Novel Buccal Film Formulation of Buprenorphine-Naloxone for the Maintenance Treatment of Opioid Dependence: A 12-Week Conversion Study

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ABSTRACT

Purpose: The purpose of this study was to provide a preliminary assessment of the safety, tolerability, symptom control, and acceptability of buprenorphine-naloxone buccal film (BBN) for the maintenance treatment of opioid dependence in patients converted from buprenorphine-naloxone sublingual tablet or film (SLBN), as well as to determine the conversion ratio for switching patients from SLBN to BBN.

Methods: This open-label study included adult opioid-dependent subjects stabilized on 8/2 to 32/8 mg/d of SLBN for a minimum of 30 days. Study subjects were converted to a bioequivalent dose of BBN and maintained for 12 weeks.

Findings: A total of 249 subjects (mean age 38.7 years, 65.9% male) were converted from SLBN to a single daily dose of BBN, and 79.1% completed the 12-week study. Adverse events and withdrawal symptoms led to discontinuation in 2.4% and 2.0% of BBN-treated subjects, respectively. Rates of constipation reported at baseline declined from 41% just before the initial BBN dose and within 24 hours of the last SLBN dose to 13% after 12 weeks of BBN treatment; treatment-emergent constipation was reported by 2.8% of BBN-treated subjects. Oral mucosal abnormalities were identified in 5% and 0.6% of systematic oral examinations in SLBN- and BBN-treated subjects, respectively. A total of 34 subjects had Clinical Opiate Withdrawal Scale total scores ranging from 10 to 25 (overall mean, 13.8) within 24 hours of taking their last SLBN dose, and scores for these subjects were reduced to a range of 0 to 3 (overall mean, 0.7) at 3 hours after the initial dose of BBN. Treatment compliance was high (108%); <1% of urine samples were buprenorphine-free, and 92.4% of BBN-treated subjects did not have a urine sample that tested positive for a non-prescribed opioid. A total of 91.3% subjects rated the taste of BBN as pleasant or neutral, and 82.5% rated BBN ease of use as easy or neutral. The overall mean final dose of BBN was 8.0/1.4 mg/d, yielding a 2:1 buprenorphine conversion ratio.

Implications: Although these results should be considered preliminary due to the open-label design, BBN was overall safe and well tolerated, and seemed to provide adequate symptom control, in the treatment of opioid-dependent subjects previously controlled on SLBN for a minimum of 30 days. There was good adherence to study medication and favorable patient acceptance of the buccal formulation. The SLBN/BBN buprenorphine conversion ratio was 2:1. ClinicalTrials.gov identifier: NCT01666119. (*Clin Ther*. 2015;37:1064–1075) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: buccal, buprenorphine, dependence, naloxone, opioid, safety.

INTRODUCTION

Opioid dependence is an important public health problem that is associated with significant morbidity and mortality.[1] In the United States, prescription opioid misuse has been described as an epidemic, with mortality now exceeding the combined rates for suicide and motor vehicle accidents, as well as the aggregate deaths from cocaine and heroin.[2] Physicians can treat their opioid-dependent patients with buprenorphine and fixed combinations of

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buprenorphine-naloxone (BN) in brand-name sublingual tablet and film formulations (SLBN)* and generic sublingual tablets. Despite evidence of their effectiveness,[3] the clinical utility of SLBN has been compromised by concerns about diversion, nonmedical use, and poor compliance with treatment.[4–7] Other concerns include challenges with palatability and tablet dissolution times,[6,8] which make it difficult for some patients to keep SLBN under their tongue, particularly when attempting to talk or swallow. In addition, talking while SLBN dissolves may affect the rate and extent of absorption.[9,10]

BN buccal film (BBN),† a novel transmucosal BN product, is a small, thin, bilayered dissolvable film that adheres to the buccal mucosa and uses Bio-Erodible MucoAdhesive (BEMA; BioDelivery Sciences International, Inc, Raleigh, North Carolina) drug delivery technology to optimize BN administration and patient convenience. BEMA delivery technology is composed of flexible water-soluble polymeric films. The mucoadhesive side contains the active ingredient buprenorphine and adheres to the moist buccal mucosa upon contact; the backing layer facilitates unidirectional buprenorphine absorption into the buccal mucosa, isolating the buprenorphine from saliva and limiting the amount of buprenorphine swallowed into the gastrointestinal tract. Because the film completely dissolves, there is no residual film to remove.

In pharmacokinetics (PK) research with the buccal formulation using BEMA technology, buprenorphine exposure was linear across doses of ~0.9, 3.5, and 5.25 mg, and the C_{max} and the AUC values for buprenorphine with a single 3.5/0.6–mg film were comparable to the equivalent dosage administered as four 0.875/0.15–mg films. These findings, which suggested that buprenorphine exposure with BBN 3.5/0.6 mg would be similar to SLBN 8/2 mg with no greater exposure to naloxone, provided the rationale for the conversion dose in the current study. Meanwhile, to determine the bioavailability of BBN 4.2/0.7 mg relative to SLBN 8/2–mg tablets and to demonstrate bioequivalent buprenorphine exposure and equal or lower naloxone exposure for BBN 4.2/0.7 mg relative to SLBN 8/2–mg tablets, an open-label, single-dose, crossover PK study in 80 healthy naltrexone-blocked volunteers was performed.[11] Buprenorphine exposure from BBN 4.2/0.7 mg was bioequivalent to an 8/2–mg SLBN tablet (Table I). Based on the comparable buprenorphine bioavailability and allowing for dosage adjustments, the current open-label study provides a preliminary assessment of the tolerability, symptom control, and patient acceptance with BBN and confirms the most appropriate conversion ratio between BBN and SLBN.

SUBJECTS AND METHODS

Subjects

This open-label study was approved by the Copernicus Group institutional review board on June 20, 2012, and was conducted between August 6, 2012, and January 8, 2013, at 10 study centers located in the United States. Study subjects included individuals diagnosed with opioid dependence according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, who had been maintained on a stable daily dose (8–32 mg) of SLBN for a minimum of 30 days. Subjects were eligible for inclusion if they were adults aged 18 to 65 years (women of childbearing potential who were not pregnant or breastfeeding and were using an acceptable method of birth control) who had been diagnosed with opioid dependence or addiction in the past 12 months; had a positive urine buprenorphine and

Table I. Pharmacokinetic parameters for buprenorphine after use of 4.2/0.7–mg buprenorphine-naloxone buccal film (BBN) and 8/2–mg buprenorphine-naloxone sublingual tablet (SLBN).

Parameter	BBN 4.2/0.7 mg (n = 65)	SLBN Tablet 8/2 mg (n = 68)
T_{max}, h*	2.25 (0.75–4.00)	1.50 (0.50–2.75)
C_{max}, ng/mL	3.41 (1.26)	3.06 (1.28)
$AUC_{0-\infty}$, ng*h/mL	27.17 (8.784)	28.67 (10.78)
$t_{½}$, h	27.53 (11.99)	28.67 (12.82)

*Median (range). Unless otherwise indicated, values are given as mean (SD)

*Trademark: Suboxone® (Reckitt Benckiser plc, Parsippany, New Jersey).

†Trademark: Bunavail® (BioDelivery Sciences International, Inc, Raleigh, North Carolina).

norbuprenorphine test at screening; and were in good general health, with no clinically significant findings on medical history, physical examination, clinical laboratory tests, and ECG.

Subjects were excluded if they had serum potassium $\leq$3.0 mEq/L or serum magnesium $\leq$1.0 mg/dL with no cardiac history or symptomatic arrhythmia; class III or IV congestive heart failure; symptomatic myocardial ischemia; a family or personal history of long QT syndrome; uncontrolled hypertension; a history of hypersensitivity, allergy, or intolerance to buprenorphine, naloxone, or related drugs; a history or current evidence of any clinically significant disorder or any other condition that would jeopardize the safety of the subject or impact the validity of the study results; a pierced tongue or mouth; or any clinically significant abnormality of the buccal mucosa that could affect drug absorption. Also excluded were those with serum creatinine, alanine aminotransferase, or aspartate aminotransferase values $\geq$3 times the upper limit of normal; pulse oximetry $\leq$93% at baseline; clinically significant abnormality on 12-lead ECG; moderate to severe hepatic impairment (Child-Pugh); or a positive urine toxicology screen for non-prescribed medications or drugs of abuse. Subjects were also excluded who had used an investigational drug or device or taken class IA or class III antiarrhythmic medications, or any medication, nutraceutical, or herbal product with cytochrome P450 3A4 inhibition or induction properties within the last 30 days; participated in a previous clinical study of BBN; or were judged to be a suicidal risk (history of suicidal ideation or suicidal behavior $\leq$3 months before baseline).

For all 10 study centers, informed consent was obtained from eligible subjects before any assessments were conducted, in accordance with written consent guidelines and the mandates of Good Clinical Practice and the Declaration of Helsinki.[12]

Study Design

Eligible subjects were converted to an approximately equivalent dose of BBN (based on earlier BBN PK studies[11]), with subsequent dose adjustments as clinically indicated to control opioid withdrawal symptoms or adverse events (AEs). Subjects were closely monitored for evidence of oral mucosal AEs attributed to the application of the BBN film. The total duration of participation for each subject was up to 18 weeks and included a screening period (subjects continued to take SLBN tablets or films), a baseline visit (the day after discontinuing SLBN; received the first dose of BBN), and a 12-week open-label treatment period with BBN films. Vital signs, AEs, risk of suicide, oral mucosa, and concomitant medications were regularly assessed throughout the study. Clinical Opiate Withdrawal Scale (COWS) assessments, pulse oximetry, clinical laboratory tests, urine toxicology screening, urine buprenorphine and norbuprenorphine testing, pregnancy testing, and 12-lead ECGs were also conducted. At the end of the 12-week treatment period, subjects resumed their previous SLBN treatment and had a follow-up visit 1 week later.

A training program to standardize the oral mucosa examination was developed by a board-certified dentist, who trained clinical investigators on the oral examination process by using a standardized protocol. The examination procedure followed a systematic assessment of the subject's mouth, with the left and right sides divided by a midline from the corner of the mouth to the tonsillar pillar, resulting in 4 quadrants. Each quadrant was assessed as normal or abnormal, and the following terms were used to describe the findings: 0 = normal, 1 = redness, 2 = swelling or raised lesions, 3 = ulceration, 4 = bleeding, and 5 = other. Any abnormalities, including pain, were recorded as AEs. Participating investigators were required to demonstrate proficiency in identification and classification of observations by testing before enrolling subjects. Oral examinations were performed at screening, baseline, and 5 additional times during the 12-week treatment period.

Subjects were monitored for clinical control of their opioid dependence in accordance with the Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction: A Treatment Improvement Protocol for the use of buprenorphine in the management of opioid dependence.[13] These guidelines included urine assessments for non-prescribed opioids as well as for buprenorphine and norbuprenorphine. Dose adjustments were permitted with this protocol as in standard clinical practice, but subjects were instructed to use BBN once daily regardless of their preference for SLBN dosing frequency.

At baseline (within 24 hours after discontinuation of SLBN and before initiating BBN dosing), a buprenorphine/naloxone–associated symptom checklist was

completed to enable assessment of any changes in symptoms while undergoing BBN treatment. Regardless of the symptom checklist, any symptom that was new or considered a worsening of a pre-existing symptom during the study was reported as an AE. The same checklist was completed again at day 84, and a comparison of symptom incidence was then performed. In addition, COWS scores and pulse oximetry were measured just before the first dose of BBN and 3 hours after the dose to assess for signs of withdrawal and respiratory depression. Beginning on day 2 (24 hours after the initial BBN dose and continuing throughout the remainder of the 12-week study), "opioid withdrawal syndrome" was recorded as an AE for subjects who experienced any symptoms that investigators considered opioid withdrawal.

Treatments

BBN film doses of 3.5/0.6–mg and 5.25/0.9–mg BN were provided for the study, with an initial conversion ratio of BBN 3.5/0.6 mg to an 8/2–mg SLBN tablet.[11] Regardless of the daily dose frequency of SLBN administration before the study, subjects started once-daily dosing with BBN at the dose that most closely approximated their total daily buprenorphine exposure from SLBN tablets or films (**Table II**). Study personnel instructed subjects on the appropriate application of the BBN film and administered the initial dose of BBN. When multiple buccal films were required to achieve the target dose, subjects applied the BBN films simultaneously to the inside of each cheek, with no more than 2 films applied on a single side.

Table II. Initial conversion of buprenorphine-naloxone sublingual tablet or film (SLBN) to buprenorphine-naloxone buccal film (BBN).

Current SLBN Dose, mg	Initial BBN Dose, mg
8/2	1 × 3.5/0.6
12/3	1 × 5.25/0.9
16/4	2 × 3.5/0.6
24/6	2 × 5.25/0.9
32/8	4 × 3.5/0.6

Assessments

Safety assessments included use of concomitant medications, opioid withdrawal (COWS), urine toxicology screen, urine buprenorphine and norbuprenorphine screen, electronic Columbia Suicide Severity Rating Scale (eC-SSRS), urine pregnancy test, standardized oral examination, physical examination, vital signs, pulse oximetry, ECGs, clinical laboratory tests (including hematology, blood chemistry, and urinalysis), and AEs. Evidence of symptom control included COWS scores after the first dose of BBN, urine opioid testing, and retention of subjects in the study.

The AE verbatim text was coded and classified according to system organ class and preferred term by using the *Medical Dictionary for Regulatory Activities* version 12.0 (March 2009). An AE was considered treatment-emergent if the onset date was on or after the first dosing date or was missing. AEs classified as possibly related, probably related, or undesignated were considered drug related. All serious AEs were collected from the start of study drug administration and were followed up by the investigator until they resolved or stabilized, the subject was lost to follow-up, the event was otherwise explained, or 30 days had passed since the last dose of study drug. Serious treatment-emergent AEs and drug-related serious treatment-emergent AEs were summarized according to system organ class and preferred term from the *Medical Dictionary for Regulatory Activities*. Subjects withdrawn due to AEs were identified on the electronic case report form as "Action Taken = Study Drug Discontinued". Abnormal physical examination findings at day 84 that were not present at screening or baseline were recorded as AEs.

Clinical laboratory tests were performed at screening; baseline; and days 28, 56, and 84 or early termination. Vital signs (seated blood pressure, heart rate, respiratory rate, and pulse oximetry) and oral temperature were recorded according to the schedule of assessments, as were normal and abnormal ECG findings at screening and day 84. Concomitant medication was coded and classified by using the World Health Organization Drug Dictionary (June 2009).

To measure opioid withdrawal, the COWS total score (including subscales for pulse rate, gastrointestinal upset, sweating, tremor, restlessness, yawning, pupil size, anxiety or irritability, bone or joint aches, gooseflesh skin, runny nose, or tearing) was assessed before the first dose of BBN and at 3 hours' post-dose.

The score was calculated as the sum of all subscales for each subject at each scheduled time.

At a minimum, the following drugs were screened in urine: amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, and opiates. Although a negative urine toxicology result (excluding prescribed medications) must have been obtained at screening for a subject to be eligible for study enrollment, a positive cannabinoid result was not necessarily considered exclusionary if the subject had been counseled and, in the opinion of the investigator, was reliable. Positive urine toxicology results after baseline were handled at the discretion of the investigator. Analysis of samples negative for non-prescribed opioids was used as a measure of symptom control.

Treatment compliance was assessed by using return film counts and urine testing for buprenorphine and norbuprenorphine. Subjects with post-baseline negative results for either analyte at 2 consecutive visits were discontinued from the study for noncompliance. Study drug compliance was calculated as follows: [total amount of study drug (number of films) taken or reported as lost by subject/total amount of study drug (number of films) prescribed] × 100 = % compliance. Mean compliance was also calculated assuming that study drug reported as "lost" was not taken by the subject. A former US Drug Enforcement Administration agent, retained as a consultant, assisted in the creation of a drug diversion reporting policy, addressed Drug Enforcement Administration accountability and reporting requirements at the investigator's meeting, and contributed to the creation of site- and subject-level study drug accountability forms.

To assess a subject's risk of suicide, the eC-SSRS was administered. Two versions of the eC-SSRS were used and electronically scored: the "baseline" version to assess lifetime suicidal ideation and behavior, and the "since last visit" version to assess suicidality since the subject's last study visit.

To determine the acceptability of the novel dose form, subjects rated BBN flavor and ease of use by using 5-point categorical scales. BBN was rated on a scale of very pleasant to very unpleasant. Likewise, BBN ease of use was rated on a scale of very easy to very difficult.

RESULTS

Subject Characteristics

Four hundred subjects were assessed for eligibility, and 151 were excluded from further participation. A total of 249 subjects stabilized on 8/2 to 32/8 mg of SLBN (105 on tablets and 144 on films) were enrolled, converted to a once-daily dose of BBN, and included in the safety population; 79.1% of subjects (107 subjects receiving SLBN films and 90 subjects receiving SLBN tablets) completed the study. Figure 1 summarizes the disposition of subjects. The mean duration of treatment was 73.8 days. Of the 52 (20.9% of 249) subjects who discontinued participation in the study before 12 weeks had elapsed, 5 (2.0%) discontinuations were due to drug withdrawal symptoms. Demographic and baseline characteristics are shown in Table III. Notably, 43% of subjects had concurrent musculoskeletal or connective tissue disease, which suggests the potential presence of concomitant pain symptoms, and 40.2% of SLBN-treated subjects had concurrent gastrointestinal disorders.

Safety and Tolerability

A total of 192 subjects (77.1%) experienced a treatment-emergent AE, and 130 subjects (52.2%) had an AE that was considered possibly drug related, drug related, or had data missing. There were no deaths; 2 (0.8%) subjects had serious AEs, and 11 (4.0%) subjects were withdrawn from the study due to an AE, including 5 subjects experiencing withdrawal symptoms. There were no clinically significant changes in vital signs and no changes in mean ECG parameters across the study period.

Oral mucosal abnormalities were identified in 6.8% (17 of 249) of SLBN-treated subjects before initiating BBN dosing and in 2.4% (6 of 249) of subjects treated with BBN over 12 weeks. Of the 6 subjects with abnormalities identified over the 12 weeks of treatment, 3 (1.2%) subjects had mucosal redness on oral examination that was considered drug related. Each of these oral events was mild in severity and resolved with continued BBN administration. No oral mucosal abnormalities were detected on day 14 or from day 56 through the end of the study period (Figure 2).

A checklist of typical BN symptoms was provided to all participating subjects; 186 subjects completed the checklist at baseline and day 84. Of these subjects, 76 (40.9%) reported constipation at the time of SLBN discontinuation but before treatment with BBN, and 24 (12.9%) subjects reported constipation after 12 weeks of BBN treatment, a decline of 68% (52 of 76)

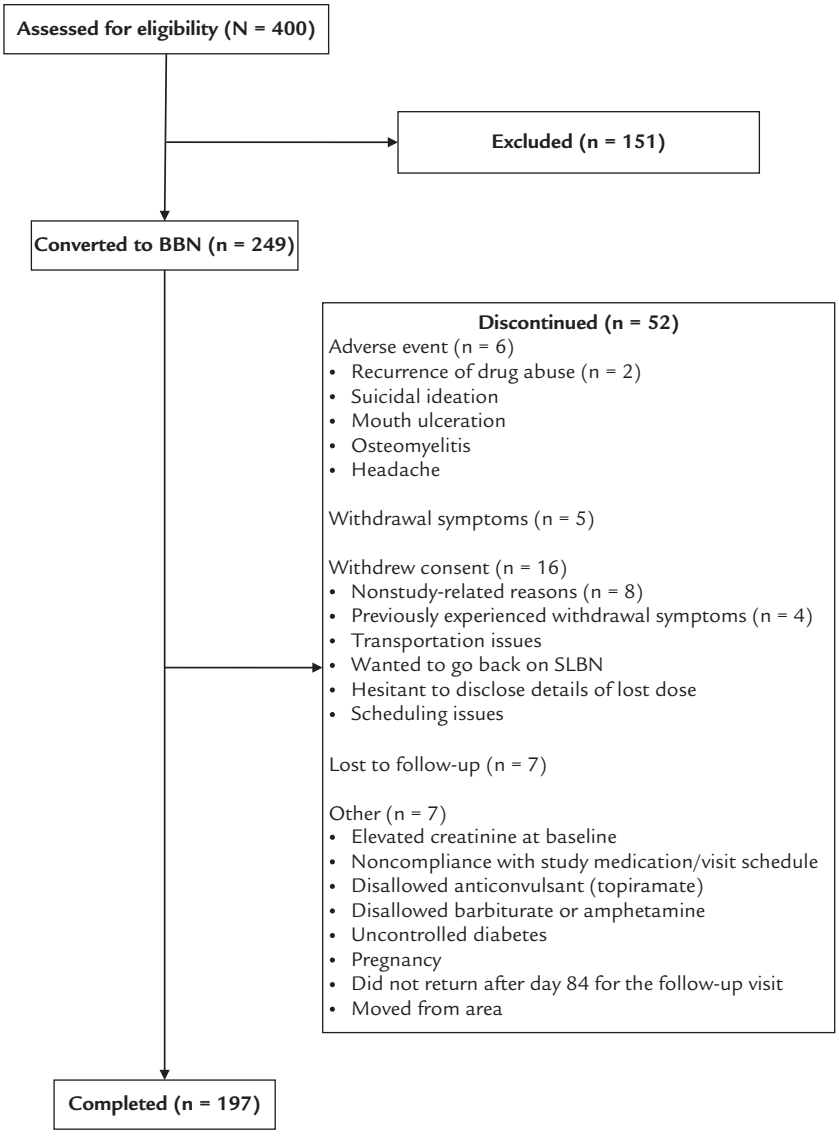


Figure 1. Subject disposition. BBN = buprenorphine-naloxone buccal film; SLBN = buprenorphine-naloxone sublingual tablets or films.

over the course of the study (Figure 3). Treatment-emergent constipation was reported by 2.8% (7 of 249) of subjects over the course of the study.

Beginning on day 2, for those subjects who reported at least 1 symptom that was considered opioid withdrawal by the investigator, "opioid withdrawal syndrome" was recorded as the AE (Table IV). The majority of subjects did not have an AE of opioid withdrawal syndrome (64.3%). Of the 89 subjects who experienced withdrawal syndrome, most experienced mild events (85.4%), and the majority of those required 0 or 1 BBN dose adjustment to abate the symptom. None was judged to be severe. The majority of dose adjustments occurred during the first 4 weeks of treatment, and most of these events resolved with a single adjustment.

Drug dependence, a term resulting from the coding of verbatim AEs containing the word "craving", was considered drug related in 2.4% (6 of 249) of subjects. Events considered possibly, probably, or definitely related to BBN that occurred in >2 subjects are summarized in Table V.

Table III. Demographic and baseline characteristics of study subjects.

Characteristic	Value
Age, y, mean (minimum, maximum)	38.7 (20.0, 62.0)
Sex, no. (%)	
Male	164 (65.9)
Female	85 (34.1)
Current medical conditions/ disorders, no. (%)*	
Psychiatric†	249 (100.0)
Nervous system	112 (45.0)
Musculoskeletal or connective tissue	107 (43.0)
Gastrointestinal	100 (40.2)
Immune system	65 (26.1)
Cardiovascular	58 (23.3)
Hepatobiliary	46 (18.5)
Reproductive system and breast	35 (14.1)
Respiratory, thoracic, and mediastinal	32 (12.9)
Skin and subcutaneous tissue	32 (12.9)
Endocrine	27 (10.8)
Prior medication usage, no. (%)‡	
SLBN	249 (100)
Clonazepam	23 (9.2)
Trazodone	21 (8.4)
Ibuprofen	18 (7.2)
Amphetamine mixed salts	17 (6.8)
Alprazolam	16 (6.4)
Gabapentin	15 (6.0)
Lisinopril	15 (6.0)
Zolpidem tartrate	14 (5.6)

SLBN = buprenorphine-naloxone sublingual tablet or film.
*Reported in >10% of subjects.
†The most common psychiatric conditions were opioid dependence, anxiety, and depression.
‡Used by >5% of subjects.

Evidence of Efficacy

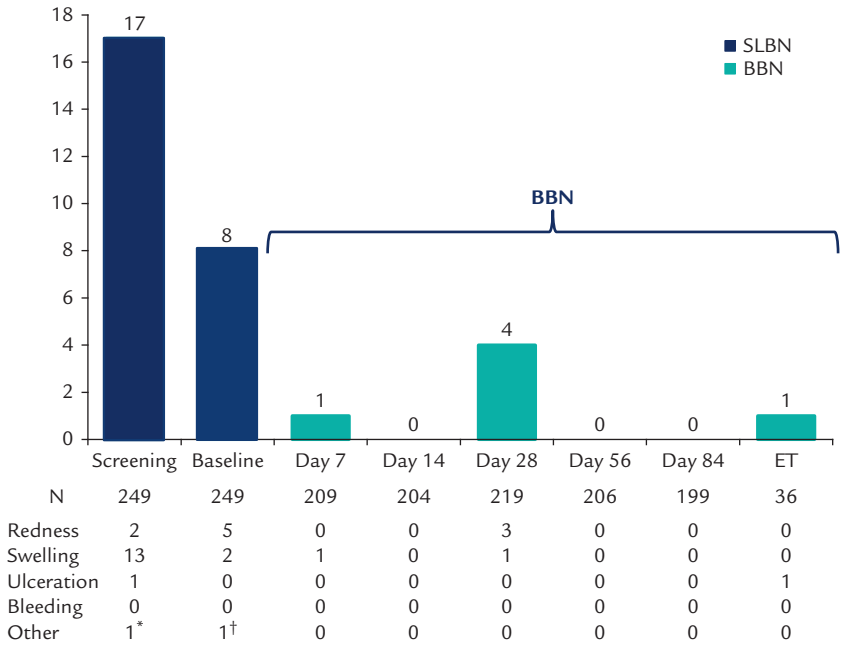
At baseline (before BBN dose administration and within 24 hours of taking the last SLBN dose), COWS scores ranged from 0 to 25, with an overall mean of 3.3 in the total population and 4.6 in subjects taking SLBN 16, 24, or 32 mg daily. Three hours after the initial BBN dose, the overall mean COWS score was ≤0.54 for the study population. Among subjects with baseline COWS scores ranging from 10 to 25 (n = 34) after discontinuation of SLBN, initiation of BBN resulted in a decline in mean scores from ≥13.1 to ≤1.1 in 3 hours (Table VI). These results depend on the bioequivalence of buprenorphine exposure from BBN 4.2/0.7 mg and an 8/2–mg SLBN tablet, which was demonstrated in the previously conducted PK study,[11] and should be considered preliminary due to the open-label design of this study.

Compliance with study drug administration (per protocol) was high; mean study drug compliance was 108% when study drug reported by the subject as "lost" was considered as "taken." During the 12-week BBN administration period, 11 subjects had buprenorphine-negative urine samples, and 11 subjects had norbuprenorphine-negative urine samples (Table VII). One subject had negative results for both, recorded at the day 84 visit. No subject had multiple buprenorphine-negative samples. Urine testing was positive for a non-prescribed opioid in 19 (7.6%) subjects during the BBN dosing period (Figure 4). Eleven of these 19 subjects had a single opioid-positive urine sample, 4 had 2 opioid-positive urine samples, and 4 had >2 opioid-positive urine samples.

The mean SLBN dose at the time of study entry was 15.74 mg of buprenorphine per day. Based on an initial conversion factor of BBN 3.5/0.6 mg = SLBN 8/2 mg, the mean BBN starting dose was 6.9/1.2 mg/d. The starting conversion dose of BBN administered as a once-daily dose was adequate for 63.5% (158 of 249) of subjects regardless of their previous SLBN dosing regimen. After dose adjustments (Table VIII), the mean final dose of BBN was 8.0/1.4 mg, yielding a 2:1 buprenorphine conversion ratio from SLBN 16 mg to BBN 8.0 mg. The established conversion ratio is further supported by the higher relative bioavailability demonstrated in the PK study comparing BBN 4.2/0.7 mg with SLBN 8/2 mg.[11]

Treatment Acceptance

The majority (91.3%) of subjects considered the flavor of BBN to be very pleasant, pleasant, or neutral, and a similarly high proportion (82.5%) rated BBN as very easy, easy, or neutral for ease of use (Figure 5). The assessments of the flavor and ease of use of BBN that were favorable or neutral were reported



	Screening	Baseline	Day 7	Day 14	Day 28	Day 56	Day 84	ET
N	249	249	209	204	219	206	199	36
Redness	2	5	0	0	3	0	0	0
Swelling	13	2	1	0	1	0	0	0
Ulceration	1	0	0	0	0	0	0	1
Bleeding	0	0	0	0	0	0	0	0
Other	1*	1†	0	0	0	0	0	0

Figure 2. Subjects with abnormal oral examination results after treatment with buprenorphine-naloxone sublingual tablets or films (SLBN) or buprenorphine-naloxone buccal film (BBN).
*Small, 1-mm mucus cyst (benign) in the upper right mucosa. †Tiny white spot in the upper right mucosa; white adherent patch in the upper left mucosa. ET = early termination.

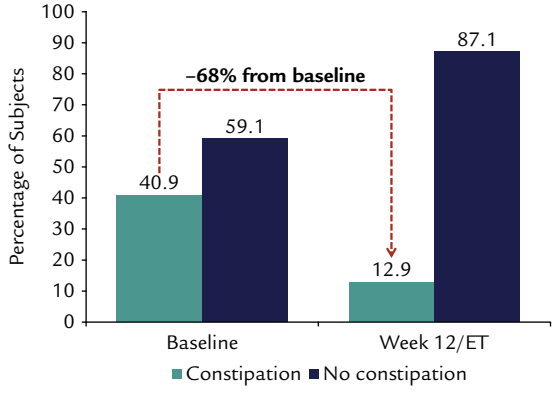


Figure 3. Constipation at the end of treatment with buprenorphine-naloxone sublingual tablets or films (baseline) and week 12 in subjects* converted to buprenorphine-naloxone buccal film (n = 186).
*A total of 186 subjects completed the symptom checklist at baseline and week 12. ET = early termination.

Table IV. Subjects with treatment-emergent drug withdrawal syndrome* grouped according to severity and required dose adjustments (N = 249).

Dose Adjustment†	Subjects With Drug Withdrawal Syndrome, no. (%)			
	Absent‡	Mild	Moderate	Severe
0	136 (54.6)	16 (6.4)	5 (2.0)	0
1	20 (8.0)	44 (17.7)	5 (2.0)	0
2	4 (1.6)	16 (6.4)	3 (1.2)	0

*Recorded as an adverse event if the subject experienced ≥1 symptom considered to be opioid withdrawal.
†Required after initial conversion from buprenorphine-naloxone sublingual tablet or film.
‡Drug withdrawal syndrome not reported.

Table V. Treatment-emergent adverse events occurring in >5% of subjects (N = 249).

Event	No. (%)
Lethargy	22 (8.8)
Headache	20 (8.0)
Nasopharyngitis	14 (5.6)

irrespective of whether subjects were switched from SLBN tablets or films.

DISCUSSION

Overall, BBN showed an acceptable safety and tolerability profile in this 12-week study for the maintenance treatment of opioid dependence in subjects previously stabilized for at least 30 days on 8- to 32-mg buprenorphine tablets or films. With each of the 10 participating investigators applying a standardized protocol of oral mucosal examination, the 64% decline in subjects experiencing abnormalities over the BBN dosing period indicates a low risk for clinically significant oral mucosal abnormalities due to BBN administration over 12 weeks. These results address the oral tolerability of the novel buccal film formulation (ie, oral mucosal irritation) and align with previous research showing that the BEMA technology provides acceptable buccal safety and rapid, consistent drug absorption, even in the presence of oral mucositis.[14]

The constipation rate reported at baseline, after the last dose of SLBN, was >60%, and subjects

Table VII. Buprenorphine- and norbuprenorphine-negative urine samples among subjects treated with buprenorphine-naloxone buccal film (N = 249).

	Buprenorphine		Norbuprenorphine	
Visit	N	No. (%)	N	No. (%)
Screening	249	1 (0.4)	249	1 (0.4)
Baseline	247	3 (1.2)	244	3 (1.2)
Day 7	237	0	237	6 (2.5)
Day 14	228	2 (0.9)	227	2 (0.9)
Day 28	218	1 (0.5)	217	4 (1.8)
Day 42	211	1 (0.5)	210	1 (0.5)
Day 56	204	1 (0.5)	204	1 (0.5)
Day 70	198	3 (1.5)	196	2 (1.0)
Day 84	197	1 (0.5)	197	3 (1.5)
ET	37	2 (5.4)	35	1 (2.9)
Total		15		24

ET = early termination

Table VI. Clinical Opiate Withdrawal Scale total score for subjects with a baseline total score ≥10 (n = 34).

BBN initial dose, mg	3.5/0.6	5.25/0.9	7.0/1.2[*]	10.5/1.7[†]	14.0/2.3[‡]
Prior SLBN daily dose mg, no. (%)	8 (0)	12 (1)	16 (15)	24 (16)	32 (2)
Predose mean (range)	—	13.0 (13 to 13)	13.8 (10 to 25)	13.8 (10 to 23)	14.5 (11 to 18)
3 Hours' post-dose mean (range)	—	1.0 (1 to 1)	1.1 (0 to 3)	0.6 (0 to 3)	0 (0 to 0)
Change from baseline to 3 hours; postdose mean (range)	—	−12.0 (−12 to −12)	−12.7 (−25 to −9)	−13.3 (−22 to −10)	−14.5 (−18 to −11)

BBN = buprenorphine-naloxone buccal film; SLBN = buprenorphine-naloxone sublingual tablet or film.
[*]2 × 3.5/0.6 mg.
[†]2 × 5.25/0.9 mg.
[‡]4 × 3.5/0.6 mg.

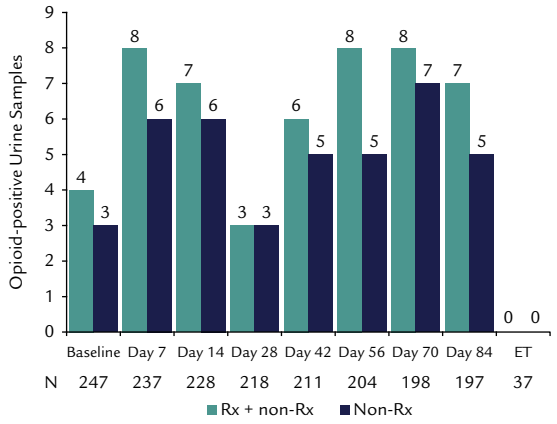


Figure 4. Number of opioid-positive urine samples during treatment (Rx) with buprenorphine-naloxone buccal film (N = 249). ET = early termination.

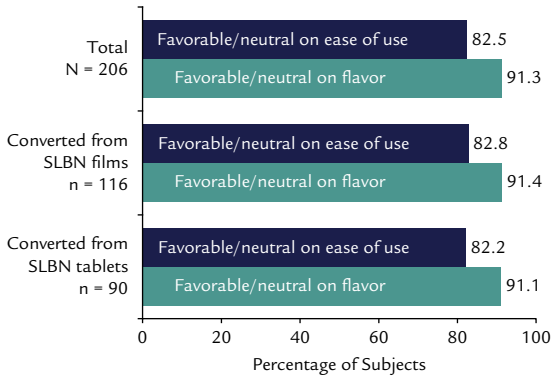


Figure 5. Subject assessment of buprenorphine-naloxone buccal film flavor and ease of use after switching from buprenorphine-naloxone sublingual tablets or films (SLBN).

experienced a substantial decrease after being switched to BBN. The novel buccal formulation might have had a role in reducing constipation, possibly due to less BN reaching opioid receptors in the gastrointestinal tract as a result of increased bioavailability and lower total buprenorphine dose. This positive finding must be interpreted with caution due to the open-label nature of the study.

The COWS total score reductions in subjects with baseline values ≥10, high retention rate, and low incidence of opioid-positive urine samples suggest that an average daily dose of 8.0/1.4 mg of buprenorphine may be effective in subjects previously stabilized on a mean daily dose of 15.74 mg of buprenorphine. Despite stable COWS scores at 3 hours after the initial BBN dose, however, some BBN-treated subjects

Table VIII. Dose adjustments in buprenorphine-naloxone buccal film (BBN). Values are given as number (%).

	Final Dose, mg						
Variable	3.5/0.6	5.25/0.9	7.0/1.2	10.5/1.7	14.0/2.3	10.5/1.7	21.0/3.6
Starting dose, mg							
3.5/0.6 (n = 48)	29 (60.4)*	8 (16.7)	9 (18.8)	2 (4.2)	0	0	0
5.25/0.9 (n = 40)	0	27 (67.5)*	10 (25.0)	3 (7.5)	0	0	0
7.0/1.2 (n = 110)	0	0	68 (61.8)*	32 (29.1)	3 (2.7)	5 (4.5)	2 (1.8)
10.5/1.7 (n=43)	0	1 (2.3)	0	26 (60.5)*	6 (14.0)	10 (23.3)	0
14.0/2.3 (n=8)	0	0	0	0	8 (100.0)*	0	0
Total no. of patients	29	36	87	63	17	15	2
No. of dose adjustments	0	9	19	37	9	15	2
Average starting dose, 6.9/1.2 mg	Average final dose, 8.0/1.4 mg						

*Patients whose starting and final buprenorphine-naloxone buccal film doses were the same (ie, no dose adjustment).

reported symptoms of drug withdrawal syndrome. This outcome may have been due to the change in dosing frequency or the slightly lower buprenorphine exposure from the initially chosen conversion ratio. However, a high level of compliance with BBN treatment was demonstrated by the nearly 80% of subjects who completed the 12-week study, as well as by the urine test results for buprenorphine and norbuprenorphine.

Subjects in this study who were converted to BBN reported high ratings for acceptability, and a large percentage of subjects who switched from SLBN tablets or films considered BBN easy to use. This finding corroborates previous research, in which 85% of subjects who used the BEMA technology rated it as excellent, good, or very good.[15] Because the favorable ratings were provided by subjects switched from SLBN tablets or films, it seems unlikely that the previous SLBN formulation will be an important factor in the decision to convert patients to BBN.

In these opioid-dependent subjects, the mean final effective dose of BBN was ~50% less than the baseline dose of SLBN. This parallels PK findings in healthy volunteers, in which BBN provided buprenorphine exposure equivalent to SLBN tablets at approximately one half the dose, with reduced exposure to naloxone.[11] The near-identical results across different cohorts demonstrate the consistency of buprenorphine delivery with the BEMA technology and suggests that, in clinical practice, switching patients to BBN should be safe and predictable.

SLBN has been widely used and is generally considered safe and effective,[3] but sublingual administration has been a concern due to suboptimal dissolve times, inconsistent absorption, risk of diversion, and unintentional exposure in children.[4–7] By permitting the use of a lower BN dose than sublingual tablets and films, BBN may help to control the symptoms of opioid dependence with a potentially lower incidence of adverse effects, favorable ease of administration, and high rate of adherence.[11,16,17] Both active ingredients have a bitter taste, but the current study suggests that BBN may address this challenge: the majority of subjects switched from SLBN considered BBN to be pleasant-tasting.

This study has some limitations due to its open-label design. First, it is possible that not blinding investigators might have influenced their assessments. In addition, the findings of symptom control that are suggestive of efficacy must be considered as preliminary. Despite these shortcomings, in opioid-dependent subjects treated with a stable dose of 8- to 32-mg buprenorphine daily for at least 30 days, BBN exhibited evidence of safety and tolerability, with a low rate of treatment-emergent AEs. Preliminary efficacy, specifically COWS scores after first dose, urine opioid testing, and retention over the course of the 12-week study, was also demonstrated. The 2:1 buprenorphine dose conversion ratio from the mean baseline SLBN dose to the mean BBN dose at the end of the study was consistent with results from a bioequivalence study in healthy volunteers.[11] Accordingly, the final marketed formulation of BBN will be based on the 2:1 ratio and the mean final BBN dose, not the doses used in this clinical trial.

CONCLUSIONS

While these results should be considered preliminary due to the open-label design, BBN was overall safe and well tolerated, and it appeared to provide adequate symptom control, in the treatment of opioid-dependent subjects previously controlled on SLBN for a minimum of 30 days. There was good adherence to study medication and favorable patient acceptance of the buccal formulation. The SLBN-BBN buprenorphine conversion ratio was 2:1.

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CONFLICTS OF INTEREST

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REFERENCES

1. Degenhardt L, Whiteford HA, Ferrari AJ, et al. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013;382:1564–1574.

2. Manchikanti L, Helm S 2nd, Fellows B, et al. Opioid epidemic in the United States. *Pain Physician*. 2012;15:ES9–38.
3. Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2009:3: CD002025.
4. Ling W. Buprenorphine for opioid dependence. *Expert Rev Neurother*. 2009;9:609–616.
5. Jones H. Practical considerations for the clinical use of buprenorphine. *Sci Pract Perspect*. 2004;2:4–20.
6. Strain EC, Stoller K, Walsh SL, Bigelow GE. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. *Psychopharmacology (Berl)*. 2000;148:374–383.
7. Boyer E, McCance-Katz E, Marcus S. Methadone and buprenorphine toxicity in children. *Am J Addict*. 2009; 19: 89–85.
8. Fischer A, Jönsson M, Hjelmström P. Pharmaceutical and pharmacokinetic characterization of a novel sublingual buprenorphine/naloxone tablet formulation in healthy volunteers. *Drug Dev Ind Pharm*. 2013:1–6. [Early Online].
9. Suboxone Prescribing Information. Available at: http://www.suboxone.com/content/pdfs/SuboxonePI.pdf. Accessed June 2014.
10. Zubsolv Prescribing Information. Available at: http://www.zubsolv.com/pdf/zubsolvFullPI-HCP.pdf. Accessed June 2014.
11. Vasisht N, Stark J, Bai SA, Finn A. Buprenorphine/naloxone buccal film has a relative buprenorphine bioavailability approximately twice that of buprenorphine/naloxone sublingual tablet. 2014 ASAM 45th Annual Medical-Scientific Conference. Poster #10. Orlando, FL: 10-13 April 2014.
12. World Medical Association. Declaration of Helsinki (2008). Available at: http://www.wma.net/en/30publications/10policies/b3/index.html. Accessed April 2014.
13. Center for Substance Abuse Treatment. *Clinical guideline for the use of buprenorphine in the treatment of opioid addiction*. Treatment Improvement Protocol (TIP) Series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004;14–18.
14. Finn AL, Hill WDC, Tagarro I, Gever LN. Absorption and tolerability of fentanyl buccal soluble film (FBSF) in patients with cancer in the presence of oral mucositis. *J Pain Res*. 2011;4:245–251.
15. Slatkin NE, Hill C, Finn A. The safety of BEMA™ (BioErodible MucoAdhesive) fentanyl use for breakthrough pain (BTP) in cancer patients (Poster #190). *Presented at the American Pain Society (APS) 27th Annual Scientific Meeting. May*. 2008:8–10. Tampa, Florida.
16. Chinna Reddy P, Chaitanya KS, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. *Daru*. 2011;19:385–403.
17. Das N, Das S. Development of mucoadhesive dosage forms of buprenorphine for sublingual drug delivery. *Drug Deliv*. 2004;11: 89–95.

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