M1530-02-07

Evaluation of the Pharmacokinetics and Abuse Potential of Intranasally Administered Extended-Release Oxycodone and Naloxone Abuse-Deterrent Formulations Milled to Different Particle Sizes

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PURPOSE

As of 2024, FDA approved eight opioid products labeled with abuse deterrent (AD) potential for the nasal route. Generic opioid products are recommended not to be inferior, with respect to AD potential, to the reference listed drug (RLD) that describes AD features. There is no literature that demonstrates the influence of particle size distributions, administered intranasally, on the bioavailability and positive subjective effect of the opioid agonist of an agonist/antagonist product. Therefore, this clinical study was designed to measure the impact of the particle size on the AD potential on manipulated agonist/antagonist product when administered intranasally.

OBJECTIVES

1) to evaluate the impact of particle size of a manipulated AD product on the nasal pharmacokinetic (PK) parameters of opioid agonist and antagonist, oxycodone and naloxone, respectively, [Primary Objective] and oxycodone active metabolite, oxymorphone [Secondary Objective]
2) to understand the effect of particle size on naloxone's ability to mitigate the drug liking and other pharmacodynamic (PD) effects of oxycodone
3) to evaluate the safety and tolerability of the manipulated products via the nasal route

METHODS

Study Design: Single-dose, randomized, double-blind, active controlled, five-way crossover study (Phase 1 study)

Study Subject: Non-dependent recreational opioid users who:
- underwent a naloxone challenge
- underwent discrimination test
- tolerate the study products

Study Product: Oxycodone HCl; Naloxone HCl ER Tablet 40mg:20mg

Treatments:
- A: Manipulated product, fine particles [106–300 µm]
- B: Manipulated product, medium particles [300–600 µm]
- C: Manipulated product, coarse particles [600–1000 µm]
- D: Active control, milled immediate release oxycodone HCl tablet
- E: Placebo, microcrystalline cellulose powder

Dose and Administration: Dose: oxycodone HCl: 40 mg, naloxone HCl :20 mg
Administration: insufflation using plastic straw

Assessment:
- Pharmacokinetic parameters: AUC, Cmax, etc.
- Pharmacodynamic endpoints: Drug liking VAS Emax, Take Drug Again VAS Emax, High VAS Emax, pupillometry, etc.
- Safety endpoints: adverse events, vital signs, lab test results, etc.

HCl: Hydrochloride **ER**: Extended-release **AUC**: Area Under the Curve
Cmax: Peak Concentration **VAS:** Visual Analog Scale **Emax:** Maximum Effect

RESULTS

Pharmacokinetic Assessment:

- Number of subjects who received at least 1 study drug during the Treatment Phase and could provide at least one reliable PK parameter is 40 (**PK population**)
- For oxycodone and oxymorphone, the rates and extents (except of early extent) of absorption were comparable between the three manipulated products (90% confidence intervals of Cmax and AUCinf were within acceptance range of 80.00-120.00 %, Figure 1).
- As particle size increased (particle size of A < B < C), the extent of absorption at the early stage (AUC0-0.5, 0-1 and 0-2) tended to decrease.
- Treatment D showed a distinct PK profile with a double peak observed for all subjects.
- For naloxone, a lower rate and extent of absorption were observed as the particle size increased (Figure 1).

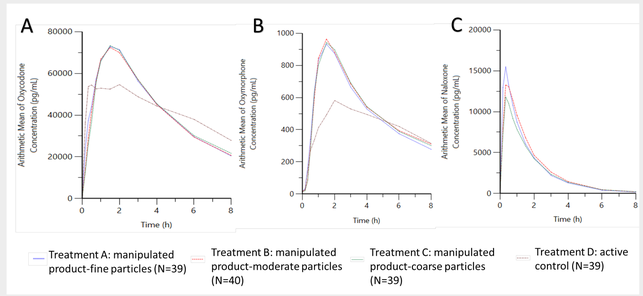

Figure 1: The Pharmacokinetic Profiles of Oxycodone (A), Oxymorphone (B), and Naloxone (C) After the Intranasal Administration of Manipulated Products of Oxycodone HCl and Naloxone HCl ER Tablet Compared to Milled Immediate-release Oxycodone HCl tablet (Active Control)

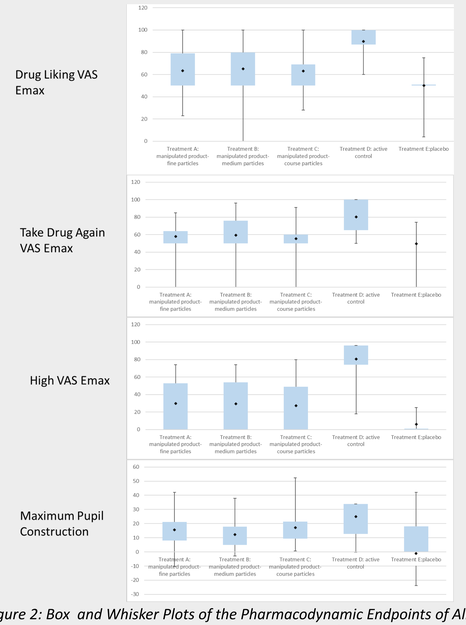

Figure 2: Box and Whisker Plots of the Pharmacodynamic Endpoints of All the Treatments Where the Box Presents the 1st and 3rd Percentiles (Q1 and Q3) , the Whiskers Present the Range (Min, Max) and the Diamond Symbol presents the Mean (N=37)

Pharmacodynamic Assessment

- **Modified Completer population** included 37 subjects who were completers and did not meet the exclusion criteria*
- The PD assessment was validated by the significant difference of Emax for Drug Liking between the active control and placebo ($p<0.001$) (Figure 2)
- The three different manipulated products demonstrated statistically significant AD potential compared to the active control ($p<0.001$)
- Comparable AD potential between the manipulated products with different particle sizes
- A cumulative of 65%, 62 % and 73 % of subjects (Treatment A, B, and C, respectively) showed at least 50 % reduction in Drug Liking Emax compared to active control (Figure 3)

*Exclusion criteria: Subjects who had similar Drug Liking E_{max} across all treatments or an E_{max} for placebo > 60 and E_{max} for placebo ≥ positive control + 5.

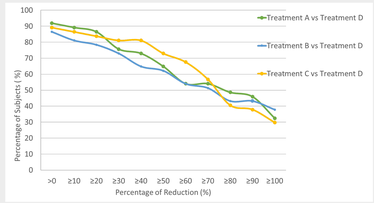

Figure 3: Responder Analysis: Percent Reduction Profiles for Emax of Drug Liking VAS Manipulated Products of Oxycodone HCl And Naloxone HCl ER Tablet (Treatment A, B, And C) Compared to Milled Immediate-release Oxycodone HCl Tablet (Active Control, Treatment D)

Safety Assessment:

- All 40 subjects in the randomized population who received 1 study drug in the Treatment phase was included in **Safety population**
- All study treatments were well tolerated without unexpected or serious adverse events
- The most common adverse events were somnolence, headache, and euphoric mood (Figure 4)
- All Treatment-Emergent Adverse Effects (TEAEs) are mild and commonly associated with treatment with opioids

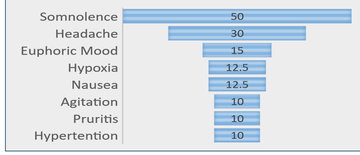

Figure 4: Most Common (≥ 10%) Treatment-Emergent Adverse Effects in Subjects of All the Treatments Expressed as Percent in Subjects (N=40)

CONCLUSIONS

- Intranasal administration of the manipulated products with smaller particles resulted in a faster and greater extent of exposure for naloxone but not for oxycodone and its active metabolite, oxymorphone.
- The change in the nasal bioavailability of naloxone did not impact the AD potential of the product as measured by Drug Liking.
- The AD potential of this product via the nasal route was not impacted by the particle size of the insufflated product.
- All study treatments were well tolerated without unexpected or serious adverse events.

ACKNOWLEDGEMENT

The work presented was conducted under contract (HHSF223201610004I-HHSF22301002T) awarded to BioPharma Service USA Inc.

DISCLAIMER

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