Buprenorphine-naloxone buccal film optimizes delivery of buprenorphine and provides a novel approach in the treatment of opioid dependence

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Background

- Buprenorphine-naloxone combinations (BN) 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

Single-dose Pharmacokinetic (PK) Study

- Compare the rate and extent of buprenorphine and naloxone absorption following single doses of BBN and sublingual BN (SLBN [Suboxone®, Reckitt Benckiser Pharmaceuticals Inc.]) tablet

12-week, Open-label, Safety Study

- Evaluate the safety and tolerability of BBN following conversion from a stable dose of SLBN tablets or films
- Determine the most appropriate conversion ratio for switching subjects from SLBN tablets or films

Methods

Study Design

- We summarize results from two studies with BBN:
  - Phase 1, open-label, single-dose, crossover PK study in 80 healthy subjects comparing buprenorphine and naloxone exposure from BBN with SLBN tablet
  - 12-week, open-label, multicenter study in 249 subjects stabilized on 8/2 to 32/8 mg/day SLBN tablet (n=105) or film (n=144) for at least 30 days assessing the safety and tolerability of BBN in the maintenance treatment of opioid dependence

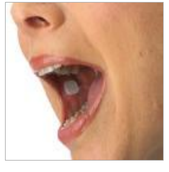
Figure 1. BBN administration

Patients administer BBN by:

- Using the moist tongue or water to wet the inside of the cheek
- Placing the dry BBN film on the tip of a finger (similar to a contact lens), with the ink-marked side facing up
- Placing the ink-marked side of BBN against the inside of the cheek
- Pressing/holding BBN in place for 5 seconds
- Films will completely dissolve

If multiple BBN films are needed:

- They may be administered in immediate succession to the inside of alternating cheeks
- No more than 2 BBN films per side



Methods (cont.)

- In the single-dose PK study:
  - Plasma concentrations of buprenorphine and naloxone for all study treatments were determined
  - Calculated PK parameters included C_{max}, T_{max}, AUC_{last}, AUC_{inf}, and $t_{½}$
  - Buprenorphine, norpbuprenorphine, and naloxone PK parameters were compared across treatments (BBN vs SLBN) using a standard bioequivalence approach; the 90% confidence intervals (CI) were reported for C_{max}, AUC_{last}, and AUC_{inf} and assessed within limits of 80–125% for buprenorphine
- In the 12-week, open-label, safety study:
  - 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 film counts and urine testing for buprenorphine, norbuprenorphine, and non-prescribed opioids
  - Treatment acceptance of the buccal film dose form was measured following completion of 12 weeks of treatment with BBN using an opioid medication preference questionnaire

Results

In the single-dose PK study (Table 1):

- For buprenorphine, 4.2/0.7 mg BBN was bioequivalent to 8/2 mg SLBN tablet (90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were well within the acceptance limits of 80-125%), showing that the bioavailability of buprenorphine from BBN was approximately twice that of SLBN tablet
- The rate of naloxone absorption after BBN relative to SLBN (based on C_{max}) was 73% and the extent of naloxone absorption from BBN relative to SLBN (based on AUC_{last} and AUC_{inf}) was 66% to 67%
- The rate and extent of norbuprenorphine from BBN relative to SLBN was 40% based on C_{max}, 48% based on AUC_{last}, and 52% based on AUC_{inf}

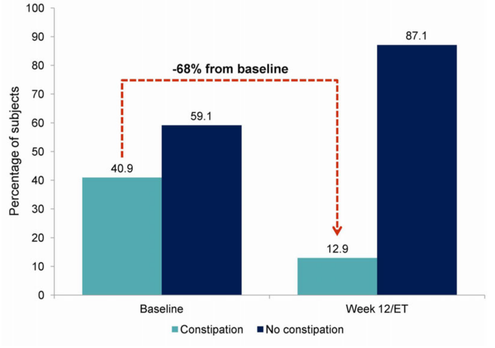
Table 1. Systemic exposure of 4.2/0.7 mg BBN and 8/2 mg SLBN (N=80)

PK Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI of the Geometric Ratio	
	BBN 4.2/0.7 mg	SLBN 8/2 mg	BBN/SLBN	Lower	Upper
Buprenorphine					
ln (C_{max})	3.15	2.89	109.07	100.49	118.39
ln (AUC_{last})	24.21	25.40	95.35	88.92	102.24
ln (AUC_{inf})	25.57	27.03	94.62	88.48	101.19
Norbuprenorphine					
ln (C_{max})	0.46	1.16	39.54	36.35	43.02
ln (AUC_{last})	16.18	33.70	48.00	43.86	52.52
ln (AUC_{inf})	18.81	36.41	51.64	48.20	55.33
Naloxone					
ln (C_{max})	117.6	161.4	72.86	65.94	80.51
ln (AUC_{last})	298.1	442.3	67.41	61.98	73.31
ln (AUC_{inf})	304.4	459.0	66.32	61.14	71.94

In the 12-week, open-label, safety study:

- SLBN mean dose at entry was 15.74mg/day; BBN mean final dose was 8.0/1.4 mg/day. Therefore a conversion ratio of 16mg SLBN to 8mg BBN is appropriate (2:1 ratio)
- BBN treatment was associated with a high rate of subject retention (79.1%) with few adverse events (AEs)
- Drug-related constipation was reported by only 4 (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 2) — which may be attributed to lower amounts of buprenorphine ingested and/or lower norbuprenorphine systemic exposure with BBN

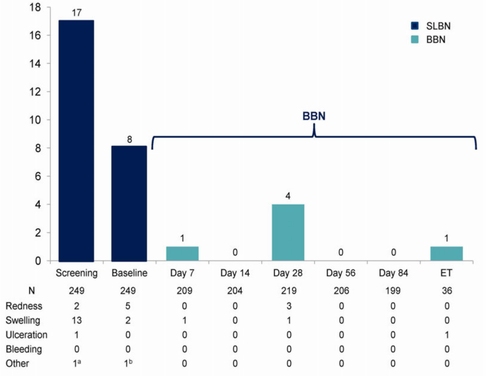
Figure 2. Constipation at baseline and at week 12



In the 12-week, open-label, safety study:

- As shown in Figure 3, oral mucosal abnormalities were infrequent and 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 3. Subjects with abnormal oral examinations

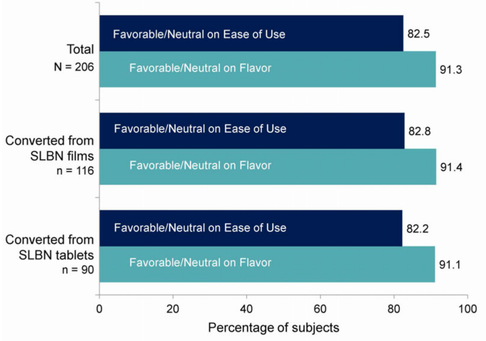


[a]Small, 1 mm mucus cyst (benign), upper right mucosa
[b]Tiny white spot, upper right mucosa; white adherent patch, upper left mucosa

In the 12-week, open-label, safety study:

- Nearly all (91.3%) subjects switched from SLBN reported that BBN had 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 flavor and ease of use (N = 206)



Conclusions

- **BBN, using BEMA technology, provides bioequivalent buprenorphine exposure at approximately half the dose of a SLBN tablet**
- **There was a low incidence of AEs, including oral irritation, among subjects switched from SLBN to BBN**
- **There was a reduced incidence of constipation in subjects switched to BBN**
- **BEMA technology provides an alternative means for administering buprenorphine for the maintenance treatment of opioid dependence, with enhanced bioavailability, good oral tolerability, a low incidence of constipation, and high ratings for taste and ease of use**

References

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

Disclosures

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