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Safety, Efficacy, and Pharmacokinetics of Probuphine®, a 6-Month Implantable Sustained-Release Formulation of Buprenorphine, for the Treatment of Opioid Addiction

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ABSTRACT

Background: Sublingual buprenorphine (SL BPN) is an effective and well-tolerated treatment for opioid addiction. However, the daily dosing associated with sublingual administration hinders treatment compliance, increases the risk of misuse and diversion, and potentially contributes to patient relapse and treatment failure. Buprenorphine implants (buprenorphine hydrochloride [HCL]/ethylene vinyl acetate [EVA]) are matchstick-sized subcutaneous implants (BPN implants) that deliver a low, continuous level of BPN for 6 months with a single treatment, thus insuring compliance and greatly reducing the risk of misuse and diversion. Safety, efficacy, and BPN plasma concentration results from two Phase 3 multicenter studies covering treatment of opioid addiction for up to one year are presented.

Study 1: Double-blind, randomized, placebo-controlled study
Methods: Following brief induction with sublingual BPN (12-16 mg/day), opioid-dependent (DSM-IV-TR) outpatients at 18 clinical sites in the U.S. were randomized (2:1) to receive either 4 BPN implants (n=108) or 4 placebo implants (n=55). Subjects received a 5th BPN implant or placebo implant if the protocol-specified threshold for rescue with SL BPN was exceeded. Urine samples were collected 3 times weekly and analyzed for the presence of illicit opioids; monthly blood samples were collected to assess plasma BPN levels. Study subjects received weekly individual drug counseling (NIDA IDC manual). Additional assessments included standard safety measures, symptoms of opioid withdrawal and craving, self-reported illicit drug use, clinical global improvement, and quality-of-life.

Results: The in-office implant insertion and removal procedures were generally well-tolerated, and BPN implants were associated with minimal adverse events. The most common adverse events in the BPN implant group were headache, insomnia, nasopharyngitis, nausea, and constipation. BPN implants were superior to placebo in the proportion of opioid negative urine samples (p=.0117), retention in treatment (p<.0001), and control of opioid withdrawal (p=.0004) and cravings (p=.0009) over the full 6-month period. Twenty percent of the BPN implant group versus 58% of the placebo group received a dose increase (5th implant) during the study. Following a dose increase, subjects who continued to require more than the protocol-specified amount of SL BPN rescue were withdrawn as treatment failures. There were no treatment failures in the BPN implant group versus 45% in the placebo group (p<.0001). There was no evidence of unscheduled implant removal or attempted removal. Consistent with findings of a Phase 1/2 study, pharmacokinetic results in patients treated with BPN implants showed an early, brief pulse of BPN release, followed by steady-state plasma levels achieved within 3-4 weeks and maintained for 6 months. The mean steady-state plasma BPN level post-implant was 941 pg/mL (n=104). Completers from this study [71 (66%) BPN implants and 17 (31%) placebo] were eligible to enroll in a 6-month open-label re-treatment study (Study 2).

Study 2: Open-label safety study
Methods: Seventy-one (81%) of the eligible subjects from Study 1 were screened following removal of their Study 1 implants. Sixty-two subjects met eligibility criteria and received a brief induction with SL BPN 12-16 mg/day, in consideration of the placebo subjects (n=12) who were not exposed to BPN implants during Study 1. All subjects initially received 4 BPN implants and were provided with drug counseling (NIDA IDC manual) and SL BPN rescue medication as clinically indicated. Following implantation, subjects were seen in the clinic at week 1 and then monthly thereafter for standard safety evaluations and clinical assessment of opioid withdrawal and craving, illicit drug use, global improvement, and quality-of-life. Monthly PK samples were also collected.

Results: Forty-six subjects (74%) completed six months of treatment. There was no evidence of unscheduled implant removal or attempted removal. The implant insertion and removal procedures were generally well-tolerated, and the incidence of adverse events was similar to Study 1. Secondary measures of efficacy indicated that treatment was associated with effective suppression of opioid withdrawal and craving symptoms, clinician- and subject-rated global improvement, and improvements in quality-of-life. Pharmacokinetic analysis of plasma BPN concentrations replicated results of the Phase 2 study and Study 1.

Conclusion: These data consistently indicate that BPN implants are an effective and well-tolerated treatment option for patients with opioid addiction.

SUPPORTED BY FUNDING FROM TITAN PHARMACEUTICALS

INTRODUCTION

- Buprenorphine, a partial mixed opioid receptor agonist and antagonist, has been shown to be safe and effective for treatment of opioid dependence.
- A novel implantable formulation of buprenorphine (BPN implants) using a polymer matrix sustained-release technology has been developed to offer treatment for opioid dependence.
  - Ethylene vinyl acetate rods (26 mm x 2.5 mm) embedded with BPN (80 mg)
  - Subcutaneous implant delivers low, continuous, steady-state levels of BPN for 6 months
  - Facilitates treatment compliance
  - Reduces risk of illicit diversion
  - Reduces side-effects and withdrawal symptoms associated with fluctuating drug levels (Lopatko et al., Drug Alcohol Depend 2003;69:317-22)
  - Efficacy achieved while reducing overall patient drug exposure
- The pharmacokinetics, safety and efficacy of BPN implants have been demonstrated in a small Phase 1/2 study (White et al, Drug Alcohol Depend 2009;103:37-43).

OBJECTIVES

- Primary: To evaluate the efficacy of BPN implants in the treatment of subjects with opioid dependence over 16 weeks of treatment
- Secondary: To evaluate the efficacy of BPN implants in the treatment of subjects with opioid dependence in the subsequent 8 weeks of treatment; to evaluate the safety of BPN implants over 24 weeks of treatment

METHODS

Study design: Study 1

- Screening period: Up to 10 days
- Induction phase: Open-label treatment with 12-16 mg/d of sublingual BPN (SL-BPN)
- Double-blind period: Randomization in a 2:1 ratio to 24 weeks of treatment with either:
  - 4 BPN implants (80 mg each) in inner side of the non-dominant arm
  - 4 placebo implants in the inner side of the non-dominant arm

Study design: Study 2

- Patients who completed 24 weeks of treatment in Study 1 and continued to meet eligibility criteria were enrolled in a 24 week open-label extension phase.
- At least 12 hours prior to receiving BPN implants, patients completed induction with 12-16 mg/d of sublingual buprenorphine.

Key study entry criteria

- Male or female, 18-65 years; use of reliable contraception by females of childbearing potential and fertile males
- Currently meets DSM-IV criteria for opioid dependence
- Excluded for any of the following:
  - Current diagnosis of acquired immune deficiency syndrome
  - Current use of agents metabolized via CYP 3A4
  - Met DSM-IV criteria for current dependence on any psychoactive substances other than opioids or nicotine
  - Acute or unstable medical condition
  - Pending legal action

Assessments

Efficacy

- Primary: the cumulative distribution function (CDF) of the percent of urine samples that were negative for opioids for Weeks 1-16
- Secondary:
  - CDF of urine samples that were negative for opioids for Weeks 17-24
  - Mean % urines negative for opioids
  - Retention: proportion (%) of study completers
  - Mean total score on the clinical opiate withdrawal scale (COWS)
  - Mean total score on the subjective opioid withdrawal scale (SOWS)
  - Mean subjective opioid craving assessment (VAS)

Safety

- Adverse events
- Laboratory evaluations
- 12-lead ECG

Pharmacokinetic

- BPN plasma concentrations were obtained monthly (at least 12 hours after any use of sublingual buprenorphine)

The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.
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RESULTS

Table 1. Study 1: Demographic and Clinical Characteristics of Patients

	BPN Implant N=108	Placebo N=55
Male, N (%)	72 (66.7)	40 (72.7)
Race, N (%)		
White	82 (75.9)	40 (72.7)
Black	14 (13.0)	6 (10.9)
Other	12 (11.1)	9 (16.4)
Ethnicity, N (%)		
Hispanic	12 (11.1)	12 (21.8)
Age, years, mean (SE)	35.8 (1.1)	39.3 (1.6)
Current primary opioid abuse, N (%)		
Heroin	69 (63.9)	34 (61.8)
Prescription pain reliever	39 (36.1)	21 (38.2)
Time since first diagnosis >5 years, N (%)	30 (27.8)	15 (27.3)
Previously treated for substance abuse/dependence, N (%)		
Counseling / meeting	15 (13.9)	10 (18.2)
Pharmacotherapy	25 (23.1)	14 (25.5)
Other	30 (27.8)	10 (18.2)
None	38 (35.2)	21 (38.2)

Figure 1. Study 1 - Flow diagram and Patient Disposition

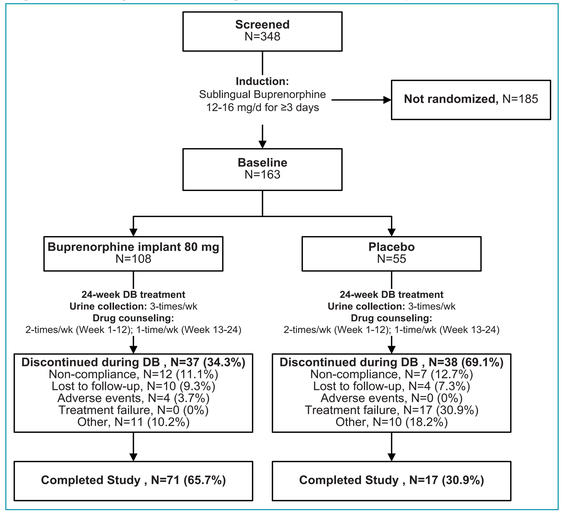


Figure 2. Study 1: Proportions of Opioid Negative Urine Samples

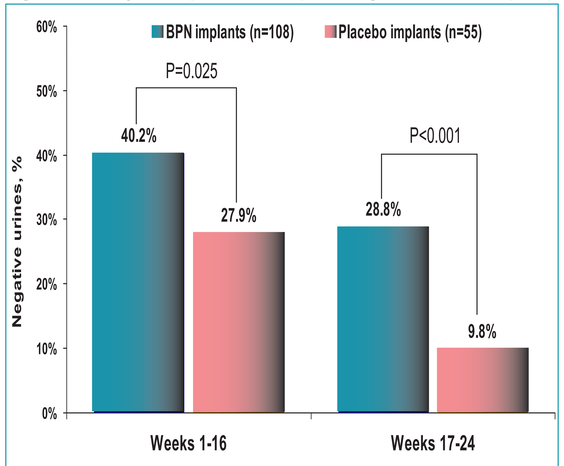
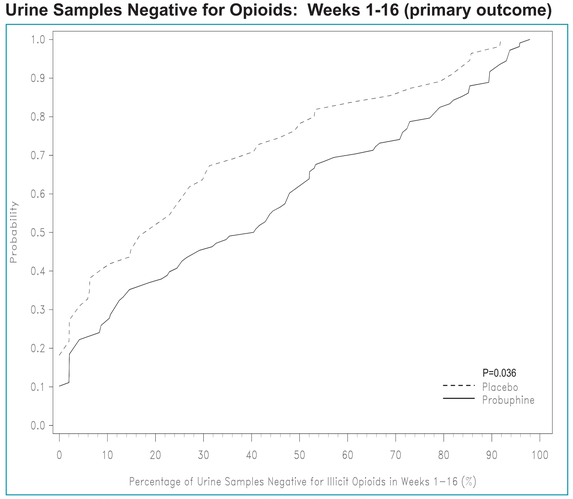
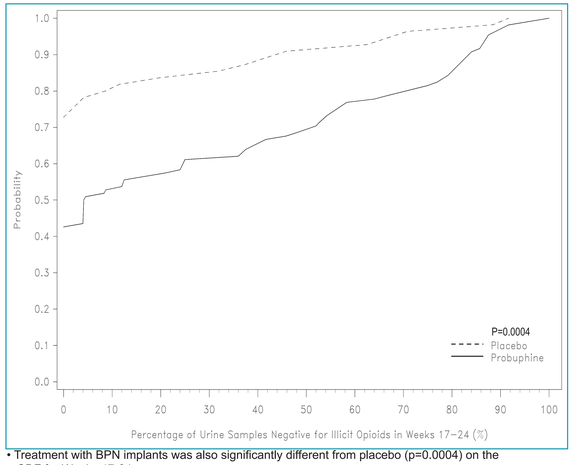


Figure 3. Study 1: Cumulative Distribution Function of the Percent of Urine Samples Negative for Opioids: Weeks 1-16 (primary outcome)



- Treatment with BPN implants was associated with a significant difference from placebo (p=0.036) on the CDF of the percent of negative urine samples for Weeks 1-16 (the primary a priori endpoint).

Figure 4. Study 1: Cumulative Distribution Function of the Percent of Urine Samples Negative for Opioids: Weeks 17-24



- Treatment with BPN implants was also significantly different from placebo (p=0.0004) on the CDF for Weeks 17-24.

Table 2. Secondary and Exploratory Efficacy Measures

	BPN Implants N=108	Placebo N=55	P-value
Proportion of study completers, N (%)	71 (65.7)	17 (30.9)	<0.0001
Clinician-rated opioid withdrawal scale (COWS), mean (SE)	2.3 (0.2)	3.4 (0.3)	0.0004
Subject-rated opioid withdrawal scale (SOWS), mean (SE)	4.1 (0.5)	6.5 (0.7)	0.0039
CGI-Improvement, Responders, N (%)*	73 (80.2)	24 (51.1)	0.0003
CGI-Severity, borderline-to-no symptoms, N (%)*	52 (57.2)	16 (34.0)	0.0086
VAS-opioid craving, LS mean (SE)	9.9 (1.1)	15.8 (1.6)	0.0009

*CGI-I and CGI-S evaluated at Visit 15 or End-of-Treatment

SAFETY

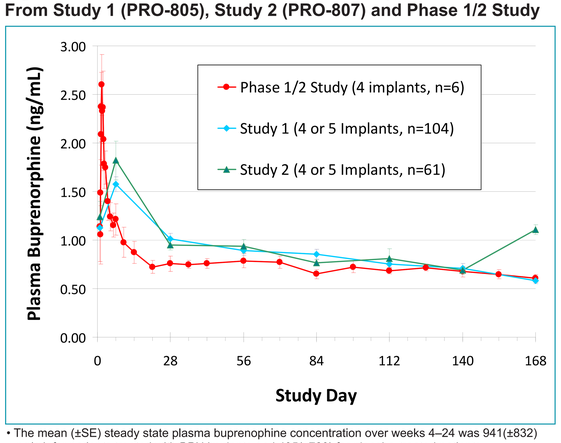
Table 3. Treatment-Emergent Adverse Events (All-Causality, Incidence >10%)

	Study 1, Weeks 1-24		Study 2, 24 week open-label extension
	BPN implants N=108	Placebo N=55	BPN implants N=62
Constipation	15 (13.9)	3 (5.5)	8 (12.9)
Diarrhea	6 (5.6)	7 (12.7)	2 (3.2)
Nausea	15 (13.9)	7 (12.7)	2 (3.2)
Toothache	12 (11.1)	3 (5.5)	3 (4.8)
Nasopharyngitis	15 (13.9)	3 (5.5)	2 (3.2)
Upper respiratory tract infection	14 (13.0)	6 (10.9)	3 (4.8)
Back pain	13 (12.0)	3 (5.5)	5 (8.1)
Headache	27 (25.0)	10 (18.2)	11 (17.7)
Anxiety	11 (10.2)	5 (9.1)	2 (3.2)
Insomnia	23 (21.3)	12 (21.8)	8 (12.9)
At least 1 severe adverse event	12 (11.1)	4 (7.3)	3 (4.8)
Serious adverse events	2 (1.9)*	4 (7.3)**	0 (0)
Implant site adverse events			
Erythema	27 (25.0)	12 (21.8)	16 (25.8)
Edema	14 (13.0)	5 (9.1)	8 (12.9)
Itching	27 (25.0)	8 (14.5)	12 (19.4)
Pain	24 (22.2)	6 (10.9)	12 (19.4)
Bleeding	13 (12.0)	7 (12.7)	10 (16.1)
Patients with implant site AEs rated as severe	1 (0.9)	0 (0)	1 (1.6)

*Burn, PE in patient with COPD; **Pneumonia, suicidal ideation, COPD, drug dependence

PHARMACOKINETICS

Figure 5. Clinical Pharmacokinetics of BPN Implants: Results From Study 1 (PRO-805), Study 2 (PRO-807) and Phase 1/2 Study



- The mean (±SE) steady state plasma buprenophine concentration over weeks 4–24 was 941(±832) pg/mL for patients treated with BPN implants and 495(±720) for placebo-treated patients.
- These levels are consistent with a constant release of 1.0-1.3 mg/day of BPN from the 4-5 implants.
- In Study 1, 22 patients (20.4%) randomized to BPN implants and 32 patients (58.2%) randomized to placebo received a 5th implant; in Study 2, six patients (9.7%) received a fifth implant.

CONCLUSIONS

- BPN implants were clinically and statistically superior to placebo in the treatment of opioid-dependent patients.
- Significance was consistently achieved for the primary and key secondary endpoints, and for other clinical parameters.
- BPN implants were found to be safe and well-tolerated in this study.
  - Adverse events were mild to moderate in ~90% of patients
  - Discontinuation due to adverse events was low (3.7%)
- The implant procedure was generally well-tolerated with no evidence of implant diversion or misuse.
- BPN implants deliver a low level of buprenorphine continuously for six months.

CONFLICT OF INTEREST STATEMENT

Dr. Beebe, Ms. Yen and Mr. Henley are full-time employees of Titan Pharmaceuticals.
Dr. Ling has received unrestricted educational grants, and has served as a consultant to Reckitt-Benckiser, and to Titan Pharmaceuticals.
Dr. Casadonte has served as a consultant to Titan Pharmaceuti**cals.**
Dr. Rotrosen has received research funding from Alkermes, and has an equity stake in Amgen, Du Pont, Biogen IDEC, Elan, St. Jude Medical Inc, Denstpy Intl.