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

James G. Sullivan1, Niraj Vasisth2, Jeffrey Stark3, Andrew Finn2

1 Parkway Medical, Birmingham, AL; 2 BioDelivery Sciences International, Inc., Raleigh, NC; 3 Worldwide Clinical Trials, Austin, TX

Background

- Buprenorphine-naloxone combinations (BH) have been shown to be effective in the treatment of opioid dependence
- Currently available sublingual formulations of BH result in relatively low and potentially variable absorption and talk back or swallowing during administration can affect the rate and extent of absorption
- BH buccal film (BBN, Suboxone®) is an oral transmucosal dosage form of buprenorphine and naloxone
- BBN utilizes BioErodible MucoAdhesive (BEMA) technology, which is 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 mucoadhesive 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 for the maintenance treatment of opioid dependence

Objectives

- Compare the rate and extent of buprenorphine and naloxone absorption following single doses of BH and sublingual BH (SLBN [Suboxone®, Reckitt Benckiser Pharmaceuticals Inc.]) tablet
- Determine the most appropriate conversion ratio for switching subjects from SLBN tablets or films

Methods

Single-dose Pharmacokinetic (PK) Study
- Compare the rate and extent of buprenorphine and naloxone absorption following single doses of BH and sublingual BH (SLBN [Suboxone®, Reckitt Benckiser Pharmaceuticals Inc.]) tablet

12-week, Open-label, Safety Study
- Evaluate the safety and tolerability of BH 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

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 following BH and SLBN tablet
  - 12-week, open-label, multicenter study in 249 subjects stabilized on 8–24 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

Methods (cont.)

- In the single-dose PK study:
  - Plasma concentrations of buprenorphine and naloxone for all subjects were determined
  - Calculated PK parameters included Tmax, T1/2, AUC0–τ, AUC0–INF, and t1/2
  - Buprenorphine, norbuprenorphine, and naloxone PK parameters were compared across treatments (BH vs SLBN) using a standard bioequivalence approach; the 90% confidence intervals (CI) were reported for T1/2, AUC0–τ, and AUC0–INF and assessed within limits of 80–125% for buprenorphine
  - In the single-dose PK study:
    - Measures providing evidence of effectiveness included change in Clinical Opiate Withdrawal Scale (COWS) scores, rate of the symptoms of opioid withdrawal syndrome after BH 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
      - Conversion treatment was assessed by reported film curie and urine testing for buprenorphine, norbuprenorphine, and non-prescription opioids
      - Treatment acceptance of the buccal film dose form was measured following completion of 12 weeks of treatment with BH using an opioid medication preference questionnaire

Methods (cont.)

- In the 12-week, open-label, safety study:
  - BH mean dose at entry was 15.74mg/day; BH mean final dose from a stable dose of SLBN tablet (90% CI of the geometric mean ratio for AUC0–INF was 0.85 (0.79–0.91) and 0.90 (0.85–0.94) for Cmax and AUC0–INF, respectively, for BBN relative to SLBN)
  - Drug-related constipation was reported by only 4 (1.6%) patients receiving BH, with no cases of incontinence
  - Patients administered BBN by:
    - Placing the BH film on the tip of a finger (similar to a contact lens), with the ink-marked side facing up
    - Pressing the BH film against the inside of the cheek
    - Film 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 BH films per side
  - In the 12-week, open-label, safety study:
    - As shown in Figure 3, oral mucosal abnormalities were infrequent and identified in 15% (9 of 60) of the buccal examinations before treatment with BH, and 0.6% (6/1073) of the exams performed during the 12-week treatment with BH
  - Patients administer BBN by:
    - Using the BH film to moisten or wash the inside of the cheek
    - Placing the BH film on the tip of a finger (similar to a contact lens), with the ink-marked side facing up
    - Pressing the BH film against the inside of the cheek
    - Films will completely dissolve

Results

- In the single-dose PK study (Table 1):
  - For the BEMA technology was bioequivalent to 8/2 mg SLBN tablet (90% CIs for Cmax, AUC0–INF, and AUC0–τ were well within the acceptance limits of 80–125%; bioavailability, good oral tolerability, and a low incidence of AEs, including oral irritation, among subjects switched from SLBN to BBN
  - BH 8mg is appropriate (2:1 ratio)

- In the 12-week, open-label, safety study:
  - Nearly all (91.3%) subjects switched from SLBN to BBN 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)

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 administrating 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


Disclosures

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