Buprenorphine-naloxone buccal film is well tolerated in opioid-dependent patients converted from buprenorphine-naloxone sublingual tablet or film

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Background

- Buprenorphine-naloxone (BN) combinations have been shown to be effective in the maintenance treatment of opioid dependence[1]
- Currently available sublingual formulations of BN result in relatively low and potentially variable absorption, and talking or swallowing during administration can affect the rate and extent of absorption
- BN buccal film (BBN, Bunavail™) is an oral transmucosal dosage form of buprenorphine and naloxone
- BBN utilizes BioErodible MucoAdhesive (BEMA®) technology, which was specifically designed to optimize drug absorption and enhance patient convenience:
  - The film adheres to the inside of the cheek within seconds, and the buprenorphine is efficiently absorbed
  - The backing layer creates a barrier to facilitate one-way absorption into the cheek
  - There is no need for patients to avoid talking or swallowing during administration, and the film completely dissolves
- The BEMA technology results in a substantial increase in buprenorphine bioavailability with substantially lower doses of buprenorphine required for the management of opioid dependence relative to other methods of administration
- BBN optimizes buprenorphine delivery and administration convenience for the maintenance treatment of opioid dependence

Objectives

- Evaluate the safety and tolerability of BBN following conversion from a stable dose of sublingual BN (SLBN [Suboxone®, Reckitt Benckiser Pharmaceuticals Inc.]) tablets or films
- Determine the most appropriate conversion ratio for switching subjects from SLBN tablets or films

Methods

- 12-week, open-label, multicenter study assessing the safety and tolerability of BBN in the maintenance treatment of opioid dependence in 249 subjects stabilized on 8/2 to 32/8 mg/day SLBN tablet or film for at least 30 days
- Safety assessments included concomitant medications; opioid withdrawal symptoms; urine toxicology, buprenorphine, and norbuprenorphine screen; electronic Columbia Suicide Severity Rating Scale; urine pregnancy test; standardized oral examination; physical examination; vital signs; pulse oximetry; ECGs; clinical laboratory tests; and adverse events (AEs)
- Measures providing evidence of effectiveness included change in Clinical Opiate Withdrawal Scale (COWS) scores, resolution of the symptoms of opioid withdrawal syndrome after BBN dose adjustment, and the presence of non-prescribed opioids in urine samples
- Oral tolerability was assessed using standardized buccal examinations performed at screening and during the 12-week treatment period
- Compliance was assessed by returned BBN and urine testing for buprenorphine, norbuprenorphine, and non-prescribed opioids
- Subject acceptance was measured following 12 weeks of BBN treatment with an opioid medication preference questionnaire

Results

Subject Disposition

- A total of 249 subjects were converted from SLBN tablet (n = 105) or film (n = 144) to a single daily dose of BBN, and 79% (197/249) completed the study
- Of the 52 (20.9% of 249) subjects who discontinued before 12 weeks had elapsed, 5 (2.0%) discontinuations were due to drug withdrawal symptoms

Preliminary Efficacy

- At baseline (pre-BBN dose administration), COWS scores ranged from 0 to 25, with a mean of 3.3 in the total population and 4.6 in subjects taking SLBN 16, 24, or 32 mg/day; 3 hours after the initial BBN dose, the mean COWS score was ≤0.6
- Among subjects with baseline COWS scores ranging from 10 to 25 (n = 34), the mean score declined from ≥13 or greater to ≤1.1 at 3 hours after the initial BBN dose (Table 1)
- There were 47 opioid-positive urine samples in 27 subjects during the BBN dosing period (Figure 1); 9 subjects had a valid prescription supporting 10 of the 47 positive samples
- Opioid testing was positive for a non-prescribed opioid in 19 (7.6%) subjects

Table 1. COWS total score for subjects with baseline COWS total scores ≥10 (n = 34)

BBN Initial Dose (mg)	SLBN Prior Dose (mg)	Predose[a]	Postdose[a]	
			3 Hrs	Baseline–3 Hrs
3.5/0.6	8 (0)	-	-	-
5.25/0.9	12 (1)	13.0 (13,13)	1.0 (1,1)	-12.0 (-12,-12)
7.0/1.2	16 (15)	13.8 (10,25)	1.1 (0,3)	-12.7 (-25,-9)
10.5/1.7	24 (16)	13.8 (10,23)	0.6 (0,3)	-13.3 (-22,-10)
14.0/2.3	32 (2)	14.5 (11,18)	0.0 (0,0)	-14.5 (-18,-11)

a. Mean (Range)

- The mean SLBN dose at the time of entry was 15.74 mg buprenorphine/day; based on a conversion factor of 3.5/0.6 mg BBN = 8/2 mg SLBN, the mean BBN starting dose was 6.9/1.2 mg/day
- The starting conversion dose of BBN administered as a once-daily dose was adequate for 63.5% (158/249) of subjects regardless of their prior SLBN dosing regimen

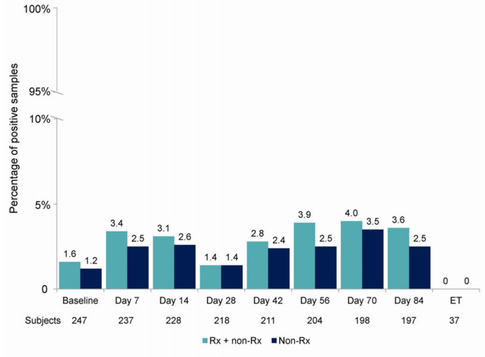
Conversion Ratio

- After dose adjustments, the mean final dose of BBN was 8.0/1.4 mg, yielding a 2:1 buprenorphine conversion ratio, from 16 mg SLBN to 8.0 mg BBN (Table 2)

Table 2. Mean dose at study entry and exit (mg/day)

SLBN Dose at Entry	BBN Dose at Exit
16/4	8.0/1.4

Figure 1. Opioid-positive urine samples during treatment with BBN



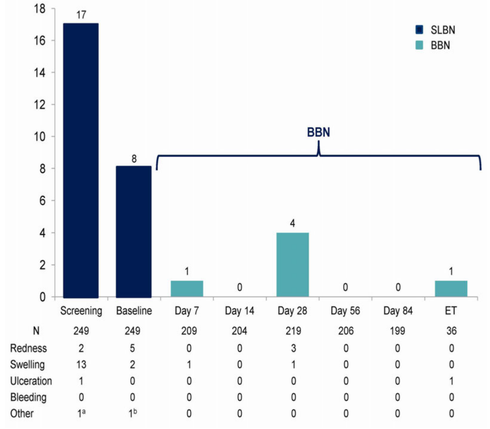
Safety and Tolerability

- Oral mucosal abnormalities were identified in 5% (25/498) of the buccal examinations before treatment with BBN and 0.6% (6/1073) of the exams performed during treatment with BBN (Figure 2)
- Drug-related constipation was reported by only 4 subjects (1.6%)
- Of the 41% of subjects who reported constipation at the time of discontinuation of SLBN and before treatment with BBN, only 13% had constipation at the end of the 12-week treatment with BBN — a decline of 68% over the course of the study (Figure 3)
- The most common drug-related AE was drug withdrawal syndrome, which was observed in 31.3% of the 249 study subjects
- Two subjects experienced serious AEs (suicidal ideation and osteomyelitis); both were severe but judged not related to BBN
- Events considered possibly, probably, or definitely related to BBN that occurred in more than 2 subjects are summarized in Table 3

Table 3. Drug-related adverse events occurring in >2 subjects (N = 249)

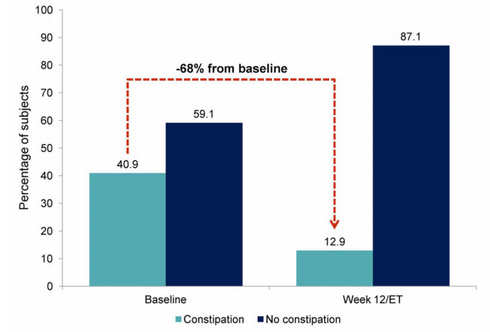
Event	n (%)	Event	n (%)
Drug withdrawal syndrome	78 (31.3)	Hyperhidrosis	5 (2.0)
Headache	13 (5.2)	Constipation	4 (1.6)
Drug dependence	6 (2.4)	Somnolence	4 (1.6)
Fatigue	6 (2.4)	Insomnia	3 (1.2)
Lethargy	6 (2.4)	Oral mucosal erythema	3 (1.2)
Chills	5 (2.0)	Rhinorrhea	3 (1.2)

Figure 2. Subjects with abnormal oral examinations



[a]Small, 1 mm mucus cyst (benign), upper right mucosa
[b]Tiny white spot, upper right mucosa; white adherent patch, upper left mucosa

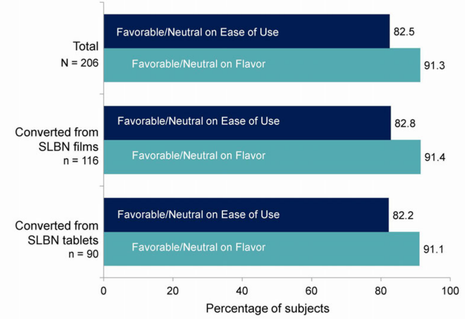
Figure 3. Constipation at baseline and at week 12



Treatment Acceptance

The vast majority (91.3%) of subjects switched from SLBN reported that BBN has a very pleasant, pleasant, or neutral flavor, and similarly high proportions (82.5%) assessed BBN as very easy, easy, or neutral for ease of use (Figure 4)

Figure 4. Subject assessment of BBN after SLBN tablets or films (N = 206)



Conclusions

- **BBN was overall safe and well-tolerated in opioid-dependent subjects**
- **The final mean daily dose of BBN was approximately half that of the SLBN mean daily dose at study entry**
- **BBN had good acceptance with respect to taste and ease of administration**
- **Preliminary analysis of data suggest BBN was efficacious in the maintenance treatment of opioid dependence**

References

1. Gowing L et al. *Cochrane Database Syst Rev*. 2009;3(3):CD002025.

Disclosures

JGS and LW were paid consultants of BioDelivery Sciences International, Inc.; TW and AF are employees of BioDelivery Sciences International, Inc.