Pharmacokinetic and Pupillometry Outcomes from a Phase 1 Placebo-controlled Trial to Compare the Effects of Buprenorphine Buccal Film and Oral Oxycodone Hydrochloride

Lynn Webster, MD[1]; Jacqueline Cater, PhD[2]; Thomas Smith, MD[3]

[1]Center for U.S. Policy, Salt Lake City, UT, USA; [2]ICON plc, Philadelphia, PA, USA; [3]BioDelivery Sciences International, Inc., Raleigh, NC, USA

Introduction

Background

- The opioid crisis has led to increased concern about the safety of opioids administered for chronic pain, especially regarding abuse and respiratory depression–associated death[1]
- As a partial μ-opioid receptor agonist, buprenorphine has unique properties that distinguish it from full μ-opioid receptor agonists
  - Buprenorphine is classified as a Schedule III drug because it has a lower abuse potential than full μ-opioid receptor agonists[2,3]
- Buprenorphine buccal film (BELBUCA®, BBF) is approved by the US Food and Drug Administration for use in patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for whom alternative treatment options are inadequate[4]
- In this phase 1 study, evaluation of the primary endpoint revealed immediate-release oxycodone administration led to a significant, dose-dependent decrease in respiratory drive, whereas BBF did not (ClinicalTrials.gov Identifier: NCT03996694)
- The pharmacokinetic and pupillometry outcomes presented here were chosen because of their relevance for respiratory safety and potential risk for abuse
  - The abuse quotient (AQ) is a quantitative measure of pharmacokinetic parameters to compare an aspect of abuse potential across opioids[5]
  - Previous studies have shown a relationship between pupil constriction and "drug liking" in the context of opioid abuse[6,7]

Purpose

- Here we report secondary outcomes from the aforementioned phase 1 clinical trial, including effects of BBF and immediate-release oral oxycodone on pharmacokinetic, and pupillometry assessments

Methods

Population and Treatments

- The study included healthy individuals who self-identified as recreational opioid users and who were not dependent on opioids as confirmed by a Naloxone Challenge Test on day −1
- Study treatments (**Figure 1**)
  - Placebo
  - 300 μg, 600 μg, and 900 μg BBF
  - 30 mg and 60 mg oral immediate-release oxycodone

Study Design

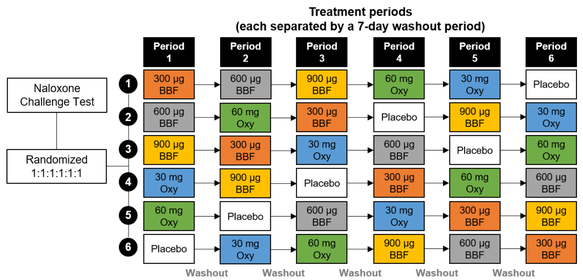
- Doses for the 2 drugs were chosen on the basis of calculations for equipotency
- In a randomized, double-blind, double-dummy, 6-treatment, 6-period, placebo-controlled crossover design, 7-day washouts were performed between treatments (**Figure 1**)
  - This study design was chosen to minimize variability by allowing each subject to serve as their own control
- An institutional review board approved the study protocol

Assessments

- Respiratory drive was evaluated by ventilatory response to hypercapnia
- Blood samples were collected for pharmacokinetic analysis
- Pupil diameter was assessed with standard pupillometry via the NeurOptics VIP® 200 pupillometer
- An institutional review board approved the study protocol

Methods (cont'd)

Figure 1. Study Design



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

Results

- A total of 19 subjects were enrolled; 15 subjects completed the study (**Table 1**)

Table 1. Subject Demographics and Disposition

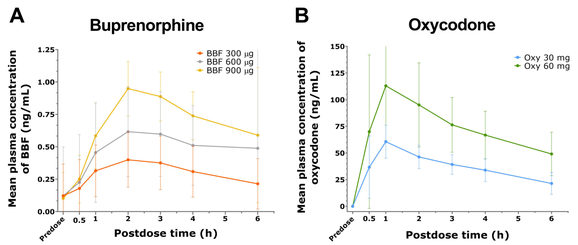
	Enrolled	Partial completers[a]	Completers
Subjects, No.	19	16	15
Age, mean (SD), y	33.1 (4.5)	32.8 (4.3)	32.9 (4.4)
Male, No. (%)	18 (94.7)	15 (93.8)	14 (93.3)
Race, No. (%)			
White	14 (73.7)	13 (81.3)	12 (80.0)
Black or African American	1 (5.3)	1 (6.3)	1 (6.7)
Asian	1 (5.3)	1 (6.3)	1 (6.7)
American Indian or Alaska Native	3 (15.8)	1 (6.3)	1 (6.7)
Weight, mean (SD), kg	78.6 (15.8)	79.3 (16.9)	80.6 (16.7)
Height, mean (SD), cm	177.1 (8.4)	177.0 (9.1)	177.4 (9.3)
BMI, mean (SD), kg/m²	24.9 (3.7)	25.1 (3.9)	25.4 (3.8)

[a]Subjects who completed at least 2 study treatment periods.
Abbreviations: BMI, body mass index; SD, standard deviation.

Results (cont'd)

- Maximum observed plasma concentration (C_{max}) increased proportionally with dose for both drugs (**Figure 2; Table 2**)
  - As expected, time to C_{max} (T_{max}) suggested faster absorption of immediate-release oxycodone than BBF
- Mean AQ (C_{max}/T_{max}) ranged from 0.2 to 0.4 for BBF and 67.4 to 110 for immediate-release oxycodone (**Table 2**)

Figure 2. Dose Response Curves for Buprenorphine and Oxycodone



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

Table 2. Plasma Pharmacokinetic Parameters

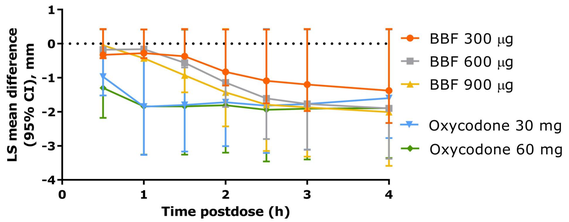
Parameter	BBF			Oral IR oxycodone	
	300 μg (n=15)	600 μg (n=17)	900 μg (n=17)	30 mg (n=15)	60 mg (n=16)
C_{max}, ng/mL mean (SD)	0.4 (0.2)	0.8 (0.9)	1.1 (0.4)	65.8 (19.1)	132 (46.2)
T_{max}, h median (min, max)	2.2 (2.1, 3.2)	3.1 (1.1, 6.0)	2.2 (2.1, 6.0)	1.2 (0.6, 3.2)	1.2 (0.7, 6.0)
AQ, C_{max}/T_{max} mean (SD)	0.2 (0.1)	0.3 (0.2)	0.4 (0.1)	67.4 (39.2)	110 (75.3)

Abbreviations: AQ, abuse quotient; BBF, buprenorphine buccal film; C_{max}, maximum observed plasma concentration; IR, immediate release; max, maximum; min, minimum; SD, standard deviation; T_{max}, time to attain maximum observed plasma concentration.

- Significant miosis (p<0.05 vs placebo) began later after BBF administration, compared with immediate-release oxycodone (**Figure 3**)

Results (cont'd)

Figure 3. Difference in Pupillometry vs Placebo



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. Significant differences from placebo were observed at all time points for both oxycodone doses; starting at 1 h and onward for BBF 900 μg; starting at 1.5 h and onward for BBF 600 μg; and starting at 2 h and onward for BBF 300 μg.
Abbreviations: BBF, buprenorphine buccal film; CI, confidence interval; LS, least squares.

Conclusions

- **The secondary outcomes of this study showed that pharmacokinetics of immediate-release oxycodone and BBF differed significantly in recreational opioid users**
- **C_{max} was higher, T_{max} was faster, and AQ was higher for immediate-release oxycodone than for estimated equianalgesic doses of BBF**
- **Significant miosis occurred faster for immediate-release oxycodone than for BBF**
- **Results from this study suggest that a single dose of BBF may have lower risks of drug liking and abuse compared with a single dose of the full μ-receptor agonist, immediate-release oxycodone**

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Author Disclosures

LW has received consultation, advisory board, and travel fees from BioDelivery Sciences International, Inc.; advisory board and travel fees from Ensysce Biosciences, Neurana Pharmaceuticals, and Salix Pharmaceuticals; consultation fees from Arbor Pharmaceuticals; and travel fees from Elysium Health. **JC** declares no conflicts of interest. **TS** is an employee of BioDelivery Sciences International, Inc.

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