

Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone

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ABSTRACT

Aims To evaluate the safety and efficacy of buprenorphine implants (BI) versus placebo implants (PI) for the treatment of opioid dependence. A secondary aim compared BI to open-label sublingual buprenorphine/naloxone tablets (BNX). **Design** Randomized, double-blind, placebo-controlled trial. Subjects received either four buprenorphine implants (80 mg/implant) ($n = 114$), four placebo implants ($n = 54$) or open-label BNX (12–16 mg/day) ($n = 119$). **Setting** Twenty addiction treatment centers. **Participants** Adult out-patients (ages 18–65) with DSM-IV-TR opioid dependence. **Measurements** The primary efficacy end-point was the percentage of urine samples negative for opioids collected from weeks 1 to 24, examined as a cumulative distribution function (CDF). **Findings** The BI CDF was significantly different from placebo ($P < 0.0001$). Mean [95% confidence interval (CI)] proportions of urines negative for opioids were: BI = 31.2% (25.3, 37.1) and PI = 13.4% (8.3, 18.6). BI subjects had a higher study completion rate relative to placebo (64 versus 26%, $P < 0.0001$), lower clinician-rated ($P < 0.0001$) and patient-rated ($P < 0.0001$) withdrawal, lower patient-ratings of craving ($P < 0.0001$) and better subjects' ($P = 0.031$) and clinicians' ($P = 0.022$) global ratings of improvement. BI also resulted in significantly lower cocaine use ($P = 0.0016$). Minor implant-site reactions were comparable in the buprenorphine [27.2% (31 of 114)] and placebo groups [25.9% (14 of 54)]. BI were non-inferior to BNX on percentage of urines negative for opioids [mean (95% CI) = 33.5 (27.3, 39.6); 95% CI for the difference of proportions = (-10.7, 6.2)]. **Conclusions** Compared with placebo, buprenorphine implants result in significantly less frequent opioid use and are non-inferior to sublingual buprenorphine/naloxone tablets.

Keywords Buprenorphine, drug addiction, drug implants, maintenance therapy, opioid dependence, treatment adherence.

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INTRODUCTION

Based on substantial efficacy data, international guidelines specify sublingual buprenorphine and methadone as first-line treatments of opioid dependence [1]. Buprenorphine can be prescribed in office-based physi-

cian practice [1]. However, rates of misuse, abuse and diversion of various forms of sublingual buprenorphine are increasing in the United States [2–5].

An implantable formulation of buprenorphine was developed to address problems with adherence, diversion and non-medical use. The implant is a polymeric ethylene

vinyl acetate and buprenorphine matrix that, following an initial pulse release, delivers a constant, low medication level over 6 months.

A 6-month placebo-controlled, multi-center study established the efficacy of the buprenorphine implant in the treatment of opioid-dependent subjects, although the comparative efficacy of the implant to the standard sublingual buprenorphine was questioned [6,7]. The primary objective of the current randomized double-blind clinical trial was to confirm the efficacy of buprenorphine implants (BI) relative to placebo implants (PI) over 24 weeks of treatment for opioid dependence. A secondary objective was to establish the non-inferiority of BI relative to BNX over weeks 1–24.

METHODS

Participants

Twenty addiction treatment centers in the United States recruited subjects between April 2010 and September 2011. Institutional Review Boards approved the study at each site, and written informed consent was obtained from all participants.

Men and non-pregnant women (aged 18–65 years) met the DSM-IV diagnosis of current opioid dependence as determined by the Mini International Neuropsychiatric Interview (MINI) [8]. Individuals were excluded if they had AIDS, a clinically low platelet count, substance dependence on other than opioids or nicotine, received methadone or buprenorphine for opioid dependence within 90 days, current diagnosis of chronic pain requiring opioid analgesics or currently using non-prescribed benzodiazepines. Subjects were also excluded with aspartate aminotransferase levels $\geq 3\times$ upper limit of normal, alanine aminotransferase levels $\geq 3\times$ upper limit of normal, total bilirubin $\geq 1.5\times$ upper limit of normal and/or creatinine $\geq 1.5\times$ upper limit of normal.

Study intervention and randomization

An open-label induction phase evaluated whether buprenorphine could be administered safely to eligible subjects. Subjects who achieved a target dose of 12–16 mg/day BNX for at least 3 consecutive days were eligible to be randomized. Those who, at the end of the induction phase, reported significant opioid withdrawal symptoms, defined as >12 on the Clinical Opiate Withdrawal Scale (COWS) [9], or significant opioid cravings, defined as >20 mm on a 100 mm opioid craving Visual Analog Scale (VAS), were excluded. Final determination for study enrollment was made by site investigators.

Subjects were randomized (stratified by gender) in a 2:1:2 ratio to four BI (80 mg each), four PI or open-label

BNX (12–16 mg/day once daily), using a computer-generated randomization scheme. An independent group of statisticians and programmers were responsible for the randomization scheme, the results of which were entered into an interactive voice response system (IVRS) program. Once enrollment began, clinical site staff would either (i) dial into the system by telephone or (ii) visit a web page to enter basic information about the subject, and receive the treatment assignment (open-label BNX or the code number corresponding to a blinded implant kit).

Implants were inserted into the subdermal space (2–3 mm below the skin) in the inner, upper side of the non-dominant arm by a physician. Implanting physicians were from various medical specialties with prior surgical training who received standardized training in implant insertion and removal from the study sponsor. All implants were removed at 6 months or upon early discontinuation. Subjects and study staff, with the exception of the implanting clinicians, were blinded to the buprenorphine or placebo implants.

During the 24-week study, all subjects could receive supplemental sublingual buprenorphine/naloxone for opiate withdrawal and cravings in 2 mg/day increments, as indicated clinically. Supplemental buprenorphine/naloxone tablets [(i.e. rescue medication (RM))] were generally administered under observation and dosing was directed by protocol-specific parameters, excepting a maximum of 3 days of take-home dosing provided over weekends/holidays.

Subjects in BI and PI could receive one additional implant. BNX subjects could receive a dose increase of 2–4 mg/day (arriving at a fixed dose not to exceed 16 mg/day) if they required ≥ 3 days/week of any RM for 2 consecutive weeks or ≥ 8 days of RM over 4 consecutive weeks. Subjects were considered a treatment failure (and withdrawn from the study) if they met criteria for a second dose increase.

Manual-guided individual drug counseling sessions [10] were provided by experienced counselors twice weekly during weeks 1–12, and then weekly for the subsequent 12 weeks.

Temperature-verified urine samples were collected three times per week. Another sample was provided if a sample was outside a valid temperature range. A second sample outside the temperature range constituted a 'missing' sample. A central laboratory conducted testing of urine samples for opioids and cocaine, and study staff and subjects remained blind to results. Subjects who failed to provide nine consecutive urines were designated as non-compliant and withdrawn from the study. The double-blind for urine results was maintained throughout the study, and subjects' participation in the study was independent of urine testing results.

Efficacy assessments

The primary efficacy end-point was the percentage of urines that were negative for opioids from weeks 1 to 24, expressed as a cumulative distribution function (CDF). As requested by the Food and Drug Administration (FDA) prior to breaking the blind, an additional primary efficacy end-point combined participants' self-reported opioid use with their urine sample analyses. Secondary efficacy end-points were the percentage of urines that were negative for opioids during weeks 1–16 and 17–24.

Additional secondary measures included the proportion of study completers, patient-report and clinician-report withdrawal scales, a craving scale and patient and clinician improvement ratings. The Subjective Opiate Withdrawal Scale (SOWS) measured patient-reported withdrawal symptoms [11]. Clinician reports of withdrawal symptoms were assessed with the COWS. Opioid craving was measured using a 100 mm VAS (0 = no cravings, 100 = maximum craving experienced). SOWS, COWS and VAS were obtained at weeks 1, 4, 8, 12, 16, 20 and 24. Self-report illicit drug use was obtained at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 24. Clinician-rated Clinical Global Impressions–severity (CGI-S) (of opioid dependence) and improvement scales (CGI-I) [12] were obtained at weeks 16 and 24 (and at baseline for the CGI-S). Hypothesis testing for primary and secondary efficacy end-points was conducted using a fixed-sequence testing procedure.

Safety and pharmacokinetic assessments

Vital signs, laboratory tests (hematology, liver function tests, coagulation, pregnancy test) and electrocardiographs (ECGs) were obtained at regular study visits. Clinical staff inspected the surgical implant location at each visit for evidence of any adverse event (AE) or unplanned removal. Levels of plasma buprenorphine were obtained from blood samples taken at baseline and monthly thereafter.

Statistical analyses

The denominator for the primary efficacy end-point was all possible urine samples that could have been collected from implantation to week 24 (72 urine samples per subject). Missed samples were counted as opioid-positive. When a subject discontinued, or was withdrawn from the study, urine samples from that point onwards were considered positive.

Using all randomized subjects who received any treatment, the primary statistical analyses used the non-parametric Wilcoxon rank-sum test, adjusted for gender and site using the van Elteren method [13], to compare BI and PI on: (i) CDFs of the percentages of urine samples

negative for opioids over 24 weeks and (ii) CDFs of the percentages of urine sample negative for opioids with imputation based on self-report of opioid use. Secondary analyses compared BI and PI on the percentage of negative urines from weeks 1 to 16 (48 urines), and separately during weeks 17–24 (24 urines).

Hypothesis testing for the primary and secondary hypotheses was conducted using a fixed-sequence testing procedure to reduce Type I error risk. The two primary hypotheses were tested using a 5% alpha level. Testing proceeded to the secondary analyses (comparison of CDFs for weeks 1–16 and 17–24 for the two implant groups) only if the null hypothesis was rejected for both primary analyses). Then, the two implant groups were compared sequentially on secondary end-points (as ordered above).

Analyses of variance examined implant group differences in mean percentage of urine samples negative for opioids separately over weeks 1–24, 1–16 and 17–24, with gender and site as covariates. Analyses of the COWS, SOWS and opioid craving VAS were conducted with a mixed-effects repeated-measures analysis of covariance using all available assessments. Terms were included for treatment, week, treatment \times week, gender and site baseline as a covariate and subject as a random effect. An autoregressive (AR1) correlation structure was specified. End-point patient and clinician-rated CGI-I scales were analyzed as categorical variables using a Cochran–Mantel–Haenszel (CMH) test stratified by gender and site.

Because of recent reports of the potential efficacy of buprenorphine on cocaine use patterns in subjects with both opioid and cocaine dependence [14], we compared BI and PI on CDFs of the percentages of urine samples negative for cocaine over 24 weeks.

Sample size for the BI versus PI comparison was calculated using 80% power to detect a shift of 20% (deemed clinically relevant) between groups on the distributions of the percentage of urines negative for opioids over 24 weeks ($\alpha = 0.05$; two-sided). Approximately 150 subjects were required, assuming the 2:1 randomization scheme, a common standard deviation of 30% and an attrition rate of approximately 40%.

Open-label comparison with BNX

For the non-blinded open-label comparison study (i.e. BI versus BNX), the non-inferiority comparison of BI to BNX was conducted by calculating the 95% confidence interval (CI) for the mean difference between the proportions of urine samples negative for opioids in the two groups. Non-inferiority would be demonstrated if the lower bound of the CI was greater than -15% . This margin was based on input from clinical experts and previous studies showing a difference between sublingual

buprenorphine and placebo in the range of 30–40% [15,16]. Thus, the 15% margin is smaller than the smallest effect that BNX can be reliably expected to have, and also ensures that the efficacy of BI would be within a clinically relevant range of BNX. Sample size determination for the non-inferiority test of difference in percentages of urine samples negative for opioids over 24 weeks for BI compared to BNX was based on a fixed 15% margin of inferiority, a one-sided significance of 0.025, 80% power, a 1:1 randomization ratio, an assumption of 50% of urines negative for opioids for BNX and a common standard deviation of 30%, yielding approximately 66 subjects per treatment group.

RESULTS

Subject characteristics and disposition

There were 480 subjects screened for the study (Fig. 1). Prior to induction, 108 of those screened did not meet inclusion/exclusion criteria. Of the remaining 372 who entered the induction phase, 71 did not complete the induction phase within 16 days of screening or did not receive a fixed dose of 12–16 mg/day sublingual buprenorphine/naloxone for at least 3 consecutive days during induction, 14 were randomized and withdrew before receiving treatment and 287 were randomized and

received treatment. Following randomization, six (5.3%) subjects in BI, nine (16.7%) in PI and no subjects in the BNX met the definition of treatment failure.

The treatment groups did not differ on available baseline characteristics (Table 1).

Efficacy

The primary end-point, comparing the two implant groups on the CDF of the percentage of opioid-negative urines from weeks 1 to 24, revealed a significant difference between BI and PI ($P < 0.0001$) (Fig. 2). The second primary end-point analysis (i.e. urines with imputation based on self-report) comparing the two implant groups was also statistically significant ($P < 0.0001$). Unadjusted mean (95% CI) proportions of urines negative for opioids, without and with imputation based on self-report, were 31.2% (25.3, 37.1) and 31.0% (25.1, 36.8) for BI, 13.4% (8.3, 18.6) and 12.8% (7.1, 17.9) for PI and 33.5% (27.3, 39.6) and 33.1% (27.0, 39.2) for the BNX, respectively. At all points on the CDE, BI was superior to PI, and the effect sizes were moderate to strong. Using some example clinical cut-points, patients assigned to BI were more likely to have at least 50% of urines negative for opioids [BI: 27 versus PI: 6%; number needed to treat (NNT) = 5], and were significantly more likely to have 30% or greater urines negative for opioids

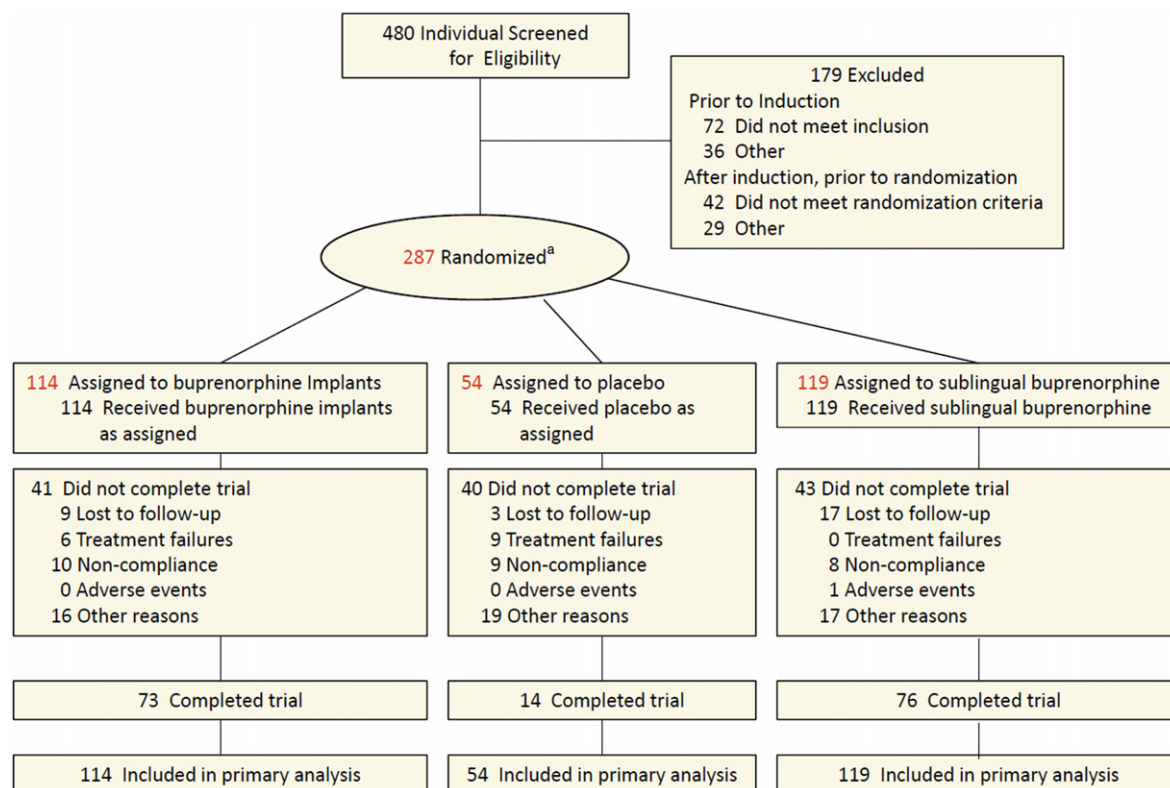
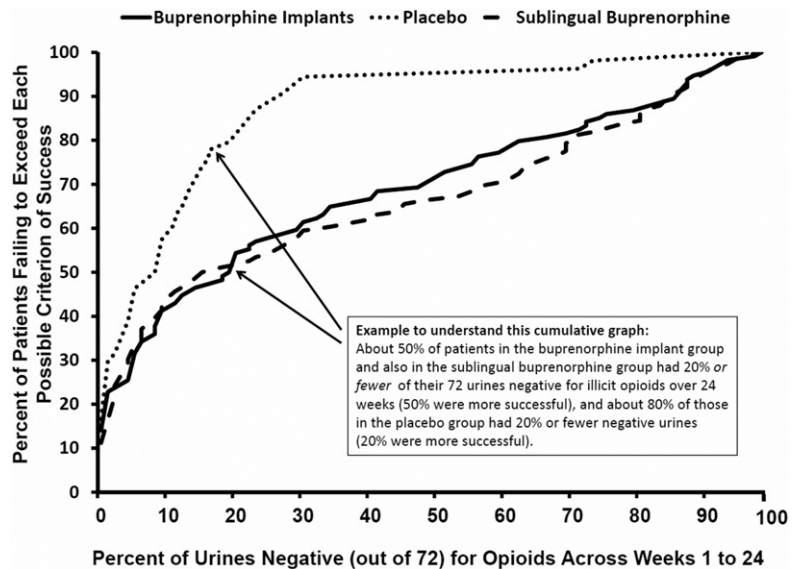


Figure 1 Flow diagram of participants through the trial. ^aWhile 301 were randomized, 287 were actually treated. There were 14 subjects who never returned to receive treatment following randomization.

Table 1 Baseline characteristics of subjects.

Characteristic	Buprenorphine implant group <i>n</i> = 114	Placebo implant group <i>n</i> = 54	Sublingual buprenorphine <i>n</i> = 119
Age, mean (SD), years	36.4 (11.0)	35.2 (10.3)	35.3 (10.9)
Male, no. (%)	72 (63.2)	31 (57.4)	72 (60.5)
Race, <i>n</i> (%)			
White	95 (83.3)	45 (83.3)	97 (81.5)
Black	14 (12.3)	7 (13.0)	16 (13.4)
Other	5 (4.4)	2 (3.8)	6 (5.0)
Hispanic ethnicity, <i>n</i> (%)	24 (21.1)	11 (20.4)	17 (14.3)
Primary opioid of abuse, <i>n</i> (%)			
Heroin	76 (66.7)	28 (51.9)	75 (63.0)
Prescription pain medication	38 (33.3)	26 (48.1)	43 (36.1)
Other	0	0	1 (0.8)
Diagnosis of opioid dependence for >5 years, <i>n</i> (%)	29 (25.4)	12 (22.2)	37 (31.1)
Previous treatment for opioid dependence, <i>n</i> (%)	63 (55.3)	31 (57.4)	68 (57.1)

SD = standard deviation.

**Figure 2** Cumulative distribution functions of percentage of urine samples negative for opioids

(BI: 42 versus PI: 7%; NNT=3). Patients assigned to PI were significantly more likely to have fewer than 5% of their urines negative for opioid use (PI: 43 versus BI: 27%; NNT=7).

According to the fixed sequential analytical plan, significant results obtained on the primary end-point permitted the secondary analyses. Comparison of BI and PI on CDFs of the percentage of opioid-negative urines during the first 16 weeks of treatment showed statistically significant differences ($P < 0.0001$). The percentage of urines negative for opioids also differed statistically between BI and PI for weeks 17–24 ($P = 0.0002$). The 95% CI around the mean difference between BI and SB in the proportions of urine samples that were negative for illicit opioids over 24 weeks of treatment was $-10.7, 6.2$.

The lower bound of this interval was greater than -15 , meeting the pre-specified criterion of non-inferiority of BI relative to BNX.

Significant differences between BI and PI were also evident on the secondary efficacy measures (Table 2). Differences in adjusted mean urines negative for opioids were statistically significant for the full 24-week period ($P < 0.0001$), weeks 1–16 ($P < 0.0001$) and weeks 17–24 ($P < 0.0001$). Treatment was completed at week 24 by 64.0% (73 of 114) of those in BI compared to 25.9% (14 of 54) ($P = 0.0002$) in PI.

For the COWS ($P < 0.0001$), SOWS ($P < 0.0001$) and opioid craving VAS ($P < 0.0001$) scales, there were higher mean scores (reflecting more withdrawal symptoms and craving) for PI compared with BI across

Table 2 Descriptive statistics on secondary efficacy measures.

	Buprenorphine implant	Placebo implant	Sublingual buprenorphine	P-value	P-value
	<i>n</i> = 114	<i>n</i> = 54	<i>n</i> = 119	Buprenorphine implant versus placebo	Buprenorphine implant versus sublingual buprenorphine
Urines negative for opioids, weeks 1–24, mean ^a	36.0	14.4	35.1	<0.0001	0.81
Urines negative for opioids, weeks 1–16, mean ^a	39.6	17.9	37.8	<0.0001	0.65
Urines negative for opioids, weeks 17–24, mean ^a	28.9	7.2	29.6	<0.0001	0.86
Proportion of study completers, <i>n</i> (%)	73 (64.0)	14 (25.9)	76 (63.9)	0.0002	0.62
Clinical Opiate Withdrawal Scale (COWS)	2.49	4.52	1.71	<0.0001	0.0005
Over 24 weeks, mean ^b					
Subjective Opiate Withdrawal Scale (SOWS)	5.30	8.42	2.83	<0.0001	0.0006
Over 24 weeks, mean ^b					
VAS-opioid craving over 24 weeks, mean ^b	10.2	21.8	7.1	<0.0001	0.054
Patient rated CGI-improvement at week 24 (or end-point), ^c <i>n</i> (%)				0.031	0.30
Very much improved	47 (41.2)	14 (25.9)	57 (47.9)		
Much improved	35 (30.7)	18 (33.3)	29 (24.4)		
Minimally improved	10 (8.8)	9 (16.7)	9 (7.6)		
No change	3 (2.6)	5 (9.3)	0		
Minimally worse	1 (0.9)	1 (1.9)	1 (0.8)		
Much worse	0	1 (1.9)	0		
Very much worse	0	0	0		
Clinician-rated CGI-improvement at week 24 (or end-point), ^c <i>n</i> (%)				0.022	0.99
Very much improved	57 (50.0)	12 (22.2)	58 (48.7)		
Much improved	17 (14.9)	8 (14.8)	22 (18.5)		
Minimally improved	15 (13.2)	11 (20.4)	9 (7.6)		
No change	6 (5.3)	10 (18.5)	3 (2.5)		
Minimally worse	0	4 (7.4)	1 (0.8)		
Much worse	0	1 (1.9)	2 (1.7)		
Very much worse	0	1 (1.9)	0		

^aSignificance tests for urine data based on analyses of variance with treatment, gender and site in the model. Adjusted means presented. ^bSignificance tests for COWS, SOWS, and Visual Analog Scale (VAS) based on mixed-effects repeated-measures analysis of variance using scores from weeks 1, 4, 8, 12, 16, 20 and 24, with treatment, week, treatment × week, baseline scores, gender and site in the model. ^cSignificance tests for patient and clinician Clinical Global Impressions (CGI) improvement scales based on the Cochran–Mantel–Haenszel (CMH) test stratified on gender and site. The COWS scale potentially ranges from 0 to 48, with 5–12 = mild, 13–24 = moderate, 25–36 = moderately severe, more than 36 = severe withdrawal. The SOWS scores potentially range from 0 to 64, with each of 16 questions rated on intensity of withdrawal on a 0 (not at all) to 4 (extremely) scale. The VAS scale ranges from 0 (no craving) to 100 mm (maximum experienced).

24 weeks of treatment. At week 24, there were significant differences on the patient-rated ($P = 0.031$) and clinician-rated ($P = 0.022$) CGI-I scales, favoring BI over PI. A *post-hoc* analysis compared the proportion of patients in each group who achieved 'responder' status defined as at least 4 weeks of continuous abstinence. For the PI group, only patients who received no RM were included ($n = 69$). Of these patients, 29% of BI participants met this responder criterion compared to 4% in PI patients (CMH test, adjusted for gender and site, $P = 0.0029$) and 29% in BNX.

A *post-hoc* analysis of the percentage of cocaine-negative urines across weeks 1–24 indicated a significant difference between BI and PI ($P = 0.0016$). For patients

randomized to BI, the mean percentage of urines negative for cocaine use across 24 weeks, assuming missing values as positive, was significantly different from PI (50.2 versus 32.0%) and not significantly different from BNX (55.1%).

Outcome data from the open-label BNX group, including urine toxicology results, patient reported cravings and physician ratings of patient cravings, are shown in Table 2. The exploratory analyses comparing BI and BNX revealed no significant differences on the percentage of treatment completers, mean percentage of urine samples negative for opioids separately over weeks 1–24, 1–16 and 17–24, or CGI-I scales. BI, compared to BNX, showed greater withdrawal symptoms on the COWS

($P = 0.0005$) and SOWS ($P = 0.0006$). VAS scale craving scores were not significantly different for BI compared to BNX.

Treatment exposure

The median (mean; range) number of weeks of exposure to implants (before removal) was 25.0 (26.9; 4–60) for BI and 15.5 (18.4; 1–56) for PI. Additional implants were received by 21.9% (25 of 114) patients randomized to BI and 38.8% (21 of 54) of patients randomized to PI. Of the 114 patients randomized to BI, 89 (78%), received four implants. The majority of BI patients ($n = 69$ of 114; 61%) took no RM. Twenty patients (22.5%) required the following amounts of RM over the 24-week study: mean days used per week = 0.10; mean mg per week = 0.91. Patients requiring RM in amounts that exceeded the pre-specified threshold were required to receive a fifth implant. In the PI group, 38.8% (21 of 54) received an additional implant. In the open-label BNX treatment arm, the median (mean; range) exposure was 25.0 (20.7; 1–65) weeks.

Safety

In the BI group, 67.5% (77 of 114) of patients had at least one AE, compared to 61.1% (33 of 54) for PI and 71.4% (85 of 119) for BNX. The events were mild in severity and were unrelated to study intervention. AEs were further described as occurring or not at the implant location. Among non-implant site AEs with incidence $\geq 5\%$ (Table 3), headache was most common in BI (13.2%) and

BNX (16.0%); insomnia (14.8%) was most common in PI. There were no significant differences between groups on any AEs. Implant-site reactions were evident for 27.2% (31 of 114) in BI and 25.9% (14 of 54) in PI, most commonly hematomas [eight (7.0%) and six (11.1%), respectively] and pain [six (5.3%) and five (9.3%), respectively; not significant (NS)]. There was no evidence of unscheduled implant removal or attempted removal.

Serious adverse events (SAEs) occurred in 16 patients. In BI, 5.3% (six of 114) experienced SAEs, compared to 5.6% (three of 54) in PI and 5.9% (seven of 119) in BNX. In BI, these were: umbilical hernia, pneumonia ($n = 2$), breast cancer, hypotension and tooth abscess. None were judged as related to treatment. SAEs resulted in five hospitalizations in BI (five of 114; 4.4%), two in PI (two of 54; 3.7%) and six in BNX (six of 119; 5.0%). There was one death in the study, which occurred in BNX (accidental overdose) 3 days following early study discontinuation initiated by the subject.

DISCUSSION

This study confirms the 24-week efficacy of BI relative to PI demonstrated in the previous trial [6]. Statistically significant differences were observed on both primary end-points and all secondary end-points. Effect sizes for primary and secondary end-points were moderate to strong (NNTs < 10), and were comparable or superior to effect sizes reported for frequently prescribed psychiatric medications, including second-generation antipsychotic [17] and attention deficit hyperactive disorder (ADHD) medications [18]. In addition, BI was found to be not inferior to BNX when comparing BI, provided on a double-blind basis, versus BNX provided as an open-label treatment. Lack of blinding is often associated with inflated treatment effects [19]. The 24-week retention rate for active treatment (BI and open-label BNX: 64%) was significantly higher than placebo (26%) and was within the range observed in other clinical studies of buprenorphine. Previous open-label and single-blind studies have reported completion rates ranging from 38 [20] to 78% [21]. Office-based treatment with buprenorphine/naloxone has reported retention rates of 55% [16].

It is unclear whether greater withdrawal symptoms found in BI, compared to BNX, relate to lower blood levels of buprenorphine; what is clear is that the difference in withdrawal symptoms does not translate into more drug use (compared to placebo). Notably, the absolute levels of withdrawal symptoms were very low for all three groups.

Diversion and misuse of sublingual buprenorphine is a significant clinical and societal concern. There was no evidence of attempted removal of the implants in the

Table 3 Non-injection site treatment emergent adverse events across 24 weeks with incidence $\geq 5\%$ in one or more groups.

Event	Buprenorphine implants $n = 114$	Placebo implants $n = 54$	Sublingual buprenorphine $n = 119$
Headache	15 (13.2)	5 (9.3)	19 (16.0)
Upper respiratory infection	10 (8.8)	4 (7.4)	11 (9.2)
Depression	10 (8.8)	3 (5.6)	4 (3.4)
Insomnia	9 (7.9)	8 (14.8)	16 (13.4)
Sore throat	8 (7.0)	1 (1.9)	4 (3.4)
Nausea	7 (6.1)	1 (1.9)	8 (6.7)
Vomiting	7 (6.1)	1 (1.9)	5 (4.2)
Nasopharyngitis	6 (5.3)	3 (5.6)	12 (10.1)
Back pain	6 (5.3)	3 (5.6)	7 (5.9)
Limb abscess	3 (2.6)	4 (7.4)	5 (4.2)
Hyperhidrosis	3 (2.6)	3 (5.6)	2 (1.7)
Anxiety	2 (1.8)	3 (5.6)	7 (5.9)
Diarrhea	2 (1.8)	3 (5.6)	2 (1.7)
Any 'severe' event	9 (7.9)	3 (5.6)	14 (11.8)
Any 'serious' event	6 (5.3) ^a	3 (5.6)	7 (5.9)

^aUmbilical hernia, pneumonia ($n = 2$), breast cancer, hypotension, tooth abscess.

current, or previous [6], trials. Supplemental sublingual buprenorphine was used by 39.5% of subjects in the BI group, primarily by those who ultimately required an implant dose increase. The pattern of AEs for BI and PI was similar to that found previously with minor implant-site reactions commonly occurring.

Regarding cocaine use, earlier *post-hoc* findings [14] were replicated, suggesting a beneficial effect of BI in reducing cocaine use in opioid-dependent subjects. It is unknown whether this effect is an indirect result of buprenorphine treatment of opioid dependence or is a direct pharmacological effect. The potential utility of implantable buprenorphine in cocaine-use disorders, at least among opioid-dependent individuals, deserves further attention.

Although the safety and efficacy of BI was confirmed in two randomized clinical trials, areas for further discussion remain. How many patients and physicians in the community would prefer buprenorphine implants instead of available forms of the medicine is unknown, and was not measured in the study. Physicians may be reluctant to prescribe implants when other formulations are available. In the current and previous trials, physicians across a variety of specialties (e.g. psychiatry, obstetrics, family medicine) performed the procedure safely with training. It is possible that clinicians would identify certain patients more suitable for either a sublingual form of the medicine or the implant. For example, clinicians could decide to recommend implants for patients with young children in the home, patients with a pattern of inconsistent adherence to prescriptions or patients who may repeatedly misplace sublingual formats. Balancing individual patient and physician concerns with the burgeoning need to minimize harm resulting from opioid abuse and diversion [3–5] is a question for clinicians, future clinical research and for public health policy.

A limitation of the non-inferiority component of the study was that the comparison with BNX was unblinded. Another limitation was the use of rescue sublingual buprenorphine/naloxone across all groups, making it difficult to compare outcome and retention results to previous studies that did not use rescue medication. In addition, the generalization of these findings is uncertain for individuals who are also dependent upon other substances, have recently received methadone or buprenorphine or have chronic pain that requires opioid analgesics.

In summary, buprenorphine implants compared with placebo implants resulted in significantly less opioid use over 24 weeks, replicating the efficacy observed in a previous randomized clinical trial. Buprenorphine implants were also found to be non-inferior to sublingual buprenorphine with regard to the proportion of urines

negative for opioids over 24 weeks of treatment for opioid dependence.

Clinical trial registration

Clinicaltrials.gov identifier: NCT01114308.

Declaration of interests

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