

Safety of a Rapidly Dissolving Buprenorphine/Naloxone Sublingual Tablet (BNX-RDT) for Treatment of Opioid Dependence: A Multicenter, Open-label Extension Study

Kent Hoffman, DO, Marvin L. Peyton, MD, and Michael Sumner, MB, BS, MRCP (UK)

Objective: To assess the safety of rapidly dissolving buprenorphine/naloxone sublingual tablets (BNX-RDT) in opioid-dependent patients.

Methods: This open-label, 24-week extension study enrolled patients who completed primary trials of BNX-RDT. Daily tablet doses ranged from 5.7 to 17.1 mg. The primary endpoint was safety; secondary assessments included opioid cravings, addiction severity, health-related quality of life (QOL), and workplace productivity at screening (final day of the primary trials) through study end, with changes measured from baseline of the primary trials.

Results: In all, 665 patients received treatment; 292 (43.9%) completed the study. A total of 258 patients (38.8%) reported 557 treatment-emergent adverse events, most commonly headache (3.2%) and constipation (3.0%). Craving scores showed continued improvement on 100-mm visual analog scale (mean change from

primary trial baseline, -52.8 at screening; mean change from extension trial baseline, -60.5 at week 24). Reductions in addiction severity from baseline of both the primary and extension trial were maintained through week 24 on multiple assessments, as were improvements in QOL on Short Form 36. Employment increased by 15% and mean (SD) hours worked per week increased by 4.6 (20.1) from baseline to study end. Mean (SD) scores for impact of opioid dependence on work productivity improved from 4.7 (3.0) at baseline to 0.9 (1.8) at study end (11-point scale).

Conclusions: Extended treatment with BNX-RDT demonstrated a safety profile similar to other BNX formulations, reduced opioid cravings, and improved both QOL and work productivity. Continued treatment may enable patients to advance in recovery and return to normal functioning.

Key Words: buprenorphine, functioning, naloxone, opioid-related disorders, quality of life, substance-related disorders

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From the Lake Howell Health Center, Maitland, FL (KH); Oklahoma Clinical Research, Oklahoma City, OK (MLP); and Orexo US, Inc., Morristown, NJ (MS).

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Send correspondence and reprint requests to Michael Sumner, MB, BS, MRCP (UK), Orexo US, Inc., 150 Headquarters Plaza East Tower, 5th Floor, Morristown, NJ 07960. E-mail: Michael.sumner@orexo.com

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Opioid addiction, considered by the US Department of Health and Human Services to be an epidemic, has resulted in an approximate 4-fold increase in deaths and a >5-fold increase in hospital admissions between 1999 and 2007 due to misuse of both prescription and illicit opioids (Volkow et al., 2014). In 2014, prescription opioids were implicated in a total of 18,893 overdose deaths compared with 10,574 deaths attributable to heroin (National Institute on Drug Abuse, 2015). In addition to mortality risk, personal and societal burdens associated with opioid addiction are substantial. The disease can have a potentially devastating impact on the quality of life (QOL) of patients, causing impairments in their physical and psychological health, financial independence, and personal or social relationships (Parran et al., 2010; Feelemyer et al., 2014). In sensitivity analyses of costs per person associated with opioid dependence (2003 dollars), healthcare costs were 8.3 times higher for those with opioid addiction compared with the nonaddicted population (Strassels, 2009). An assessment of the societal costs related to prescription opioid misuse (2007 dollars) reported that \$25.6 of \$55.7 billion total societal costs (46%) resulted from lost workplace productivity (Birnbaum et al., 2011).

With effective treatment, most patients with opioid dependence can be expected to respond and regain functional

capacity (Volkow et al., 2014). However, opioid medication-assisted treatment (MAT) remains underutilized. Methadone is considered effective, but in the United States, its availability is limited to specialist clinics, which presents a barrier to use for many patients (Ridge et al., 2009). Alternatively, sublingual buprenorphine and buprenorphine/naloxone (BNX) combinations, provided as tablet or film formulations, are effective options for office-based treatment (Apelt et al., 2013).

As improvements in QOL may improve patient adherence and deter misuse, clinical trials of patients with opioid dependence have included patient-rated assessments of QOL after treatment with methadone or buprenorphine (Mitchell et al., 2015), and have demonstrated substantial benefits of treatment using numerous QOL measures (Zubaran and Foresti, 2009; Mitchell et al., 2015). A long-term, retrospective chart review of patients who maintained treatment with a BNX regimen for at least 18 months demonstrated significant improvements in QOL for specific measures of employment ($P=0.03$), negative impulsive behaviors ($P=0.03$), personal relationships ($P=0.01$), family relationships ($P=0.004$), negative personality changes ($P=0.04$), and financial issues ($P=0.02$) (Parran et al., 2010).

A rapidly dissolving BNX sublingual combination tablet (BNX-RDT; Zubsolv, Orexo US, Inc., Morristown, NJ) is approved by the US Food and Drug Administration (FDA) for the induction and maintenance treatment of adults with opioid dependence as part of a complete treatment plan to include counseling and psychosocial support (Zubsolv prescribing information, 2015). BNX-RDT is a higher-bioavailability formulation (administration of a 30% lower dose of buprenorphine with equivalent systemic exposure was seen compared with a previously available BNX sublingual tablet) with inclusion of certain patient-preferred characteristics (Fischer et al., 2014, 2015).

Findings from 2 randomized studies conducted in 1068 patients with opioid dependence provide robust evidence supporting the safety and efficacy of BNX-RDT during induction and maintenance (Webster et al., 2014; Gunderson et al., 2015). The primary objective of the current extension study, which included patients who completed the primary efficacy trials, was to further evaluate the safety of longer-term treatment with BNX-RDT using assessments of treatment-emergent adverse events (TEAEs). Opioid cravings, addiction severity, QOL, and work-related health economic measures were included as secondary efficacy assessments.

METHODS

Study Design

This multicenter, open-label, uncontrolled extension study, conducted between July 2013 and September 2014 at 50 study centers in the United States, enrolled patients who had completed 1 of 2 studies of induction/stabilization treatment using BNX-RDT. One primary study (study 006) compared BNX-RDT with generic buprenorphine during treatment induction, followed by a comparison of BNX-RDT with a BNX sublingual film (Suboxone; buprenorphine and naloxone sublingual film CIII; Reckitt Benckiser

Healthcare [UK] Ltd.) for maintenance treatment (Gunderson et al., 2015). The other primary study (study 007) compared BNX-RDT with generic buprenorphine during treatment induction, followed by maintenance treatment with BNX-RDT (Webster et al., 2014). The current extension study comprised a total of 7 treatment visits, including the first study visit (which was also the final study visit for each of the primary studies) and 6 follow-up visits every 4 weeks thereafter; the total study period was approximately 24 weeks.

The study was conducted in accordance with Good Clinical Practice as required by US FDA regulations, International Council for Harmonisation guidelines, and standard operating procedures for clinical investigation. The study protocol and related study documentation was reviewed and approved by a central Institutional Review Board. All patients provided written informed consent before enrollment and receipt of study medication.

Study Population and Treatments

Completion of one of the primary studies (study 006 or 007) was required for inclusion in this study; the primary studies enrolled male and female patients aged 18 to 65 years who met criteria for opioid dependence, as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*.

All eligible patients had received buprenorphine-based opioid substitution therapy for at least 22 days in the primary studies. During the 24-week extension trial, patients received once-daily treatment with BNX-RDT, administered using various combinations of 1.4/0.36 and 5.7/1.4 mg. Patients who were receiving BNX-RDT at completion of the primary studies were continued at the same dose; those who were receiving BNX sublingual film at the completion of study 006 were initiated on a BNX-RDT dose based on a fixed conversion factor (5.7 mg BNX-RDT to 8.0 mg BNX sublingual film). The BNX-RDT dosage was titrated, if necessary, between 5.7/1.4 and 17.1/4.2 mg/d to achieve optimal relief of opioid cravings and withdrawal symptoms while minimizing adverse effects. Titration was initially performed in buprenorphine dosage increments of 2.8 mg, with increments of 1.4 mg used as needed. During treatment, Clinical Opiate Withdrawal Scale assessments were conducted to monitor long-term control of withdrawal symptoms. For patients who experienced withdrawal symptoms, the BNX-RDT dose could be modified as permitted by the patient's titrated dose level with up to 1 to 2 hours between doses to avoid worsening of symptoms.

Study Assessments

Safety assessments, the primary endpoint of this study, included the incidence of TEAEs, vital signs, and laboratory values. These evaluations were conducted at screening and at each study visit.

Assessments of BNX-RDT efficacy were evaluated as secondary endpoints. At the screening visit (study day 1 of the extension trial) and at each subsequent study visit, patients were evaluated for intensity of opioid cravings; each patient rated opioid cravings on a 100 mm visual analog scale (VAS; 0 mm = "no cravings" and 100 mm = "most intensive craving I have ever had") (Grusser et al., 2000). At day 1,

week 12, and week 24 study visits, patients were assessed for severity of addiction/opioid dependence using the patient-rated Addiction Severity Index-Lite (ASI-Lite) and the investigator-rated Clinical Global Impression-Severity (CGI-S). The ASI-Lite is a semistructured, multidimensional interview that evaluates medical, employment, drug use, alcohol use, legal, family/social, and psychiatric status, with empirically developed composite scores generated with regard to the past 30 days and lifetime status (Cacciola et al., 2007). The CGI-S is investigator-rated on a 7-point scale (1 = “normal, not at all ill”; 7 = “among the most seriously ill patients”) (Guy, 1976). Patients were also assessed on study day 1, week 12, and week 24 for improvement in severity of opioid dependence using the investigator-rated Clinical Global Impression-Improvement (CGI-I) and the patient-rated Patient Global Impression-Improvement (PGI-I; adapted from the CGI-I); both the CGI-I and PGI-I are rated on a 7-point scale (1 = “very much improved”; 7 = “very much worse”) (Guy, 1976).

At the day 1, week 12, and week 24 study visits, patients were assessed for health-related QOL using the Short Form 36 version 2 (SF-36) questionnaire, a patient-rated assessment tool which includes questions regarding current state of general health compared with 1 year ago, and also assessments under the subdomains of Bodily Pain, General Health, Mental Health, Physical Functioning, Role–Emotional, Role–Physical, Social Functioning, and Vitality (Ware and Sherbourne, 1992; Francois et al., 2015). Scores for current general health compared with 1 year ago are rated on a 5-point Likert scale, with lower scores being more favorable (1, best health; 5, worst health). Scores for the 8 subdomains are measured on a scale of 0 to 100, with higher scores being more favorable (0, worst possible health status; 100, best possible health status); thus, higher scores indicate improved QOL. T-scores for the Mental Component Summary (MCS) are generated based on the Vitality, Social Functioning, and Role–Emotional subdomains, and the Physical Component Summary (PCS) T-scores are calculated based on the Physical Functioning and Role–Physical subdomains; T-scores are rated similarly to subdomain scores. The SF-36 and the ASI-Lite were not administered to patients in withdrawal.

Health economic outcomes (HEOs) were assessed on study day 1 and at each subsequent study visit using the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), which includes questions regarding current employment status (question 1: yes/no), hours worked or missed (questions 2–4), and the impact of opioid dependence on work productivity and daily activities (questions 5 and 6) in the past 7 days (Reilly et al., 1993). The WPAI:SHP was not administered to patients who were in withdrawal.

Urine Drug Screening

Urine drug screens for buprenorphine and for illicit nonbuprenorphine-opioid and nonopioid drug use were performed on day 1 and weeks 4, 8, 12, 16, 20, and 24.

Statistical Analysis

All assessments were evaluated in the safety population, which included all patients who took at least 1 dose of study

treatment. Endpoints were summarized using descriptive statistics, including 95% confidence intervals (CIs), when appropriate. Total VAS craving scores were summarized as change from primary study baseline to extension study day 1 and weeks 4, 8, 12, 16, 20, and 24 (end of study; for study completers only), and at study endpoint (defined as the last recorded postbaseline value for the endpoint in question). Changes from primary study baseline to extension study day 1 and weeks 12 and 24 were summarized for the CGI-S, CGI-I, PGI-I, ASI-Lite, SF-36 subdomains, and SF-36 MCS and PCS scores. Change from primary study baseline for the WPAI:SHP scores was summarized at extension study day 1 and weeks 4, 8, 12, 16, 20, 24, and study endpoint. Formal assessments of statistical significance were not conducted for study endpoints. All data were analyzed on an observed basis with no statistical methods employed to handle missing values.

RESULTS

Study Population

A total of 668 patients entered the study after completion of one of the primary studies. Three patients did not receive any study medication during the extension study and were excluded from statistical analyses; therefore, analyses are based on a total of 665 patients. Of these 665 patients, 475 (71.4%) were initially enrolled in study 006 and 190 (28.6%) were initially enrolled in study 007.

A total of 292 patients (43.9%) completed the extension study. Of the 373 (56.1%) patients who withdrew from the study, the most common reasons for withdrawal were patients being lost to follow-up ($n = 168$, 25.1%), patient nonadherence ($n = 110$, 16.5%), and patient request for discontinuation ($n = 42$, 6.3%). Demographic and baseline characteristics are summarized in Table 1.

BNX-RDT Dosing

The most frequently used BNX-RDT dose was 11.4/2.8 mg at screening ($n = 169$, 25.7%) through the week 12 visit ($n = 105$, 24.7%). However, at weeks 16 and 20, the lowest BNX-RDT dose (5.7/1.4 mg) was the most commonly used (week 16: $n = 96$, 25.1%; week 20: $n = 94$, 28.4%).

Primary Endpoint: Safety

In all, 258 patients (38.8%) experienced 557 TEAEs, of which headache (21 patients; 3.2%) and constipation (20 patients; 3.0%) were the most frequently reported. A total of 71 patients (10.7%) had 100 TEAEs considered related to treatment with BNX-RDT; constipation was the most common (19 patients, 2.9%). Most treatment-related TEAEs were mild or moderate, with the exception of 3 that were considered severe in 4 patients: constipation ($n = 2$), depression ($n = 1$), and drug withdrawal syndrome ($n = 1$). Of 14 patients (2.1%) who discontinued due to TEAEs, 6 patients had TEAEs possibly related to treatment with BNX-RDT (abnormal laboratory values, $n = 3$; vomiting, $n = 1$; depression, $n = 1$; constipation, $n = 1$). Nine patients (1.4%) experienced treatment-emergent serious adverse events (SAEs); severe depression in 1 patient was considered to be related to treatment.

TABLE 1. Patient Demographics and Baseline Characteristics, Safety Population

Parameter	Primary Study		Overall (N = 665)
	Study 006 (n = 475)	Study 007 (n = 190)	
Age, mean (SD), y	35.9 (11.4)	39.0 (10.8)	36.8 (11.3)
Sex, n (%)			
Male	279 (58.7)	127 (66.8)	406 (61.1)
Female	196 (41.3)	63 (33.2)	259 (38.9)
Race, n (%)			
White	402 (84.6)	167 (87.9)	569 (85.6)
Black or African American	62 (13.1)	21 (11.1)	83 (12.5)
Asian	1 (0.2)	0 (0)	1 (0.2)
American Indian or Alaskan Native	2 (0.4)	0 (0)	2 (0.3)
Mixed race	3 (0.6)	2 (1.0)	5 (0.8)
Not recorded	5 (1.1)	0 (0)	5 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	65 (13.7)	17 (8.9)	82 (12.3)
Not Hispanic or Latino	410 (86.3)	173 (91.1)	583 (87.7)
Height, mean (SD), cm	172.0 (9.43)	173.4 (10.01)	172.4 (9.61)
Weight, mean (SD), kg	78.34 (18.99)	78.98 (20.73)	78.53 (19.49)
BMI, mean (SD), kg/m ²	26.47 (6.11)	26.26 (6.63)	26.41 (6.26)
Duration of opioid use, median, y	7.20	9.60	7.95
Original randomized treatment, n (%)			
BNX-RDT	241 (50.6)*	89 (46.4)†	330 (49.4)‡
Generic buprenorphine/BNX sublingual film	235 (49.4)*	103 (53.6)†	338 (50.6)‡

*n = 476.

†n = 192.

‡n = 668.

BMI, body mass index; SD, standard deviation.

Two patients experienced SAEs (not treatment emergent or treatment related) that resulted in death (toxic effects of heroin, n = 1; cardiovascular disease, n = 1).

In all, 29 patients had laboratory abnormalities that were considered TEAEs; 3 patients discontinued the study due to increased levels of aspartate and alanine aminotransferase (n = 2), and gamma glutamyl transferase (n = 1), which were primarily related to hepatitis C and liver function, but also considered possibly related to treatment. Seven patients experienced vital sign abnormalities that were considered TEAEs; 1 patient had an increase in blood pressure of moderate intensity that was determined to be possibly related to treatment.

Opioid Cravings

Patient-rated VAS scores for intensity of opioid cravings demonstrated a substantial reduction from primary study baseline to extension study day 1 (mean change [95% CI] of -52.8 [-55.0 , -50.6] from mean primary study baseline score of 70.8) (Fig. 1). Continued improvement was seen throughout the extension study, with mean change from primary study baseline (95% CI) of -60.5 (-63.8 , -57.2) at week 24.

Severity of Opioid Addiction

From primary study baseline to extension study week 24, patients demonstrated reductions (improvement) in all 7 subscale composite scores of the ASI-Lite (Table 2).

Patients showed substantial improvement in mean CGI-S scores (SD) from primary study baseline (4.3 [1.16]; moderately ill) to extension study day 1 (2.3 [1.16]; borderline ill; mean change from baseline [95% CI] -2.0 [-2.1 , -1.9]).

Improvement was maintained at week 12 (2.3 [1.17]; mean change from baseline [95% CI] -2.0 [-2.2 , -1.9]) and week 24 (2.4 [1.23]; mean change from baseline [95% CI] -2.0 [-2.1 , -1.8]).

Results for the CGI-I demonstrated substantial improvements from primary study baseline at all points of the extension study. Mean CGI-I scores (SD) were 1.9 (0.78) at day 1, 1.7 (0.75) at week 12, and 2.0 (0.99) at week 24; the mean scores indicate that most patients were considered by clinicians to be, at minimum, “much improved” (score of 2). Results for the

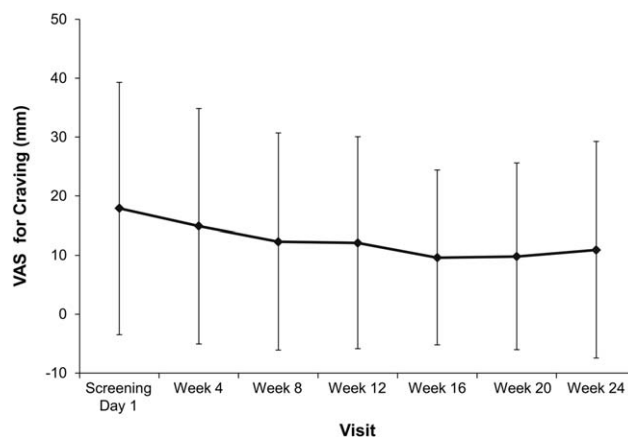


FIGURE 1. Mean (SD) VAS craving scores versus primary study baseline mean score of 70.8, safety population. Patients treated with BNX-RDT rated scores for cravings on a 100-mm VAS for which 0 mm = “no cravings” and 100 mm = “the most intensive craving I have ever had.”

TABLE 2. Change in Addiction Severity Index-Lite Composite Scores From Primary Study Baseline to Extension Study Week 24, Safety Population

Composite Measure	N	Baseline Score, Mean (SD)	Week 24 Score, Mean (SD)	Change From Baseline to Week 24, Mean (95% CI)
Alcohol use	392	0.05 (0.10)	0.03 (0.06)	-0.026 (-0.04, -0.02)
Drug use	392	0.32 (0.10)	0.06 (0.09)	-0.26 (-0.27, -0.24)
Employment status	393	0.55 (0.32)	0.52 (0.32)	-0.03 (-0.05, -0.01)
Family/social status	389	0.15 (0.21)	0.08 (0.13)	-0.08 (-0.10, -0.06)
Legal status	391	0.08 (0.15)	0.02 (0.08)	-0.05 (-0.07, -0.04)
Medical status	393	0.19 (0.31)	0.14 (0.27)	-0.05 (-0.08, -0.02)
Psychiatric status	392	0.14 (0.19)	0.09 (0.16)	-0.05 (-0.07, -0.03)

PGI-I were similar, with mean (SD) scores of 1.7 (0.75), 1.6 (0.69), and 1.7 (0.95) for day 1, week 12, and week 24, respectively. These scores indicate that most patients considered themselves to be “very much improved” or “much improved.”

QOL and HEO Measures

Clinically meaningful improvements in all subdomains of the SF-36 were observed from primary study baseline and were generally maintained during the study (Fig. 2). For the MCS, the mean primary study baseline T-score of 36.20 increased to 46.27 at extension study week 24, representing a mean increase (95% CI) of 10.06 (8.60, 11.52). For the PCS, the mean primary study baseline T-score of 46.09 increased to 50.27 at week 24, representing a mean increase (95% CI) of 4.17 (3.26, 5.08).

For question 1 of the WPAI:SHP regarding employment status, 35 patients (6.0%) who answered “yes” at primary study baseline were not employed at extension study endpoint (last recorded postbaseline value), and 124 patients (21.3%) who answered “no” at primary study baseline were employed at extension study endpoint. Thus, the resulting net gain in employment was 15.3%. Improvements were also observed for responses to WPAI:SHP questions 2 through 6 at extension study endpoint. Specifically, the mean (SD) number of missed work hours due to opioid dependence declined by 4.8 (15.4)

hours, and mean (SD) hours worked per week increased by 4.6 (20.1) hours from primary study baseline to extension study endpoint. Mean (SD) scores for impact of opioid dependence on work productivity improved from 4.7 (3.0) at primary study baseline to 0.9 (1.8) at extension study endpoint (mean [SD] change of -3.8 [3.1] on 11-point scale); improvements in scores for regular daily activities were similar (mean [SD] change from primary study baseline of -4.3 [3.6] on 11-point scale). Changes from primary study baseline to extension study week 24 (study completers only) for questions 2 through 6 of the WPAI:SHP were similar to those observed at extension study endpoint, and are summarized in Table 3.

Urine Drug Screening

Urinalysis results were positive for buprenorphine in more than 90% of participants through the week 20 assessment, and were positive in 88.8% at week 24. Positive screens for nonbuprenorphine opiates were observed in 24.4% of participants on day 1, 29.6% at week 4, 24.7% at week 8, 22.0% at week 12, 24.6% at week 16, 21.0% at week 20, and 24.1% at week 24.

DISCUSSION

Previous primary efficacy studies conducted in large populations of patients with opioid dependence have demonstrated the efficacy, safety, and tolerability of BNX-RDT in

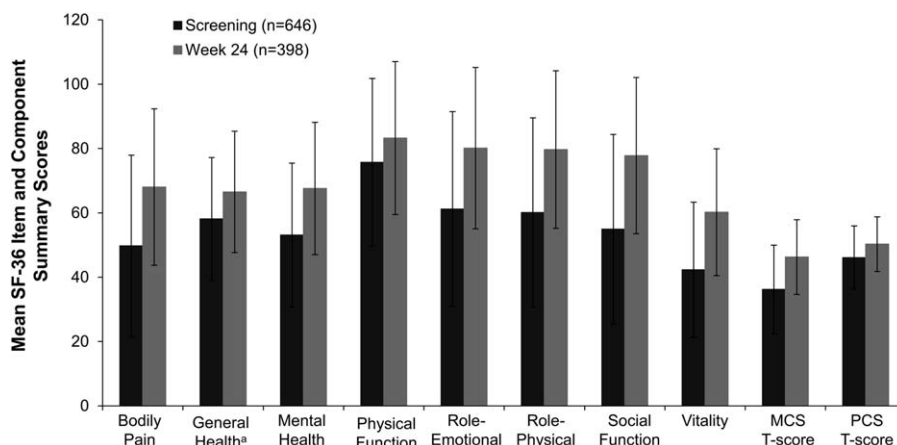


FIGURE 2. Mean (SD) SF-36 item and component summary scores at screening and week 24, safety population. Normalized scores for the 8 subdomains and MCS and PCS T-scores are measured on a scale of 0 to 100, with higher scores being more favorable. Mean general population (2005–2006) SF-36 item scores ranged from 49.47 (Role-Physical) to 54.27 (Mental Health); component summary scores were 49.22 for the PCS and 53.78 for the MCS (Maglinter et al., 2012). ^aOne patient did not have data available for the assessment of General Health at day 1 or week 24.

TABLE 3. Change in Responses to Questions 2 to 6 on the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) From Primary Study Baseline To Extension Study Week 24, Safety Population

WPAI:SHP Item	N	Baseline Score, Mean (SD)	Week 24 Score, Mean (SD)	Change From Baseline to Week 24 Mean (95% CI)
Q2. During the past 7 days, how many hours did you miss from work because of problems associated with your opioid dependence?	79	7.30 (10.16)	2.54 (10.51)	-4.75 (-8.06, -1.45)
Q3. During the past 7 days, how many hours did you miss from work because of any other reason, such as vacation, holidays, or time off to participate in this study?	79	2.17 (5.63)	2.00 (5.02)	-0.17 (-1.85, 1.52)
Q4. During the past 7 days, how many hours did you actually work?	78	28.55 (14.89)	36.24 (18.35)	7.69 (3.43, 11.95)
Q5. During the past 7 days, how much did your opioid dependence affect your productivity while you were working?	70	4.70 (3.05)	0.80 (1.54)	-3.90 (-4.68, -3.12)
Q6. During the past 7 days, how much did your opioid dependence affect your ability to do regular daily activities, other than work at a job?	283	5.84 (3.01)	1.49 (2.25)	-4.35 (-4.76, -3.93)

Question 1 ascertained employment status with a response of yes or no (see “Results” section).

Questions 2 to 4 captured the total actual hours worked or missed in the previous 7 days.

Questions 5 and 6 were assessed using an 11-point scale (0 = no effect; 10 = completely prevented patient from working or conducting daily activities).

retaining patients in treatment and controlling symptoms of opioid withdrawal and cravings (Webster et al., 2014; Gunderson et al., 2015). Findings of this open-label extension study add to those findings, demonstrating that the favorable safety profile of BNX-RDT in opioid-dependent patients established during these primary induction/stabilization studies were sustained through up to 24 weeks of subsequent BNX-RDT maintenance therapy, with no new safety signals identified. Whereas safety assessments were the primary endpoint of this study, secondary assessments of efficacy demonstrated that these findings were maintained and/or improved as well. A majority of patients who required a BNX-RDT dose of 11.4/2.8 mg at the beginning of the current extension trial required a much lower dose (5.7/1.4 mg) by study end.

The large percentage of patients that withdrew from the study (56.1%) is comparable with rates of withdrawal observed in other studies and typical of clinical trials conducted in patients with opioid dependence (Hser et al., 2014; Schuman-Olivier et al., 2014). Participant withdrawal rates may have also resulted from the lack of adjunct therapies typically used in clinical practice. Notably, these findings were observed with pharmacotherapy alone in the absence of adjunctive counseling programs; true MAT (ie, pharmacotherapy with BNX-RDT in combination with psychotherapy) may lead to even greater gains for physicians and their patients.

With respect to reductions in opioid cravings, mean VAS cravings scores were reduced by 75% at day 1 and by 85% at week 24 of open-label extension treatment with BNX-RDT compared with primary study baseline. Similar improvements were observed in addiction severity, with reductions demonstrated from primary study baseline to extension study week 24 for all 7 composite scores of the ASI-Lite. These improvements were further supported by a substantial 2-point

reduction in the CGI-S, and also mean ratings of “much improved” and/or “very much improved” on the clinician-rated CGI-I and patient-rated PGI-I scales.

Improvements in patient-rated QOL were maintained during open-label extension treatment with BNX-RDT. Mean improvements from primary study baseline in the MCS and PCS T-scores of the SF-36 QOL assessment were maintained at extension study week 24. The mean change from baseline in MCS and PCS T-scores in the current study (mean increases of 10.06 and 4.17, respectively) were greater than the improvements observed in a post hoc analysis of patients with alcohol dependence after 24 weeks of treatment with the opioid system modulator nalmefene (statistically significant mean increase of 5.74 and 2.35 vs placebo, respectively) (Francois et al., 2015). Improvements in all subdomains of the SF-36 were observed from primary study baseline and were generally maintained during the extension study.

Also of note are the improvements observed in responses to the WPAI:SHP questionnaire during maintenance therapy with BNX-RDT. At extension study endpoint, patients had a net gain in employment, a substantial increase in the number of hours worked, and a marked decline in the number of work hours missed due to opioid dependence. Taken together with the sustained improvements in QOL, these findings provide evidence that maintenance treatment with BNX-RDT can improve QOL, functioning, and productivity at work, allowing patients who misuse opioids to recover and return to normal daily activities.

Limitations of the current study include its open-label design, which precludes the ability to compare BNX-RDT with other forms of maintenance treatment, and also the high rate of discontinuations, which are typical in trials of patients with opioid dependence. The latter raises questions regarding the impact of patients discontinuing treatment on the overall population efficacy results. For example, it could be

hypothesized that several of the patients who dropped out of treatment are indeed treatment refractory, and therefore would not achieve the same level of improvement. Additional studies are needed with adequate retention rates or follow-up of discontinued patients to establish the true long-term effectiveness of treatment with BNX-RDT. In addition, at study end (week 24), although 88.8% of patients had a positive urine drug screen for buprenorphine (ie, BNX-RDT), 24.1% also tested positive for nonbuprenorphine opioids. This outcome may have resulted from the lack of adjunctive treatment options offered to potentially increase patient adherence (eg, counseling, participation in 12-step programs, warnings against continued positive urinalysis results, etc). However, correlations between abstinence and improvement were not analyzed. An additional limitation is that approximately 85% of the study population was white, and subgroup analyses were not performed, so it is unknown whether results are generalizable to other racial subgroups.

CONCLUSIONS

Administration of BNX-RDT over 6 months after stabilization on buprenorphine-based therapy was well-tolerated with no new safety signals identified. Whereas efficacy was not the primary objective of the current study, improvements were observed in opioid cravings, addiction severity, QOL, and HEOs in patients with opioid dependence. In the real-world clinical setting, treatment with BNX-RDT may help individuals who misuse opioids advance in their recovery, as those who continue an effective treatment regimen can expect improvements in social, emotional, and physical functioning, and also increased presence and productivity in the workplace.

REFERENCES

- Apelt SM, Scherbaum N, Golz J, et al. Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. *Pharmacopsychiatry* 2013;46:94–107.
- Birnbaum HG, White AG, Schiller M, et al. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. *Pain Med* 2011;12:657–667.
- Cacciola JS, Alterman AI, McLellan AT, et al. Initial evidence for the reliability and validity of a “Lite” version of the Addiction Severity Index. *Drug Alcohol Depend* 2007;87:297–302.
- Feelemyer JP, Des Jarlais DC, Arasteh K, et al. Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: an international systematic review. *Drug Alcohol Depend* 2014;134:251–258.
- Fischer A, Johansson K, Gruden S. Zubsolv[®]: a novel sublingual tablet with improved bioavailability of buprenorphine for treatment of opioid dependence [poster]. Presented at: Annual Conference of the Association for Medical Education and Research in Substance Abuse; November 6-7, 2014; San Francisco, CA.
- Fischer A, Jonsson M, Hjelmstrom P. Pharmaceutical and pharmacokinetic characterization of a novel sublingual buprenorphine/naloxone tablet formulation in healthy volunteers. *Drug Dev Ind Pharm* 2015;41:79–84.
- Francois C, Rahlhali N, Chalem Y, et al. The effects of as-needed nalmefene on patient-reported outcomes and quality of life in relation to a reduction in alcohol consumption in alcohol-dependent patients. *PLoS One* 2015; 10:e0129289.
- Grusser SM, Heinz A, Flor H. Standardized stimuli to assess drug craving and drug memory in addicts. *J Neural Transm (Vienna)* 2000;107: 715–720.
- Gunderson EW, Hjelmstrom P, Sumner M. 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. *Clin Ther* 2015;37:2244–2255.
- Guy W. Clinical Global Impressions In: ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare; 1976, 217–222.
- Hser YI, Saxon AJ, Huang D, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. *Addiction* 2014;109:79–87.
- Maglinte GA, Hays RD, Kaplan RM. US general population norms for telephone administration of the SF-36v2. *J Clin Epidemiol* 2012;65:497–502.
- Mitchell SG, Gryczynski J, Schwartz RP, et al. Changes in quality of life following buprenorphine treatment: relationship with treatment retention and illicit opioid use. *J Psychoactive Drugs* 2015;47:149–157.
- National Institute on Drug Abuse. Overdose Death Rates. Bethesda, MD; 2015. Available at: <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>. Accessed March 18, 2016.
- Feelemyer JP, Des Jarlais DC, Arasteh K, et al. Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: an international systematic review. *Drug Alcohol Depend* 2014;134:251–258.
- Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–365.
- Ridge G, Gossop M, Lintzeris N, et al. Factors associated with the prescribing of buprenorphine or methadone for treatment of opiate dependence. *J Subst Abuse Treat* 2009;37:95–100.
- Schuman-Olivier Z, Weiss RD, Hoepfner BB, et al. Emerging adult age status predicts poor buprenorphine treatment retention. *J Subst Abuse Treat* 2014;47:202–212.
- Strassels SA. Economic burden of prescription opioid misuse and abuse. *J Manag Care Pharm* 2009;15:556–562.
- Volkow ND, Frieden TR, Hyde PS, et al. Medication-assisted therapies: tackling the opioid-overdose epidemic. *N Engl J Med* 2014;370: 2063–2066.
- Ware Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–483.
- Webster L, Helmstrom P, Sumner M. Assessing buprenorphine/naloxone efficacy during induction therapy in opioid-dependent patients: what is the ideal measure? [poster]. Presented at: Annual Meeting and Symposium of the American Academy of Addiction Psychiatry; December 4-7, 2014; Aventura, FL.
- Zubaran C, Foresti K. Quality of life and substance use: concepts and recent tendencies. *Curr Opin Psychiatry* 2009;22:281–286.
- Zubsolv [package insert]. Orexo US, Inc.: Morristown, NJ; 2015.