SYNOPSIS

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Company: ALZA Corporation **Investigational Product:** OROS hydromorphone HCl **Active ingredient:** hydromorphone HCl		

Title: A Phase 3, Randomized, Double-Blind, Fixed-Dose, Parallel-group Comparison of Controlled-Release Hydromorphone HCl vs. Placebo in Patients with Osteoarthritis	
Investigator(s)/Study Center: Multicenter	
Publication (reference): none	
Study period: First patient treated: 21 November 2003 Last patient completed: 04 May 2005	**Phase of Development:** 3
Objective: To compare the analgesic efficacy and safety of OROS hydromorphone HCl 8 mg and 16 mg to placebo in patients with osteoarthritis (OA).	
Methodology: This was a Phase 3, randomized, placebo-controlled, double-blind, fixed-dose, parallel-group, multicenter study in adult patients≥21 years old with OA who were unable to consistently control or treat their pain with nonopioid medications, or who had received an opioid for treatment of the pain. Eligible patients were randomized in an equal ratio to receive 1 of 3 treatments: OROS hydromorphone HCl 8 mg, OROS hydromorphone HCl 16 mg, or placebo. All patients could take acetaminophen (≤2000 mg per day) as rescue medication for osteoarthritic pain. Rescue medication was not permitted during the washout period or 6 hours before an efficacy assessment. The study was comprised of the following periods: an analgesic taper and washout period (≤2 weeks), a Titration Phase (≤16 days), a Maintenance Phase (12 weeks), and a study drug taper period (≤1 week). At the end of the washout period, all patients received OROS hydromorphone HCl 8 mg or matching placebo to be taken once daily. After 1 week, patients were to return to the study site to receive new supplies of study drug. During the second week of titration, patients randomized to the OROS hydromorphone 16 mg group had their dose increased from 8 mg daily to 16 mg daily of OROS hydromorphone. No dose adjustments were allowed. After completing the Maintenance Phase or upon early termination, study drug was tapered for up to 1 week as follows: one 8 mg tablet or placebo once daily for the first 2 days then taken every other day as appropriate to taper off the study medication.	
Number of patients (planned and analyzed): Planned n=900; Randomized n=990; Treated n=981; Completed n= 473; Efficacy n= 980 (excludes 1 patient who did not have baseline efficacy measurements); Safety n= 981	
Diagnosis and main criteria for inclusion: Patients ≥21 years who met criteria (functional Class I-III in the hip or knee) for OA.	
Test product, dose and mode of administration, batch number: OROS hydromorphone 8 mg tablets, Batch Nos. MV0310175, MV0322465, and MV041378 OROS hydromorphone 16 mg tablets, Batch Nos. MV0310195, MV0322481, and MV0413750	
Duration of trial: ~19 months	
Duration of individual participation: ~17 weeks	

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Reference therapy:
Placebo tablets matching OROS hydromorphone 8 mg, Batch Nos. MV0310180, MV0322486, and MV0413744
Placebo tablets matching OROS hydromorphone 16 mg, Batch Nos. MV0310201, MV0322496, MV0322501, and MV0413757

Breakthrough-pain medication:
Rescue medication included over-the-counter acetaminophen (≤2000 mg daily).

Criteria for evaluation:
Efficacy Measures: Office visit pain intensity (primary measure); WOMAC pain subscale; WOMAC Osteoarthritis Index; WOMAC stiffness subscale; WOMAC physical function subscale; MOS sleep scale including 7 subscales and 2 overall indexes; Patient global assessment; Treatment responders; Weekly pain intensity using IVRS; and Rescue medication use.

Safety Measures: AEs, clinical laboratory test results, and vital signs.

Pharmacokinetics: Values for the pharmacokinetic parameters of hydromorphone, including clearance (CL/F) were calculated.

Statistical methods:
All statistical tests were 2-sided and were considered statistically significant if the p-value was less than or equal to 0.05 (when rounded to 3 decimal places). For all efficacy analyses and safety summaries the primary comparison was made between the OROS hydromorphone HCl 16 mg treatment group and the placebo group. In general, all statistical comparisons were performed using an analysis of variance (ANOVA) with treatment group as the main effect for continuous variables and Chi-squared test for categorical variables for: demographics, baseline pain assessments, primary, and secondary efficacy endpoints. For continuous primary and secondary variables where ANOVA was used, in addition to treatment group, center was also used as a factor.

Efficacy Analysis:
The primary efficacy measurement was the time-interval weighted area under the curve (AUC) divided by the maximum AUC benefit possible for an individual (observed baseline score multiplied by the planned (14 week) duration for office visit pain intensity. Pain intensity AUC was estimated using the linear trapezoidal rule. The AUC was a measure of cumulative pain intensity differences from baseline for the Titration and Maintenance phases. Upon discontinuation, patients were assigned their baseline pain value for the remainder of the trial, baseline observation carried forward (BOCF). To demonstrate how the method of imputation influenced the results, several imputation methods were explored.

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Statistical methods (continued):

All of the following imputation methods were used for the analysis of the primary efficacy endpoint:

- No imputation (Observed Cases)
- Baseline observation carried forward (BOCF)
- Last observation carried forward (LOCF)
- Worst observation carried forward (WOCF)
- Group means imputation (GMI)
- Placebo means imputation (PMI)
- Imputation utilizing dropout reason (IUDR)

The various imputation methods were applied to the primary office visit pain intensity measure and the WOMAC pain subscale for the AUC ratio and the change from baseline analyses at each time point up to and including Maintenance Week 12. The WOMAC overall index score, physical function and joint stiffness subscales were analyzed using the AUC ratio and change from baseline using no imputation, and the BOCF and LOCF imputation methods. Patient global assessment, responder analysis, pain intensity via IVRS, rescue medication use and MOS Sleep Scale were analyzed per protocol.

Efficacy Results Summary:

- The protocol-specified analysis of the office visit pain AUC ratio using the BOCF imputation method showed statistically significant treatment differences between OROS hydromorphone 16 mg and placebo through Maintenance Week 4; no statistically significant differences were seen at study end (Maintenance Week 12). The protocol-specified analysis of the pain AUC ratio was significantly better for OROS hydromorphone 16 mg than placebo through Maintenance Week 10 using the observed cases analysis and through Maintenance Week 12 using clinically relevant alternate imputation methods (LOCF, WOCF, GMI, and IUDR).

- The protocol-specified analysis of the office visit pain AUC ratio at each visit showed statistically significant treatment differences between OROS hydromorphone 16 mg than placebo through the first 6 weeks of treatment, independent of the method of imputation.

- The WOMAC Pain Subscale AUC ratio analysis over time was significantly better for OROS hydromorphone 16 mg than placebo at each time point up to and including Maintenance Week 12 for the observed cases analysis and for the LOCF, WOCF, GMI, PMI, and IUDR imputation methods.

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Efficacy Results Summary (continued):

- On both the office visit pain AUC ratio over time and the WOMAC pain subscale AUC ratio over time, the BOCF imputation method yielded different results from the observed cases analysis and the other clinically relevant alternate imputation methods. In this fixed-dose trial, the BOCF method appeared to inappropriately bias the treatment effects in the setting of a high and differential dropout rate and a continued improvement in placebo response over time.

- Efficacy results for OROS hydromorphone 8mg showed that it was an effective treatment for titration, demonstrating statistical significance over placebo during the first 2 weeks of treatment using office visit pain intensity AUC ratio and for at least 6 weeks using the WOMAC pain subscale AUC ratio.

Pharmacokinetic Results Summary:

Using the demographic and other information from 407 participants with osteoarthritis (OA) who received OROS hydromorphone, a population pharmacokinetic (PK) model was developed to investigate covariate effects on the steady-state clearance (CL/F) of OROS hydromorphone. Three plasma samples were drawn from each participant at three different visits (Maintenance Weeks 1, 3, and 6). NONMEM software (NONMEM V.1.1, Globomax LLC) was used to analyze the OROS hydromorphone plasma concentration data and to test the statistical significance of covariate effect using likelihood ratio test combined with forward addition – backward elimination method. A total of 10 covariates were tested including sex, race, age, weight, height, body mass index, target joint, sedative medication use, prior opioid use in the past 13 weeks, and radiographic osteoarthritis index. Body weight and age were identified as significant covariates ($p<0.001$), and accounted for a 5.1% decrease in the inter-patient variability. None of the other covariates including sex and race had a significant effect on the steady-state clearance (CL/F) of OROS hydromorphone.. The final model produced a good fit to the observed concentration data. The typical value of clearance (CL/F) was 484 ± 11.4 L/hr, which was comparable to the value of 429 ± 57.1 L/hr obtained from a healthy volunteer study D-101. The analysis indicated that body weight and age appeared to have an impact on the clearance of OROS hydromorphone, with values generally higher in patients with increased body weight and reduced oral clearance in older patients. Based on the median age of 58.5 years for the PK population, every 10 kg increase in weight is predicted to increase CL/F by 5%. Based on the median weight of 98 kg of the PK population, every 10 year increase in age is predicted to decrease CL/F by 9%.

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Safety Results Summary:

Overall, approximately 64%, 81%, and 88% of patients in the placebo, OROS hydromorphone 8 mg, and OROS hydromorphone 16 mg groups, respectively, experienced at least one treatment-emergent AE. The most common AEs were gastrointestinal (GI) events, with constipation and nausea occurring in >10% of patients in both active treatment groups. Nervous system disorders of somnolence, dizziness, and headache were reported in >10% of patients in both active treatment groups. Vomiting and pruritus were reported in >10% of patients in the OROS hydromorphone group 16 mg, and in <10% of patients in the OROS hydromorphone 8 mg and placebo groups. Most of these events were considered to be opioid-related, and are commonly reported with opioid use. Most AEs were mild to moderate in severity. Severe AEs that occurred in more than one patient in the active treatment groups were opioid-related. Most AEs were considered related to the study treatments. The overall incidence of treatment-related AEs was 34.6% for placebo, 68.3% for OROS hydromorphone 8 mg, and 75.5% for OROS hydromorphone 16 mg.

No deaths occurred during the study or within 30 days after termination of study medication. Serious adverse events were reported in 5 patients (1.5%) in the placebo group, 8 patients in the OROS hydromorphone 8 mg group (2.5%), and in 13 patients (3.9 %) in the OROS hydromorphone 16 mg group. Of these, none of the SAEs for patients in the placebo group were considered treatment-related; 2 patients experienced treatment-related SAEs in the OROS hydromorphone 8 mg group; and 4 patients experienced treatment-related SAEs in the OROS hydromorphone 16 mg group.

Early discontinuation from the study due to an AE occurred in 20 (6.0%) patients who received placebo, in 81 (25.4%) patients who received OROS hydromorphone 8 mg, and in 127 (38.5%) patients who received OROS hydromorphone 16 mg. Nausea and constipation were the most common reasons for early discontinuation from the study.

There were no clinically significant mean changes from baseline in vital signs in any treatment group and there was no case of respiratory depression based on AEs or vital signs.

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Conclusions:

The efficacy of OROS hydromorphone was established based on the following:

- Although the primary analysis based on the BOCF method of imputation failed to show a statistically significant difference among treatment groups at the end of the trial, clinically relevant and alternative methods of imputation established the efficacy of OROS hydromorphone 16 mg qd in patients with osteoarthritis.
- Application of the alternative methods of imputation to the WOMAC Pain Subscale, a primary measure of efficacy in many clinical trials evaluating arthritis, further established the efficacy of OROS hydromorphone 16 mg qd in patients with osteoarthritis.
- Regardless of the imputation method, OROS hydromorphone 16 mg qd was effective through the first 6 weeks of treatment.
- The 8 mg dose of OROS hydromorphone was significantly more effective than placebo in managing pain intensity for the first 2 weeks of treatment. Therefore, OROS hydromorphone 8 mg may be appropriate for individual dose titration.

A population pharmacokinetic model indicated that sex and race did not have a significant effect on the steady-state clearance (CL/F) of OROS hydromorphone whereas body weight and age were identified as significant covariates and accounted for a 5.1% decrease in the inter-patient variability.

The safety profile of OROS hydromorphone in this study was consistent with that of other opioid treatments for chronic pain conditions and most of the adverse events were of mild or moderate severity.

Date of the report: 20 April 2006

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