Study Number: EN3288-114

Title of Study: A Randomized Double-blind, Single-Dose, Placebo-Controlled, Four-Period, Crossover Study to Evaluate the Subjective Effects and Systemic Exposure of Manipulated OPANA® ER Administered Intranasally Compared with Oxymorphone Hydrochloride Powder Administered Intranasally in Healthy, Non-Dependent Subjects Who Recreationally Administer Opioids Intranasally

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Publications (reference): None

Studied Period (years):	**Phase of Development**: 1
Date first subjects enrolled: 14-Apr-2014	
Date last subjects completed: 04-Sep-2014	

Objectives:

Primary Objectives:

- To evaluate the subjective effects of manipulated OPANA ER administered intranasally compared with oxymorphone HCl powder administered intranasally in healthy non-dependent subjects who recreationally administer opioid medications intranasally

Secondary Objective:

- To characterize the systemic exposure of oxymorphone following intranasal administration of manipulated OPANA ER and oxymorphone HCl powder in healthy non-dependent subjects who recreationally administer opioid medications intranasally
- To evaluate the safety of manipulated OPANA ER and oxymorphone HCl powder administered intranasally in healthy non-dependent subjects who recreationally administer opioid medications intranasally

Exploratory Objective:

- To evaluate the subjective effects of OPANA ER placebo administered intranasally compared to placebo powder administered intranasally in healthy non-dependent subjects who recreationally administer opioid medications intranasally

Methodology: This study utilized a randomized, double-blind, single-dose, placebo-controlled, 4-period, crossover design in healthy, non-dependent subjects who recreationally administer opioids intranasally. Each subject participated in a screening visit, a qualification phase and a treatment phase consisting of 4 back-to-back treatment periods.

Prior to receipt of the first dose in the qualification phase, each subject had a naloxone challenge test to determine if he/she was physically dependent on opioids. In the qualification phase, subjects received oxymorphone HCl powder 7.5 mg and placebo intranasally in a randomized, double-blind, crossover manner to ensure that he/she could discriminate between active drug and placebo, and could tolerate oxymorphone HCl powder 7.5 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 72 hours between the end of the qualification phase and the beginning of the treatment phase.

In the treatment phase subjects were confined to the study unit for 16 days, from the day prior to dose administration (day -1) of treatment period 1 until the morning of day 3 (48 hours post-dose) of treatment period 4. Subjects were administered OPANA ER 7.5 mg tablet manipulated using a common

method, OPANA ER placebo tablet manipulated using the same common method, oxymorphone HCl powder 7.5 mg, and placebo powder, intranasally. Each dose was separated by at least a 4-day washout period.

Pharmacodynamic measurements were obtained through 24 hours, safety assessments and blood samples for pharmacokinetics were obtained through 48 hours postdose.

End of study evaluations were to be conducted on day 3 of treatment period 4 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 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	36 to complete
Enrolled and Randomized	104 enrolled, 98 randomized	49
Safety Population	103	49
Pharmacodynamic Population	Not applicable	38
Pharmacokinetic Population	Not applicable	47

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: OPANA ER 7.5-mg tablets, manipulated and prepared for intranasal administration (approximately 230 mg total mass). OPANA ER 7.5-mg tablets (lot B12275), were manufactured by PMRS for Endo Pharmaceuticals Inc.

Duration of Treatment:

Qualification Phase: Confinement began on the day subjects received the naloxone challenge (day -1) and continued until the day 3 (4^{th} day); each randomized subject received a single dose of study medication on day 1 and day 2; there were at least 72 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 16 (at least 48 hours after the period 4 dose); the treatment periods ran back-to-back, and there were 4 days between doses. Each subject received a single intranasal dose of study drug on day 1 of each of the 4 periods (days 2, 6, 10, and 14).

Subjects randomized into the qualification phase only, were administered oxymorphone HCl powder 7.5 mg by insufflation and placebo powder by insufflation. Subjects randomized into the treatment phase were administered intranasal doses of OPANA ER 7.5 mg manipulated tablet; OPANA ER Placebo manipulated tablet, oxymorphone HCl powder 7.5 mg, and placebo powder.

Reference Therapy, Dose and Mode of Administration, Batch Number: The powders and manipulated tablets for insufflation were prepared by the clinical research facility.

Qualification Phase:

- Oxymorphone HCl powder 7.5 mg manufactured by Mallinckrodt and supplied by Endo Pharmaceuticals Inc. (Lot 1304000913), administered with lactose powder manufactured by DFE Pharma (Lot 10711892) and supplied by Frontage Laboratories (total dose of approximately 120 mg)
- Lactose powder, approximately 120 mg, manufactured by DFE Pharma (Lot 10711892) and supplied by Frontage Laboratories

Treatment Phase:

- OPANA ER placebo tablets, approximately 230 mg, manipulated using a common method. OPANA ER placebo tablets (Lot B14016), manufactured by PMRS and supplied by Endo Pharmaceuticals Inc.
- Oxymorphone HCl powder 7.5 mg manufactured by Mallinckrodt and supplied by Endo Pharmaceuticals Inc. (Lot 1304000913), administered with lactose powder manufactured by DFE Pharma (Lot 10711892) and supplied by Frontage Laboratories (total dose of approximately 120 mg)
- Lactose powder, approximately 120 mg, manufactured by DFE Pharma (Lot 10711892) and supplied by Frontage Laboratories

Other Product, Dose and Mode of Administration, Batch Number:

Qualification Phase: Naloxone HCl 0.8 mg, intravenous administration (Lot 35-441-EV and Lot 39-540-EV) manufactured by Hospira.

Criteria for Evaluation:

Pharmacodynamics: A number of visual analog scales (VASs) assessing a range of subjective effects (ie, balance, positive, negative, and other subjective effects) were included to assess the subjective response to the study drugs. During each treatment phase, VASs were Drug Liking (at this moment), Overall Drug Liking, Take Drug Again, Good Effects, High, Bad Effects, Sick, and Any Drug Effects. VASs were administered for 8 hours during the qualification phase, and at intervals from predose to 24 hours after each dose during the treatment phase.

Pupil diameter was measured once after each dose of the qualification phase, and at intervals from predose to 24 hours after each dose during the treatment phase. Numerical Rating Scales (NRS) for Intranasal Tolerability (intranasal discomfort, itching, burning, pain, runny nose, and stuffiness) were also obtained 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 48-hour interval, measured after each intranasal dose during the treatment phase. 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 and at end of the qualification phase, and at day -1 and at end of the treatment (end of 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 qualification phase dose and 48 hours after the last intranasal dose (treatment phase); and electrocardiograms (ECGs) obtained at screening, the end of the qualification phase, and the end of the study.

Statistical Methods:

Pharmacodynamic Analyses: Visual analog scales for Drug Liking "at this moment," Overall Drug Liking, Take Drug Again, Any Drug Effects, High, Good Drug Effects, Bad Drug Effects, Sick; Intranasal Tolerability NRS; and pupillometry were summarized by peak effect, the area under the response curve (AUE), and area over the curve relative to baseline, as appropriate for each dose group. Descriptive statistics were computed for mean responses at each time point and for pertinent pharmacodynamics parameters after each dose. Pairwise comparisons of responses during the treatment phase were obtained by linear mixed effect model analysis.

Pharmacokinetic Analyses: Plasma oxymorphone and 6-OH-oxymorphone concentrations, measured after each treatment phase 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. Pairwise comparisons of responses during the treatment phase were obtained by linear mixed effect model analysis of logarithmically transformed pharmacokinetic parameters.

Safety: 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 data were available from 38 subjects, who completed the treatment phase of the study. Pharmacokinetic data were available from 43 subjects administered insufflated OPANA ER 7.5 mg manipulated tablet, and 45 subjects administered insufflated oxymorphone HCl powder 7.5 mg. For 49 subjects who qualified and were randomized into the treatment phase, mean age was 27.6 years; 41 (84%) were men and 8 (16%) were women; 21 (43%) were White, and 28 (57%) were Black or African American.

For 104 subjects enrolled in the study, mean age was 27.6 years; 84 (82%) were men and 19 (18%) were women; 35 (34%) were White, 65 (63%) were Black or African American, 1 (1%) was Asian, and 2 (2%) were American Indian or Alaskan Native.

The median percentage of each treatment actually insufflated in the treatment phase ranged from 96% to 97%.

PHARMACODYNAMIC RESULTS:

As displayed in the tables below, the validity of the study was demonstrated by significantly higher Drug Liking VAS E_{max} after insufflated oxymorphone HCl powder 7.5 mg compared to placebo powder. The primary endpoint of a statistically significantly lower Drug Liking VAS E_{max} after insufflated OPANA ER 7.5 mg manipulated tablet compared to oxymorphone HCl powder 7.5 mg was observed. Responder analysis showed 55% subjects had at least 30% reduction in Drug Liking VAS E_{max}.

Pharmacodynamic effects for most VAS and for pupillometry were lower and occurred later after insufflated OPANA ER 7.5 mg manipulated tablet compared to oxymorphone powder 7.5 mg.

No statistically significant differences in the subjective effects of insufflated OPANA ER Placebo manipulated tablets and placebo powder were observed.

Nonparametric Analyses of Primary Endpoint - E_{max} (mm) of Drug Liking
Pharmacodynamic Population (N=38)

Parameters (unit)	Treatment Difference	Median of the Difference	Interquartile Range	p-value
Study Validation	C-D	38.5	19.0	<.0001
Primary Analysis	C-A	15.5	33.0	<.0001

A = OPANA ER manipulated tablet 7.5 mg; B = OPANA ER placebo manipulated tablet; C = Oxymorphone HCl powder 7.5 mg, D = Placebo powder.

Subjective Effects Measures E_{max} (mm): Pharmacodynamic Population (N=38) (Mean±SD)

Effect	OPANA ER Manipulated Tablet 7.5 mg (N=38)	OPANA ER Placebo Manipulated Tablet (N=38)	Oxymorphone HCl Powder 7.5 mg (N=38)	Placebo Powder (N=38)
Drug Liking VAS	70.3±16.20	53.3±8.69	87.8±10.33	50.3±0.65
Overall Drug Liking VAS[a]	57.4±21.77	49.5±12.09	76.5±18.85	50.9±6.79
Take Drug Again VAS[a]	56.5±23.88	47.1±16.46	78.3±19.00	50.4±11.85
High VAS	45.3±37.06	9.2±21.03	83.0±16.60	2.5±8.85
Good Effect VAS	45.8±36.35	10.8±22.17	81.3±18.58	4.7±12.71
Bad Effects VAS	16.2±25.70	4.9±16.59	12.4±21.06	1.9±8.57
Sick VAS	12.0±21.57	1.3±2.47	9.6±19.37	1.8±7.76
Any Drug Effects	47.7±36.58	10.7±22.11	81.7±17.99	2.5±7.97

[a] Average of 2 assessments.

Statistical Comparison of Derived Pharmacodynamic Parameters: VAS E_{max} (mm) after Oxymorphone HCl Powder 7.5 mg Minus OPANA ER 7.5 mg Manipulated Tablet - Pharmacodynamic Population (N=38)

Effect	Difference in LS Means	95% Confidence Interval	p-value
Drug Liking	17.15	12.53;21.77	<0.0001
Overall Drug Liking[a]	18.84	12.22;25.46	<0.0001
Take Drug Again[a]	21.43	13.70; 29.17	<0.0001
High	36.65	26.24;47.06	<0.0001
Good Effect	34.52	23.78; 45.26	<0.0001
Bad Effects	-4.44	-12.18; 3.30	0.258
Sick	-2.74	-8.81; 3.33	0.373
Any Drug Effects	33.08	22.74; 43.41	<.0001

[a] Average of 2 assessments

Median maximum NRS response for Burning, Runny Nose/Nasal Discharge, and Facial Pain were zero for all treatments. The median responses for Itching were approximately 1 for the oxymorphone treatments compared to zero for the placebo treatments. For Need to Blow Nose and for Nasal Congestion, the median responses were approximately 2 for the manipulated ER tablets (OPANA ER manipulated tablet 7.5 mg and OPANA ER placebo manipulated tablet) compared to zero for the 2 powder treatments.

The maximum effect (decrease in pupil diameter) of insufflated OPANA ER 7.5 mg manipulated tablet was less and occurred later than the effects of insufflated oxymorphone HCl powder 7.5 mg. PC_{min}, and area above the effect curve up to 1 hour and up to 2 hours ($PAOC_{0-1h}$, $PAOC_{0-2h}$) showed a statistically significantly greater effect after insufflated oxymorphone HCl powder 7.5 mg than after OPANA ER 7.5 mg manipulated tablet: Difference in LS means (and 95% CI): PC_{min} -0.42 mm (-0.79 to -0.05 mm); $PAOC_{0-1h}$ 1.33 mm.hr (1.12 to 1.54 mm.hr); and $PAOC_{0-2h}$ 2.36 mm.hr (1.88 to 2.85 mm.hr). There was no significant difference in $PAOC_{0-8h}$.

PHARMACOKINETIC RESULTS:

Systemic absorption of the insufflated oxymorphone HCl powder 7.5 mg was rapid, with maximum concentrations observed at 0.25 hours compared with the slower absorption of oxymorphone from

insufflated OPANA ER manipulated tablet 7.5 mg, with significantly lower maximum concentrations observed at 1.50 hours. C_{max} LS means ratio 0.42; 90% CI, 0.37-0.49. There was no significant difference in extent of systemic exposure (AUC_{0-t}).

Similarly, maximum 6-hydroxy-oxymorphone concentration was lower after insufflated OPANA ER manipulated tablet 7.5 mg. C_{max} LS means ratio 0.41; 90% CI, 0.35-0.49.

Plasma Pharmacokinetics of Oxymorphone After Single Intranasal Doses of Manipulated OPANA ER 7.5 mg and Oxymorphone HCl Powder 7.5 mg Administered to Fasted Healthy Subjects (N=47), Arithmetic Mean±SD (%CV)

	Oxymorphone HCl	
Parameter	**OPANA ER Manipulated Tablet 7.5 mg (N=43)**	**Oxymorphone HCl Powder 7.5 mg (n=45)**
AUC_{0-t} (ng•h/mL)	20.59±12.64 (61)	16.38±5.70 (35)
AUC_{0-inf} (ng•h/mL)	20.91±12.97 (62)[a]	16.516±5.77 (35)[b]
C_{max} (ng/mL)	2.84±1.46 (52)	6.03±2.33 (39)
T_{max} (h)[c]	1.50 (0.75;10.02)	0.25 (0.25;2.00)
C_{max}/T_{max} (ng/ml.hr) [c]	1.43 (0.23;8.80)	19.20 (2.08;48.00)
$t_{1/2}$ (h)	4.36±1.73 (40) [a]	4.12±1.09 (27) [b]

[a] n=41; [b] n=38; [c] Median (Range)

Statistical Analyses of Pharmacokinetic Parameters for Oxymorphone: Pharmacokinetic Population (N=49)

	Least Squares Geometric Mean				
Parameter	**A: OPANA ER Manipulated Tablet 7.5 mg (N=43)**	**C: Oxymorphone HCl Powder 7.5 mg (N=45)**	**Geometric Ratio A/C**	**90% Confidence Interval**	**p-value**
C_{max} (ng/mL)	2.44	5.75	0.42	0.37; 0.49	<.0001
AUC_{0-t} (ng•h/mL)	16.03	15.76	1.02	0.83; 1.24	0.8906
AUC_{0-inf} (ng•h/mL)	16.12[a]	15.38[b]	1.05	0.85; 1.29	0.7048

[a] n=41; [b] n=38

Plasma Pharmacokinetics of 6-Hydroxy-Oxymorphone After Single Intranasal Doses of Manipulated OPANA ER 7.5 mg and Oxymorphone HCl Powder 7.5 mg Administered to Fasted Healthy Subjects (N=47), Arithmetic Mean±SD (%CV)

	Oxymorphone HCl	
Parameter	**OPANA ER Manipulated Tablet 7.5 mg (N=43)**	**Oxymorphone HCl Powder 7.5 mg (n=45)**
AUC_{0-t} (ng•h/mL)	2.67±1.83 (69)	3.61±1.55 (43)
AUC_{0-inf} (ng•h/mL)	3.23±2.26 (70)[a]	3.91±1.62 (42)[b]
C_{max} (ng/mL)	0.168±0.085 (51)	0.39±0.23 (59)
T_{max} (h)[c]	3.00 (0.75,16.00)	0.75 (0.25,5.00)
$t_{1/2}$ (h)	12.86±7.13 (56) [a]	12.21±4.75 (39) [b]

[a] n=28; [b] n=23; [c] Median (Range)

SAFETY RESULTS:

One hundred three (103) subjects entered the qualification phase, 98 were randomized into the qualification phase, 49 were randomized into the treatment phase of the study. Overall 38 completed the study, 41 did not meet the qualification criteria for the treatment phase, 6 subjects were discontinued as a result of an adverse event, 2 subjects were lost to follow-up, 6 subjects withdrew from the study, 6 subjects did not complete the study because of personal or family events, 1 subject failed the naloxone challenge, 1 subject had a positive drug screen, and the physician excluded 2 subjects from qualification phase randomization.

No deaths occurred during the study. One SAE was reported for a subject screened but not entered into the qualification phase of the study (this subject was not 1 of the 103 subjects who entered the study). There were no SAEs or deaths observed for the 103 subjects who were administered any study drug. Six (6) subjects were discontinued from the study due to TEAEs; 5 were treatment related; 2 after a placebo dose and 3 after a dose of active drug substance.

At least 1 treatment-related TEAE occurred in 51 of 103 subjects (49.5%) in the qualification phase. In the treatment phase, at least 1 treatment-related TEAE occurred in 38 of 49 subjects (77.6%). TEAEs related to insufflation of oxymorphone HCl 7.5 mg as powder or manipulated OPANA ER 7.5 mg tablet and experienced by at least 5% of subjects after any treatment are tabulated:

Treatment-Related TEAEs Experience by ≥5% Subjects After Active Treatments – Qualification and Treatment Phases

	Qualification Phase	Treatment Phase	
Parameter	Oxymorphone HCl Powder 7.5 mg N=97 n(%)	OPANA ER 7.5 mg Tablet, manipulated N=43 n(%)	Oxymorphone HCl Powder 7.5 mg N=97 n(%)
Vomiting	21 (21.6)	11 (25.6)	6 (13.3)
Nausea	12 (12.4)	8 (18.6)	4 (8.9)
Hyperhidrosis	11 (11.3)	2 (4.7)	4 (8.9)
Feeling of relaxation	8 (8.2)	4 (9.3)	8 (17.8)
Pruritis	7 (7.2)	6 (14.0)	3 (6.7)
Elevated mood	6 (6.2)	2 (4.7)	3 (6.7)
Hot flush	6 (6.2)	1 (2.3)	1 (2.2)
Dizziness	5 (5.2)	0	2 (4.4)
Sedation	4 (4.1)	2 (4.7)	5 (11.1)
Headache	2 (2.1)	4 (9.3)	2 (4.4)
Feeling hot	0	3 (7.0)	3 (6.7)
Abdominal pain	0	1 (2.3)	3 (6.7)

The remaining TEAEs were experienced by only 1 or 2 subjects after any active treatment: dry mouth, lethargy, euphoric mood, dyspepsia, salivary hypersecretion, paraesthesia, feeling abnormal, palpitations, sinus tachycardia, vertigo, blurred vision, feeling drunk, irritability, respiratory tract congestion, decreased appetite, urinary hesitation, dyspnea, ventricular extrasystoles. Most treatment-related TEAEs were mild, about 10% were moderate, none was serious. All resolved (except 1 outcome was unknown). Three (3) TEAEs were treated with medication.

Small, if any, mean decreases in pulse rate were observed after active treatments. Sinus tachycardia was listed as a mild, possibly treatment-related, TEAE for 1 subject after insufflated oxymorphone HCl 7.5 mg during the qualification phase. No other vital signs measurement was considered to be clinically

significant. Ventricular extrasystoles were listed as a mild, possibly-related TEAE for 1 subject after insufflated oxymorphone HCl 7.5 mg during the treatment phase.

There was no clinically significant change in physical examination findings related to study treatments. Nasal irritation scores indicated no problem in most cases, with a few observations regarded as a moderate problem. Three (3) laboratory test results were listed as TEAEs but none was treatment-related.

Most of the treatment-related TEAEs for oxymorphone that occurred in this study are listed in the OPANA labeling.