation [45%] and nausea [30%]), and the nervous system body system (in particular somnolence [30%]). A similar trend was observed in the placebo group, but with a lower frequency (31 subjects [21%] and 27 subjects [18%] in the gastrointestinal and nervous system, respectively).

A higher proportion of subjects in the OROS hydromorphone hydrochloride group (76%) experienced "opioid-typical" and gastrointestinal-related TEAEs compared to placebo (31%), overall and per body system. The most frequently reported "opioid-typical" and gastrointestinal-related TEAEs were constipation, nausea and vomiting in the in the gastrointestinal body system, and somnolence and dizziness in the nervous system body system.

TEAEs resolved for the majority of subjects in either treatment group (77% of subjects in the OROS hydromorphone hydrochloride group and 81% of subjects in the placebo group).

No notable differences were observed between treatment groups for the remaining safety variables.

Overall, the safety outcomes of the trial were consistent with the known characteristics of OROS hydromorphone hydrochloride. TEAEs of clinical interest namely contusion, fall and depression are more commonly observed with the disease under study and may also be secondary to known adverse effects of the study treatment. Similarly, mild and moderate oliguria was observed in 3 subjects. In all cases, the subjects fully recovered.

CONCLUSIONS:

The primary endpoint has not been met in this study, i.e., superiority for OROS hydromorphone hydrochloride compared to placebo in its analgesic effect in subjects with moderate-to-severe pain induced by OA of the hip or knee has not been proven. The secondary variables have not demonstrated significant differences between the two treatment groups. This study confirms the already well-documented safety profile of OROS hydromorphone hydrochloride, and shows that AEs are generally similar in a subject group who are naive to strong opioid analgesics such as OROS hydromorphone hydrochloride.

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