Secondary Outcomes of a Phase 1 Placebo-Controlled Trial Comparing the Effects of Buprenorphine Buccal Film and Oral Oxycodone Hydrochloride on Respiratory Drive

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Introduction

Background

- Buprenorphine is a Schedule III atypical opioid with partial μ-opioid receptor agonist activity, which is thought to contribute to its decreased risk of respiratory depression relative to that of full μ-opioid receptor agonists (eg, fentanyl, morphine, oxycodone)[1]
  - Partial agonism refers to receptor-level activity and not analgesic efficacy, as buprenorphine has analgesic efficacy comparable to that of full μ-opioid receptor agonists[1]
- Buprenorphine also has functions at other opioid receptors, including antagonism at the κ- and δ- opioid receptors and agonism at the nociceptin receptor (formerly known as opioid receptor-like 1 or ORL-1)[1]
- This unique receptor activation profile of buprenorphine translates to effective analgesia and potentially greater safety than Schedule II opioids for the management of chronic pain

Purpose

- As the primary cause of death related to opioid overdose is hypoxia caused by opioid-induced respiratory depression,[2] this phase 1 study was conducted to directly compare the effects of buprenorphine buccal film (BBF; BELBUCA®, BioDelivery Sciences International, Inc.) and the full μ-opioid receptor agonist oxycodone hydrochloride (immediate release) on respiratory drive (clinicaltrials.gov, NCT03996694)
- The primary outcome of the study evaluated respiratory drive by observing the maximum decrease in minute ventilation after the administration of each study drug via the ventilatory response to hypercapnia (VRH)
- Relative to placebo, BBF did not significantly impact respiratory drive at any of the doses tested, whereas oxycodone decreased respiratory drive in a dose-dependent fashion
- Presented here are additional secondary outcomes that were assessed throughout the study, including changes in minute ventilation, peak expiratory flow rate (PEFR), and oxygen saturation over time

Methods

Subjects

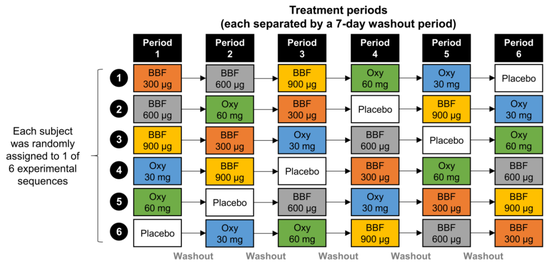
- Subjects were healthy men and women who self-identified as recreational opioid users and were not dependent on opioids (confirmed via a Naloxone Challenge Test at Day –1)

Study Design

- Effects on respiratory drive were assessed using a randomized, double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled, crossover design
- Treatments were BBF 300, 600, and 900 μg; oral immediate-release oxycodone 30 and 60 mg; and placebo
- Each subject received every treatment once, following a computer-generated randomization treatment sequence (**Figure 1**)
  - All treatments were separated by a minimum 7-day washout period to avoid any potential carryover effects
- This study design was chosen to minimize variability by allowing each subject to serve as their own control

Methods (cont'd)

Figure 1. Study Design



Abbreviations: BBF, buprenorphine buccal film; oxy, oxycodone.

Assessments

- Respiratory drive was evaluated by testing the VRH, which was performed once predose and at 0.5, 1, 2, 3, and 4 hours postdose
  - At each time point, subjects were allowed a period of acclimation to room air to establish a regular breathing pattern; this was immediately followed by breathing of a hypercapnic gas mixture (7% CO_2, 21% O_2, 72% N_2) for a 5-minute capture period, unless the subject reached an end-tidal CO_2 of 60 mm Hg for 3 consecutive breaths, in which case the procedure was terminated
- During VRH testing, minute ventilation, PEFR, and oxygen saturation were monitored continuously

Statistical Analyses

- For minute ventilation and PEFR, least squares (LS) mean differences between each treatment were calculated, along with differences in LS means with 95% CIs and *P* values
- Statistical analyses were performed using a linear mixed-effects model with treatment, period, and sequence as fixed effects, and time point and treatment-by-time-point interaction as repeated fixed effects

Results

Table 1. Subject Disposition and Demographics

Disposition		
Subjects, no.		
Screened	40	
Enrolled	19	
Safety[a]	19	
Completers[b]	15	
Demographics		
Category	**Safety[a]**	**Completers[b]**
Men, no. (%)	18 (94.7)	14 (93.3)
Age, mean (SD), y	33.1 (4.5)	32.9 (4.4)
Race, no. (%)		
White	14 (73.7)	12 (80.0)
Black or African American	1 (5.3)	1 (6.7)
Asian	1 (5.3)	1 (6.7)
American Indian or Alaska Native	3 (15.8)	1 (6.7)
Weight, mean (SD), kg	78.6 (15.8)	80.6 (16.7)
Height, mean (SD), cm	177.1 (8.4)	177.4 (9.3)
Body mass index, mean (SD), kg/m^2	24.9 (3.7)	25.4 (3.8)

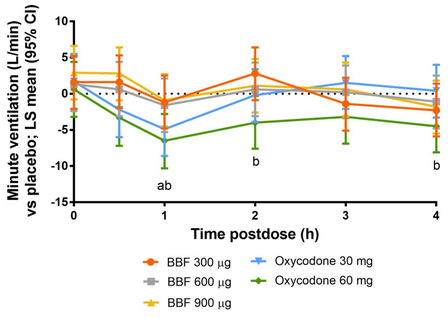
[a]Subjects who received at least 1 dose of any study drug in the treatment phase.
[b]Subjects who completed all 6 treatment periods with valid primary endpoint measurements.

Results (cont'd)

Respiratory Outcomes

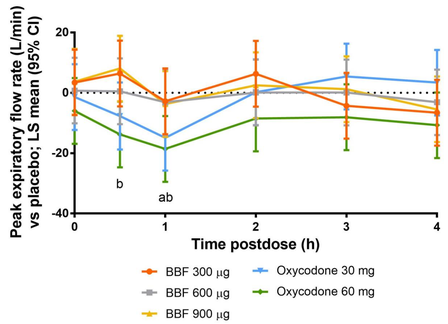
- For all BBF doses, mean minute ventilation was similar to that seen with placebo across all time points; whereas treatment with oxycodone 30 mg led to a significant (*P*<0.05) decrease at 1 hour postdose and oxycodone 60 mg led to significant (*P*<0.05) decreases at 1, 2, and 4 hours postdose, relative to placebo (**Figure 2**)
- Oxycodone 30 and 60 mg led to a significant (*P*<0.05) decrease in PEFR at 1 hour postdose, with 60 mg also resulting in a significant (*P*<0.05) decrease at 30 minutes, relative to placebo; whereas the PEFR for BBF was similar to that for placebo for all postdose time points (**Figure 3**)
- Mean oxygen saturation levels were mostly stable (≥95%) after treatment with each study drug (**Figure 4**), but 1 subject had an oxygen saturation level of 86% approximately 1.5 hours after receiving oxycodone 60 mg
  - This moderately severe adverse event was considered by the investigator to be likely related to the study drug

Figure 2. Minute Ventilation (Study Completers, n=15)



[a]*P*<0.05, oxycodone 30 mg vs placebo. [b]*P*<0.05, oxycodone 60 mg vs placebo.
Abbreviations: BBF, buprenorphine buccal film; LS, least squares.

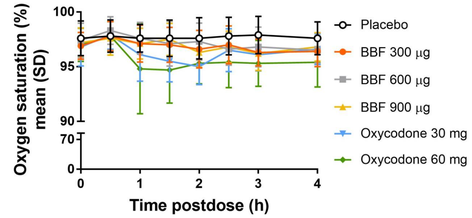
Figure 3. Peak Expiratory Flow Rate (Study Completers, n=15)



[a]*P*<0.05, oxycodone 30 mg vs placebo. [b]*P*<0.05, oxycodone 60 mg vs placebo.
Abbreviations: BBF, buprenorphine buccal film; LS, least squares.

Results (cont'd)

Figure 4. Oxygen Saturation (Safety Population, n=19)



Abbreviation: BBF, buprenorphine buccal film.

Conclusions

- **Unlike oxycodone, BBF was not associated with significant decreases in minute ventilation or PEFR and did not cause any adverse reactions related to decreased oxygen saturation levels**
- **These findings support the results from the study's primary endpoint by affirming the enhanced respiratory safety profile of BBF relative to that of the full μ-opioid receptor agonist oxycodone**
- **Overall, BBF may be a better-tolerated treatment option and should be considered before a full μ-opioid receptor agonist for the treatment of chronic pain**

References

1. Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: a unique opioid for the treatment of chronic pain. *Pain Ther*. 2020;9(1):41-54. doi:10.1007/s40122-019-00143-6
2. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction*. 1999;94(7):961-72.

Author Disclosures

- In the previous 3 years, LW has received consultation, advisory board, and travel fees from Charleston Laboratories, Depomed, Egalet, Insys Therapeutics, Mallinckrodt Pharmaceuticals, Pfizer, Teva, and Trevena; consultation and travel fees from Alcobra, Bonti, Cassava Sciences, Daiichi Sankyo, Elysium, Indivior, KemPharm, Pernix, and Shionogi; advisory board and travel fees from BioDelivery Sciences International, Inc., Ensysce Biosciences, and Inspirion Pharmaceuticals; travel fees from Cara Therapeutics; and consultation fees from Jefferies, Merck, Trevi, Vallon, and Vector Pharma. JC has no conflicts of interest. TS is an employee of BioDelivery Sciences International, Inc.

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