SYNOPSIS

Name of Sponsor/Company	Xian-Janssen Pharmaceutical Ltd
Name of Finished Product	JURNISTA®
Name of Active Ingredient(s)	JNJ-6606769-AAC (OROS® hydromorphone hydrochloride)

Status: Approved

Date: 13 March 2013

Prepared by: Xian-Janssen Pharmaceutical Ltd

Protocol No.: 42801-PAI-1012

Title of Study: An Open-Label Study to Evaluate the Single Dose Pharmacokinetic Profile and Safety of OROS® Hydromorphone in Chinese Subjects With Cancer who are not Opioid Tolerant.

Coordinating Investigator: Dr. Zeyuan Liu, Ph.D. of Clinical Pharmacology, Affiliated Hospital of Academy of Military-307 Hospital, Beijing, China, 100071

Study Center(s): Two centers in China (Affiliated Hospital of Academy of Military-307 Hospital, Beijing, China; and The Third Xiangya Hospital of Central South University, Changsha, Hunan Province, China.

Publication (Reference): None

Study Period: 07 February 2012 to 27 August 2012. Final database lock: 08 November 2012

Phase of Development: 1

Objectives: The objectives of this study were to

- Investigate the pharmacokinetics (PK) of OROS hydromorphone in Chinese subjects with cancer following the oral administration of a single 8 mg dose
- To assess the safety and tolerability of 8 mg OROS hydromorphone.

Methodology: This was an open-label, single-dose study in adult Chinese subjects with cancer. Approximately 12 subjects, between 18 and 65 years of age, who were not opioid tolerant were to be enrolled in the study. Subjects who withdrew were to be replaced to achieve a minimum of 12 PK evaluable subjects.

This study consisted of a screening phase (within 21 to 1 days before admission to the study research center on Day -1) followed by a 4-day open-label treatment phase (Day -1 to Day 3) and end-of-study or withdrawal assessments (done upon completion of the 48-hour PK sampling on Day 3 or upon withdrawal).

Each subject received a single oral 8 mg dose of OROS hydromorphone in the morning of Day 1. Serial blood samples were to be collected through 48 hours after dosing for the determination of plasma hydromorphone concentrations.

The subject also received a regimen of naltrexone 50 mg, to block the opioid effects of hydromorphone. The subject was administered with naltrexone 14 hours before, 2 hours before, and 10 hours after study drug administration. After the 10-hour dose, additional doses of naltrexone were administered every 12 hours up to 34 hours postdose.

Number of Subjects (planned and analyzed):

Planned: Approximately 12 subjects were to be enrolled in the study. Dropped-out subjects were to be replaced to achieve a minimum of 12 PK evaluable subjects.

Analyzed: A total of 12 subjects received the dose of study drug and were included in the safety and PK analysis set.

Diagnosis and Main Criteria for Inclusion:

Eligible Chinese male or female subjects with cancer between 18 and 65 years of age (inclusive); diagnosed with early stage cancer, with no active metastases, or severe intercurrent systemic disease, who met all of the inclusion criteria and none of the exclusion criteria were to be enrolled in the study.

Test Product, Dose and Mode of Administration, Batch No.: A single dose of an OROS hydromorphone tablet of 8 mg (Batch number: 0NA243; Expiry date: August 2012) were to be administered orally on Day 1 under fasting conditions. Naloxone injection (used for screening opioid challenge test [0.8 mg] and as rescue medication [0.4 mg to 2 mg] subcutaneously every 2 to 3 minutes as needed). Naltrexone 50-mg oral tablet (5 single doses during each period: 14 hours and 2 hours before the morning dose of study medication on Day 1 and every 12 hours afterwards, up to 34 hours postdose).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The planned total duration of the study for each subject was approximately 24 days (including screening and follow-up visits).

Criteria for Evaluation:

Pharmacokinetic evaluations: Serial blood samples for determination of hydromorphone plasma concentration levels were collected before and up to 48 hours following the administration of study drug. The following PK parameters were calculated: C_{max}, t_{max}, $AUC_{0\text{-}48h}$, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, $t_{1/2,\lambda}$, λ_z, Vd/F, and CL/F. In addition, t_{lag}, the time period between the time of dosing and the time of the first measurable concentration, was also calculated.

Safety evaluations: Safety and tolerability were evaluated by assessment of adverse events (AE), clinical laboratory tests (blood and urine), electrocardiogram (ECG), vital signs (blood pressure, pulse, respiratory rate until 48 hours after dosing of OROS hydromorphone, and temperature), oxygen saturation, sleep respirations, and physical examination.

Statistical Methods:

Sample size: Using an estimated intersubject coefficient of variation (CV) of 35% for cancer patients, a sample size of 12 subjects was considered sufficient to estimate the mean AUC and C_{max} of hydromorphone to be within 80% and 125% of their true values with 95% confidence. Drop-out subjects were to be replaced to ensure that a minimum of 12 subjects completed the study.

Pharmacokinetic analysis: All hydromorphone plasma concentrations were obtained during co-administration of naltrexone. Factors that could influence the plasma concentration (vomiting, diarrhea, comedication, fever, or high predose concentration) were checked. If an influencing factor was present, a decision was made by the responsible pharmacokineticist, whether to include or exclude the specific sample or subject.

Reasons for exclusion of a subject or a sample from the analysis could include the following: (1) vomiting within 48 hours after OROS hydromorphone administration; (2) If the $\%AUC_{\infty,ex}$ exceeds 20% for a given subject, that subject was excluded from the statistical analysis of AUC_{∞} ; (3) Too few data (greater than 10% missing values per each subject); (4) Noncompliance with study procedures affecting PK (eg, co-medication).

All subjects and samples excluded from the analysis are clearly documented in the study report.

Log-linear and linear-linear individual and mean hydromorphone plasma concentration-time profiles were plotted. All estimated PK parameters of hydromorphone were summarized with arithmetic mean and geometric mean, median, minimum value, maximum value, standard deviation, and coefficient of variation.

Safety analysis: All subjects who received study drug were included in the safety analysis. Safety was evaluated by examining the incidence and type of AEs, and changes in clinical laboratory test values, serial vital signs and pulse oximetry measurements, sleep respiration assessments and physical examination results, from the screening phase through study completion. ECG results were described.

RESULTS:

STUDY POPULATION:

A total of 14 subjects were screened, 2 subjects were screen failures. Twelve subjects were enrolled, received the study drug and completed the study. All 12 subjects were Chinese with equal distribution of male (6 [50%]) and female (6 [50%]) subjects. The mean (SD) age was 47.1 (6.73) years. The median (range) weight and BMI at baseline were 62.75 kg (50.5 to 75.0 kg) and 24.24 kg/m² (19.48 to 29.67 kg/m²), respectively. No protocol deviations were reported during the study.

PHARMACOKINETIC RESULTS

Following oral administration of a single dose of 8 mg OROS hydromorphone to 12 Chinese subjects with cancer who are not opioid tolerant, after 2 hours lag time, OROS hydromorphone was absorbed into the systemic circulation with the median t_{max} ranging from 8.0 to 24.0 hours after dosing. The mean C_{max} and drug exposure (AUC_{0-48h}) was 0.71 ng/mL and 16.5 h*ng/mL, respectively, with an inter-subject CV of 14.5% for C_{max}, and 21.9% for AUC_{0-48h}.

The estimated CL/F ranged from 410 to 477 L/hour and the estimated Vd/F ranged from 4950 to 12000 L, indicating extensive tissue distribution of OROS hydromorphone.

SAFETY RESULTS:

Of the 12 subjects treated, 2 subjects (16.7%) had 3 treatment emergent adverse events (TEAEs). The reported TEAEs were nausea and asthenia for 1 subject (Subject 08600302) and dizziness for the other subject (Subject 08600101). All these TEAEs were mild in intensity. The event of nausea and asthenia were considered to be doubtfully related and dizziness was considered to be probably related to the study drug by the investigator. All these events recovered/resolved without sequelae and no action was taken with the study drug due to these events.

No deaths, other SAEs, persisting TEAEs or TEAEs leading to discontinuation of study medication were reported during the study.

Changes in vital signs and physical examination from baseline were generally small and not clinically significant. One subject (Subject 08600101) with a medical history of hypertension and diabetes who had sinus rhythm and T wave changes at baseline also had ST-T changes during the study which was considered clinically significant but not reported as AE. No other clinically significant ECG abnormalities were reported in the study.

No clinically relevant changes from baseline were observed for hematology, chemistry, and urinalysis parameters.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

After a single dose of oral 8 mg OROS hydromorphone co-administered with naltrexone, the mean C_{max} and drug exposure (AUC_{0-48h}) of hydromorphone was 0.71 ng/mL and 16.5 h*ng/mL, respectively, with an inter-subject CV of 14.5% for C_{max}, and 21.9% for AUC_{0-48h}.The large values of calculated CL/F and Vd/F indicated extensive tissue distribution of hydromorphone.

The oral administration of OROS hydromorphone 8 mg as single dose co-administered with naltrexone appeared to be safe and well tolerated in Chinese subjects with cancer.

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