Effects of a Higher-bioavailability Buprenorphine/Naloxone Sublingual Tablet Versus Buprenorphine/Naloxone Film for the Treatment of Opioid Dependence During Induction and Stabilization: A Multicenter, Randomized Trial

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ABSTRACT

Purpose: Sublingual buprenorphine and combination buprenorphine/naloxone (BNX) are effective options for the treatment of opioid dependence. A BNX sublingual tablet approved by the US Food and Drug Administration for the induction and maintenance treatment of opioid-dependence in adults was developed as a higher-bioavailability formulation, allowing for a 30% lesser dose of buprenorphine with bioequivalent systemic exposure compared with another BNX sublingual tablet formulation. No data were previously available comparing the higher-bioavailability BNX sublingual tablet to generic buprenorphine or BNX sublingual film; we therefore evaluated treatment retention during induction and stabilization with the higher-bioavailability BNX sublingual tablet versus generic buprenorphine or BNX sublingual film.

Methods: This multicenter, prospective, randomized, parallel-group noninferiority trial was conducted at 43 centers in the United States. Eligible patients were adults aged 18 to 65 years who met the criteria for opioid dependence and had at least mild withdrawal symptoms. On days 1 and 2, patients received blinded, fixed-dose induction with the higher-bioavailability BNX sublingual tablet or generic buprenorphine. On days 3 to 14, patients induced with BNX received open-label, titrated doses of the BNX tablet for stabilization; patients induced with buprenorphine received sublingual BNX film. Co-primary end points were treatment retention on days 3 and 15; noninferiority was concluded if the lower limit of the 95% CI of the between-group difference in treatment retention was $\geq -10\%$. Tolerability was assessed throughout the study period.

Findings: A total of 758 opioid-dependent patients were included in the study (BNX sublingual tablet, 383 patients; generic buprenorphine, 375). Day-3 retention rates were 93.9% (309/329) and 92.6% (302/326) with the BNX tablet and buprenorphine, respectively (between-group difference 95% CI, −2.6 to 5.1). Day-15 retention rates were 83.0% (273/329) and 82.5% (269/326) with the BNX tablet and BNX film, respectively (between-group difference 95% CI, –5.3 to 6.3). No unexpected tolerability issues were identified; the safety profile of the BNX sublingual tablet was similar to those of generic buprenorphine and BNX film.

Implications: Based on the findings from this study in patients with opioid dependence, the higher-bioavailability BNX sublingual tablet formulation was noninferior to both generic buprenorphine (induction) and BNX film (stabilization). These findings suggest that BNX sublingual tablets are an efficacious and well-tolerated option for induction and early stabilization treatment of opioid dependence. ClinicalTrials.gov identifier: NCT01908842. (*Clin Ther.* 2015;37:2244–2255) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: buprenorphine, buprenorphine/naloxone combination, induction therapy, maintenance therapy, treatment retention.

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INTRODUCTION

Sublingual buprenorphine and combination buprenorphine/naloxone (BNX) are effective options for office-based treatment of opioid dependence.[1,2] Buprenorphine is a partial μ-opioid receptor agonist that promotes treatment retention, reduces illicit drug use, and relieves cravings in patients dependent on full μ-opioid agonists.[3] Unlike other partial opioid agonists, buprenorphine binds with high affinity to the μ-opioid receptor.[4] From a clinical perspective, the tight binding blocks the effects of exogenous opioids, which is important for the prevention of relapse. However, displacement of full μ-opioids by the higher-affinity partial agonist can lead to precipitated withdrawal,[5,6] which poses a clinical challenge during induction as patients transition from full μ-opioids. The μ-receptor antagonist naloxone is included in combination products to deter abuse, as it precipitates withdrawal symptoms when taken parenterally by opioid-dependent patients.[7,8] Naloxone has no or limited systemic effects when administered sublingually due to its low bioavailability via this route.[4]

The use of a BNX sublingual tablet formulation* was approved in 2002 by the US Food and Drug Administration for the treatment of opioid dependence in adults. Although the branded product was discontinued from the market, generic formulations remain available. Subsequently, a sublingual BNX film formulation† was approved in 2010 for use as maintenance treatment of opioid dependence in adults and in 2014 for the induction of treatment in those transitioning from short-acting opioids.[9,10] No BNX formulation is licensed for induction therapy in both patients dependent on long-acting opioids and patients dependent on short-acting opioids. The induction of therapy in patients dependent on long-acting opioids (eg, methadone) might be complicated by an increased risk for precipitated or prolonged withdrawal.[11–13] Limited clinical evidence exists regarding the efficacy of BNX film for induction in patients dependent on long-acting opioids, or among those transitioning from long-acting extended-release preparations.[14,15] Thus, buprenorphine monotherapy is the only treatment approved and recommended[11] for induction in patients transitioning from long-acting opioids. After successful induction, adherence of opioid-dependent patients to maintenance BNX therapy is important for preventing relapse and future illicit opioid use.[16] In addition, successful maintenance therapy might integrate psychosocial treatment to promote behavioral and/or lifestyle changes, as well as to address psychosocial challenges that might contribute to a patient's addiction.[9,11]

A higher-bioavailability BNX sublingual tablet formulation‡ was approved by the FDA in July 2013 for use as maintenance treatment in adult patients with opioid dependence and was made available for clinical use in September 2013. An indication for induction treatment in adult patients with opioid dependence followed in August 2015. This higher-bioavailability BNX sublingual product allows for the administration of a 30% lesser dose of buprenorphine with systemic exposure (ie, bioavailability) equivalent to that of a previously available BNX sublingual tablet formulation; the development of this tablet formulation also incorporated specific characteristics to address patients' preferences.[9] The technology used in the formulation, comprising micronized buprenorphine in an associative admixture with a citric acid buffer system, demonstrates rapid disintegration, an immediate but temporary reduction in pH, and synchronized buprenorphine release in vitro. These properties contribute to its increased dissolution rate and improved bioavailability.[17]

The clinical development of this higher-bioavailability sublingual tablet focused initially on comparisons to the previously available BNX tablet formulation. In a comparative bioavailability study in healthy participants who received naltrexone blockade, the use of a 5.7/1.4 mg dose of the BNX sublingual tablet (a 30% lesser buprenorphine dose) maintained bioequivalent buprenorphine systemic exposure[9] and 12% less naloxone exposure,[17] as well as significantly faster sublingual dissolve time ($P < 0.0001$),[9] compared with those of the other, 8/2-mg, BNX tablet.

Although these pharmacokinetic data on the higher-bioavailability BNX sublingual tablet[9] were sufficient for FDA approval, no published clinical studies have compared the effects of the BNX sublingual tablet formulation with either the generic buprenorphine sublingual tablet or BNX sublingual film. Given the importance of such data for guiding physicians' and patients' decision making, the clinical

*Trademark: Suboxone® (Reckitt Benckiser, Richmond, Virginia).

†Trademark: Suboxone® sublingual film (Reckitt Benckiser).

‡Trademark: Zubsolv® (Orexo US, Inc, Morristown, New Jersey).

efficacy and tolerability of the higher-bioavailability BNX sublingual tablet in opioid-dependent patients were assessed in the Induction, Stabilization, Adherence and Retention Trial. This study compared the efficacy and tolerability of the higher-bioavailability BNX sublingual tablet with those of generic buprenorphine, and stabilization with higher-bioavailability BNX sublingual tablet with that of the BNX film. To better reflect patients treated in clinical practice, the study enrolled patients being transitioned from short- or long-acting opioid use. The primary objective was to assess the efficacy of the BNX sublingual tablet formulation, measured as retention in treatment during the induction and stabilization phases. Secondary objectives included the assessment of treatment effects on opioid withdrawal symptoms and cravings, and treatment tolerability.

PATIENTS AND METHODS

Study Design

This prospective, multicenter, randomized, parallel-group, noninferiority trial was conducted at 43 centers in the United States from August 2013 to April 2014. A noninferiority design was used because the BNX sublingual tablet and BNX film contain the same active components, and it would have been considered unethical to have included a placebo arm. This study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions, and in compliance with the International Conference on Harmonisation Good Clinical Practice guideline and all applicable laws and regulations. The study protocol was approved by an institutional review board at each site, and all patients provided written informed consent to participate.

The study comprised an induction phase of 2 days and a stabilization phase of 20 days, with study visits scheduled on days 1, 2, 3, 4, 8, 15, and 22. Eligible opioid-dependent patients were randomly assigned (1:1) within 14 days after screening to receive induction with either the higher-bioavailability BNX sublingual tablet or a generic buprenorphine tablet for 2 days. Generic buprenorphine was selected as the comparator drug for induction in this trial as it was the only product approved for use as induction therapy when the study was designed. In addition, it is currently the only formulation indicated for induction after both short- and long-acting opioid use.[10] Randomization and allocation of treatments were made through an Interactive Response Technology service. The doses on days 1 and 2 were provided in kits allocated through the Interactive Response Technology randomization procedure.

On day 3, patients allocated to induction using the higher-bioavailability BNX sublingual tablet were continued on the same treatment during the stabilization phase, whereas those allocated to induction using buprenorphine were switched to BNX film.

On day 15, patients on BNX sublingual tablets were switched to BNX film, and those receiving BNX film were switched to BNX sublingual tablets. At the final study visit on day 22, patients were offered the option of continuing in an open-labeled follow-up study of the higher-bioavailability BNX sublingual tablet.

Inclusion and Exclusion Criteria

Male or female adults aged 18 to 65 years, in generally good health, and who met the criteria for opioid dependence as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) in the 12 months before the start of the study were eligible for inclusion if they agreed to abstain from opioid utilization (other than study drug) and from the use of other addictive drugs, and if they demonstrated at least *mild withdrawal symptoms,* defined as a score of ≥ 9 on the Clinical Opiate Withdrawal Scale (COWS) predose on day 1. Eligibility also required a buprenorphine-negative urine drug screen and, in female participants, a negative urine pregnancy test and agreement to use a reliable method of contraception throughout the study. Treatment with any opioid prescribed for pain management was discontinued before induction and after clearance was obtained from the prescribing physician.

Patients were excluded from the study if they had any serious, untreated *DSM-IV-TR*–defined Axis I psychiatric comorbidity and/or were considered at risk for suicide; any clinically significant medical disorder or other condition that might have compromised the participant's safety or the validity of the study results; and/or any tongue or other oral deformity that might have affected the absorption of the study drugs. Other exclusion criteria were the use of any of the following: generic buprenorphine monotherapy within 90 days before the start of the study; methadone at a dose of >30 mg/d within the week

before the start of the study; any methadone within 30 hours before the initial study treatment; or any medication or product with strong cytochrome P-450 3A4 inhibition or induction properties within 14 days before screening.

Study Treatment

The study medications included the higher-bioavailability BNX sublingual tablet (5.7/1.4 or 1.4/0.36 mg), BNX sublingual film (8/2 or 2/0.5 mg), and generic buprenorphine sublingual tablets (8 or 2 mg[§]). The patients, investigators, and sponsor were blinded to the treatment assignments; however, because no buprenorphine-matched placebo was available, the achievement of an identical appearance of the study medications was not possible. To maintain blinding of the investigators to treatment assignments during induction, study medications were placed in identical packaging with blinded labels, and induction therapy was administered with the supervision of a staff member who was not involved in the clinical assessments.

On days 1 and 2, patients received a total fixed dose of higher-bioavailability BNX sublingual tablet (5.7/1.4 mg and 5.7/1.4 mg or 11.4/2.8 mg, respectively) or generic buprenorphine (8 mg and 8 mg or 16 mg, respectively). On day 3, the start of the stabilization phase, the patients receiving generic buprenorphine were switched to BNX film. Patients were allowed rescue medication if needed. Dosing during stabilization was open-labeled; stabilization doses were titrated to maximal daily doses of 17.1/4.2 mg and 24/6 mg of the BNX sublingual tablet and BNX film, respectively, on the basis of clinical symptoms. On day 15, treatments were switched according to a fixed conversion factor (5.7 to 8 mg) on the basis of the corresponding dose strengths of the BNX sublingual tablets and BNX film.

Efficacy and Tolerability Assessments

The co-primary efficacy end points were retention in treatment on days 3 and 15. Retention in treatment on day 3 was added as a co-primary efficacy end point in a protocol amendment for the purpose of assessing the efficacy and tolerability of the higher-bioavailability BNX sublingual tablet formulation used for the induction phase of treatment in patients with opioid dependence. Secondary efficacy end points included opioid withdrawal symptoms, as assessed using the COWS (total-score range, 0–48, with a lesser score being more favorable) and the Subjective Opiate Withdrawal Scale (SOWS; total-score range, 0–64, with a lesser score being more favorable), and opioid cravings, as assessed using a visual analog scale ranging from 0 ("no cravings") to 100 ("most intense craving I have ever had"). The staff at each study site was trained by the study sponsor or monitor on the proper administration of the scales. These assessments were performed before dosing on treatment visit days, and additionally at 0.5, 1.5, 3, and 6 hours after dosing on day 1.

Tolerability was assessed at all visits using adverse-events monitoring, including vital signs measurements. Physical examinations and clinical laboratory tests were done at screening and at the end of the study. We report results from all end points through day 15.

Statistical Analysis

The sample-size calculation was made using nQuery + nTerim version 2.0 (Statistical Solutions, Boston, Massachusetts). Assuming a retention rate of 80% on day 15, and assuming that 5% of patients would not be eligible for the primary efficacy analysis, a sample size of 708 patients was determined to have 90% power to ensure that the lower limits of the 2-tailed 95% CIs of the true between-treatment differences in retention on days 3 and 15 would be $\geq -10\%$.

The primary efficacy analysis of retention in treatment on days 3 and 15 was based on noninferiority testing, as determined by the primary efficacy end point of treatment retention, between treatment groups in the per-protocol population (all randomized patients who met eligibility criteria and correctly received the study treatment to which they were assigned). A priori noninferiority was concluded if the lower limit of the 95% CI of the difference in retention rate between treatments was $\geq -10\%$. Sensitivity analyses of retention rate and analyses of all other efficacy end points were performed on data from all randomized patients who received at least 1 dose of study treatment. For the sensitivity analysis of retention rate, a logistic regression model was used, with treatment and center as factors and day 1 predose COWS score as a covariate. Adverse events

[§]Manufacturer: Roxane Laboratories (Columbus, Ohio).

were coded using the Medical Dictionary for Regulatory Activities version ≥15.1, and the prevalences of each were compared between treatment groups using the χ^2 test. Other tolerability parameters were assessed using descriptive statistics.

RESULTS

Study Population

A total of 758 opioid-dependent patients were randomly assigned to induction with the higher-bioavailability BNX sublingual tablet (n = 383) or generic buprenorphine (n = 375) (Figure 1). The 2 treatment arms were comparable in terms of patients' demographic characteristics and baseline clinical characteristics, including recent methadone use (Table I). The mean age of the study cohort was 35.6 years; most patients were male (59.6%) and white (83.1%). The mean duration of opioid dependence reported was 10.6 years.

Efficacy

Retention Rate

In the primary efficacy analysis of data from the per-protocol population, 309 of 329 patients (93.9%) in the group that received the higher-bioavailability BNX sublingual tablet and 302 of 326 patients (92.6%) in the group that received generic buprenorphine were retained in treatment on day 3 (Table II). On day 15, retention in treatment was achieved in 273 patients (83.0%) in the group that received the BNX sublingual tablet and in 269 patients (82.5%) in the BNX film group. In both cases, the lower limit of the 95% CI was above the predefined noninferiority limit of −10%. Thus, in the primary efficacy analysis of data from the per-protocol population, BNX sublingual tablets were determined as noninferior to buprenorphine tablets in the induction phase of treatment, and as noninferior to BNX film in the stabilization phase of treatment. Comparable results were obtained

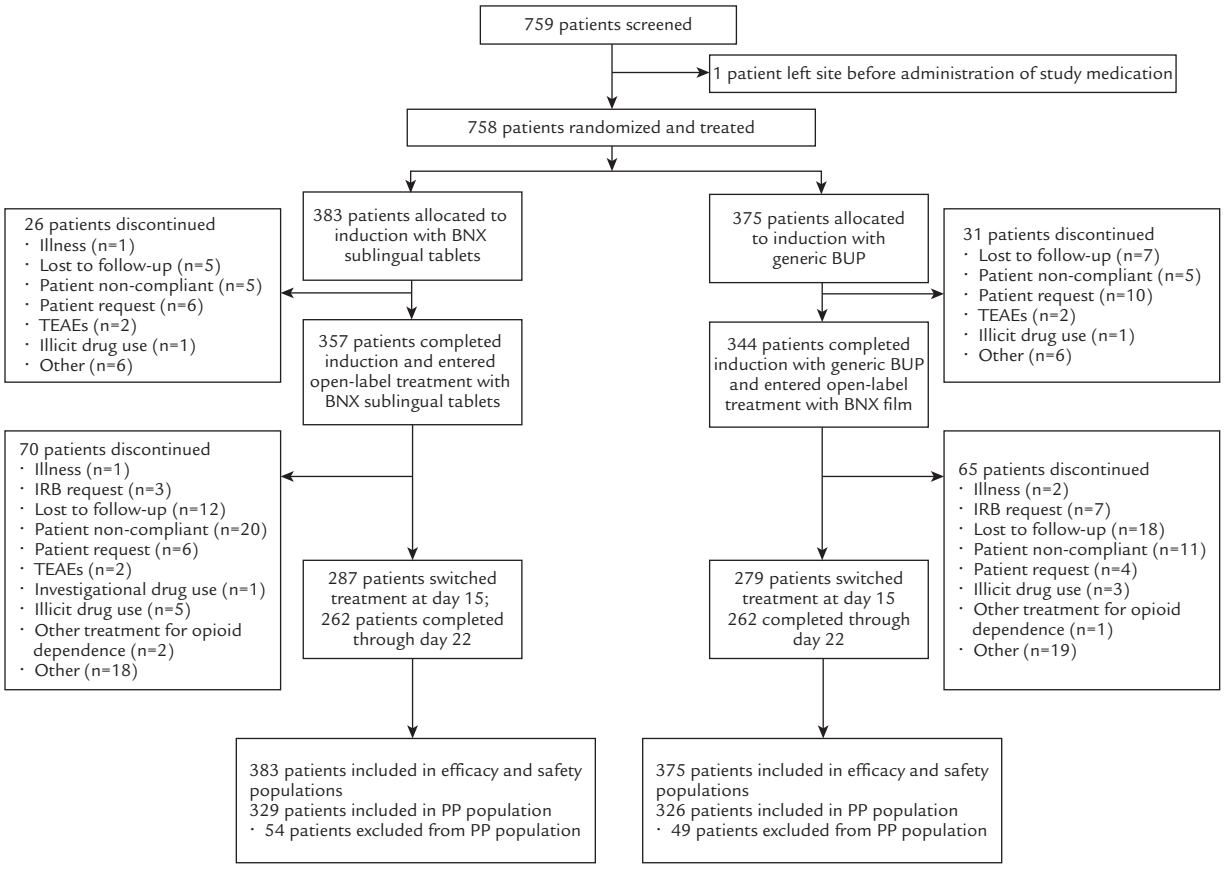

Figure 1. Patient disposition. BNX = buprenorphine/naloxone; BUP = buprenorphine; IRB = institutional review board; PP = per protocol; TEAE = treatment-emergent adverse event.

Table I. Demographics and baseline clinical characteristics.

Characteristic	BNX Sublingual Tablets (n = 383)	Generic BUP/BNX Film (n = 375)	All Patients (N = 758)
Age, y			
Mean (SD)	35.7 (11.26)	35.6 (11.28)	35.6 (11.26)
Range	18–64	18–65	18–65
Sex, no. (%)			
Male	216 (56.4)	236 (62.9)	452 (59.6)
Female	167 (43.6)	139 (37.1)	306 (40.4)
Race, no. (%)			
White	318 (83.0)	312 (83.2)	630 (83.1)
Black/African American	51 (13.3)	49 (13.1)	100 (13.2)
Other or not recorded	14 (3.7)	14 (3.7)	28 (3.7)
Duration of opioid dependence, mean (SD), y	10.7 (9.57)	10.5 (9.01)	10.6 (9.29)
Self-report of substance use over previous 30 days, no. (%)*			
Heroin	212 (55.5)	199 (53.4)	411 (54.4)
Methadone	51 (13.4)	48 (12.9)	99 (13.1)
Buprenorphine	41 (10.7)	29 (7.8)	70 (9.3)
Other opioids/analgesics	240 (62.8)	235 (63.0)	475 (62.9)
Self-report of substance use in patient's lifetime, no. (%)*			
Heroin	235 (61.8)	236 (63.4)	471 (62.6)
Methadone	127 (33.5)	129 (34.7)	256 (34.1)
Buprenorphine	125 (32.9)	108 (29.0)	233 (31.0)
Other opioids/analgesics	304 (79.8)	288 (77.4)	592 (78.6)

*Percentages based on number of patients with available responses.

Table II. Retention in treatment on days 3 and 15.

	Retention, No. (%)		Between-Group Difference, %*		
	BNX Sublingual Tablets	Generic BUP	Estimate (SE)	95% CI	*P*
Per protocol					
Day 3	309/329 (93.9)	302/326 (92.6)	1.3 (1.96)	−2.6 to 5.1	0.512
Day 15	273/329 (83.0)	269/326 (82.5)	0.5 (2.95)	−5.3 to 6.3	0.875
All patients					
Day 3	357/383 (93.2)	344/375 (91.7)	1.5 (1.92)	−2.3 to 5.2	0.440
Day 15	287/383 (74.9)	279/375 (74.4)	0.5 (3.16)	−5.7 to 6.7	0.866

BNX = buprenorphine/naloxone; BUP = buprenorphine.
*Difference in retention rate for the higher-bioavailability BNX sublingual tablet group minus the generic BUP/BNX film group.

in the sensitivity analysis conducted on data from the entire study cohort (Table II). In the logistics regression model, the odds ratios of retention in treatment in the group that received the BNX sublingual tablet compared with the combined group that received generic buprenorphine/BNX film were 1.10 (95% CI, 0.61–1.96) on day 3 and 1.02 (95% CI, 0.72–1.45) on day 15. A Kaplan-Meier survival plot for retention in treatment is shown in Figure 2. Retention in treatment did not differ significantly between groups on the basis of recent methadone use. In the full analysis population, treatment-retention rates on day 3 in a subgroup of patients who used methadone 30 days before being induced with the higher-bioavailability BNX sublingual tablet or with generic buprenorphine were 80.4% and 79.2%, respectively (between-group difference, 1.2%; 95% CI, –14.6 to 17.1). On day 15, treatment-retention rates in the subgroup that used methadone 30 days before being induced with the BNX sublingual tablet or with generic buprenorphine were 68.6% and 64.6%, respectively (between-group difference, 4%; 95% CI, –14.5 to 22.6).

Opioid Withdrawal Symptoms

Both treatments similarly reduced opioid withdrawal symptoms, as assessed using COWS and SOWS scores (Figure 3). The least squares (LS) mean AUC values of COWS total score from days 1 to 15 were 5.43 and 5.53 in the group that received the BNX sublingual tablet and the combined group that received generic buprenorphine/BNX film, respectively; the between-group difference in LS mean values was −0.10 (95% CI, −0.54 to 0.34). Similarly, the LS mean AUC values of SOWS total score were 11.17 and 11.25, respectively, and the between-group difference in LS mean values was −0.07 (95% CI, −1.33 to 1.18).

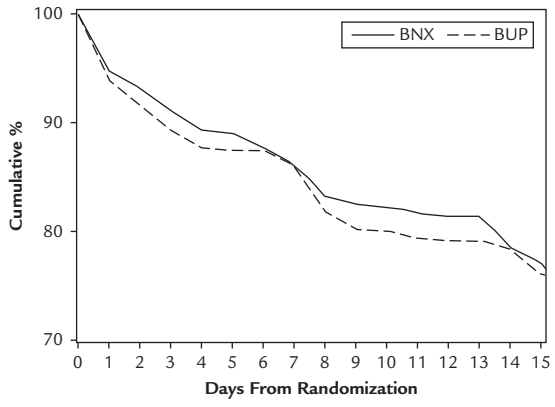

Figure 2. Kaplan-Meier plot of retention in treatment. BNX = buprenorphine/naloxone; BUP = buprenorphine.

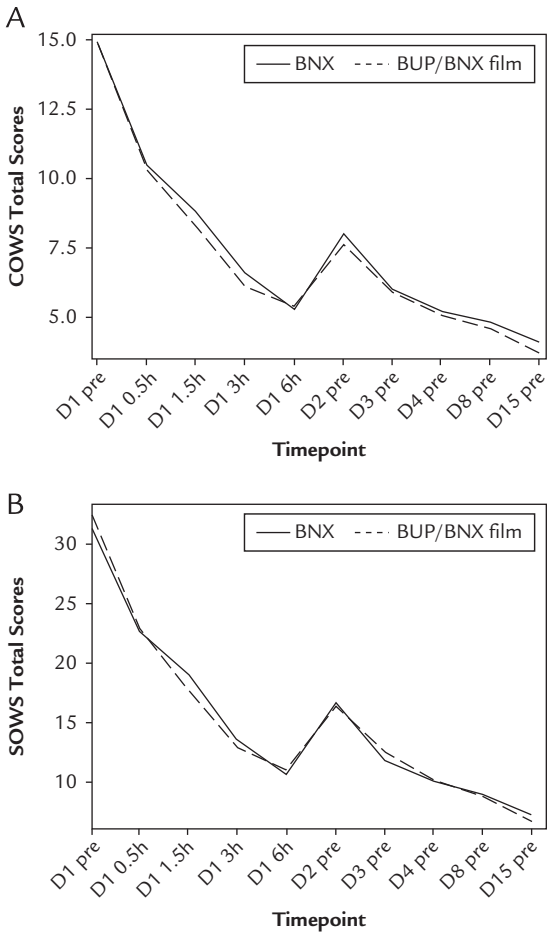

Figure 3. Mean time profile of total scores on the Clinical Opiate Withdrawal Scale (COWS) (A) and Subjective Opiate Withdrawal Scale (SOWS) (B), by treatment group. COWS total scores range from 0–48, with a lesser score being more favorable. SOWS total scores range from 0–64, with a lesser score being more favorable. BNX = buprenorphine/naloxone; BUP = buprenorphine.

Opioid Cravings

Both treatments similarly reduced opioid cravings with a time course that paralleled the reduction in

opioid withdrawal symptoms (Figure 4). On the visual analog scale for cravings, the LS mean AUC values for days 1 to 15 were 30.76 in the group that received the BNX sublingual tablet and 30.07 in the combined group that received generic buprenorphine/BNX film. The between-group difference in LS mean was 0.70 (95% CI, −2.41 to 3.80).

Doses of Study Treatment

On day 1 of the double-blinded induction phase, patients received the higher-bioavailability BNX sublingual tablet at a fixed dose of 5.7/1.4 mg or generic buprenorphine 8 mg. The mean buprenorphine doses prescribed on day 3 were 10.9 and 14.6 mg in the groups that received the BNX sublingual tablet and BNX film, respectively. On day 15, the mean prescribed buprenorphine doses were 10.8 and 15.9 mg in the group that received the BNX sublingual tablet and BNX film, respectively.

Tolerability

The prevalences of treatment-related adverse events did not differ significantly between treatment groups (Table III). In the induction phase (days 1 and 2), 61 patients (15.9%) in the group that received the higher-bioavailability BNX sublingual tablet and 55 patients (14.7%) in the group that received generic buprenorphine reported 1 or more treatment-related adverse events ($P = 0.63$). The most commonly reported adverse events were headache, nausea, and vomiting. In the open-label stabilization phase (days 3–15), the proportions of patients reporting treatment-related adverse events in the groups that received the BNX sublingual tablet and BNX film were 11.8% and 10.8%, respectively ($P = 0.67$). The most commonly reported adverse events (all patients) were constipation (3.1%) and headache (1.7%). There were no treatment-related serious adverse events reported during either period. Four patients discontinued study treatment due to treatment-related adverse events during induction generic buprenorphine group: moderate nausea and vomiting [n = 1]; moderate diaphoresis [n = 1]; BNX sublingual tablet group: moderate flushed face and torso, moderate vomiting, and mild stomach cramps [n = 1]; moderate nausea and vomiting [n = 1]. Two patients in the group that received the BNX sublingual tablet in the open-labeled phase discontinued study treatment due to treatment-related adverse events (moderate lethargic, vomiting, abdominal cramping, and no bowel bovement [n = 1]; moderate worsening of dizziness, mild nausea and fatigue [n = 1]).

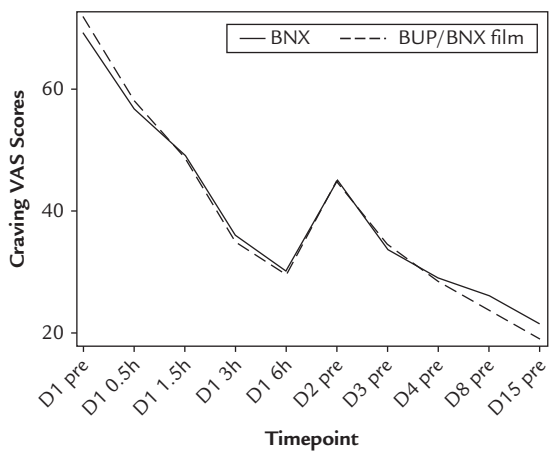

Figure 4. Mean time profile of visual analog scale (VAS) for opioid craving (ranging from 0 ["no cravings"] to 100 ["most intense craving I have ever had"]). BNX = buprenorphine/naloxone; BUP = buprenorphine.

DISCUSSION

The findings from this study, notable for its large-scale patient population, support the clinical efficacy and tolerability of a higher-bioavailability BNX sublingual tablet formulation during initiation of buprenorphine maintenance treatment of opioid dependence. Specifically, the efficacy of the higher-bioavailability BNX sublingual tablet during induction was comparable to that of generic buprenorphine, and the efficacy of the BNX sublingual tablet during early stabilization was comparable to that of BNX film. These findings were consistent when assessed by treatment retention and by reductions in withdrawal symptoms and opioid cravings. Opioid withdrawal symptoms and craving were nearly eliminated by the end of the stabilization period with the use of the higher-bioavailability BNX sublingual tablet or BNX film, consistent with treatment goals during the early phases of medication-assisted treatment[18] and with previously reported findings during induction with BNX film.[6] Together, treatment retention and the reduction of clinical symptoms are important factors in the stabilization of patients and in the prevention of illicit opioid use.

Generic buprenorphine is currently the only formulation indicated for the induction of maintenance

Table III. Prevalence of treatment-related adverse events reported in >1% of patients. Data are given as number (%) of patients.

MedDRA Preferred Term	BNX Sublingual Tablets	Generic BUP/BNX Film	All Patients
Double-blind period (days 1 and 2)	n = 383	n = 375	N = 758
Any	61 (15.9)	55 (14.7)	116 (15.3)
Headache	20 (5.2)	19 (5.1)	39 (5.1)
Vomiting	12 (3.1)	11 (2.9)	23 (3.0)
Nausea	8 (2.1)	15 (4.0)	23 (3.0)
Dry mouth	8 (2.1)	2 (0.5)	10 (1.3)
Somnolence	6 (1.6)	2 (0.5)	8 (1.1)
Insomnia	5 (1.3)	4 (1.1)	9 (1.2)
Constipation	4 (1.0)	3 (0.8)	7 (0.9)
Open-label period (days 3–15)	n = 357	n = 344	N = 701
Any	42 (11.8)	37 (10.8)	79 (11.3)
Constipation	10 (2.8)	12 (3.5)	22 (3.1)
Headache	5 (1.4)	7 (2.0)	12 (1.7)
Nausea	5 (1.4)	1 (0.3)	6 (0.9)
Somnolence	5 (1.4)	1 (0.3)	6 (0.9)
Vomiting	4 (1.1)	2 (0.6)	6 (0.9)

BNX = buprenorphine/naloxone; BUP = buprenorphine; MedDRA = Medical Dictionary for Regulatory Activities.

treatment both in patients dependent on short-acting opioids and in those dependent on long-acting opioids[10]; however, the findings from the present study suggest that the higher-bioavailability BNX sublingual tablet formulation may be appropriate for induction therapy in patients dependent on short- or long-acting opioids, including methadone. Between-group differences in treatment retention on days 3 and 15 in the subgroup of patients who had used methadone within the 30 days before treatment induction were small and associated with tightly overlapping 95% CIs. When interpreting these data, it is important to note that only a small number of patients included in the study had a history of methadone use in the 30 days before induction (n = 99); therefore, the study was underpowered to detect small differences in treatment retention among these patients.

No unexpected tolerability issues were identified during this study. The safety profile of the higher-bioavailability BNX sublingual tablet formulation was similar to that of generic buprenorphine during the blinded induction phase and similar to that of BNX film during the open-labeled stabilization phase. Moreover, the findings on the tolerability of the higher-bioavailability BNX sublingual tablet were comparable to those reported in a previous study of this proprietary formulation[19] and are aligned with the safety profiles of both buprenorphine sublingual tablets[20,21] and BNX sublingual film.[6]

In this study, the investigators were permitted to titrate the doses of the BNX sublingual tablet and BNX film. Although the BNX sublingual tablet formulation retains the 4:1 ratio of buprenorphine to naloxone, it contains amounts of buprenorphine and naloxone (5.7/1.4 mg) that are less than those in the corresponding film formulation (8/2 mg) due to enhanced transmucosal absorption of the active ingredients.[17] Consistent with the pharmacokinetic properties of the product, comparable efficacy of the 2 formulations was achieved with doses of buprenorphine and naloxone that are less in the BNX sublingual tablet than in the BNX film. The mean buprenorphine doses measured on days 3 and 15 were 26% and 32% less, respectively, in the group that received the BNX sublingual tablet compared with those in the group that received the BNX film. The extent of the public health benefits due to the lesser buprenorphine dose in the higher-bioavailability

BNX sublingual tablet formulation may be related to the product being less attractive for misuse or diversion; however, this concept remains to be determined. The availability of higher dose strengths of this BNX sublingual tablet (8.6/2.1 and 11.4/2.9 mg) might simplify dosing and allow patients to be treated with fewer tablets daily. In addition, less buprenorphine in this formulation may result in a decreased preference for the BNX sublingual tablet by injection-drug users. However, further research is necessary for determining whether the higher-bioavailability BNX sublingual tablet reduces misuse and diversion compared with such reductions with use of other medications used for treating opioid dependence.

Strengths of the clinical study described herein included the use of a noninferiority, prospective design; a large-scale population of opioid-dependent patients transitioning from the use of a broad array of short- and long-acting opioids; and standardized measures of treatment retention, opioid withdrawal symptoms, and opioid craving. This study also had several limitations. Although the investigators and patients were blinded to induction-therapy assignments, patients previously treated with buprenorphine-containing products may have distinguished the treatment assignment based on differences in aftertaste and mouth-feel; however, such recognition might be a disadvantage for the higher-bioavailability formulation under investigation given the likely greater familiarity with the higher unit dose products. For example, the findings from the subjective measures used during the open-label phase might have been affected by patients' bias toward BNX film, a well-known opioid-dependence treatment product. In addition, this study was conducted at selected clinical research sites, and the findings might not be generalizable to all office-based practices. For example, retention may be greater in patients treated at dedicated treatment centers with integrated, specialized counseling and other supportive services. Finally, the study was not specifically designed or statistically powered to establish the efficacy of the higher-bioavailability BNX sublingual tablet formulation in patients transferring from long-acting opioid use. Notably, the subgroup with recent methadone use before study entry had reduced treatment-retention rates of ~10% to 15% compared with the entire patient population. Similar reductions in treatment-retention rates were observed in both treatment arms in this subgroup. The challenge of buprenorphine induction among patients transitioning from methadone has been previously reported,[12,13,22] and further studies are needed for elucidating treatment protocols regarding induction in patients transitioning from the use of long-acting opioids such as methadone.

CONCLUSIONS

Noninferiority was established between the higher-bioavailability sublingual BNX tablet formulation and the generic buprenorphine tablet formulation during the induction phase and between the higher-bioavailability BNX tablet and BNX film during the early stabilization phase of treatment among these patients dependent on short- or long-acting opioids. Treatment-retention rates on day 3 (after induction) and on day 15 (after stabilization) were similar between treatment groups, as were the decreases in withdrawal symptoms and opioid cravings. Comparable efficacy between treatments was achieved despite the administration of less buprenorphine in the BNX sublingual tablet compared with generic buprenorphine or BNX film, which is consistent with the enhanced transmucosal absorption of active ingredients from the BNX sublingual tablet formulation. The findings from this study suggest that the higher-bioavailability BNX sublingual tablet formulation is an efficacious and well-tolerated option for induction and early stabilization treatment of opioid dependence. Overall, the findings from this study provide important information for guiding informed treatment decisions by prescribers and patients during the induction and maintenance phases of treatment, as well as potentially to lessen the public health epidemic of opioid dependence.

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CONFLICTS OF INTEREST

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