Study Number: EN3288-113

Title of Study: A Double-blind, Dose-Ranging, Pilot Study to Evaluate the Safety, Subjective Effects, and Pharmacokinetics of Oxymorphone Hydrochloride in Healthy Subjects Who Recreationally Administer Opioids Intranasally

Principal Investigator: Debra Kelsh, MD

Study Center(s): Vince & Associates Clinical Research, 10103 Metcalf Avenue, Overland Park, KS 66212, USA

Publications (reference): None

Studied period (years):	**Phase of development**: Phase 1
Date first subjects enrolled: 28-Oct-2013	
Date last subjects completed: 8-Jan-2014	

Objectives:

Primary Objectives:

- To evaluate the safety of oxymorphone HCl administered intranasally in healthy subjects who recreationally administer opioid medications
- To evaluate the pharmacodynamic effects of oxymorphone HCl administered intranasally over a range of doses in healthy subjects who recreationally administer opioid medications

Secondary Objective:

- To evaluate the pharmacokinetics of oxymorphone HCl administered intranasally in healthy subjects who recreationally administer opioid medications

Methodology: This pilot study was a randomized, double-blind, ascending-dose, placebo-controlled design. Healthy, non-dependent recreational opioid users with experience in using opioids intranasally participated in a screening visit, a qualification phase and a treatment phase.

In the qualification phase, subjects received OPANA 30 mg (3 × 10 mg) and placebo orally (on consecutive days) in a randomized, double-blind, crossover manner to ensure that he/she could discriminate between active drug and placebo, and could tolerate OPANA 30 mg (3 × 10 mg). They were confined to the study unit beginning on the day prior to the first dose (day -1) until the morning of day 3 (24 hours after the second dose).

There was a washout period of at least 48 hours between the end of the qualification phase and the beginning of the treatment phase. In the treatment phase subjects were divided into 2 cohorts of 9 subjects and administered up to 3 ascending intranasal doses of oxymorphone HCl in an alternating panel design. At each dose level, 6 subjects were randomized to receive oxymorphone HCl and 3 subjects were randomized to receive placebo, and they were confined to the study unit beginning on the day prior to dosing (day -1) until the afternoon of day 2 (approximately 30 hours postdose).

Pharmacodynamic measured were obtained through 24 hours, and blood samples for pharmacokinetics were obtained through 30 hours postdose. Escalation to any dose level was determined by safety results and pharmacodynamic effects from the preceding dose level administered to the other cohort of subjects.

End of study evaluations were to be conducted on day 2 of the final treatment dose or upon early termination from the study. Seven (7) days (± 1 day) after the last dose of study medication, a follow-up telephone call was to be conducted to collect information regarding adverse events (AEs) and concomitant medications.

Number of Subjects (Planned and Analyzed):

	Qualification Phase	Treatment Phase
Planned	As needed for treatment phase	18
Enrolled and Randomized	32	19 (18 + 1 replacement)
Safety Population	32	19
Pharmacodynamic Population	Not applicable	19
Pharmacokinetic Population	Not applicable	19

Diagnosis and Main Criteria for Inclusion: Subjects included in the study were healthy males or females, of any race, between 18 and 55 years of age, inclusive; recreational prescription opioid users, who were not currently physically dependent on opioids; and experienced with intranasal use of prescription opioid formulations.

Test Product, Dose and Mode of Administration, Batch Number: Oxymorphone HCl powder prepared for intranasal administration: 2.5 mg, 5 mg, 7.5 mg, and 10 mg. Oxymorphone HCl was supplied by Frontage Laboratories (Lot 1304000913).

Subjects in cohort 1 were administered 2 of the following: placebo, 2.5 mg, and 7.5 mg oxymorphone HCl. The dose may have been escalated to 12.5 mg if necessary. There were at least 96 hours between treatments.

Subjects in cohort 2 were administered 2 of the following: placebo, 5 mg, and 10 mg oxymorphone HCl. The dose may have been escalated to 15 mg if necessary. There were at least 96 hours between treatments.

Duration of Treatment:

Qualification Phase: Confinement began on day -1 and continued until day 3; each subject received a single dose of study medication on day 1 and day 2; there were at least 48 hours between the end of the qualification phase and the beginning of the treatment phase

Treatment Phase: Confinement began on day -1 and continued until day 2 (at least 30 hours postdose) of each period; 2 alternating cohorts received 1 of 2 doses of study medication on the morning of day 1; there were at least 48 hours between dosing periods.

Subjects randomized into the qualification phase only, were administered a single oral dose of OPANA. Subjects randomized into the qualification phase and the treatment phase were administered a single oral dose of OPANA then 1 or 2 single intranasal oxymorphone HCl doses over a period of 16 to 37 days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Qualification Phase: The supplies used for the qualification phase were prepared/over-encapsulated by the clinical research facility.

- OPANA 30 mg (3 × 10-mg tablets), oral administration, manufactured by Endo Pharmaceuticals Inc. (Lot T011212A)
- Placebo (microcrystalline cellulose), oral administration, manufactured by Fargron (Lot 13721-U06-012275)

T*reatment Phase*: Placebo powder, intranasal administration, lactose powder manufactured by PFE Pharma (Lot 10597908)

Criteria for Evaluation:

Pharmacodynamics: A number of visual analog scales (VASs) assessing a range of subjective effects (eg, positive, negative, balance, and other subjective effects) were included to assess the subjective response to the study drugs. During each treatment phase, VASs were Good Effects, High, Bad Effects,

Sick, Drug Liking (at this moment), Overall Drug Liking, Take Drug Again, Any Drug Effects, and Numerical Rating Scales (NRS) for Intranasal Tolerability (intranasal discomfort, itching, burning, pain, runny nose, and stuffiness). Selected VASs were administered during the qualification phase, and all were administered at intervals from predose to 24 hours after each dose during the treatment phase.

The Addiction Research Center Inventory (ARCI) for mood states typically associated with certain classes of drugs such as euphoria for stimulants and opioids (morphine-benzedrine group [MBG]) was administered during the qualification phase and at intervals from predose to 24 hours after each dose during the treatment phase.

Pupil diameter was measured during the qualification phase, at intervals from predose to 24 hours after each dose during the treatment phase.

Pharmacokinetics: Plasma oxymorphone and 6-hydroxy-oxymorphone (6-OH-oxymorphone) concentrations were determined over a 30-hour interval, measured after each intranasal dose of oxymorphone HCl. From plasma concentrations, peak concentration (C_{max}), corresponding peak time (T_{max}), area under the concentration versus time curve (AUC_{0-t} and AUC_{0-inf}), last measured concentration (C_t), terminal rate constant (λ_z), and terminal half-life ($t_{½}$) were calculated for each analyte when possible. Non-compartmental methods were used in determination of various pharmacokinetic parameters.

Safety: Safety assessments included monitoring and recording of AEs from signing of the informed consent through 7 days after the last dose of study medication; physical examination and routine clinical laboratory tests (hematology, serum chemistry, and urinalysis) performed at screening, on day -1 of the qualification phase and at the end of the study (or early discontinuation); vital signs measurements conducted at screening, on day -1 of the qualification and treatment phases, and at intervals after each dose, until 24 hours after the last oral dose (qualification phase) and 30 hours after the last intranasal dose (treatment phase); and electrocardiograms (ECGs) obtained at screening and the end of the study.

Statistical Methods:

Pharmacodynamic Analyses: Visual analog scales for Drug Liking "at this moment," Overall Drug Liking, Any Drug Effects, Good Drug Effects, Bad Drug Effects, High, Sick, Take Drug Again, and Intranasal Tolerability; ARCI-MBG; and pupillometry were summarized by mean, peak, the area under the response curve (AUE), and area over the curve relative to baseline, as appropriate for each dose group.

Pharmacokinetic Analyses: Plasma oxymorphone and 6-OH-oxymorphone concentrations, measured after each intranasal dose, were listed by time points and displayed graphically in both linear and semi-logarithmic coordinates. Descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, geometric mean, median, minimum, and maximum) were computed for pertinent pharmacokinetic parameters and for drug concentrations at each time point after each dose.

Safety: The occurrence of dose-limiting toxicity data for intranasal administration of oxymorphone HCl was to be analyzed using a mixed effects logistic regression model with dose as a continuous independent variable and subject as a random effect. If possible, the minimum intolerable dose and its 95% confidence interval were calculated using the mixed effects logistic regression model inversely.

All data collected in the study were listed by subject, treatment, date, and time. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 16.1). The occurrence of treatment-emergent adverse events (TEAEs) was summarized by treatment, system organ class, and preferred term for all TEAEs, TEAEs by severity, and treatment-related TEAEs. Descriptive statistics for vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation) were calculated for each treatment by time point and for change from baseline. Clinical laboratory test results were reviewed for the presence of any clinically significant result. Physical examination data were reviewed for any treatment-emergent abnormalities.

SUMMARY:

The pharmacodynamic/pharmacokinetic data were available from all 19 subjects randomized into the treatment phase, 10 in cohort 1 and 9 in cohort 2. There are data from 12 placebo doses and 6 doses each of 2.5, 5, 7.5, and 10 mg oxymorphone HCl. The mean age was 30 years; 18 (95%) were men and 1 (5%) was a woman; 15 (79%) were White, 3 (16%) were Black or African American, and 1 (5%) was Asian.

The median percentage of oxymorphone HCl dose actually insufflated was 63%, 96%, 97%, and 98% for the 2.5-, 5-, 7.5-, and 10-mg doses, respectively. The median percentage of placebo insufflated was 96%.

PHARMACODYNAMIC RESULTS:

A sigmoidal oxymorphone HCl dose response, with the steep slope between 2.5and 7.5 mg, was evident for many of the subjective drug effects and for the objective decrease in pupil diameter. The responses for balance effects, positive effects, and other subjective effects VAS maximum effect (E_{max}) and for the objective minimum pupil diameter, increased successively from placebo to the 2.5-, 5-, and 7.5-mg oxymorphone HCl doses. The dose-response E_{max} reached an asymptote such that the effects of the 7.5-mg and 10-mg doses were comparable. No such oxymorphone HCl dose response was evident for the negative subjective drug effects or low subjective measures of nasal tolerability.

Subjective Effects Measures E_{max}: Pharmacodynamic Population (N=19) (Mean±SD)

Effect	Placebo (N=12)[a]	Oxymorphone HCl Dose			
		2.5 mg (N=6)	5 mg (N=6)	7.5 mg (N=6)	10 mg (N=6)
Drug Liking VAS	55.3±10.73	63.3±16.46	76.2±15.77	96.3±4.76	92.7±7.89
Overall Drug Liking VAS	55.0±11.31	61.4±15.22	74.8±17.08	89.0±9.27	83.8±13.69
Take Drug Again VAS	58.2±16.78	59.6±14.88	77.2±14.08	90.7±10.65	90.0±12.17
High VAS	16.8±31.48	31.5±35.92	62.8±30.84	98.8±2.86	93.8±8.70
Good Effect VAS	16.8±31.50	33.3±39.41	63.0±29.51	99.0±2.00	98.5±2.51
ARCI-MBG	3.4±4.27	3.7±2.50	8.5±5.61	10.7±4.18	9.3±6.12
Bad Effects VAS	3.3±4.41	17.3±33.71	12.2±18.08	3.5±5.32	3.7±5.13
Sick VAS	3.0±4.05	3.7±4.13	13.7±29.59	7.3±16.50	29.7±41.39
Any Drug Effects	16.9±31.73	32.7±37.57	61.5±30.38	99.5±1.22	98.5±2.51

[a] The overall total N=19: 3 each dosed with placebo and 2.5 mg, placebo and 7.5 mg, placebo and 5 mg, placebo and 10 mg, 5 mg and 10 mg, 2 dosed with 2.5 mg and 7.5 mg, 1 subject dosed with 2.5 mg, and 1 subject dosed with 7.5 mg

Nasal Tolerability: All NRS scores were low. For all nasal tolerability scales, E_{max} values for NRS after oxymorphone doses were similar to E_{max} after placebo.

Pupillometry: Minimum pupil diameters were 6.18±0.631, 5.43±1.344, 4.20±1.145, 2.77±0.455, and 2.62±0.366 mm after insufflated doses of placebo, 2.5, 5, 7.5, and 10 mg oxymorphone HCl.

PHARMACOKINETIC RESULTS:

Systemic absorption of the insufflated oxymorphone HCl dose was rapid, with maximum concentrations observed by 0.25 hours.

Once the low percentage of the 2.5-mg dose actually insufflated by the subjects was taken into account, systemic exposure to oxymorphone and 6-OH-oxymorphone was approximately proportional to doses of 2.5 mg and 5 mg, but increased less than proportionately to doses of 7.5 mg and 10 mg oxymorphone HCl.

Systemic exposure to 6-OH-oxymorphone was much lower than systemic exposure to oxymorphone, at an average of 20%.

Plasma Pharmacokinetics of Oxymorphone After Intranasal Doses Administered to Fasted Healthy Subjects: (N=19), Arithmetic Mean±SD

	Oxymorphone HCl			
Parameter	**2.5 mg (n=6)**	**5 mg (n=6)**	**7.5 mg (n=6)**	**10 mg (n=6)**
AUC_{0-t} (ng•h/mL)	3.55±0.703	14.20±6.660	17.57±3.747	22.43±4.936
AUC_{0-inf} (ng•h/mL)	3.81±0.924	14.73±6.707	18.12±3.687	23.14±4.847
C_{max} (ng/mL)	1.78±0.505	5.95±1.719	7.84±3.553	9.84±3.207
T_{max} (h)[a]	0.28 (0.3-0.3)	0.25 (0.3-0.8)	0.25 (0.3-0.3)	0.25 (0.3-0.6)
$t_{½}$ (h)	2.59±0.874	7.42±3.460	6.92±1.440	8.43±1.068

[a] Median (range)

Plasma Pharmacokinetics of 6-Hydroxy-Oxymorphone After Intranasal Oxymorphone Doses Administered to Fasted Healthy Subjects: (N=19), Arithmetic Mean±SD

	Oxymorphone HCl Dose			
Parameter	**2.5 mg (n=6)**	**5 mg (n=6)**	**7.5 mg (n=6)**	**10 mg (n=6)**
AUC_{0-t} (ng•h/mL)	0.42±0.203	2.82±1.400	3.42±0.882	4.79±1.030
C_{max} (ng/mL)	0.099±0.0262	0.29±0.152	0.33±0.097	0.48±0.073
T_{max} (h) [a]	0.79 (0.8-1.5)	0.75 (0.6-5.0)	2.39 (0.6-5.0)	2.53 (0.6-5.0)

[a] Median (range)

SAFETY RESULTS:

Thirteen (13) subjects entered and completed the qualification phase but were not randomized into the treatment phase of the study.

Nineteen (19) subjects completed the qualification phase and were randomized into the treatment phase: 15 completed the study; 3 completed the treatments, pharmacokinetic and pharmacodynamic assessments but were lost to follow-up, and 1 withdrew consent during period 1. No subject in the treatment phase experienced a dose-limiting AE, so a maximum tolerable insufflated dose was not defined in this study. Consequently, no statistical analysis of dose-limiting toxicity was possible.

No deaths and no serious adverse events (SAEs) occurred during the study. No subject was discontinued from the study due to TEAEs.

At least 1 treatment-related TEAE occurred in 2 subjects after placebo and in 12 of 32 subjects after 30 mg OPANA in the qualification phase. At least 1 treatment-related TEAE occurred in 1 subject after insufflation of 5 mg, 3 subjects after insufflation of 7.5 mg, and 5 subjects after insufflation of 10 mg oxymorphone HCl. The number of treatment-related TEAEs increased as the insufflated oxymorphone HCl dose increased. TEAEs related to administration of 30 mg OPANA were nausea (5 cases), vomiting (4 cases), hyperhidrosis (3 cases), pruritis (3 cases), dizziness (2 cases), and visual field defect, abdominal pain, chills, hot flush, headache and dyspnoea (1 case each). Treatment-related TEAEs after insufflation of oxymorphone HCl were pruritis (5 cases), vomiting (3 cases), nausea (2 cases), hyperhidrosis (2 cases), hiccups (1 case), and headache (1 case).

Most treatment-related TEAEs were mild, 2 were moderate, none was serious, and all resolved without medication.

Small, if any, mean changes in vital signs were observed after 30 mg OPANA and after 2.5, 5, 7.5, or 10 mg insufflated oxymorphone HCl; none was clinically significant. There was no clinically significant change in physical examination findings related to study treatments. There were no clinically significant changes in clinical laboratory test results.

All but 2 treatment-related TEAEs (chills and hiccups) for oxymorphone that occurred in this study are listed in the OPANA labeling.