16.1 Study Information
16.1.1 Protocol and Protocol Amendments

This section contains the following documents:

Original protocol dated 14 May 2014
Amendment 1 dated 14 August 2014
Amendment 2 dated 24 September 2014
Amendment 3 dated 30 March 2015
Clinical Trial Protocol
PRO-814

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

PROBUPHINE®
(BUPRENOHRPHINE HYDROCHLORIDE IMPLANT)

BRAEBURN PHARMACEUTICALS:
47 Hulfish Street, Suite 441
Princeton, NJ 08542

Original Protocol: 1.0, 14-MAY-2014

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1. **SPONSOR AND KEY PERSONNEL CONTACT INFORMATION**

<table>
<thead>
<tr>
<th>ROLE IN STUDY</th>
<th>NAME</th>
<th>CONTACT INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Sponsor</strong></td>
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</tr>
</tbody>
</table>
2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Product: Probuphine® (buprenorphine hydrochloride implant)

Name of Active Ingredient: buprenorphine hydrochloride

Study Title:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Objectives:

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of sublingual (SL) buprenorphine (BPN), to 4 Probuphine implants compared to SL BPN.

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

Methodology:

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN. The study will include 3 Phases: Screening, Maintenance and Follow-up.

Medical and eligibility screening should occur within 2 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history.

All subjects who have provided written informed consent and have met the other study entry criteria will be eligible for randomization. Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit). On Post-Implant Visit, additional follow-up safety and implant assessment procedures will be conducted. Subjects will return for monthly study visits on Weeks 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). In addition to the monthly scheduled visits, subjects will provide 4 random
Clinical Trial Protocol  
PRO-814  
Braeburn Pharmaceuticals  
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urine toxicology samples throughout the 24-week treatment period.

A total of 10 urine toxicology samples will be collected; 6 at scheduled visits (1 per month) and 4 at random urine toxicology visits throughout the 24-week treatment period. At the scheduled visits, other assessments of efficacy and safety will be collected. Implants will be removed at the End of Treatment Visit on Week 24.

Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects. and Week 26 will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

Number of Subjects (Planned):

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized in the Maintenance Phase.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for at least 6 months.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days prior to Screening.
   c. No positive urine toxicology results for illicit opioids in the last 90 days.
5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

Exclusion Criteria

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.

6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).

7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.

8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).

9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.

10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

**Investigational Product, Dosage and Mode of Administration:**

All subjects will receive either four 80 mg Probuphine implants or four matching placebo implants for a period of 24 weeks.

**Reference Therapy, Dosage and Mode of Administration:**

Buprenorphine will be administered as 2 mg or 8 mg SL BPN tablets at doses of ≤8 mg (the same dose subjects had been previously stable on) per day or matching placebo SL tablets for a period of 24 weeks.

**Duration of Study:**

Subjects will participate in this study for up to 28 weeks, including Screening (up to 2 weeks), Maintenance/active study drug treatment (24 weeks), and Follow-up (2 weeks).

**Criteria for Evaluation:**

**Primary Efficacy Endpoint:** The primary efficacy endpoint is a responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Illicit opioid use is defined as a positive opioid urine toxicology result or self-
reported illicit opioid use.

**Secondary Efficacy Endpoints**

Secondary efficacy endpoints will include measures of desire/need to use (Desire to Use VAS, Need to Use VAS) and measures of withdrawal (Clinical Opiate Withdrawal Scale [COWS] and Subjective Opioid Withdrawal Scale [SOWS])

**Exploratory Efficacy Variables:**

Exploratory variables include: Urine toxicology for other drugs of abuse, supplemental SL BPN use, unscheduled visits, phone calls, additional psychosocial counseling and other pharmacological interventions, and treatment discontinuation, including reasons for discontinuation.

**Safety Variables**

Safety endpoints include: adverse events (AEs), clinical laboratory tests, electrocardiogram, physical and implant site examinations, implant site insertion and removal assessments, concomitant medications, and vital signs.

**Statistical Methods (Data Analysis):**

**Primary efficacy analysis:**

A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta=20\%$ will be employed to define non-inferiority. Let $\pi_C$ and $\pi_T$ be the rate of response at 24-weeks on the control arm (SL BPN) and experimental treatment arm (Probuphine), respectively. The null hypothesis ($H_0$) of inferiority is

$$H_0 : \pi_T \leq \pi_C - 0.20.$$ 

The alternative hypothesis ($H_A$) of non-inferiority is

$$H_A : \pi_T > \pi_C - 0.20.$$ 

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).

**Secondary efficacy analysis:**

The secondary endpoints will include change from baseline (Day 1) in the secondary efficacy variables at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.
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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE Adverse event
AIDS Acquired Immune Deficiency Syndrome
ANCOVA Analysis of covariance
BMI Body Mass Index
BPN Buprenorphine (may refer to buprenorphine/naloxone or buprenorphine alone)
C_avg Average plasma concentration
CFR Code of Federal Regulations
CNS Central nervous system
COWS Clinical Opioid Withdrawal Scale
CRF Case Report Form (may include electronic data capture systems or paper forms)
CS Clinically significant
CSA Clinical Study Agreement
CYP Cytochrome P450
ECG Electrocardiogram
EDC Electronic data capture
EE Efficacy Evaluable
EVA Ethylene vinyl acetate
FDA Food and Drug Administration
GCP Good Clinical Practice
HIV Human Immunodeficiency Virus
ICF Informed consent form
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-Treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MAT</td>
<td>Medication-assisted treatment</td>
</tr>
<tr>
<td>MINI</td>
<td>Mini International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>MOP</td>
<td>Manual of Procedures</td>
</tr>
<tr>
<td>NCS</td>
<td>Not clinically significant</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
</tr>
<tr>
<td>SOC</td>
<td>System Organ Class</td>
</tr>
<tr>
<td>SOWS</td>
<td>Subjective Opioid Withdrawal Scale</td>
</tr>
<tr>
<td>RBC</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>THC</td>
<td>Tetrahydrocannabinol</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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5. INTRODUCTION

5.1. Background

Opioid dependence is a serious chronic, debilitating, and sometimes fatal disorder. The process of recovery from opioid dependence is, for most individuals, a long-term and non-linear endeavor that is subject to recurrent relapse. It is well understood that medication-assisted treatment (MAT) without a broader treatment program is generally insufficient to achieve recovery for most opioid-dependent individuals. However, it is also known that MAT has proved to be effective in enabling many individuals to succeed on the long-term path to recovery. The primary agents used in MAT are methadone, buprenorphine hydrochloride (BPN), and naltrexone. Buprenorphine, a partial \( \mu \)-opioid receptor agonist, is effective and safe (marketed in 34 countries), and has expanded access to treatment for individuals who might otherwise remain untreated. Sublingual (SL) BPN, first approved in 2002, has become widely-available and highly-effective treatment for opioid dependence.

Although daily dosing of SL BPN has proven effective, this route of delivery has several shortcomings. First, SL BPN can easily be diverted for illicit use, injected for greater effect, or accidentally ingested especially by children (Winstock et al., 2008). Second, adherence to daily medication is a challenge, and a conscious decision to discontinue BPN treatment in anticipation of exposure to illicit drugs can also be achieved. Medication non-adherence may lead to relapse, treatment failure, and mortality in the opioid-dependent population. Such limitations are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently), or to those who have difficulty managing the responsibility of daily dosing.

Probuphine\(^\circledast\) (buprenorphine hydrochloride implant; herein referred to as Probuphine) is a subdermally implantable, abuse- and diversion-deterrent formulation of BPN under development for the maintenance treatment of opioid dependence. Probuphine was developed as an additional therapeutic alternative in maintenance treatment of opioid dependence by providing a long-acting six-month BPN implant that is inherently less susceptible to accidental ingestion (especially by children), abuse and diversion than SL BPN, and is intended to facilitate medication adherence. Probuphine is inserted subdermally in a brief in-office procedure under local anesthetic. Probuphine is designed to provide sustained release of BPN for up to 6 months. At the end of each 6-month treatment, Probuphine is removed in a brief, in-office procedure.
under local anesthetic. Each Probuphine implant consists of 80 mg of BPN that has been blended and extruded with ethylene vinyl acetate (EVA).

5.2. Safety and Efficacy of Buprenorphine

The safety and efficacy of BPN in the treatment of opioid dependence are well-established (Eder et al., 1998; Johnson et al., 1992; Johnson et al., 1995; Johnson et al., 2000; Lopatko et al., 2003; Strain et al., 1994). As a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor, a ceiling or plateauing effect is observed whereby higher doses of BPN are less likely to cause complications of overdose relative to full µ-opioid receptor agonists (Walsh et al., 1994). This results in a safety profile superior to methadone and levo-acetyl-methadol, though efficacy of these treatments for opioid dependence is comparable (Johnson et al., 2000).

In controlled clinical trials with SL BPN, the most common adverse events (AEs) (i.e., those occurring in >10% of subjects) included headache, pain, withdrawal syndrome, asthenia, anxiety, depression, insomnia, rhinitis, nausea, constipation, back pain, infection, and sweating (Reckitt Benckiser Pharmaceuticals, Inc., 2013). From published clinical studies, additional common side effects reported with BPN include drowsiness (increased with alcohol), vomiting, orthostatic hypotension, and sweating. In addition, due to its κ-receptor antagonist activity, BPN can cause withdrawal symptoms if administered with a µ-opioid agonist (such as heroin). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in patients receiving BPN, both in clinical trials and in post-marketing AE reports (Reckitt Benckiser Pharmaceuticals, Inc., 2013). Available data cannot exclude the role of BPN as either causative or contributory in the development of these hepatic abnormalities.

Buprenorphine is metabolized by the 3A4 isoenzyme of cytochrome P450 (CYP3A4). Therefore, concomitant use of CYP 3A4 inhibitors, such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) may increase plasma concentrations of BPN.

Respiratory and central nervous system (CNS) depression can be magnified with concomitant use of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedatives/hypnotics, or other CNS depressants (including alcohol). There have been post-marketing reports of coma and death associated with the concomitant intravenous (IV) misuse of SL BPN and benzodiazepines. In many of these cases, SL BPN was misused by self-injection of crushed SL BPN tablets. In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if
required. Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine.

Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Subjects should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BPN therapy does not adversely affect their ability to engage in such activities. Like other opioids, BPN may produce orthostatic hypotension in ambulatory subjects.

As with other µ-opioid receptor agonists, the administration of BPN may obscure the diagnosis or clinical course of subjects with acute abdominal conditions.

### 5.3. Safety and Efficacy of Probuphine

The safety and efficacy of Probuphine have been studied for the maintenance treatment of opioid dependence in two six-month randomized controlled trials and two six-month, open-label re-treatment trials (Table 1). The pharmacokinetic properties of Probuphine have been evaluated in two relative bioavailability studies, in which plasma concentrations of BPN derived from four 80 mg Probuphine implants were observed to be comparable to the average of those measured in subjects receiving 8 mg or less of SL BPN per day. The subjects in these Phase 3 studies were adults who had not received any MAT for at least 90 days prior to entering the studies, and who underwent a brief induction with SL BPN 12 to 16 mg daily prior to randomization in the controlled trials or continuation in the re-treatment trials.

The medical literature, the completed studies with Probuphine, and an additional pharmacometric analyses performed by the Sponsor demonstrate:

1. Safety and effectiveness of SL BPN in the maintenance treatment of opioid dependence;
2. Effective use of lower SL BPN doses for maintenance treatment of individuals stabilized on daily doses of SL BPN 8 mg or less;
3. Four 80 mg Probuphine implants yield average BPN plasma concentrations of 0.74 to 0.76 ng/mL (average concentration \([C_{avg}]\) over weeks 4 to 24 in subjects who received 4 implants and did not take supplemental SL BPN in PRO-805/PRO-806 studies), which is within a range of approximately 0.5 to 1.0 ng/mL, comparable to the average of those observed following daily doses of 8 mg or less of SL BPN;
4. Probuphine implants provide stable and consistent therapeutic BPN concentrations resulting from continuous delivery of BPN over 6 months, with low intra- and inter-subject variability, and without risk of non-adherence that may be associated with SL BPN;
5. Safety and efficacy of Probuphine in a more difficult-to-treat population of opioid-dependent patients (induced on 12 to 16 mg/day) (Ling et al., 2010; Rosenthal et al., 2013), allowing a potential downward extrapolation of efficacy to a more stable population of patients on longer-term maintenance treatment with 8 mg SL BPN or less.

In addition to the above, Probuphine may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy. Thus, Probuphine is expected to provide patients and clinicians with an additional treatment option with the potential for more stable plasma concentrations, enhanced adherence and reduced public health consequences of diverted and abused SL BPN.

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Study Number</th>
<th>Subjects</th>
<th>Key Findings for Current Study</th>
</tr>
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<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>TTP-400-02-01</td>
<td>N=12 (N=6 with 4 implants; N=6 with 2 implants)</td>
<td>Four 80 mg Probuphine implants yield BPN plasma concentrations comparable to those observed upon administration of SL doses of 8 mg or less daily. Probuphine implants provide stable BPN concentrations over 6 months, with low intra and inter-subject variability.</td>
</tr>
<tr>
<td></td>
<td>PRO-810</td>
<td>N=9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-805 PRO-806</td>
<td>Population Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>PRO-805 PRO-806</td>
<td>N=262</td>
<td>Statistical significance of pre-specified endpoints met in a population of subjects stabilized for as little as 3 days. Efficacy &gt; Placebo (with SL rescue) on multiple outcome measures. Efficacy similar to SL BPN according to PRO-806 and published data (Rosenthal et al., 2013 In PRO-806, retention rates were 64% for both Probuphine and SL BPN</td>
</tr>
<tr>
<td>Safety</td>
<td>PRO-805 PRO-806 PRO-807 PRO-811</td>
<td></td>
<td>Common adverse events (AEs) and safety issues similar to those seen with SL BPN 2% of subjects discontinued treatment due to implant-related AEs.</td>
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</tbody>
</table>

Overall, the safety data indicate that Probuphine is well-tolerated over two 24-week implant periods, and exclusive of implant-related treatment emergent AEs, the safety profile is consistent with other marketed buprenorphine-containing products. Including patients receiving Probuphine in safety studies after completing a placebo arm, a total 262 patients have received Probuphine in
the efficacy and safety studies (201 subjects for at least 24 weeks and 82 subjects for at least 48 weeks). With the exception of implant-related AEs, the most common AEs with Probuphine are similar to those observed with SL BPN, and include AEs such as headache, insomnia, nausea, back pain, and diarrhea.

Additional safety information is available in the Probuphine Investigator’s Brochure.

5.4. Study Rationale

Medication-assisted treatment (MAT) is one of the most effective therapies available for opioid dependence and is associated with substantial reductions in illicit opioid use, criminal activity, deaths, and HIV transmission. Because patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, treatment strategies that keep patients in treatment longer may have additional advantages (WHO, 2004). Limitations associated with SL BPN are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently) or to those who have difficulty managing the responsibility of daily dosing. Probuphine offers a valuable opportunity to overcome adherence issues, and to deliver the expected exposure levels that only patients who are compliant with SL BPN may achieve. In addition, although daily dosing of SL BPN has proven effective, SL tablets or even film can easily be diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (Winstock et al., 2008).

Four 80 mg Probuphine implants are expected to approximate the plasma concentrations of BPN observed following daily SL BPN doses of 8 mg or less. Previous clinical trials have demonstrated the efficacy of SL BPN doses of 8 mg/day or less for the maintenance treatment for opioid dependence (Johnson et al., 1992; Johnson et al., 1995; Ling et al., 1998). In addition, post-market studies have shown that clinicians are effectively treating many patients with maintenance BPN doses of 8 mg or less (Apelt et al., 2013; Mattick et al., 2008; Meade et al., 2010). The needs of patients who have been effectively maintained on relatively low SL BPN doses and require less frequent follow-up visits, may be better met by Probuphine than by SL formulations. In addition, Probuphine provides an alternative dosage form that can reduce diversion and enhance abuse deterrence. Therefore, the purpose of this study is to demonstrate the maintenance of the safety and efficacy by an alternate delivery form of BPN, Probuphine, in
the continuing treatment of opioid dependence in clinically stabilized SL BPN\textsuperscript{a} maintenance patients.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN, to 4 Probuphine implants compared to SL BPN.

6.2. Secondary Objective

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN.

The study will include 3 Phases; Screening, Maintenance and Follow-up. Subjects will participate in this study for up to 28 weeks, including 2 weeks of the Screening Phase, 24 weeks of study drug treatment (Maintenance Phase) and 2 weeks of the Follow-up Phase.

All subjects who have provided written informed consent and have met the other study entry criteria will be enrolled and randomized into the Maintenance Phase. At least 180 subjects will be randomized to one of 2 treatment groups in a 1:1 ratio.

The overall study design is illustrated in Figure 1. Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2).

\textsuperscript{a} Note that throughout this protocol, SL BPN may refer to either sublingual buprenorphine or sublingual buprenorphine/naloxone products, unless otherwise indicated.
All subjects will be seen for a total of approximately 14 visits (total of 10 urine toxicology samples will be collected) as outlined in the Schedule of Assessments:

- 1 Screening visit
- 12 main study visits:
  - 8 Maintenance Phase visits, including 1 Baseline and Initiation of Study Drugs Visit (post-randomization Implant Day [Day 1]), 1 Post-Implant Follow-up Visit, and 6 additional monthly Maintenance Phase visits, including the End of Treatment Visit at Week 24
  - 4 Random urine toxicology visits
- A Post-Treatment Telephone Contact will occur 1 week after the End of Treatment Visit (~1 week prior to the Follow-Up Visit).
- 1 Follow-Up Visit (2 weeks after the End of Treatment Visit)

Additional visits may be scheduled at the discretion of the subject or Investigator.

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects (regardless of randomized group) will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of all study-related medications and counseling will also be covered by the Sponsor.

Section 10 provides additional information on the baseline, efficacy and safety assessments included in the study. Efficacy endpoints and statistical analyses are described in Section 10.6 and Section 12, respectively.

### 7.1.1. Screening Phase (Week -2 to -1)

Medical and eligibility screening should occur within 2 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history. Data on urine toxicology results for the duration of historical stable maintenance dosing (e.g., at least 90 days prior to Screening,) and the treating Health Care Practitioner’s documentation on the patient’s clinical stability (including the length of time that they have judged the patient to be stable) will be obtained via the clinical stability form (provided in the MOP).

Following the Screening Phase, subjects will be eligible for randomization if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.
7.1.2. Maintenance Phase (Month 1 to 6; Week 1 to Week 24)

Eligibility for randomization will be confirmed after the Screening visit and prior to implantation on Day 1 (Baseline and Initiation of Study Drugs Visit). Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Subjects in Treatment Group A will be transitioned to the same dose of SL BPN on which they were previously maintained. Treatment Group B will be transitioned to four Probuphine implants that are expected to yield BPN plasma concentration within a range of approximately 0.5 to 1 ng/mL, comparable to the average of those observed following daily dose of 8 mg or less of SL BPN.

All subjects will be blinded to their treatment group assignment, as will all study staff with the exception of the clinician(s) performing the implant procedure and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets). To maintain blinding, all subjects will receive 4 implants (Probuphine or placebo) and SL tablets (BPN equivalent to their daily dose during the Screening Phase or placebo). Implants will be surgically inserted on Day 1. After Day 1, there will be a Post-Implant Follow-up Visit (to occur within 5 days after implantation) to conduct implant site examination and any additional safety assessments. Further information on implantation procedures can be found in Section 9.1.1.

During the first month, subjects will be required to attend 3 scheduled visits: Baseline and Initiation of Study Drugs Visit (Probuphine/placebo implant insertion and SL BPN/SL placebo administration [Day 1]), Post-Implant Follow-up Visit, and Week 4 first study assessment Visit (evaluation of outcome measures and safety assessments).

During months 2 to 6, subjects will return for monthly study visits for evaluation of outcome measures and safety assessments as described in Table 2. Subjects will be provided with sufficient take home medication for the daily dose of SL BPN or placebo for the subsequent month, as appropriate.

In order to assess number of opioid-free months throughout the 6 months (24 weeks) of treatment, a total of 6 monthly study visits (6 scheduled monthly urine toxicology samples) and 4 random visits (4 random urine samples throughout the 6 months) will be obtained for each subject.
Each investigator will be instructed to treat additional symptoms (e.g., withdrawal, desire/need to uses, etc.) as they usually would under normal clinical practice, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions (other than those identified as prohibited in Section 9.7). Subjects will be told that their study dose of BPN is comparable to the dose they have been stable on and is expected to be adequate to maintain stability. Therefore, it is generally not anticipated that they will need any additional SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine), but additional counseling and other pharmacological interventions may be available at the discretion of the investigator. Any additional interventions that the subjects receive will be recorded.

Final outcome measures will be collected at the final treatment visit at Week 24 (End of Treatment Visit) and implants will be removed as described in Section 9.1.1

7.1.3. Follow-up Phase

Additional post-implant removal and other assessments will be performed on Week 25 to 26 as outlined in Table 2. Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects, 1 week (± 3 days) after the End of Treatment Visit to capture any AEs that may have occurred. Week 26 (± 3 days) will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).
Figure 1: Overview of Study Design

Screening

- Clinically stable, Daily ≤ 8 mg
- SL BPN for at least 90 days,
- No positive urine toxicology
  for last 90 days
- Up to 2 Weeks
  (Weeks -2 to -1)

Maintenance Phase

- Group A:
  - Daily SL BPN ≤ 8 mg
  - 4 placebo implants
- Group B:
  - 4 Probuphine implants
  - Daily SL placebo

Follow-up

- 2 Weeks
  (25 to 26)
- 6 Scheduled Urine Toxicology & Other Study Assessments (one per month)
- 4 Random Urine Toxicology
- 24 Weeks (Weeks 1 to 24)
- Monthly Visits

Randomization takes place on Day 1 (day of implant)

SL BPN = sublingual buprenorphine or sublingual buprenorphine/naloxone
7.2. Discussion of Overall Study Design

The design selected to meet the objectives of the study is a 24-week randomized double-blind, double-dummy study with SL BPN as an active comparator in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN. Probuphine will be compared to SL BPN using a non-inferiority analysis. Given the pharmacokinetic data showing that four 80 mg Probuphine implants produce BPN plasma concentrations similar to a daily SL BPN dose of 8 mg or less, the proposed design is consistent with other trials evaluating the transfer of subjects to alternative dosage forms, where the overall plasma concentrations have been demonstrated to be similar, such as the transfer from once-daily to weekly dosing of anti-diabetics (Gastaldelli et al., 2013).

Research indicates that for most people with drug dependence, the threshold of significant improvement is reached after about 3 months in treatment, with further gains as treatment is continued (WHO, 2004). Therefore, subjects in maintenance treatment for at least 6 months will be included in the study. Investigators will be required to gain confirmation of clinical stability for subjects according to the clinical judgement of the patients’ treating physician. The clinical judgement should be confirmed by both objective and subjective measures, as described below:

1. According to the results from the Sponsor survey of addiction specialists, clinicians generally consider duration of stability on a given dose to be a proxy for clinical stability. Therefore, one criterion for entry into the study will be a treatment dose of SL BPN (≤8 mg) for at least 90 days.

2. In addition to being on a stable dose for at least 90 days, clinicians will also attest to their patients’ clinical stability as characterized by absence of withdrawal symptoms and no evidence of positive urine toxicology tests for illicit opioids in the previous 90 days. Other elements of clinical stability include, social, emotional and psychological stability (i.e., stable family/home life and employment, treated emotional/psychological issues), compliance to clinic visits, and ongoing counseling.

The current study will enroll patients who have had no evidence of positive urine toxicology results for illicit opioids in the past 90 days. Nevertheless, addiction specialists state that clinically stable patients may have occasional opioid-positive urine toxicology. This is also supported by studies in the literature, that demonstrate subjects undergoing prescribed treatment for at least 3 months report monthly illicit opioid use in the range of 13% to 46.5% (Carrieri et al., 2003; Galanter et al., 2003; Guichard et al., 2003; Jones et al., 2009). While self-reports may
be somewhat less reliable, similar data have been reported using urine toxicology. In these studies, positive opioid urine toxicology screen results in stable subjects maintained on buprenorphine were in the range of 10% up to approximately 25% (Fiellen et al., 2008; Jones et al., 2009; Kakko et al., 2003; Maremmani et al., 2007).

The study will include 24 weeks of study drug treatment (Maintenance Phase). The patient population is clinically stable and accustomed to less frequent visits. Therefore, the study assessment visits will be monthly throughout the 6-month Maintenance Phase of the study starting with Week 4 Visit (Weeks 4 to 24). While previous studies of opioid dependence treatment have required subjects to attend up to thrice weekly visits, the clinically stable subjects under investigation in the current trial do not routinely receive such frequent and intense monitoring for their treatment. The proposed study visit schedule is designed to potentially increase study feasibility as well as improve retention. In addition to the 6 scheduled monthly study assessment visits, subjects will be required to provide 4 random urine toxicology samples throughout the Maintenance Phase of the study, which should be sufficient to detect any abuse of opioids during the 24 weeks of treatment. Subjects will also be encouraged to contact their investigator for unscheduled visits should they experience any signs of inadequate treatment.

8. **SELECTION OF STUDY POPULATION**

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized into the Maintenance Phase.

This study will enroll adult outpatients with opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR), who have been on a stable dose of 8 mg or less of SL BPN for at least 90 days prior to Screening, and meet their treating healthcare provider's criteria for clinical stability.

8.1. **Inclusion Criteria**

Subjects must meet each of the following inclusion criteria at Screening to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for at least 6 months.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days prior to Screening.
   c. No positive urine toxicology results for illicit opioids in the last 90 days.

5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.

6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met at Screening:

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.
6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.
8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).
9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.
10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.
11. Any pending legal action that could prohibit participation or compliance in the study.
12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥ 3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A subject’s participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study for any of the following reasons:

- Evidence of implant removal or attempted removal of the implant
- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent, require discontinuation of study drug, or both
- At the request of the Sponsor, Regulatory, or IRB
  - Subject is lost to follow-up
  - Death of subject

A subject may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Subject refusal or unable to adhere to the study protocol
- Protocol violation
- Pregnancy
- Requirement for continual use of opioid analgesics > 7 days or requirement for general anesthesia for surgery

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to
obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

For any case of early discontinuation (whether or not the subject is at the clinical site), the subject will be required to return for, at minimum, the End of Treatment Visit to remove the implants. The Investigator should ask the subject to return for the Follow-up assessments (i.e., Week 26 assessments), provided that the subject has not withdrawn consent for those assessments. If a subject refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

9. TREATMENTS

9.1. Treatment Administration

Following confirmation of a signed informed consent document, eligibility and randomization:

- Subjects randomized to Treatment Group A will receive daily doses of SL BPN (containing BPN and naloxone) equivalent to their usual single daily dose of BPN (≤8 mg per day) for 24 weeks. Subjects randomized to this group will also receive 4 placebo implants on Day 1.

- Subjects randomized to Treatment Group B will receive 4 Probuphine implants on Day 1, which are expected to deliver BPN to the subject for at least a period of 24 weeks. Subjects randomized to this group will also receive daily SL placebo tablets.

9.1.1. Implant Insertion and Removal Procedures

All Probuphine and placebo implants will be implanted and removed by trained clinicians. The Sponsor will institute the Probuphine Clinical and Procedure Training and Evaluation program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards. The Sponsor will also provide an Implant Insertion/Removal Instruction for Use slide deck, training DVD, as well as live training on the instructions for aseptic subdermal insertion and removal of Probuphine or placebo implants.

Prior to randomization and Day 1 (Implant Day), it will be recommended that subjects discontinue SL BPN and have implants inserted subdermally within 12-24 hours after their last SL BPN dose. In addition, it will be recommended that subjects discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to and bathe the day of insertion and removal of implants.
Implantation under the skin of the upper arm will be performed using a specialized applicator provided by the Sponsor. The Probuphine Applicator has been utilized in previous Probuphine studies and is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon®. Additional details on Insertion/Removal procedures and training will be provided in the Study Manual of Procedures (MOP) and the Implant Training DVD. Subjects should be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff. The Implant Clinician will also complete the Implant Insertion Procedure Assessment form provided in the Study MOP.

Subjects will have their implants removed during the End of Treatment Visit. Implant removal procedures are described in detail in the MOP and the Implant Training DVD. If, upon removal, the Implanting Clinician has difficulty locating the implants, ultrasound may be used to facilitate their localization. The Implant Clinician will also complete the Implant Removal Procedure Assessment form provided in the Study MOP.

### 9.2. Identity of Investigational Products

Probuphine and placebo implants are sterile, approximately 26 mm in length, and 2.5 mm in diameter. The implants are translucent to off-white in appearance. Each Probuphine implant contains 80 mg of BPN HCl, which has been blended and extruded with EVA. Buprenorphine HCl is a Schedule III controlled substance that is chemically derived from thebaine. One milligram of buprenorphine HCl is equal to 0.93 mg of buprenorphine as base. Placebo implants contain only EVA.

Each implant is individually packaged in a foil-lined, heat-sealed pouch. Pouches are then sterilized using gamma radiation. Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants or 4 placebo implants.

Subjects will be required to take daily SL BPN (BPN/naloxone) during the Maintenance Phase. These products will be supplied by the Sponsor or designee. Matching SL placebo tablets will be provided for each dosage strength. More information regarding the SL BPN and near-matching SL placebo products can be found in the MOP.

For potential supplemental SL BPN needs, a different brand of SL BPN will be utilized to prevent the unblinding of study drug. Information on this brand of SL BPN can be found in the MOP.
All containers/packages/boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

9.2.1. Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

All Patient Kits should be stored at room temperature (15–25°C / 59–77°F) in a secured, double-locked area and in accordance with applicable laws, regulations and institutional requirements. SL BPN should be stored in a secured area and in accordance with the product labeling (a copy is located in the MOP) and all applicable laws, regulations, and local/institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor’s drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site. The Investigator or designee must maintain an inventory record of all SL BPN dispensed to subjects for the purpose of treatment and supplemental use. The drug accountability records for returned SL BPN and placebo tablets will be handled by the unblinded study site personnel. Additional details are provided in the Study MOP.

Following implant removal, appropriate collection and disposal of all implants is outlined in the Study MOP.

Buprenorphine is a Schedule III controlled substance and study drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

9.2.2. Dispensing and Administration Procedures

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects. Subjects will be provided with a monthly supply of study medications.
Subjects will be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, tablets should be placed in different areas under the tongue at the same time.

9.2.3. **Supplemental SL BPN**

Investigator will be instructed to treat additional symptoms as they would usually, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions. However, subjects will be told that while additional counseling and other pharmacological interventions could be available, their current dose of BPN is expected to be adequate to maintain stability and their physician does not expect that they will need any additional supplemental SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine).

Any supplemental SL BPN, additional counseling, and other pharmacological interventions provided by the Investigator will be recorded, along with the reasons for determining the need for any supplemental interventions.

9.3. **Method of Assigning Subjects to Treatment Groups**

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.

Subjects who have met the eligibility criteria (Section 8) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group A: Daily SL BPN plus placebo implants or Treatment Group B: four Probuphine implants plus SL placebo tablets). Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2.
9.4. **Selection of Doses in the Study**

The dose of 4 Probuphine implants was selected based on efficacy, safety and pharmacokinetic data from Studies PRO-805, PRO-806, TPP-400, and PRO-810 (Investigator’s Brochure for Probuphine). Four Probuphine implants are expected to yield BPN plasma concentrations comparable to a SL BPN dose of 8 mg or less per day.

9.5. **Selection and Timing of Dose for Each Subject**

Subjects will be randomized to receive either 4 Probuphine implants or SL BPN. The SL BPN will be administered at a dose level equivalent to their usual care/Screening Phase dose.

No fasting or special dietary requirements are required for the study; however, when taking the SL BPN or placebo tablets, subjects should be advised to not eat or drink anything until the tablet(s) are completely dissolved. To ensure consistency in bioavailability, subjects should follow the same manner of dosing for the duration of the study.

9.6. **Blinding**

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo.

Due to minor potential differences between active and placebo SL tablets initiated after randomization, subjects will be told that clinical supplies of SL BPN have been specifically developed for this study and may look or taste different than commercially available products they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets. To provide additional assurance of maintaining the blind, a different brand of SL BPN will be utilized for any potential supplemental SL BPN needs. Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects.

Since the placebo implants have a slightly different appearance than the Probuphine implants, the following will be agreed upon in a signed document by the Implanting Clinician and the Investigator in order to maintain the blind:
The Implanting Clinician and any other staff involved in the implant insertion and removal procedures must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.

In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct the subject’s view of the procedure, etc.).

The study staff must not ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject’s safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

### 9.7. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject’s eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:

- NSAID or aspirin-containing medications should not be used during the week prior to implant insertion and the week prior to implant removal.

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take several days following discontinuation of Probuphine or SL BPN treatment. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be fully documented for subjects.
who have a requirement for any opioid analgesic for >7 days continually or general
anesthesia for surgery.

- Buprenorphine is metabolized via CYP3A4. Because CYP 3A4 inhibitors may increase
plasma concentrations of BPN, if CYP3A4 inhibitors such as azole antifungals (e.g.,
ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors
(e.g., ritonavir, indinavir, and saquinavir) are required, the Medical Monitor must be
consulted. Interactions with CYP 3A4 inducers have not been investigated; therefore it is
recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin
and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor
must be consulted prior to starting subjects on any of these agents.

- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other
tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) may
cause respiratory and CNS depression. Use of these substances should be minimized
during treatment with Probuphine or SL BPN. If these sedatives are required during the
study, the Medical Monitor must be consulted. Subjects should be advised of the danger
of concomitant use of sedatives while participating in the study. Subjects should be
explicitly advised of the danger of IV abuse of benzodiazepines while under treatment
with implants or SL BPN.

### 9.8. Subject Study Drug Accountability

Although it is difficult to divert the subdermal Probuphine implants for abuse (removal of
implants and extraction of the active BPN HCl from the EVA), diversion can theoretically occur.

Subjects must therefore be carefully monitored for such diversion. The implant site will be
visually inspected and palpated (for accountability of the implants) at each visit, and, if there is
any evidence of removal of the implants by the subject, the subject will be withdrawn from
study. If there is evidence of attempted removal, the subject will be withdrawn from the study
and all implants will be removed (Section 9.1.1). Due to the non-biodegradable nature of the
Probuphine and placebo implants, it is vital that no subject is lost to follow-up to ensure proper
implant removal, and that the End of Treatment Visit is completed as outlined in this protocol.

Subjects will be reminded to bring any remaining unused dispensed SL tablets to every visit.
10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2); the following sections outline the details and procedures associated with the assessments. Additional details on the assessments, including copies of questionnaires, logs, manuals, and information sheets are provided in the Study MOP.
### Table 2: Schedule of Assessments

<table>
<thead>
<tr>
<th>Study Period/Phase</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month:</strong></td>
<td>-</td>
<td>Month 1 Visits</td>
<td>Month 2 to 5 Visits</td>
</tr>
<tr>
<td><strong>Week:</strong></td>
<td>-2 to -1</td>
<td>Week 1</td>
<td>Week 4</td>
</tr>
<tr>
<td><strong>Day:</strong></td>
<td>-</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- **Informed Consent<sup>d</sup>**
  - X
- **Eligibility Criteria Review<sup>e</sup>**
  - X
  - X
- **Medical and Medication History / Substance Abuse and Treatment History**
  - X
- **DSM-IV-TR, MINI, v 6.0**
  - X
- **Physical Examination<sup>f</sup>**
  - X
- **Abbreviated Review of Systems**
  - X
- **Vital Signs<sup>g</sup>**
  - X
  - X<sup>b</sup>
  - X
  - X
  - Monthly
  - X<sup>b</sup>
  - X
- **ECG**
  - X
- **Chemistry, Hematology, Urinalysis and Coagulation Profile**
  - X

<sup>a</sup> Treatment Visits should be conducted within a window of ±7 days for the monthly visits, except for Post-Implant Visit, which should occur within a window of 1 to 5 days after Day 1. Visits for Weeks 25 and 26 should occur within ±3 days. If a subject misses a visit or completes a visit early or late, the original schedule should be resumed at the subsequent visit such that the ensuing visits occur as originally scheduled, relative to Day 1.<br><br>**<sup>b</sup> Baseline and Initiation of Study Drugs Visit.**<br><br>**<sup>c</sup> Post-Implant Visit.**<br><br>**<sup>d</sup> Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.**<br><br>**<sup>e</sup> Prior to enrollment in the randomization and Maintenance Phase of this study, all Inclusion and Exclusion criteria must be met.**<br><br>**<sup>f</sup> A complete physical exam of all major body systems will be performed at the Screening Visit.**<br><br>**<sup>g</sup> Includes temperature, blood pressure, pulse rate, respiration rate, and weight. Height will be captured at Screening Visit. BMI will be auto-calculated.**<br><br>**<sup>h</sup> Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implant insertion/removal, and then 15 minutes and 30 minutes after implant insertion/removal.
### Study Period/Phase:

<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month:</td>
<td>-</td>
<td>Month 1 Visits</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 2 to 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visits</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 6/</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visit</td>
<td></td>
</tr>
<tr>
<td>Week:*a</td>
<td>-2 to -1</td>
<td>Week 1</td>
<td>Week 24</td>
</tr>
<tr>
<td>Day:</td>
<td>-</td>
<td>Week 4</td>
<td>Week 25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 8, 12, 16, 20</td>
<td>Week 26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 24</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 26</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy test</strong>i</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Hepatitis B/C, HIV</strong>j</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Implant Site Examination</strong>k</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Dispense Treatment Identification Card</strong></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine Toxicology</strong></td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Random Urine Toxicology</strong></td>
<td></td>
<td></td>
<td>4 Random Urine Toxicology Tests</td>
</tr>
<tr>
<td><strong>Illicit Drug Use Self-Report</strong></td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Withdrawal and Desire to Use/Need to Use (SOWS, COWS, VAS)</strong></td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>SL BPN or placebo dispensing</strong></td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td><strong>Probuphine or placebo [four (4) implants] Insertion</strong></td>
<td>Xj</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Implant removal procedure</strong></td>
<td></td>
<td></td>
<td>Xm</td>
</tr>
<tr>
<td><strong>Additional interventions</strong>n</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

---

1 A serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit (Week 24). An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed prior to start of SL BPN and Probuphine treatment.

2 It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site’s IRB prohibits such testing.

3 The implant site will be visually inspected and palpated.

4 Subjects should be instructed to arrive having bathed with soap and water on Day 1.

5 It is recommended that subjects return 7 days post implant for suture removal.

6 Subjects may receive additional counseling, supplemental SL BPN, or other pharmacological interventions deemed appropriate by the investigator, at any time after implantation, at the investigator’s discretion.

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### Study Period/Phase:

<table>
<thead>
<tr>
<th>Month:</th>
<th>Screening</th>
<th>Month 1 Visits</th>
<th>Month 2 to 5 Visits</th>
<th>Month 6/End of Treatment Visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week:*</td>
<td>-</td>
<td>Week 1</td>
<td>Week 4</td>
<td>Week 24</td>
<td>Week 25</td>
</tr>
<tr>
<td>Day:</td>
<td>-</td>
<td>Day 1b</td>
<td>Post-Implant*</td>
<td></td>
<td>Week 26</td>
</tr>
</tbody>
</table>

- **Implant Insertion Procedure Assessment**  
  X |
- **Implant Removal Procedure Assessment**  
  X |
- **Psychosocial Counseling**  
  X  Monthly  X |
- **Adverse Events**  
  X  X  X  X  Monthly  X  X  X |
- **Concomitant Medications/Procedures**  
  X  X  X  X  Monthly  X  X  X |
- **Wound Care Information Sheet**  
  X  X |
- **Telephone Contact**  
  X (As Needed)  X

---

* AE events that are reported by the subject at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.

† Subjects will be monitored for at least 30 minutes after implantation for AEs. AEs will be recorded both prior to and after implant removal at Week 24.

‡ During removal process, careful inspection of the implant site, difficulty of removal and/or fracturing of the implants will be recorded.

§ If a significant AE is described by the subject and is judged by the Investigator as being possibly related to study treatment, the subject will visit the study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).

* A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent
The nature of the study and its risks and benefits will be explained to the participant by the Investigator or designated study personnel. The participant must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject’s medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. Demographics and Psychosocial History
The following demographics will be recorded: age (birthdate), sex, race, and ethnicity. A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.3. Medical History
The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

A psychiatric interview will be conducted using the Mini International Neuropsychiatric Interview, Version 6.0 (MINI). The MINI is a valid and reliable structured diagnostic interview for DSM-IV-TR psychiatric disorders.

10.1.4. Medication History
All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatments will be collected separately.
10.1.5. Substance Use and Treatment History

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences and concomitant medications, using a timeline follow-back type of interview (Fals-Stewart, 2000). Validation of historical clinical stability, including duration of treatment and dose at which patient has been stable, and any data available on urine toxicology results, will be captured and reported on the study entry form. Detailed information on substance use and treatment history is provided in the Study MOP.

10.2. Eligibility Review and Randomization

Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of randomization in the Maintenance Phase.

Randomization will be accomplished centrally, using an Interactive Voice Response System and/or by an Interactive Web Response System managed by the Sponsor.

10.3. Efficacy Assessments

Details regarding primary, secondary and exploratory endpoints are provided in Section 10.6 (Efficacy Variables); and discussed further in Section 12.3 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Study MOP.

10.3.1. Urine Toxicology for Opioids

Urine toxicology samples will be collected at each visit (both scheduled and random) using a urine collection cup containing a temperature sensor. Specimen authenticity will be verified at the site using this sensor to measure the urine temperature immediately following collection. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the
subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as ‘missing’, and should not be sent for analysis (any such samples must be documented in the subject’s records). Direct observation approach to obtaining urine samples may be used if the investigator deem necessary. Urine samples will be logged and numbered and then sent to a central laboratory for analysis for the presence of opioids (e.g., codeine, morphine, hydrocodone, oxymorphone, hydromorphone, oxycodone, methadone, and fentanyl). In addition, it is recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

10.3.2. Self-Reported Illicit Drug Use
Subjects will be questioned about illicit drug use, including illicit or prescription opioids and other drugs of abuse using a timeline follow-back type of interview (Fals-Stewart, 2000). A copy of the Illicit Drug Use Self-Report form is provided in the Study MOP.

10.3.3. Measures of Desire and Need to Use
Desire to Use and Need to Use will be administered using unipolar 100 mm VAS (“Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm = Strongest possible desire, and from 0 = No need to use and 100 mm = Strongest possible need, respectively) (Kozlowski et al., 1989).

Copies of these VASs are provided in the Study MOP. NOTE: Only VAS copies provided by the Sponsor should be used with study subjects; photocopies made locally may result in changes to the length of the scale, leading to inaccurate results.

A separate VAS will be provided for each Desire to Use and Need to Use and measurements must be taken separately (i.e., separated in time or by other procedures).

10.3.4. Measures of Withdrawal

10.3.4.1. Subjective Opioid Withdrawal Scale (SOWS)
Subjects will complete a self-assessment of withdrawal symptoms using the SOWS. This form contains 16 questions that rate the intensity of withdrawal from 0 (“Not at all”) to 4 (“Extremely”). A copy of the SOWS is provided in the Study MOP.
10.3.4.2. Clinical Opioid Withdrawal Scale (COWS)

Study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater. A copy of the SOWS is provided in the Study MOP.

10.3.5. Urine Toxicology for Other Drugs of Abuse

Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative methods. Positive results will not be confirmed using quantitative methods.

10.3.6. Supplemental Visits, Medication and Counseling

Supplemental SL BPN use will be allowed, as described in Section 9.2.3. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for supplemental visits, supplemental SL BPN needs, phone calls or additional counseling or other pharmacological interventions, will be recorded.

10.4. Safety Assessments and Other Procedures

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF. Appropriate medical intervention should be provided and, if necessary, implants may be removed or SL BPN treatment discontinued as clinically indicated.

10.4.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
### 10.4.1.1. Adverse Event Reporting

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Relationship to insertion / removal procedure
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the End of Treatment Visit (i.e., implant removal and discontinuation of SL BPN/placebo treatment). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

### 10.4.1.2. Serious Adverse Event

A serious adverse event (SAE) or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
• Is a congenital anomaly/birth defect (in an offspring)

• An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the End of Treatment Visit AND are not considered to be drug-related by the Investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

10.4.1.2.1. Serious Adverse Event Reporting

Serious Adverse Events (SAEs) must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the End of Treatment Visit are reportable within 24 hours. During the follow-up period beyond 14 days from implant removal or discontinuation of SL BPN assigned treatment, only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

• Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.

• The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.

• The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
  o Subject ID
  o Basic demographic information (age, gender, weight)
Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)

- Onset date and severity of the event
- Brief description of the event including frequency and severity of symptoms leading to diagnosis, and information on supplemental SL BPN
- List of relevant test results and lab data
- Any other relevant history
- Dates of implantation and removal, if applicable
- Dates and doses of supplemental SL BPN usage
- Whether the study drug was discontinued
- Whether the event abated after implants removed and/or assigned treatment SL BPN discontinued and/or supplemental SL BPN discontinued, as applicable
- Investigator’s assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB / Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

### 10.4.2. Pregnancy

Pregnancies among trial participants should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant may withdraw their consent and discontinue the study and be referred back to the care of their usual provider. Follow-up information will be obtained where possible (with the consent of the participant or their partner).
regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

10.4.3. **Clinical Laboratory Assessments**

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not clinically significant) or “CS” (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., “CS/mild anemia.” In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 3.
Table 3: Clinical Laboratory Assessments

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Sodium</td>
<td>Color</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Potassium</td>
<td>pH</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Magnesium</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>RBC Morphology</td>
<td>Calcium</td>
<td>Ketones</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Glucose (random)</td>
<td>Protein</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Bicarbonate</td>
<td>Glucose</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Chloride</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>concentration</td>
<td>Creatinine</td>
<td>Nitrite</td>
</tr>
<tr>
<td>Total and differential (absolute)</td>
<td>Total protein</td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>white blood cell count</td>
<td>Blood urea nitrogen</td>
<td>Occult blood</td>
</tr>
<tr>
<td>Platelets</td>
<td>Albumin</td>
<td>Microscopic examination of</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin</td>
<td>sediment, only if urinalysis</td>
</tr>
<tr>
<td></td>
<td>Alanine transferase</td>
<td>dipstick results are abnormal</td>
</tr>
<tr>
<td></td>
<td>Aspartate transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic dehydrogenase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine phosphokinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total cholesterol (non-fasting)</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the Follow-up Visit. An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of SL BPN and Probuphine treatment.

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed for all subjects, unless a site’s IRB prohibits such testing. It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.
10.4.4. Vital Signs
Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

10.4.5. 12-Lead Electrocardiogram (ECG)
12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

10.4.6. Physical Examination
A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be determined as described in Table 2

10.4.7. Implant Site Examination and Wound Care
Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs. Copies of the wound care information sheets must be reviewed and approved by each site’s IRB, prior to providing them to subjects.

Implant site reactions can occur with the implantation and removal of Probuphine or placebo implants. The most frequently-reported AEs related to the insertion/removal procedure (occurring in greater than 10% of subjects) in previous Phase III clinical studies were erythema, edema, itching, pain, bleeding, bruising, and scarring. The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities, including implant expulsion or implant migration. The implant site should also be palpated to ensure that the four implants have not been removed. If there is any evidence of removal or attempted removal of the implants, or if the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and any remaining implants will be removed.
10.4.8.  **Psychosocial Counseling**

All subjects will receive manual-guided drug counseling during the study, as outlined in Table 2 and described in more detail in the Individual Drug Counseling Manual (provided in the Study MOP) (Mercer & Woody). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

10.4.9.  **Treatment Identification Card**

Subjects will receive a wallet card indicating that they are receiving BPN as part of the study. This card should be presented to health care providers by the subject in the event of an emergency or if medications such as opioid analgesics are required (see Section 9.7). Sample wallet cards will be provided for IRB submission.

10.4.10. **Other Safety Considerations**

Buprenorphine may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction and after implant insertion, and to exercise caution in performing activities requiring alertness such as driving a car during the first few days after implant insertion, or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

10.5.  **Appropriateness of Measures**

The efficacy outcome measures were selected to provide an efficacy assessment of the study medications with regards to both objective (i.e., urine toxicology results for opioids), and patient-based assessment (i.e., subject-reported desire/need to use and desire/need to use opiates). The most direct method to ascertain the frequency and amount of illicit opiate use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (Zanis et al., 1994). Thus, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. Urine toxicology has been used in many efficacy assessments of buprenorphine and will be used as the primary outcome measure in the definition of responders in this study (Section 10.6). Urine toxicology results will be adjusted for self-reported drug use at each study visit.

Secondary outcome measures were selected as a series of measures and scales to provide a complete assessment of the effectiveness and efficiency of transfer from SL BPN to Probuphine implants with regard to patient-based assessments (i.e., subject-reported desire and need to use...
opioids, withdrawal), as well as measures of the subject’s functional impairment status (Sheehan Disability Scale).

Desire to Use VAS and Need to Use VAS were selected over the typical Craving VAS because the latter term is ambiguous and may have different meaning to different individuals, while the Desire/Need to Use VAS more directly assess the potential behavioral outcome (Kozlowski et al., 1989).

Standard and widely used measures of withdrawal will be included in this study (COWS and SOWS) (Wesson & Ling, 2003; Handelsman et al., 1987) in order to ensure that subject’s withdrawal symptoms are adequately controlled by the Probuphine implants as compared to SL BPN.

In addition, although expected to be relatively rare in this study, supplemental SL BPN use will be evaluated. Finally, to ensure that potential signs of treatment failure are not missed, additional measures of potentially inadequate treatment will include subject- or Investigator-requested additional visits or counseling.

10.6. Efficacy Variables

10.6.1. Primary Efficacy Endpoint
The primary efficacy endpoint is a responder analysis. A subject will be designated as a responder (meaning they have maintained stability) if they have no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

10.6.2. Secondary Efficacy Endpoints
Secondary efficacy endpoints will include average scores over 24 weeks of treatment and average change from baseline (Day 1) scores over 24 weeks of treatment for the following outcome measures:

- Measures of desire/need to use:
  - Desire to Use VAS
  - Need to Use VAS

- Measures of withdrawal:
  - Clinical Opiate Withdrawal Scale (COWS)
  - Subjective Opioid Withdrawal Scale (SOWS)
10.6.3. Exploratory Efficacy Variables

Exploratory variables include:

- Urine toxicology for other drugs of abuse
- Supplemental SL BPN use, unscheduled visits, phone calls and additional psychosocial counseling and other pharmacological interventions, including reasons for use
- Treatment discontinuation, including reasons for discontinuation

10.7. Safety Variables

Safety variables include:

- AEs
- Clinical laboratory tests
- ECG
- Physical and implant site examinations
- Implant site insertion and removal assessments
- Concomitant medications
- Vital signs

11. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. The Sponsor or designee will review source documents for accuracy and completeness during on-site
monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with
the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted
when appropriate. Failure to comply with remedial actions may result in investigational site
termination and regulatory authority notification.

11.1. **Data Collection**

Source documents include but are not limited to original documents, data and records such as
hospital/medical records (including electronic health records), clinic charts, lab results,
participant diaries, data recorded in automated instruments, microfilm or magnetic media, and
pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data
required by the protocol should have supporting source documentation for entries in the EDC
system.

All CRFs will be completed by the site staff prior to review by the Sponsor’s monitor or
designated representative. The Sponsor’s monitor or designated representative will review all
source records on-site and compare them to the data collected on the CRF. All entries,
corrections, and alterations will be made by the Investigator or other authorized study personnel.
All data entries will be verified for accuracy and correctness by independent monitors. The
electronic data capture system maintains a full audit trail.

11.2. **Study Auditing and Monitoring**

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and
completeness) will be performed by the Sponsor’s designated monitor(s). The extent, nature, and
frequency of on-site visits will be based on such considerations as the study objectives and/or
endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the
protocol, the Investigator agrees that, within local regulatory restrictions and institutional and
ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or
an IRB may visit the site to perform audits or inspections, including the drug storage area, study
drug stocks, drug accountability records, participant charts and source documents, and other
records related to study conduct. The purpose of the Sponsor audit or inspection is to
systematically and independently examine all study-related activities and documents to
determine whether the study-related activities were conducted, and data recorded, analyzed, and
accurately reported according to the protocol, the site’s standard operating procedures, GCP
guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the study data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

12.2. Analysis Populations

The study analysis populations will consist of:

- **Randomized Population**: All subjects who are randomized into the Maintenance Phase
- **Intent-to-Treat (ITT) Population**: All subjects who have been randomized and have received an implant and/or received SL BPN/placebo. Analyses based on this population will group subjects according to the treatment they were randomized to receive, regardless of actual treatment received, and this will be the primary analysis population.
- **Safety Population**: All subjects who are randomized and treated with implants or who received any dose of SL BPN/placebo in the Maintenance Phase. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.
- **Per Protocol Population**: All subjects in the ITT population with no major protocol violations. Major protocol violation criteria will be established prior to the database lock.

12.3. Planned Analyses

12.3.1. Disposition, Demographics and Other Baseline Characteristics

Disposition for all randomized subjects will be summarized by the randomized treatment group. Reasons for discontinuation will be tabulated for each treatment group and overall.
Demographic data and baseline psychosocial characteristics will be summarized.

Tabular summaries and/or listings will be provided for baseline clinical characteristics such as illicit drug and treatment use history, medical and psychiatric history, inclusion/exclusion criteria, and medication history.

12.3.2. Analysis of Efficacy Measures

12.3.2.1. Primary Endpoint

The primary efficacy variable will be responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

A total of 10 urine toxicology samples will be collected throughout the 6 months of the study treatment period with 6 scheduled visits (1 visit per month) plus 4 random urine toxicology visits.

12.3.2.2. Analysis of Primary Endpoint

A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of \( \delta = 20\% \) will be employed to define non-inferiority. Let \( \pi_C \) and \( \pi_T \) be the rate of response at 24-weeks on the control arm and experimental treatment arm, respectively. The null hypothesis \( (H_0) \) of inferiority is

\[
H_0: \pi_T \leq \pi_C - 0.20
\]

The alternative hypothesis \( (H_A) \) of non-inferiority is

\[
H_A: \pi_T > \pi_C - 0.20
\]

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above \(-0.20\)).

Rationale for 20% non-inferiority margin: The 20% margin is appropriate from a scientific validity perspective as well as meeting Food and Drug Administration (FDA) guidelines for non-inferiority margin selection (FDA, 2010). In this study with 180 subjects, the observed data that meet the statistical 20% margin will meet scientific face-validity for the equivalency of the treatment arms. The table below (Table 4) summarizes the required Probuphine Treatment Group’s response rate (% of responders) to satisfy non-inferiority based on the 20% margin and...
the sample size of 90 subjects per group at the two-sided 5% significance level for a range of observed SL BPN arm’s response rate (Note: due to discreteness some percentages are not possible).

### Table 4: Response Rates and Non-Inferiority Margins

<table>
<thead>
<tr>
<th>Observed SL BPN Arm’s Response Rate (% of Responders)</th>
<th>Required Minimum Observed Probuphine Arm’s Response Rate (% of Responders) to Satisfy Non-inferiority (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
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</tr>
<tr>
<td>84.4</td>
<td>76.7</td>
</tr>
<tr>
<td>80</td>
<td>73.3</td>
</tr>
<tr>
<td>74.4</td>
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<tr>
<td>64.4</td>
<td>58.9</td>
</tr>
<tr>
<td>60</td>
<td>54.4</td>
</tr>
</tbody>
</table>

The table demonstrates that utilizing the 20% margin to satisfy non-inferiority, the Probuphine Treatment Group’s response rate should be at least similar to the rate for SL BPN control arm.

Although there is little literature on SL BPN treatment in long-term stabilized maintenance subjects, there is some empirical information available to lend credence to the 20% non-inferiority margin:

1. With patients on longer term BPN or methadone treatment, blinded taper (detoxification) studies indicate rates of continued opioid abstinence following complete withdrawal of about 18 to 31%. Although little data is available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15%. A summary of literature is provided in Section 16.

2. A survey of addiction experts was performed by the Sponsor to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN.
   a. The results demonstrated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability) to illicit opioid use if these patients were taken off their stable dose of 8 mg or
3. Finally, the FDA Draft Guidance notes that circumstances might support a less conservative choice for the margin, including:

a) **Pharmacologic properties of the test drug that are very similar to those of the active control** – Probuphine is an alternative dosage form of the same active entity with the expectation of similar overall plasma concentrations to the SL BPN arm;

b) **Use of a persuasive biomarker** – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success;

c) **If the drug has been shown to be effective in closely-related clinical settings** – Probuphine has already been shown to be effective relative to placebo in two trials in harder-to-treat populations;

d) **If the test drug were shown to have some important advantage (e.g., on safety or on a secondary endpoint)** – The safety issues associated with abuse of SL BPN are well-known; the Drug Abuse Warning Network confirmed an increasing trend to adverse medical outcomes associated with BPN abuse, i.e., a total of 21,483 emergency department visits related to abuse/misuse were reported in 2011 (DAWN, 2013). Probuphine has the potential to reduce misuse/abuse associated with SL BPN and have a significant positive public health impact, in addition to potentially increasing adherence.

Thus, the overall data and circumstances associated with this study support the use of a 20% non-inferiority margin.

### 12.3.2.2.1. Handling of Dropouts or Missing Data

If all missing values (urine toxicology results for illicit opioids) are replaced with extreme values (i.e., either all replaced with “negative” or all replaced with “positive”), biases will be introduced. For example, if all missing values are replaced with “positive,” the results will be biased in favor of the group with the smaller dropout rate. To avoid such biases, in the primary
analyses, missing values within a treatment arm will be replaced by randomly generated binary indicator (1=“Opioid-Positive” and 0=“Opioid-Negative”). The probability of having 1 will be the proportion of “Opioid-Positive” samples out of all available samples within that treatment arm. The random binary outcomes will be generated using seed=1374809352 in SAS.

12.3.2.3. Sensitivity Analyses
The following sensitivity analyses will be performed:

- Analysis based on completers (i.e., analysis based on all subjects who provided all required samples);
- Analysis based on missing values replaced with “Opioid-Positive;”
- Per protocol analysis (i.e., analysis based on subjects who do not have major protocol violations).

12.3.2.4. Analysis of Secondary Efficacy Endpoints
The secondary endpoints will include change from baseline (Day 1 prior to implantation) in two measurements of desire/need to use (Desire to Use VAS, Need to Use VAS), two measurements of withdrawal (COWS and SOWS), and the measure of functional impairment (Sheehan Disability Scale) at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.

Details of additional measures of efficacy and their analysis will be described prospectively, prior to final database lock and unblinding, in the SAP for this study.

12.3.3. Analysis of Safety
Exposure will be summarized by treatment group.

AEs will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to study drug or implant insertion/removal, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.
Data for clinical laboratory tests, ECG, vital signs, and physical and implant examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate.

Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics.

By-subject listings will be provided for all safety data.

12.4. Determination of Sample Size

The sample size of 90 per treatment arm (180 total) was selected to achieve 87.3% power, assuming both arms have a 75% rate of responders. If the true rates are lower, but equal in both arms, with a 65% rate of response, the power of the trial to determine non-inferiority is 80.3%. If each treatment arm has an 85% rate of response, then the trial with 180 subjects would have 96.4% power to determine non-inferiority.
13. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the Sponsor and the investigational site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor’s representatives and/or regulatory authority’s representatives at any time.

13.1.2. Ethics Approval

The investigational site’s IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

13.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant’s legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided...
13.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant’s chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant’s name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such as the United States FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant’s initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of
the subject’s information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

13.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

13.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:

Version: Final 1.0, 14-MAY-2014
A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or

A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator’s portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

13.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.
13.6. Protocol Amendments

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

13.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
14. SPONSOR APPROVAL PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 1.0

Date: 14-MAY-2014

Braeburn Pharmaceuticals

Frank E. Young, MD, PhD
Executive Vice President, Clinical and Regulatory Affairs

Date: 14 May 2014
15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 1.0

Date: 14-MAY-2014

I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonization/Good Clinical Practice Guidelines.

Investigator’s Name (please print or type)

Signature ___________________________ Date ___________________________

Version: Final 1.0, 14-MAY-2014
16. SUMMARY OF LITERATURE TO SUPPORT NON-INFRINGEMENT MARGIN

A meta-analysis of tapered discontinuation following long-term methadone or BPN treatment found an average abstinence rate of 33% (Korner & Waal, 2005). However, because of the differences in methodology (single or double-blinding, naturalistic, etc.), definitions of abstinence, treatments administered during MAT and durations of follow-up, some studies are more relevant than others. In addition, this article didn’t report on the baseline rates of percentage abstinence or urine toxicology results.

Breen et al., (2003) reported on a study of stable methadone patients (for at least 6 months) to BPN and then gradual reduction to 0 mg BPN (i.e., blinded) over an average duration of 11 weeks showed that subjects at 1 month follow-up after complete BPN discontinuation had 31% negative opioid samples (relative to about 73% negative at baseline, 89% negative during BPN induction, and 91% negative during BPN taper).

One double-blind, double-dummy study in methadone users found 25% abstinence overall during 1 month follow-up after complete discontinuation following gradual taper regimens. Abstinence was 18% in the "rapid" withdrawal group (taper over 10 weeks) (versus 100% negative urine opioid results for 4 weeks preceding study entry and 92% negative for the 6 months prior to the study) (Senay, 1977).

Most of the studies used tapered discontinuation, but in terms of abrupt discontinuation, one survey study in Australia reported that 15% of patients who abruptly discontinued opioid maintenance therapy (BPN or methadone) were abstinent for at least 3 months, while 26-27% were abstinent with either self- or physician-directed taper regimens (Winnstock et al., 2011).
# 17. SUMMARY OF SURVEY RESULTS FROM ADDICTION SPECIALISTS

<table>
<thead>
<tr>
<th>PI #</th>
<th>% Negative UDS Over 6 mths*</th>
<th>% Negative UDS Over Next 6 mths*</th>
<th>% Relapse upon BPN Discontinuation (Over 6 mths)</th>
<th>Maximum Reasonable Change in % UDS positive</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
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<td>85</td>
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NOTES: DNAQ = response given did not match question asked and is not useful for the averages; NNR = no numerical response; UDS=urine opioid toxicology
* Some answered as % positive some as % negative, for ease, results have been converted to % negative.
- If range was given; the average of the range has been entered here (i.e., 30-40% = 35% for purposes of these calculations)
- If answer given as < or >, response was entered as the numeric value
- “X of 6 responses were calculated as: 0 of 6 = 0%; 1 of 6 = 17%; 2 of 6 = 33%; 3 of 6 = 50%; 4 of 6 = 67%; 5 of 6 = 83%; 6 of 6 = 100%
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Clinical Trial Protocol
PRO-814

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

PROBUPHINE®
(BUPRENORPHINE HYDROCHLORIDE IMPLANT)

BRAEBURN PHARMACEUTICALS:
47 Hulfish Street, Suite 441
Princeton, NJ 08542

Original Protocol: 1.0, 14-MAY-2014
Amendment No. 1: 2.0, 14-AUGUST-2014

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SUMMARY OF CHANGES

Study Title: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Original Protocol: Version 1.0, 14-MAY-2014
Amendment No. 1: Version 2.0, 14-AUGUST-2014

AMENDMENT No. 1, DESCRIPTION OF CHANGES

1. Protocol Synopsis, section, Duration of Study – revision of Screening from 2 to 3 weeks.
2. Table of Contents 7.1.1, Section 7.1.1, Figure 1: Overview of Study Design, and Table 2: Schedule of Assessments - revision of Screening Phase (Week -2 to -1) to (Week -3 to -1).
3. Figure 1: Overview of Study Design – revision of “up to 2 Weeks” screening to “up to 3 Weeks”.
4. Section 7.1 – revision of “subjects will participate in this study for up to 28 weeks, including 2 weeks of the Screening Phase” to “subjects will participate for up to 29 weeks, including 3 weeks of the Screening Phase”.
5. Section 9.7 – revision to “It is recommended that subjects discontinue NSAID or aspirin containing medications during the week prior to implant insertion and the week prior to implant removal” to be consistent with Section 9.1.1.
6. Section 10.3.4.2 – revision of last sentence from “SOWS” to “COWS”.
7. Section 10.4.3 – revision: serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit (not Follow-up Visit).

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## 1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

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<th>ROLE IN STUDY</th>
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<th>CONTACT INFORMATION</th>
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<tr>
<td>Study Sponsor</td>
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<td>47 Hulfish Street, Suite 441 Princeton, NJ 08542</td>
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2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Product: Probuphine® (buprenorphine hydrochloride implant)

Name of Active Ingredient: buprenorphine hydrochloride

Study Title:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitionsed from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Objectives:

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of sublingual (SL) buprenorphine (BPN), to 4 Probuphine implants compared to SL BPN.

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

Methodology:

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN. The study will include 3 Phases; Screening, Maintenance and Follow-up.

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history.

All subjects who have provided written informed consent and have met the other study entry criteria will be eligible for randomization. Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit). On Post-Implant Visit, additional follow-up safety and implant assessment procedures will be conducted. Subjects will return for monthly study visits on Weeks 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). In addition to the monthly scheduled visits, subjects will provide 4 random
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urine toxicology samples throughout the 24-week treatment period.

A total of 10 urine toxicology samples will be collected; 6 at scheduled visits (1 per month) and 4 at random urine toxicology visits throughout the 24-week treatment period. At the scheduled visits, other assessments of efficacy and safety will be collected. Implants will be removed at the End of Treatment Visit on Week 24.

Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects and Week 26 will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

**Number of Subjects (Planned):**

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized in the Maintenance Phase.

**Inclusion and Exclusion Criteria**

**Inclusion Criteria**

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for at least 6 months.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days prior to Screening.
   c. No positive urine toxicology results for illicit opioids in the last 90 days.
5. Free from significant withdrawal symptoms (score of \( \leq 5 \) on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

**Exclusion Criteria**

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.

6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).

7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.

8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).

9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.

10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

**Investigational Product, Dosage and Mode of Administration:**

All subjects will receive either four 80 mg Probuphine implants or four matching placebo implants for a period of 24 weeks.

**Reference Therapy, Dosage and Mode of Administration:**

Buprenorphine will be administered as 2 mg or 8 mg SL BPN tablets at doses of ≤8 mg (the same dose subjects had been previously stable on) per day or matching placebo SL tablets for a period of 24 weeks.

**Duration of Study:**

Subjects will participate in this study for up to 29 weeks, including Screening (up to 3 weeks), Maintenance/active study drug treatment (24 weeks), and Follow-up (2 weeks).

**Criteria for Evaluation:**

**Primary Efficacy Endpoint:** The primary efficacy endpoint is a responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Illicit opioid use is defined as a positive opioid urine toxicology result or self-
reported illicit opioid use.

**Secondary Efficacy Endpoints**

Secondary efficacy endpoints will include measures of desire/need to use (Desire to Use VAS, Need to Use VAS) and measures of withdrawal (Clinical Opiate Withdrawal Scale [COWS] and Subjective Opioid Withdrawal Scale [SOWS]).

**Exploratory Efficacy Variables:**

Exploratory variables include: Urine toxicology for other drugs of abuse, supplemental SL BPN use, unscheduled visits, phone calls, additional psychosocial counseling and other pharmacological interventions, and treatment discontinuation, including reasons for discontinuation.

**Safety Variables**

Safety endpoints include: adverse events (AEs), clinical laboratory tests, electrocardiogram, physical and implant site examinations, implant site insertion and removal assessments, concomitant medications, and vital signs.

**Statistical Methods (Data Analysis):**

**Primary efficacy analysis:**

A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta=20\%$ will be employed to define non-inferiority. Let $\pi_C$ and $\pi_T$ be the rate of response at 24-weeks on the control arm (SL BPN) and experimental treatment arm (Probuphine), respectively. The null hypothesis ($H_0$) of inferiority is

\[ H_0: \pi_C - \pi_T \leq -\delta \]

The alternative hypothesis ($H_A$) of non-inferiority is

\[ H_A: \pi_C - \pi_T > -\delta \]

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).

**Secondary efficacy analysis:**

The secondary endpoints will include change from baseline (Day 1) in the secondary efficacy variables at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.
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4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE  Adverse event
AIDS Acquired Immune Deficiency Syndrome
ANCOVA Analysis of covariance
BMI Body Mass Index
BPN Buprenorphine (may refer to buprenorphine/naloxone or buprenorphine alone)
$C_{avg}$ Average plasma concentration
CFR Code of Federal Regulations
CNS Central nervous system
COWS Clinical Opioid Withdrawal Scale
CRF Case Report Form (may include electronic data capture systems or paper forms)
CS Clinically significant
CSA Clinical Study Agreement
CYP Cytochrome P450
ECG Electrocardiogram
EDC Electronic data capture
EE Efficacy Evaluable
EVA Ethylene vinyl acetate
FDA Food and Drug Administration
GCP Good Clinical Practice
HIV Human Immunodeficiency Virus
ICF Informed consent form
ICH | International Conference on Harmonization
IRB | Institutional Review Board
ITT | Intent-to-Treat
IV | Intravenous
MAT | Medication-assisted treatment
MINI | Mini International Neuropsychiatric Interview
MOP | Manual of Procedures
NCS | Not clinically significant
NSAID | Non-steroidal anti-inflammatory
SAE | Serious adverse event
SL | Sublingual
SOC | System Organ Class
SOWS | Subjective Opioid Withdrawal Scale
RBC | Red blood cell
SAP | Statistical Analysis Plan
THC | Tetrahydrocannabinol
US | United States
VAS | Visual analogue scale
5. INTRODUCTION

5.1. Background

Opioid dependence is a serious chronic, debilitating, and sometimes fatal disorder. The process of recovery from opioid dependence is, for most individuals, a long-term and non-linear endeavor that is subject to recurrent relapse. It is well understood that medication-assisted treatment (MAT) without a broader treatment program is generally insufficient to achieve recovery for most opioid-dependent individuals. However, it is also known that MAT has proved to be effective in enabling many individuals to succeed on the long-term path to recovery. The primary agents used in MAT are methadone, buprenorphine hydrochloride (BPN), and naltrexone. Buprenorphine, a partial µ-opioid receptor agonist, is effective and safe (marketed in 34 countries), and has expanded access to treatment for individuals who might otherwise remain untreated. Sublingual (SL) BPN, first approved in 2002, has become widely-available and highly-effective treatment for opioid dependence.

Although daily dosing of SL BPN has proven effective, this route of delivery has several shortcomings. First, SL BPN can easily be diverted for illicit use, injected for greater effect, or accidentally ingested especially by children (Winstock et al., 2008). Second, adherence to daily medication is a challenge, and a conscious decision to discontinue BPN treatment in anticipation of exposure to illicit drugs can also be achieved. Medication non-adherence may lead to relapse, treatment failure, and mortality in the opioid-dependent population. Such limitations are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently), or to those who have difficulty managing the responsibility of daily dosing.

Probuphine® (buprenorphine hydrochloride implant; herein referred to as Probuphine) is a subdermally implantable, abuse- and diversion-deterrent formulation of BPN under development for the maintenance treatment of opioid dependence. Probuphine was developed as an additional therapeutic alternative in maintenance treatment of opioid dependence by providing a long-acting six-month BPN implant that is inherently less susceptible to accidental ingestion (especially by children), abuse and diversion than SL BPN, and is intended to facilitate medication adherence. Probuphine is inserted subdermally in a brief in-office procedure under local anesthetic. Probuphine is designed to provide sustained release of BPN for up to 6 months. At the end of each 6-month treatment, Probuphine is removed in a brief, in-office procedure.
under local anesthetic. Each Probuphine implant consists of 80 mg of BPN that has been blended and extruded with ethylene vinyl acetate (EVA).

5.2. Safety and Efficacy of Buprenorphine

The safety and efficacy of BPN in the treatment of opioid dependence are well-established (Eder et al., 1998; Johnson et al., 1992; Johnson et al., 1995; Johnson et al., 2000; Lopatko et al., 2003; Strain et al., 1994). As a partial agonist at the µ-opioid receptor and an antagonist at the κ-opioid receptor, a ceiling or plateauling effect is observed whereby higher doses of BPN are less likely to cause complications of overdose relative to full µ-opioid receptor agonists (Walsh et al., 1994). This results in a safety profile superior to methadone and levo-acetyl-methadol, though efficacy of these treatments for opioid dependence is comparable (Johnson et al., 2000).

In controlled clinical trials with SL BPN, the most common adverse events (AEs) (i.e., those occurring in >10% of subjects) included headache, pain, withdrawal syndrome, asthenia, anxiety, depression, insomnia, rhinitis, nausea, constipation, back pain, infection, and sweating (Reckitt Benckiser Pharmaceuticals, Inc., 2013). From published clinical studies, additional common side effects reported with BPN include drowsiness (increased with alcohol), vomiting, orthostatic hypotension, and sweating. In addition, due to its κ-receptor antagonist activity, BPN can cause withdrawal symptoms if administered with a µ-opioid agonist (such as heroin). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in patients receiving BPN, both in clinical trials and in post-marketing AE reports (Reckitt Benckiser Pharmaceuticals, Inc., 2013). Available data cannot exclude the role of BPN as either causative or contributory in the development of these hepatic abnormalities.

Buprenorphine is metabolized by the 3A4 isoenzyme of cytochrome P450 (CYP3A4). Therefore, concomitant use of CYP 3A4 inhibitors, such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) may increase plasma concentrations of BPN.

Respiratory and central nervous system (CNS) depression can be magnified with concomitant use of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedatives/hypnotics, or other CNS depressants (including alcohol). There have been post-marketing reports of coma and death associated with the concomitant intravenous (IV) misuse of SL BPN and benzodiazepines. In many of these cases, SL BPN was misused by self-injection of crushed SL BPN tablets. In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if
required. Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine.

Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Subjects should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BPN therapy does not adversely affect their ability to engage in such activities. Like other opioids, BPN may produce orthostatic hypotension in ambulatory subjects.

As with other µ-opioid receptor agonists, the administration of BPN may obscure the diagnosis or clinical course of subjects with acute abdominal conditions.

5.3. Safety and Efficacy of Probuphine

The safety and efficacy of Probuphine have been studied for the maintenance treatment of opioid dependence in two six-month randomized controlled trials and two six-month, open-label re-treatment trials (Table 1). The pharmacokinetic properties of Probuphine have been evaluated in two relative bioavailability studies, in which plasma concentrations of BPN derived from four 80 mg Probuphine implants were observed to be comparable to the average of those measured in subjects receiving 8 mg or less of SL BPN per day. The subjects in these Phase 3 studies were adults who had not received any MAT for at least 90 days prior to entering the studies, and who underwent a brief induction with SL BPN 12 to 16 mg daily prior to randomization in the controlled trials or continuation in the re-treatment trials.

The medical literature, the completed studies with Probuphine, and an additional pharmacometric analyses performed by the Sponsor demonstrate:

1. Safety and effectiveness of SL BPN in the maintenance treatment of opioid dependence;
2. Effective use of lower SL BPN doses for maintenance treatment of individuals stabilized on daily doses of SL BPN 8 mg or less;
3. Four 80 mg Probuphine implants yield average BPN plasma concentrations of 0.74 to 0.76 ng/mL (average concentration [C_avg] over weeks 4 to 24 in subjects who received 4 implants and did not take supplemental SL BPN in PRO-805/PRO-806 studies), which is within a range of approximately 0.5 to 1.0 ng/mL, comparable to the average of those observed following daily doses of 8 mg or less of SL BPN;
4. Probuphine implants provide stable and consistent therapeutic BPN concentrations resulting from continuous delivery of BPN over 6 months, with low intra- and inter-subject variability, and without risk of non-adherence that may be associated with SL BPN;
5. Safety and efficacy of Probuphine in a more difficult-to-treat population of opioid-dependent patients (inducted on 12 to 16 mg/day) (Ling et al., 2010; Rosenthal et al., 2013), allowing a potential downward extrapolation of efficacy to a more stable population of patients on longer-term maintenance treatment with 8 mg SL BPN or less.

In addition to the above, Probuphine may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy. Thus, Probuphine is expected to provide patients and clinicians with an additional treatment option with the potential for more stable plasma concentrations, enhanced adherence and reduced public health consequences of diverted and abused SL BPN.

Table 1: Summary of Previous Data to Support Probuphine Safety and Efficacy

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Study Number</th>
<th>Subjects</th>
<th>Key Findings for Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>TTP-400-02-01</td>
<td>N=12</td>
<td>Four 80 mg Probuphine implants yield BPN plasma concentrations comparable to those observed upon administration of SL doses of 8 mg or less daily.</td>
</tr>
<tr>
<td></td>
<td>PRO-810</td>
<td>N=9</td>
<td>Probuphine implants provide stable BPN concentrations over 6 months, with low intra- and inter-subject variability.</td>
</tr>
<tr>
<td>Efficacy</td>
<td>PRO-805</td>
<td>N=262</td>
<td>Statistical significance of pre-specified endpoints met in a population of subjects stabilized for as little as 3 days. Efficacy &gt; Placebo (with SL rescue) on multiple outcome measures. Efficacy similar to SL BPN according to PRO-806 and published data (Rosenthal et al., 2013) In PRO-806, retention rates were 64% for both Probuphine and SL BPN</td>
</tr>
<tr>
<td>Safety</td>
<td>PRO-805</td>
<td>N=262</td>
<td>Common adverse events (AEs) and safety issues similar to those seen with SL BPN 2% of subjects discontinued treatment due to implant-related AEs.</td>
</tr>
<tr>
<td></td>
<td>PRO-806</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-807</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-811</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overall, the safety data indicate that Probuphine is well-tolerated over two 24-week implant periods, and exclusive of implant-related treatment emergent AEs, the safety profile is consistent with other marketed buprenorphine-containing products. Including patients receiving Probuphine in safety studies after completing a placebo arm, a total 262 patients have received Probuphine in
the efficacy and safety studies (201 subjects for at least 24 weeks and 82 subjects for at least 48 weeks). With the exception of implant-related AEs, the most common AEs with Probuphine are similar to those observed with SL BPN, and include AEs such as headache, insomnia, nausea, back pain, and diarrhea.

Additional safety information is available in the Probuphine Investigator’s Brochure.

5.4. Study Rationale

Medication-assisted treatment (MAT) is one of the most effective therapies available for opioid dependence and is associated with substantial reductions in illicit opioid use, criminal activity, deaths, and HIV transmission. Because patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, treatment strategies that keep patients in treatment longer may have additional advantages (WHO, 2004). Limitations associated with SL BPN are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently) or to those who have difficulty managing the responsibility of daily dosing. Probuphine offers a valuable opportunity to overcome adherence issues, and to deliver the expected exposure levels that only patients who are compliant with SL BPN may achieve. In addition, although daily dosing of SL BPN has proven effective, SL tablets or even film can easily be diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (Winstock et al., 2008).

Four 80 mg Probuphine implants are expected to approximate the plasma concentrations of BPN observed following daily SL BPN doses of 8 mg or less. Previous clinical trials have demonstrated the efficacy of SL BPN doses of 8 mg/day or less for the maintenance treatment for opioid dependence (Johnson et al, 1992; Johnson et al., 1995; Ling et al., 1998). In addition, post-market studies have shown that clinicians are effectively treating many patients with maintenance BPN doses of 8 mg or less (Apelt et al., 2013; Mattick et al., 2008; Meade et al., 2010). The needs of patients who have been effectively maintained on relatively low SL BPN doses and require less frequent follow-up visits, may be better met by Probuphine than by SL formulations. In addition, Probuphine provides an alternative dosage form that can reduce diversion and enhance abuse deterrence. Therefore, the purpose of this study is to demonstrate the maintenance of the safety and efficacy by an alternate delivery form of BPN, Probuphine, in
the continuing treatment of opioid dependence in clinically stabilized SL BPN* maintenance patients.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN, to 4 Probuphine implants compared to SL BPN.

6.2. Secondary Objective

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN.

The study will include 3 Phases; Screening, Maintenance and Follow-up. Subjects will participate in this study for up to 29 weeks, including 3 weeks of the Screening Phase, 24 weeks of study drug treatment (Maintenance Phase) and 2 weeks of the Follow-up Phase.

All subjects who have provided written informed consent and have met the other study entry criteria will be enrolled and randomized into the Maintenance Phase. At least 180 subjects will be randomized to one of 2 treatment groups in a 1:1 ratio.

The overall study design is illustrated in Figure 1. Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2).

* Note that throughout this protocol, SL BPN may refer to either sublingual buprenorphine or sublingual buprenorphine/naloxone products, unless otherwise indicated.
All subjects will be seen for a total of approximately 14 visits (total of 10 urine toxicology samples will be collected) as outlined in the Schedule of Assessments:

- 1 Screening visit
- 12 main study visits:
  - 8 Maintenance Phase visits, including 1 Baseline and Initiation of Study Drugs Visit (post-randomization Implant Day [Day 1]), 1 Post-Implant Follow-up Visit, and 6 additional monthly Maintenance Phase visits, including the End of Treatment Visit at Week 24
  - 4 Random urine toxicology visits
- A Post-Treatment Telephone Contact will occur 1 week after the End of Treatment Visit (~1 week prior to the Follow-Up Visit).
- 1 Follow-Up Visit (2 weeks after the End of Treatment Visit)

Additional visits may be scheduled at the discretion of the subject or Investigator.

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects (regardless of randomized group) will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of all study-related medications and counseling will also be covered by the Sponsor.

Section 10 provides additional information on the baseline, efficacy and safety assessments included in the study. Efficacy endpoints and statistical analyses are described in Section 10.6 and Section 12, respectively.

### 7.1.1. Screening Phase (Week -3 to -1)

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history. Data on urine toxicology results for the duration of historical stable maintenance dosing (e.g., at least 90 days prior to Screening,) and the treating Health Care Practitioner’s documentation on the patient’s clinical stability (including the length of time that they have judged the patient to be stable) will be obtained via the clinical stability form (provided in the MOP).

Following the Screening Phase, subjects will be eligible for randomization if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.
7.1.2. Maintenance Phase (Month 1 to 6; Week 1 to Week 24)  
Eligibility for randomization will be confirmed after the Screening visit and prior to implantation on Day 1 (Baseline and Initiation of Study Drugs Visit). Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- **Treatment Group A:** Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- **Treatment Group B:** Four 80 mg Probuphine implants + daily SL placebo tablets

Subjects in Treatment Group A will be transitioned to the same dose of SL BPN on which they were previously maintained. Treatment Group B will be transitioned to four Probuphine implants that are expected to yield BPN plasma concentration within a range of approximately 0.5 to 1 ng/mL, comparable to the average of those observed following daily dose of 8 mg or less of SL BPN.

All subjects will be blinded to their treatment group assignment, as will all study staff with the exception of the clinician(s) performing the implant procedure and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets). To maintain blinding, all subjects will receive 4 implants (Probuphine or placebo) and SL tablets (BPN equivalent to their daily dose during the Screening Phase or placebo). Implants will be surgically inserted on Day 1. After Day 1, there will be a Post-Implant Follow-up Visit (to occur within 5 days after implantation) to conduct implant site examination and any additional safety assessments. Further information on implantation procedures can be found in Section 9.1.1.

During the first month, subjects will be required to attend 3 scheduled visits: Baseline and Initiation of Study Drugs Visit (Probuphine/placebo implant insertion and SL BPN/SL placebo administration [Day 1]), Post-Implant Follow-up Visit, and Week 4 first study assessment Visit (evaluation of outcome measures and safety assessments).

During months 2 to 6, subjects will return for monthly study visits for evaluation of outcome measures and safety assessments as described in Table 2. Subjects will be provided with sufficient take home medication for the daily dose of SL BPN or placebo for the subsequent month, as appropriate.

In order to assess number of opioid-free months throughout the 6 months (24 weeks) of treatment, a total of 6 monthly study visits (6 scheduled monthly urine toxicology samples) and 4 random visits (4 random urine samples throughout the 6 months) will be obtained for each subject.
Each investigator will be instructed to treat additional symptoms (e.g., withdrawal, desire/need to use, etc.) as they usually would under normal clinical practice, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions (other than those identified as prohibited in Section 9.7). Subjects will be told that their study dose of BPN is comparable to the dose they have been stable on and is expected to be adequate to maintain stability. Therefore, it is generally not anticipated that they will need any additional SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine), but additional counseling and other pharmacological interventions may be available at the discretion of the investigator. Any additional interventions that the subjects receive will be recorded.

Final outcome measures will be collected at the final treatment visit at Week 24 (End of Treatment Visit) and implants will be removed as described in Section 9.1.1

7.1.3. Follow-up Phase
Additional post-implant removal and other assessments will be performed on Week 25 to 26 as outlined in Table 2. Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects, 1 week (± 3 days) after the End of Treatment Visit to capture any AEs that may have occurred. Week 26 (± 3 days) will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).
Figure 1: Overview of Study Design

Screening
Clinically stable, Daily ≤ 8 mg SL BPN for at least 90 days, No positive urine toxicology for last 90 days
Up to 3 Weeks (Weeks 1 to 3)

Maintenance Phase

Group A:
Daily SL BPN ≤ 8 mg
4 placebo implants

Group B:
4 Probuphine implants
Daily SL placebo

6 Scheduled Urine Toxicology & Other Study Assessments (one per month)
4 Random Urine Toxicology

24 Weeks (Weeks 1 to 24)
Monthly Visits

Follow-up

2 Weeks (25 to 26)

24 Weeks (6 months) on Treatment

Randomization takes place on Day 1 (day of implant)
SL. BPN = sublingual buprenorphine or sublingual buprenorphine/naloxone
7.2. Discussion of Overall Study Design

The design selected to meet the objectives of the study is a 24-week randomized double-blind, double-dummy study with SL BPN as an active comparator in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN. Probuphine will be compared to SL BPN using a non-inferiority analysis. Given the pharmacokinetic data showing that four 80 mg Probuphine implants produce BPN plasma concentrations similar to a daily SL BPN dose of 8 mg or less, the proposed design is consistent with other trials evaluating the transfer of subjects to alternative dosage forms, where the overall plasma concentrations have been demonstrated to be similar, such as the transfer from once-daily to weekly dosing of anti-diabetics (Gastaldelli et al., 2013).

Research indicates that for most people with drug dependence, the threshold of significant improvement is reached after about 3 months in treatment, with further gains as treatment is continued (WHO, 2004). Therefore, subjects in maintenance treatment for at least 6 months will be included in the study. Investigators will be required to gain confirmation of clinical stability for subjects according to the clinical judgement of the patients’ treating physician. The clinical judgement should be confirmed by both objective and subjective measures, as described below:

1. According to the results from the Sponsor survey of addiction specialists, clinicians generally consider duration of stability on a given dose to be a proxy for clinical stability. Therefore, one criterion for entry into the study will be a treatment dose of SL BPN (≤8 mg) for at least 90 days.

2. In addition to being on a stable dose for at least 90 days, clinicians will also attest to their patients’ clinical stability as characterized by absence of withdrawal symptoms and no evidence of positive urine toxicology tests for illicit opioids in the previous 90 days. Other elements of clinical stability include, social, emotional and psychological stability (i.e., stable family/home life and employment, treated emotional/psychological issues), compliance to clinic visits, and ongoing counseling.

The current study will enroll patients who have had no evidence of positive urine toxicology results for illicit opioids in the past 90 days. Nevertheless, addiction specialists state that clinically stable patients may have occasional opioid-positive urine toxicology. This is also supported by studies in the literature, that demonstrate subjects undergoing prescribed treatment for at least 3 months report monthly illicit opioid use in the range of 13% to 46.5% (Carrieri et al., 2003; Galanter et al., 2003; Guichard et al., 2003; Jones et al., 2009). While self-reports may
be somewhat less reliable, similar data have been reported using urine toxicology. In these studies, positive opioid urine toxicology screen results in stable subjects maintained on buprenorphine were in the range of 10% up to approximately 25% (Fiellen et al., 2008; Jones et al., 2009; Kakko et al., 2003; Maremmani et al., 2007).

The study will include 24 weeks of study drug treatment (Maintenance Phase). The patient population is clinically stable and accustomed to less frequent visits. Therefore, the study assessment visits will be monthly throughout the 6-month Maintenance Phase of the study starting with Week 4 Visit (Weeks 4 to 24). While previous studies of opioid dependence treatment have required subjects to attend up to thrice weekly visits, the clinically stable subjects under investigation in the current trial do not routinely receive such frequent and intense monitoring for their treatment. The proposed study visit schedule is designed to potentially increase study feasibility as well as improve retention. In addition to the 6 scheduled monthly study assessment visits, subjects will be required to provide 4 random urine toxicology samples throughout the Maintenance Phase of the study, which should be sufficient to detect any abuse of opioids during the 24 weeks of treatment. Subjects will also be encouraged to contact their investigator for unscheduled visits should they experience any signs of inadequate treatment.

8. SELECTION OF STUDY POPULATION

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized into the Maintenance Phase.

This study will enroll adult outpatients with opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR), who have been on a stable dose of 8 mg or less of SL BPN for at least 90 days prior to Screening, and meet their treating healthcare provider’s criteria for clinical stability.

8.1. Inclusion Criteria

Subjects must meet each of the following inclusion criteria at Screening to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for at least 6 months.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days prior to Screening.
   c. No positive urine toxicology results for illicit opioids in the last 90 days.
5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met at Screening:

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.
6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.
8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).
9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.
10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.
11. Any pending legal action that could prohibit participation or compliance in the study.
12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A subject’s participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study for any of the following reasons:

- Evidence of implant removal or attempted removal of the implant
- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent, require discontinuation of study drug, or both
- At the request of the Sponsor, Regulatory, or IRB
  - Subject is lost to follow-up
  - Death of subject

A subject may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Subject refusal or unable to adhere to the study protocol
- Protocol violation
- Pregnancy
- Requirement for continual use of opioid analgesics > 7 days or requirement for general anesthesia for surgery

The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to
obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

For any case of early discontinuation (whether or not the subject is at the clinical site), the subject will be required to return for, at minimum, the End of Treatment Visit to remove the implants. The Investigator should ask the subject to return for the Follow-up assessments (i.e., Week 26 assessments), provided that the subject has not withdrawn consent for those assessments. If a subject refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

9. TREATMENTS

9.1. Treatment Administration

Following confirmation of a signed informed consent document, eligibility and randomization:

- Subjects randomized to Treatment Group A will receive daily doses of SL BPN (containing BPN and naloxone) equivalent to their usual single daily dose of BPN (≤8 mg per day) for 24 weeks. Subjects randomized to this group will also receive 4 placebo implants on Day 1.
- Subjects randomized to Treatment Group B will receive 4 Probuphine implants on Day 1, which are expected to deliver BPN to the subject for at least a period of 24 weeks. Subjects randomized to this group will also receive daily SL placebo tablets.

9.1.1. Implant Insertion and Removal Procedures

All Probuphine and placebo implants will be implanted and removed by trained clinicians. The Sponsor will institute the Probuphine Clinical and Procedure Training and Evaluation program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards. The Sponsor will also provide an Implant Insertion/Removal Instruction for Use slide deck, training DVD, as well as live training on the instructions for aseptic subdermal insertion and removal of Probuphine or placebo implants.

Prior to randomization and Day 1 (Implant Day), it will be recommended that subjects discontinue SL BPN and have implants inserted subdermally within 12-24 hours after their last SL BPN dose. In addition, it will be recommended that subjects discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to and bathe the day of insertion and removal of implants.
Implantation under the skin of the upper arm will be performed using a specialized applicator provided by the Sponsor. The Probuphine Applicator has been utilized in previous Probuphine studies and is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon®. Additional details on Insertion/Removal procedures and training will be provided in the Study Manual of Procedures (MOP) and the Implant Training DVD. Subjects should be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff. The Implant Clinician will also complete the Implant Insertion Procedure Assessment form provided in the Study MOP.

Subjects will have their implants removed during the End of Treatment Visit. Implant removal procedures are described in detail in the MOP and the Implant Training DVD. If, upon removal, the Implanting Clinician has difficulty locating the implants, ultrasound may be used to facilitate their localization. The Implant Clinician will also complete the Implant Removal Procedure Assessment form provided in the Study MOP.

**9.2. Identity of Investigational Products**

Probuphine and placebo implants are sterile, approximately 26 mm in length, and 2.5 mm in diameter. The implants are translucent to off-white in appearance. Each Probuphine implant contains 80 mg of BPN HCl, which has been blended and extruded with EVA. Buprenorphine HCl is a Schedule III controlled substance that is chemically derived from thebaine. One milligram of buprenorphine HCl is equal to 0.93 mg of buprenorphine as base. Placebo implants contain only EVA.

Each implant is individually packaged in a foil-lined, heat-sealed pouch. Pouches are then sterilized using gamma radiation. Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants or 4 placebo implants.

Subjects will be required to take daily SL BPN (BPN/naloxone) during the Maintenance Phase.a These products will be supplied by the Sponsor or designee. Matching SL placebo tablets will be provided for each dosage strength. More information regarding the SL BPN and near-matching SL placebo products can be found in the MOP.

For potential supplemental SL BPN needs, a different brand of SL BPN will be utilized to prevent the unblinding of study drug. Information on this brand of SL BPN can be found in the MOP.
All containers/packages/boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

**9.2.1. Handling, Storage, and Accountability**

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

All Patient Kits should be stored at room temperature (15–25°C / 59–77°F) in a secured, double-locked area and in accordance with applicable laws, regulations and institutional requirements.

SL BPN should be stored in a secured area and in accordance with the product labeling (a copy is located in the MOP) and all applicable laws, regulations, and local/institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor’s drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site.

The Investigator or designee must maintain an inventory record of all SL BPN dispensed to subjects for the purpose of treatment and supplemental use. The drug accountability records for returned SL BPN and placebo tablets will be handled by the unblinded study site personnel. Additional details are provided in the Study MOP.

Following implant removal, appropriate collection and disposal of all implants is outlined in the Study MOP.

Buprenorphine is a Schedule III controlled substance and study drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

**9.2.2. Dispensing and Administration Procedures**

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects. Subjects will be provided with a monthly supply of study medications.
Subjects will be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, tablets should be placed in different areas under the tongue at the same time.

9.2.3. **Supplemental SL BPN**

Investigator will be instructed to treat additional symptoms as they would usually, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions. However, subjects will be told that while additional counseling and other pharmacological interventions could be available, their current dose of BPN is expected to be adequate to maintain stability and their physician does not expect that they will need any additional supplemental SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine).

Any supplemental SL BPN, additional counseling, and other pharmacological interventions provided by the Investigator will be recorded, along with the reasons for determining the need for any supplemental interventions.

9.3. **Method of Assigning Subjects to Treatment Groups**

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.

Subjects who have met the eligibility criteria (Section 8) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group A: Daily SL BPN plus placebo implants or Treatment Group B: four Probuphine implants plus SL placebo tablets). Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2.
9.4. Selection of Doses in the Study

The dose of 4 Probuphine implants was selected based on efficacy, safety and pharmacokinetic data from Studies PRO-805, PRO-806, TPP-400, and PRO-810 (Investigator’s Brochure for Probuphine). Four Probuphine implants are expected to yield BPN plasma concentrations comparable to a SL BPN dose of 8 mg or less per day.

9.5. Selection and Timing of Dose for Each Subject

Subjects will be randomized to receive either 4 Probuphine implants or SL BPN. The SL BPN will be administered at a dose level equivalent to their usual care/Screening Phase dose.

No fasting or special dietary requirements are required for the study; however, when taking the SL BPN or placebo tablets, subjects should be advised to not eat or drink anything until the tablet(s) are completely dissolved. To ensure consistency in bioavailability, subjects should follow the same manner of dosing for the duration of the study.

9.6. Blinding

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets initiated after randomization, subjects will be told that clinical supplies of SL BPN have been specifically developed for this study and may look or taste different than commercially available products they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets. To provide additional assurance of maintaining the blind, a different brand of SL BPN will be utilized for any potential supplemental SL BPN needs. Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects.

Since the placebo implants have a slightly different appearance than the Probuphine implants, the following will be agreed upon in a signed document by the Implanting Clinician and the Investigator in order to maintain the blind:
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- The Implanting Clinician and any other staff involved in the implant insertion and removal procedures must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.

- In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct the subject’s view of the procedure, etc.).

- The study staff must not ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject’s safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

9.7. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject’s eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:

- It will be recommended that subjects discontinue NSAID or aspirin-containing medications during the week prior to implant insertion and the week prior to implant removal.

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take several days following discontinuation of Probuphine or SL BPN treatment. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity.
with opioid administration. The clinical course should be fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.

- Buprenorphine is metabolized via CYP3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of BPN, if CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) are required, the Medical Monitor must be consulted. Interactions with CYP 3A4 inducers have not been investigated; therefore it is recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.

- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with Probuphine or SL BPN. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in in the study. Subjects should be explicitly advised of the danger of IV abuse of benzdiazepines while under treatment with implants or SL BPN.

### 9.8. Subject Study Drug Accountability

Although it is difficult to divert the subdermal Probuphine implants for abuse (removal of implants and extraction of the active BPN HCl from the EVA), diversion can theoretically occur.

Subjects must therefore be carefully monitored for such diversion. The implant site will be visually inspected and palpated (for accountability of the implants) at each visit, and, if there is any evidence of removal of the implants by the subject, the subject will be withdrawn from study. If there is evidence of attempted removal, the subject will be withdrawn from the study and all implants will be removed (Section 9.1.1). Due to the non-biodegradable nature of the Probuphine and placebo implants, it is vital that no subject is lost to follow-up to ensure proper implant removal, and that the End of Treatment Visit is completed as outlined in this protocol.

Subjects will be reminded to bring any remaining unused dispensed SL tablets to every visit.
10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2); the following sections outline the details and procedures associated with the assessments. Additional details on the assessments, including copies of questionnaires, logs, manuals, and information sheets are provided in the Study MOP.
### Table 2: Schedule of Assessments

<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Month 1 Visits</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month:</td>
<td>Month 2 to 5 Visits</td>
<td>Month 6/End of Treatment Visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week:*</td>
<td>Week 8, 12, 16, 20</td>
<td>Week 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day:</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Informed Consent&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eligibility Criteria Review&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical and Medication History / Substance Abuse and Treatment History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-IV-TR, MINI, v 6.0</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviated Review of Systems</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistry, Hematology, Urinalysis and Coagulation Profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment Visits should be conducted within a window of ±7 days for the monthly visits, except for Post-Implant Visit, which should occur within a window of 1 to 5 days after Day 1. Visits for Weeks 25 and 26 should occur within ±3 days. If a subject misses a visit or completes a visit early or late, the original schedule should be resumed at the subsequent visit such that the ensuing visits occur as originally scheduled, relative to Day 1.

<sup>b</sup> Baseline and Initiation of Study Drugs Visit.

<sup>c</sup> Post-Implant Visit.

<sup>d</sup> Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.

<sup>e</sup> Prior to enrollment in the randomization and Maintenance Phase of this study, all Inclusion and Exclusion criteria must be met.

<sup>f</sup> A complete physical exam of all major body systems will be performed at the Screening Visit.

<sup>g</sup> Includes temperature, blood pressure, pulse rate, respiration rate, and weight. Height will be captured at Screening Visit. BMI will be auto-calculated.

<sup>h</sup> Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implant insertion/removal, and then 15 minutes and 30 minutes after implant insertion/removal.
## Study Period/Phase: Screening

<table>
<thead>
<tr>
<th>Month</th>
<th>Month 1 Visits</th>
<th>Month 2 to 5 Visits</th>
<th>Month 6/End of Treatment Visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week:</td>
<td></td>
<td>Week 1</td>
<td>Week 4</td>
<td>Week 24</td>
</tr>
<tr>
<td>Day:</td>
<td></td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
</tr>
</tbody>
</table>

### Study Period/Phase: Screening

- **Pregnancy test**: X  X  X  Monthly  X
- **Hepatitis B/C, HIV**: X
- **Implant Site Examination**: X  X  Monthly  X  X
- **Dispense Treatment Identification Card**: X
- **Urine Toxicology**: X  X  Monthly  X
- **Random Urine Toxicology**: 4 Random Urine Toxicology Tests
- **Illicit Drug Use Self-Report**: X  X  Monthly  X
- **Withdrawal and Desire to Use/Need to Use (SOWS, COWS, VAS)**: X  X  Monthly  X
- **SL BPN or placebo dispensing**: X  X  Monthly
- **Probuphine or placebo [four (4) implants] Insertion**: X<sup>1</sup>
- **Implant removal procedure**: X<sup>m</sup>
- **Additional interventions**: X

---

<sup>1</sup> A serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit (Week 24). An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed prior to start of SL BPN and Probuphine treatment.

<sup>2</sup> It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site’s IRB prohibits such testing.

<sup>3</sup> The implant site will be visually inspected and palpated.

<sup>4</sup> Subjects should be instructed to arrive having bathed with soap and water on Day 1.

<sup>m</sup> It is recommended that subjects return 7 days post implant for suture removal.

<sup>u</sup> Subjects may receive additional counseling, supplemental SL BPN, or other pharmacological interventions deemed appropriate by the investigator, at any time after implantation, at the investigator’s discretion.
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<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month:</strong></td>
<td>-</td>
<td>Month 1 Visits</td>
<td>-</td>
</tr>
<tr>
<td><strong>Month 2 to 5:</strong></td>
<td>-</td>
<td>Week 4</td>
<td>-</td>
</tr>
<tr>
<td><strong>Month 6/End of Treatment Visit:</strong></td>
<td>-</td>
<td>Week 24</td>
<td>-</td>
</tr>
<tr>
<td><strong>Follow-up:</strong></td>
<td>-</td>
<td>Week 25</td>
<td>Week 26</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Week:</strong></th>
<th>-3 to -1</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Week 8, 12, 16, 20</th>
<th>Week 24</th>
<th>Week 25</th>
<th>Week 26</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day:</strong></td>
<td>-</td>
<td>Day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Implant Insertion Procedure Assessment</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant Removal Procedure Assessment</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial Counseling</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events&lt;sup&gt;o,p,q&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
<td>X&lt;sup&gt;r&lt;/sup&gt;</td>
</tr>
<tr>
<td>Concomitant Medications/Procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Wound Care Information Sheet&lt;sup&gt;s&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone Contact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X (As Needed)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>o</sup> AEs that are reported by the subject at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.

<sup>p</sup> Subjects will be monitored for at least 30 minutes after implantation for AEs. AEs will be recorded both prior to and after implant removal at Week 24.

<sup>q</sup> During removal process, careful inspection of the implant site, difficulty of removal and/or fracturing of the implants will be recorded.

<sup>r</sup> If a significant AE is described by the subject and is judged by the Investigator as being possibly related to study treatment, the subject will visit the study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).

<sup>s</sup> A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
10.1. **Demographics and Other Baseline Characteristics**

10.1.1. **Informed Consent**

The nature of the study and its risks and benefits will be explained to the participant by the Investigator or designated study personnel. The participant must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject’s medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. **Demographics and Psychosocial History**

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity. A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.3. **Medical History**

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

A psychiatric interview will be conducted using the Mini International Neuropsychiatric Interview, Version 6.0 (MINI). The MINI is a valid and reliable structured diagnostic interview for DSM-IV-TR psychiatric disorders.

10.1.4. **Medication History**

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatments will be collected separately.
10.1.5. **Substance Use and Treatment History**
A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences and concomitant medications, using a timeline follow-back type of interview (Fals-Stewart, 2000). Validation of historical clinical stability, including duration of treatment and dose at which patient has been stable, and any data available on urine toxicology results, will be captured and reported on the study entry form. Detailed information on substance use and treatment history is provided in the Study MOP.

10.2. **Eligibility Review and Randomization**
Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of randomization in the Maintenance Phase.

Randomization will be accomplished centrally, using an Interactive Voice Response System and/or by an Interactive Web Response System managed by the Sponsor.

10.3. **Efficacy Assessments**
Details regarding primary, secondary and exploratory endpoints are provided in Section 10.6 (Efficacy Variables); and discussed further in Section 12.3 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Study MOP.

10.3.1. **Urine Toxicology for Opioids**
Urine toxicology samples will be collected at each visit (both scheduled and random) using a urine collection cup containing a temperature sensor. Specimen authenticity will be verified at the site using this sensor to measure the urine temperature immediately following collection. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the
subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and should not be sent for analysis (any such samples must be documented in the subject’s records). Direct observation approach to obtaining urine samples may be used if the investigator deem necessary. Urine samples will be logged and numbered and then sent to a central laboratory for analysis for the presence of opioids (e.g., codeine, morphine, hydrocodone, oxymorphone, hydromorphone, oxycodone, methadone, and fentanyl). In addition, it is recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

10.3.2. Self-Reported Illicit Drug Use
Subjects will be questioned about illicit drug use, including illicit or prescription opioids and other drugs of abuse using a timeline follow-back type of interview (Fals-Stewart, 2000). A copy of the Illicit Drug Use Self-Report form is provided in the Study MOP.

10.3.3. Measures of Desire and Need to Use
Desire to Use and Need to Use will be administered using unipolar 100 mm VAS (“Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm= Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively) (Kozlowski et al., 1989).

Copies of these VASs are provided in the Study MOP. **NOTE: Only VAS copies provided by the Sponsor should be used with study subjects; photocopies made locally may result in changes to the length of the scale, leading to inaccurate results.**

A separate VAS will be provided for each Desire to Use and Need to Use and measurements must be taken separately (i.e., separated in time or by other procedures).

10.3.4. Measures of Withdrawal

10.3.4.1. Subjective Opioid Withdrawal Scale (SOWS)
Subjects will complete a self-assessment of withdrawal symptoms using the SOWS. This form contains 16 questions that rate the intensity of withdrawal from 0 (“Not at all”) to 4 (“Extremely”). A copy of the SOWS is provided in the Study MOP.
10.3.4.2. Clinical Opioid Withdrawal Scale (COWS)

Study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater. A copy of the COWS is provided in the Study MOP.

10.3.5. Urine Toxicology for Other Drugs of Abuse

Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative methods. Positive results will not be confirmed using quantitative methods.

10.3.6. Supplemental Visits, Medication and Counseling

Supplemental SL BPN use will be allowed, as described in Section 9.2.3. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for supplemental visits, supplemental SL BPN needs, phone calls or additional counseling or other pharmacological interventions, will be recorded.

10.4. Safety Assessments and Other Procedures

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF. Appropriate medical intervention should be provided and, if necessary, implants may be removed or SL BPN treatment discontinued as clinically indicated.

10.4.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
10.4.1.1. **Adverse Event Reporting**

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Relationship to insertion / removal procedure
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the End of Treatment Visit (i.e., implant removal and discontinuation of SL BPN/placebo treatment). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

10.4.1.2. **Serious Adverse Event**

A serious adverse event (SAE) or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in an offspring)
- An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the End of Treatment Visit AND are not considered to be drug-related by the Investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

10.4.1.2.1. Serious Adverse Event Reporting

Serious Adverse Events (SAEs) must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the End of Treatment Visit are reportable within 24 hours. During the follow-up period beyond 14 days from implant removal or discontinuation of SL BPN assigned treatment, only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
  - Subject ID
  - Basic demographic information (age, gender, weight)
Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)

- Onset date and severity of the event
- Brief description of the event including frequency and severity of symptoms leading to diagnosis, and information on supplemental SL BPN
- List of relevant test results and lab data
- Any other relevant history
- Dates of implantation and removal, if applicable
- Dates and doses of supplemental SL BPN usage
- Whether the study drug was discontinued
- Whether the event abated after implants removed and/or assigned treatment SL BPN discontinued and/or supplemental SL BPN discontinued, as applicable
- Investigator’s assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB / Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

10.4.2. Pregnancy

Pregnancies among trial participants should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant may withdraw their consent and discontinue the study and be referred back to the care of their usual provider. Follow-up information will be obtained where possible (with the consent of the participant or their partner)
regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

10.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not clinically significant) or “CS” (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., “CS/mild anemia.” In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 3.
### Table 3: Clinical Laboratory Assessments

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Sodium</td>
<td>Color</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Potassium</td>
<td>pH</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Magnesium</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>RBC Morphology</td>
<td>Calcium</td>
<td>Ketones</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Glucose (random)</td>
<td>Protein</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Bicarbonate</td>
<td>Glucose</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration</td>
<td>Chloride</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Total and differential (absolute)</td>
<td>Creatinine</td>
<td>Nitrite</td>
</tr>
<tr>
<td>white blood cell count</td>
<td>Total protein</td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>Platelets</td>
<td>Blood urea nitrogen</td>
<td>Occult blood</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Albumin</td>
<td>Microscopic examination of sediment, only if urinalysis dipstick results are abnormal</td>
</tr>
<tr>
<td>Prothrombin time (PT), INR</td>
<td>Total bilirubin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alanine transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic dehydrogenase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine phosphokinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total cholesterol (non-fasting)</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit. An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of SL BPN and Probuphine treatment.

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed for all subjects, unless a site’s IRB prohibits such testing. It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.
10.4.4. Vital Signs
Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

10.4.5. 12-Lead Electrocardiogram (ECG)
12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

10.4.6. Physical Examination
A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be determined as described in Table 2.

10.4.7. Implant Site Examination and Wound Care
Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs. Copies of the wound care information sheets must be reviewed and approved by each site’s IRB, prior to providing them to subjects.

Implant site reactions can occur with the implantation and removal of Probuphine or placebo implants. The most frequently-reported AEs related to the insertion/removal procedure (occurring in greater than 10% of subjects) in previous Phase III clinical studies were erythema, edema, itching, pain, bleeding, bruising, and scarring. The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities, including implant expulsion or implant migration. The implant site should also be palpated to ensure that the four implants have not been removed. If there is any evidence of removal or attempted removal of the implants, or if the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and any remaining implants will be removed.

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10.4.8. Psychosocial Counseling

All subjects will receive manual-guided drug counseling during the study, as outlined in Table 2 and described in more detail in the Individual Drug Counseling Manual (provided in the Study MOP) (Mercer & Woody). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

10.4.9. Treatment Identification Card

Subjects will receive a wallet card indicating that they are receiving BPN as part of the study. This card should be presented to health care providers by the subject in the event of an emergency or if medications such as opioid analgesics are required (see Section 9.7). Sample wallet cards will be provided for IRB submission.

10.4.10. Other Safety Considerations

Buprenorphine may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction and after implant insertion, and to exercise caution in performing activities requiring alertness such as driving a car during the first few days after implant insertion, or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

10.5. Appropriateness of Measures

The efficacy outcome measures were selected to provide an efficacy assessment of the study medications with regards to both objective (i.e., urine toxicology results for opioids), and patient-based assessment (i.e., subject-reported desire/need to use and desire/need to use opiates). The most direct method to ascertain the frequency and amount of illicit opiate use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (Zanis et al., 1994). Thus, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. Urine toxicology has been used in many efficacy assessments of buprenorphine and will be used as the primary outcome measure in the definition of responders in this study (Section 10.6). Urine toxicology results will be adjusted for self-reported drug use at each study visit.

Secondary outcome measures were selected as a series of measures and scales to provide a complete assessment of the effectiveness and efficiency of transfer from SL BPN to Probuphine implants with regard to patient-based assessments (i.e., subject-reported desire and need to use...
opioids, withdrawal), as well as measures of the subject’s functional impairment status (Sheehan Disability Scale).

Desire to Use VAS and Need to Use VAS were selected over the typical Craving VAS because the latter term is ambiguous and may have different meaning to different individuals, while the Desire/Need to Use VAS more directly assess the potential behavioral outcome (Kozlowski et al., 1989).

Standard and widely used measures of withdrawal will be included in this study (COWS and SOWS) (Wesson & Ling, 2003; Handelsman et al., 1987) in order to ensure that subject’s withdrawal symptoms are adequately controlled by the Probuphine implants as compared to SL BPN.

In addition, although expected to be relatively rare in this study, supplemental SL BPN use will be evaluated. Finally, to ensure that potential signs of treatment failure are not missed, additional measures of potentially inadequate treatment will include subject- or Investigator-requested additional visits or counseling.

10.6. Efficacy Variables

10.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is a responder analysis. A subject will be designated as a responder (meaning they have maintained stability) if they have no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

10.6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include average scores over 24 weeks of treatment and average change from baseline (Day 1) scores over 24 weeks of treatment for the following outcome measures:

- Measures of desire/need to use:
  - Desire to Use VAS
  - Need to Use VAS

- Measures of withdrawal:
  - Clinical Opiate Withdrawal Scale (COWS)
  - Subjective Opioid Withdrawal Scale (SOWS)
10.6.3. **Exploratory Efficacy Variables**

Exploratory variables include:

- Urine toxicology for other drugs of abuse
- Supplemental SL BPN use, unscheduled visits, phone calls and additional psychosocial counseling and other pharmacological interventions, including reasons for use
- Treatment discontinuation, including reasons for discontinuation

10.7. **Safety Variables**

Safety variables include:

- AEs
- Clinical laboratory tests
- ECG
- Physical and implant site examinations
- Implant site insertion and removal assessments
- Concomitant medications
- Vital signs

11. **DATA QUALITY ASSURANCE**

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. The Sponsor or designee will review source documents for accuracy and completeness during on-site
monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigational site termination and regulatory authority notification.

11.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor’s monitor or designated representative. The Sponsor’s monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

11.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor’s designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site’s standard operating procedures, GCP.
guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the study data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

12.2. Analysis Populations

The study analysis populations will consist of:

- **Randomized Population:** All subjects who are randomized into the Maintenance Phase
- **Intent-to-Treat (ITT) Population:** All subjects who have been randomized and have received an implant and/or received SL BPN/placebo. Analyses based on this population will group subjects according to the treatment they were randomized to receive, regardless of actual treatment received, and this will be the primary analysis population.
- **Safety Population:** All subjects who are randomized and treated with implants or who received any dose of SL BPN/placebo in the Maintenance Phase. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.
- **Per Protocol Population:** All subjects in the ITT population with no major protocol violations. Major protocol violation criteria will be established prior to the database lock.

12.3. Planned Analyses

12.3.1. Disposition, Demographics and Other Baseline Characteristics

Disposition for all randomized subjects will be summarized by the randomized treatment group. Reasons for discontinuation will be tabulated for each treatment group and overall.
Demographic data and baseline psychosocial characteristics will be summarized.
Tabular summaries and/or listings will be provided for baseline clinical characteristics such as illicit drug and treatment use history, medical and psychiatric history, inclusion/exclusion criteria, and medication history.

12.3.2.  Analysis of Efficacy Measures

12.3.2.1. Primary Endpoint
The primary efficacy variable will be responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.
A total of 10 urine toxicology samples will be collected throughout the 6 months of the study treatment period with 6 scheduled visits (1 visit per month) plus 4 random urine toxicology visits.

12.3.2.2. Analysis of Primary Endpoint
A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta=20\%$ will be employed to define non-inferiority. Let $\pi_C$ and $\pi_T$ be the rate of response at 24-weeks on the control arm and experimental treatment arm, respectively. The null hypothesis (of inferiority is

$$H_0: \pi_T \leq \pi_C - 0.20$$

The alternative hypothesis (of non-inferiority is

$$H_A: \pi_T > \pi_C - 0.20$$

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above –0.20).

Rationale for 20% non-inferiority margin: The 20% margin is appropriate from a scientific validity perspective as well as meeting Food and Drug Administration (FDA) guidelines for non-inferiority margin selection (FDA, 2010). In this study with 180 subjects, the observed data that meet the statistical 20% margin will meet scientific face-validity for the equivalency of the treatment arms. The table below (Table 4) summarizes the required Probuphine Treatment
Group’s response rate (% of responders) to satisfy non-inferiority based on the 20% margin and the sample size of 90 subjects per group at the two-sided 5% significance level for a range of observed SL BPN arm’s response rate (Note: due to discreteness some percentages are not possible).

Table 4: Response Rates and Non-InferiorityMargins

<table>
<thead>
<tr>
<th>Observed SL BPN Arm’s Response Rate (% of Responders)</th>
<th>Required Minimum Observed Probuphine Arm’s Response Rate (% of Responders) to Satisfy Non-inferiority (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>81.1</td>
</tr>
<tr>
<td>84.4</td>
<td>76.7</td>
</tr>
<tr>
<td>80</td>
<td>73.3</td>
</tr>
<tr>
<td>74.4</td>
<td>67.8</td>
</tr>
<tr>
<td>70</td>
<td>64.4</td>
</tr>
<tr>
<td>64.4</td>
<td>58.9</td>
</tr>
<tr>
<td>60</td>
<td>54.4</td>
</tr>
</tbody>
</table>

The table demonstrates that utilizing the 20% margin to satisfy non-inferiority, the Probuphine Treatment Group’s response rate should be at least similar to the rate for SL BPN control arm.

Although there is little literature on SL BPN treatment in long-term stabilized maintenance subjects, there is some empirical information available to lend credence to the 20% non-inferiority margin:

1. With patients on longer term BPN or methadone treatment, blinded taper (detoxification) studies indicate rates of continued opioid abstinence following complete withdrawal of about 18 to 31%. Although little data is available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15%. A summary of literature is provided in Section 16.

2. A survey of addiction experts was performed by the Sponsor to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN.

   a. The results demonstrated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability)
to illicit opioid use if these patients were taken off their stable dose of 8 mg or less of SL BPN. The FDA Draft Guidance would suggest a 37.5% margin to be appropriate, based on an estimate of 75% effect size (i.e., assuming all patients being stable at study randomization). However, a 37.5% margin, estimating 50% preservation of the effect size may not be clinically acceptable. The proposed 20% margin would estimate preserving >70% of the effect and should be considered clinically acceptable (Section 17).

3. Finally, the FDA Draft Guidance notes that circumstances might support a less conservative choice for the margin, including:

   a) **Pharmacologic properties of the test drug that are very similar to those of the active control** – Probuphine is an alternative dosage form of the same active entity with the expectation of similar overall plasma concentrations to the SL BPN arm;

   b) **Use of a persuasive biomarker** – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success;

   c) **If the drug has been shown to be effective in closely-related clinical settings** – Probuphine has already been shown to be effective relative to placebo in two trials in harder-to-treat populations;

   d) **If the test drug were shown to have some important advantage (e.g., on safety or on a secondary endpoint)** – The safety issues associated with abuse of SL BPN are well-known; the Drug Abuse Warning Network confirmed an increasing trend to adverse medical outcomes associated with BPN abuse, i.e., a total of 21,483 emergency department visits related to abuse/misuse were reported in 2011 (DAWN, 2013). Probuphine has the potential to reduce misuse/abuse associated with SL BPN and have a significant positive public health impact, in addition to potentially increasing adherence.

Thus, the overall data and circumstances associated with this study support the use of a 20% non-inferiority margin.

12.3.2.2.1. Handling of Dropouts or Missing Data

If all missing values (urine toxicology results for illicit opioids) are replaced with extreme values (i.e., either all replaced with “negative” or all replaced with “positive”), biases will be introduced. For example, if all missing values are replaced with “positive,” the results will be
biased in favor of the group with the smaller dropout rate. To avoid such biases, in the primary analyses, missing values within a treatment arm will be replaced by randomly generated binary indicator (1="Opioid-Positive" and 0="Opioid-Negative"). The probability of having 1 will be the proportion of “Opioid-Positive” samples out of all available samples within that treatment arm. The random binary outcomes will be generated using seed=1374809352 in SAS.

12.3.2.3. Sensitivity Analyses
The following sensitivity analyses will be performed:

- Analysis based on completers (i.e., analysis based on all subjects who provided all required samples);
- Analysis based on missing values replaced with “Opioid-Positive;”
- Per protocol analysis (i.e., analysis based on subjects who do not have major protocol violations).

12.3.2.4. Analysis of Secondary Efficacy Endpoints
The secondary endpoints will include change from baseline (Day 1 prior to implantation) in two measurements of desire/need to use (Desire to Use VAS, Need to Use VAS), two measurements of withdrawal (COWS and SOWS), and the measure of functional impairment (Sheehan Disability Scale) at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.

Details of additional measures of efficacy and their analysis will be described prospectively, prior to final database lock and unblinding, in the SAP for this study.

12.3.3. Analysis of Safety
Exposure will be summarized by treatment group.

AEs will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to study drug or implant insertion/removal, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment
group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Data for clinical laboratory tests, ECG, vital signs, and physical and implant examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate.

Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics.

By-subject listings will be provided for all safety data.

12.4. **Determination of Sample Size**

The sample size of 90 per treatment arm (180 total) was selected to achieve 87.3% power, assuming both arms have a 75% rate of responders. If the true rates are lower, but equal in both arms, with a 65% rate of response, the power of the trial to determine non-inferiority is 80.3%. If each treatment arm has an 85% rate of response, then the trial with 180 subjects would have 96.4% power to determine non-inferiority.
13. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the Sponsor and the investigational site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Study
The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor’s representatives and/or regulatory authority’s representatives at any time.

13.1.2. Ethics Approval
The investigational site’s IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

13.1.3. Subject Informed Consent
The Investigator (or authorized designee) will ensure that the participant (or the participant’s legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided
in a language understandable to the participant and must not include any language that waives the participant’s legal rights. Prospective participants must also be informed of their right to withdraw consent without prejudice at any time during the study. If the participant chooses to participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain the original, signed ICF in the participant’s source documents. A copy of the signed ICF must be given to the study participant.

13.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the participant’s chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each participant’s name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor, representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such as the United States FDA) may inspect medical records related to the study to check the validity and accuracy of the data gathered in this study. Participant medical records (with participant’s initials and/or date of birth) may be copied. Confidentiality of participant records will be maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a participant withdraws consent, some of
the subject’s information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

13.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

13.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:
A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or

A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator’s portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

13.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.
13.6. **Protocol Amendments**

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

13.7. **Financial Disclosure**

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
14. SPONSOR APPROVAL PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 2.0

Date: 14-AUGUST-2014

Braeburn Pharmaceuticals

Frank E. Young, MD, PhD
Executive Vice President, Clinical and Regulatory Affairs

14 August 2014
15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 2.0

Date: 14-AUGUST-2014

I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonization/Good Clinical Practice Guidances.

Investigator’s Name
(please print or type)

Signature

Date
16. SUMMARY OF LITERATURE TO SUPPORT NON-INFERIORITY MARGIN

A meta-analysis of tapered discontinuation following long-term methadone or BPN treatment found an average abstinence rate of 33% (Korner & Waal, 2005). However, because of the differences in methodology (single or double-blinding, naturalistic, etc.), definitions of abstinence, treatments administered during MAT and durations of follow-up, some studies are more relevant than others. In addition, this article didn’t report on the baseline rates of percentage abstinence or urine toxicology results.

Breen et al., (2003) reported on a study of stable methadone patients (for at least 6 months) to BPN and then gradual reduction to 0 mg BPN (i.e., blinded) over an average duration of 11 weeks showed that subjects at 1 month follow-up after complete BPN discontinuation had 31% negative opioid samples (relative to about 73% negative at baseline, 89% negative during BPN induction, and 91% negative during BPN taper).

One double-blind, double-dummy study in methadone users found 25% abstinence overall during 1 month follow-up after complete discontinuation following gradual taper regimens. Abstinence was 18% in the "rapid" withdrawal group (taper over 10 weeks) (versus 100% negative urine opioid results for 4 weeks preceding study entry and 92% negative for the 6 months prior to the study) (Senay, 1977).

Most of the studies used tapered discontinuation, but in terms of abrupt discontinuation, one survey study in Australia reported that 15% of patients who abruptly discontinued opioid maintenance therapy (BPN or methadone) were abstinent for at least 3 months, while 26-27% were abstinent with either self- or physician-directed taper regimens (Winnstock et al., 2011).
### 17. SUMMARY OF SURVEY RESULTS FROM ADDICTION SPECIALISTS

<table>
<thead>
<tr>
<th>PI #</th>
<th>% Negative UDS Over 6 mths*</th>
<th>% Negative UDS Over Next 6 mths*</th>
<th>% Relapse upon BPN Discontinuation (Over 6 mths)</th>
<th>Maximum Reasonable Change in % UDS positive</th>
<th>% of Patients</th>
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<tr>
<td>Mean (Median):</td>
<td>92 (97)</td>
<td>89 (90)</td>
<td>70 (75)</td>
<td>14 (17)</td>
<td>63 (65)</td>
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</table>

**Range:**
- **75-100**
- **65-100**
- **30-95**
- **0-33**
- **10-95**

**NOTES:**
- DNAQ = response given did not match question asked and is not useful for the averages; NNR = no numerical response; UDS=urine opioid toxicology
- Some answered as % positive some as % negative, for ease, results have been converted to % negative.
- If range was given; the average of the range has been entered here (i.e., 30-40% = 35% for purposes of these calculations)
- If answer given as < or >, response was entered as the numeric value
- "X of 6 responses were calculated as: 0 of 6 = 0%; 1 of 6 = 17%; 2 of 6 = 33%; 3 of 6 = 50%; 4 of 6 = 67%; 5 of 6 = 83%; 6 of 6 = 100%
18. REFERENCES


Clinical Trial Protocol
PRO-814, Amendment 1

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Kozlowski LT1, Mann RE, Wilkinson DA, Poulos CX. "Cravings" are ambiguous: ask about urges or desires. Addict Behav. 1989;14(4):443-5.


Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center.


Suboxone® (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets) and Subutex® (buprenorphine HCl sublingual tablets) US Prescribing Information. Richmond, VA: Reckitt Benckiser Pharmaceuticals, Inc., November 2013.


position paper / UNAIDS, 2004, url:  

Clinical Trial Protocol
PRO-814

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

PROBUPHINE®
(BUPRENOHRPHINE HYDROCHLORIDE IMPLANT)

BRAEBURN PHARMACEUTICALS:
47 Hulfish Street, Suite 441
Princeton, NJ 08542

Original Protocol: 1.0, 14-MAY-2014
Amendment No. 1: 2.0, 14-AUGUST-2014
Amendment No. 2: 3.0, 24-SEPTEMBER-2014

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SUMMARY OF CHANGES

Study Title: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Original Protocol: Version 1.0, 14-MAY-2014
Amendment No. 1: Version 2.0, 14-AUGUST-2014
Amendment No. 2: Version 3.0, 24-September-2014

AMENDMENT No. 2, DESCRIPTION OF CHANGES

1. Change in Sponsor Project Manager to Scott Smith.

2. Protocol Synopsis, section, Inclusion Criteria – Revision of Inclusion Criteria 4(a) to clarify definition of 6 months to be at least 24 weeks. Also to clarify the requirement for at least 24 weeks by time of randomization. Revision of Inclusion Criteria 4(b) to replace “prior to Screening” to “at time of randomization”. Revision of Inclusion Criteria 4(c) to add, “at time of randomization”.

3. Protocol Synopsis, section, Secondary Efficacy Endpoints – Addition of “illicit opioid use by month by opioid urine toxicology and self-reported illicit drug use, and time to first evidence of illicit opioid use”.

4. Section 7.1.1, Screening Phase (Week -3 to -1) – Addition of “at time of randomization” to at least 90 days without evidence of illicit opioid use.

5. Section 8 –Selection of Study Population – Addition of “at time of randomization” treatment with 8 mg or less of SL BPN.

6. Section 8.1, Inclusion Criteria - Revision of Inclusion Criteria 4(a) to clarify definition of 6 months to be at least 24 weeks. Also to clarify the requirement for at least 24 weeks by time of randomization. Revision of Inclusion Criteria 4(b) to replace “prior to Screening” to “at time of randomization”. Revision of Inclusion Criteria 4(c) to add, “at time of randomization”.

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7. Section 8.3, Removal of Subjects from Therapy or Assessment – Per advice from the FDA, addition on of, “All efforts should be made by the investigator to continue collection of urine samples at the protocol-defined study visit intervals (monthly and random), concomitant medications, and adverse events in subjects that discontinue study drugs, unless the subject withdraws his/her consent at time of early discontinuation”.

8. Section 10.6.2, Secondary Efficacy Endpoints – Addition of “illicit opioid use by month by opioid urine toxicology and self-reported illicit drug use, and time to first evidence of illicit opioid use”.

9. Section 12.3.2.2.1, Handling of Dropouts or Missing Data – Revision to, “Imputation methods to handle dropouts and/or missing data will be detailed in the SAP”. Additional imputation methods are being discussed with the FDA and will be revised and updated in the final SAP.

10. Section 12.3.2.4, Sensitivity Analysis – Addition of, “Additional sensitivity analysis will be conducted as outlined in the SAP for this study”. The SAP will be updated with additional sensitivity analysis as needed with advice from the FDA.

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## 1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

<table>
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<tr>
<th>ROLE IN STUDY</th>
<th>NAME</th>
<th>CONTACT INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Sponsor</td>
<td>Braeburn Pharmaceuticals, Inc.</td>
<td>47 Hulfish Street, Suite 441&lt;br&gt;Princeton, NJ 08542</td>
</tr>
<tr>
<td>Medical Monitor(s)</td>
<td>PPD, Inc.</td>
<td>PPD, Inc.&lt;br&gt;929 North Front Street&lt;br&gt;Wilmington, NC 28401&lt;br&gt;Telephone-800-201-8725&lt;br&gt;Fax: 888-488-9697</td>
</tr>
<tr>
<td>Sponsor Project Manager</td>
<td>Scott Smith</td>
<td>PPD, Inc.&lt;br&gt;10476 N. Sugarloaf Dr.&lt;br&gt;Cedar Hills, Utah 84062&lt;br&gt;Telephone: 512-913-6731&lt;br&gt;Fax: 512-747-9612&lt;br&gt;Email: <a href="mailto:Scott.Smith@ppdi.com">Scott.Smith@ppdi.com</a></td>
</tr>
<tr>
<td>Principal Investigators</td>
<td>Frank Vocci, PhD</td>
<td>Friends Research Institute, Inc.&lt;br&gt;1040 Park Avenue, Suite 103&lt;br&gt;Baltimore, MD 21201&lt;br&gt;Phone: 410-837-3977 x 255&lt;br&gt;Fax: 410-752-4218</td>
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<td>Richard N. Rosenthal, MD</td>
<td>Icahn School of Medicine at Mount Sinai&lt;br&gt;Medical Director of Addiction Psychiatry,&lt;br&gt;Mount Sinai Behavioral Health System&lt;br&gt;425 West 59th St., Suite 7C&lt;br&gt;New York, NY 10019&lt;br&gt;Tel: (212) 523-5366&lt;br&gt;Fax: (212) 523-7720</td>
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</table>
2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Product: Probuphine® (buprenorphine hydrochloride implant)

Name of Active Ingredient: buprenorphine hydrochloride

Study Title:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Objectives:

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of sublingual (SL) buprenorphine (BPN), to 4 Probuphine implants compared to SL BPN.

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

Methodology:

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN. The study will include 3 Phases; Screening, Maintenance and Follow-up.

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history.

All subjects who have provided written informed consent and have met the other study entry criteria will be eligible for randomization. Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit). On Post-Implant Visit, additional follow-up safety and implant assessment procedures will be conducted. Subjects will return for monthly study visits on Weeks 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). In addition to the monthly scheduled visits, subjects will provide 4 random
urine toxicology samples throughout the 24-week treatment period.

A total of 10 urine toxicology samples will be collected; 6 at scheduled visits (1 per month) and 4 at random urine toxicology visits throughout the 24-week treatment period. At the scheduled visits, other assessments of efficacy and safety will be collected. Implants will be removed at the End of Treatment Visit on Week 24.

Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects and Week 26 will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

**Number of Subjects (Planned):**

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized in the Maintenance Phase.

**Inclusion and Exclusion Criteria**

**Inclusion Criteria**

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for 6 months (at least 24 weeks) at time of randomization.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.
   c. No positive urine toxicology results for illicit opioids in the last 90 days at time of randomization.
5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

**Exclusion Criteria**

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or
naloxone.

5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.

6. Requires current use of agents metabolized through CYP 3A4 such asazole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).

7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.

8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).

9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.

10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

**Investigational Product, Dosage and Mode of Administration:**

All subjects will receive either four 80 mg Probuphine implants or four matching placebo implants for a period of 24 weeks.

**Reference Therapy, Dosage and Mode of Administration:**

Buprenorphine will be administered as 2 mg or 8 mg SL BPN tablets at doses of ≤8 mg (the same dose subjects had been previously stable on) per day or matching placebo SL tablets for a period of 24 weeks.

**Duration of Study:**

Subjects will participate in this study for up to 29 weeks, including Screening (up to 3 weeks), Maintenance/active study drug treatment (24 weeks), and Follow-up (2 weeks).
Criteria for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint is a responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

Secondary Efficacy Endpoints

Secondary efficacy endpoints will include measures of desire/need to use (Desire to Use VAS, Need to Use VAS) and measures of withdrawal (Clinical Opiate Withdrawal Scale [COWS] and Subjective Opioid Withdrawal Scale [SOWS]), illicit opioid use by month by opioid urine toxicology and self-reported illicit drug use, and time to first evidence of illicit opioid use.

Exploratory Efficacy Variables:

Exploratory variables include: Urine toxicology for other drugs of abuse, supplemental SL BPN use, unscheduled visits, phone calls, additional psychosocial counseling and other pharmacological interventions, and treatment discontinuation, including reasons for discontinuation.

Safety Variables

Safety endpoints include: adverse events (AEs), clinical laboratory tests, electrocardiogram, physical and implant site examinations, implant site insertion and removal assessments, concomitant medications, and vital signs.

Statistical Methods (Data Analysis):

Primary efficacy analysis:

A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta=20\%$ will be employed to define non-inferiority. Let $\pi_C$ and $\pi_T$ be the rate of response at 24-weeks on the control arm (SL BPN) and experimental treatment arm (Probuphine), respectively. The null hypothesis (of inferiority is

$H_0: \pi_C - \pi_T \geq \delta$.

The alternative hypothesis (of non-inferiority is

$H_1: \pi_C - \pi_T < \delta$.

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).

Secondary efficacy analysis:

The secondary endpoints will include change from baseline (Day 1) in the secondary efficacy variables at all post baseline visits where the measurements are assessed. These variables will be
analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.
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4. **LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPN</td>
<td>Buprenorphine (may refer to buprenorphine/naloxone or buprenorphine alone)</td>
</tr>
<tr>
<td>( C_{\text{avg}} )</td>
<td>Average plasma concentration</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COWS</td>
<td>Clinical Opioid Withdrawal Scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (may include electronic data capture systems or paper forms)</td>
</tr>
<tr>
<td>CS</td>
<td>Clinically significant</td>
</tr>
<tr>
<td>CSA</td>
<td>Clinical Study Agreement</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EE</td>
<td>Efficacy Evaluable</td>
</tr>
<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
</tbody>
</table>
ICH  International Conference on Harmonization
IRB  Institutional Review Board
ITT  Intent-to-Treat
IV   Intravenous
MAT  Medication-assisted treatment
MINI Mini International Neuropsychiatric Interview
MOP  Manual of Procedures
NCS  Not clinically significant
NSAID Non-steroidal anti-inflammatory
SAE  Serious adverse event
SL   Sublingual
SOC  System Organ Class
SOWS Subjective Opioid Withdrawal Scale
RBC  Red blood cell
SAP  Statistical Analysis Plan
THC  Tetrahydrocannabinol
US   United States
VAS  Visual analogue scale
5. **INTRODUCTION**

5.1. **Background**

Opioid dependence is a serious chronic, debilitating, and sometimes fatal disorder. The process of recovery from opioid dependence is, for most individuals, a long-term and non-linear endeavor that is subject to recurrent relapse. It is well understood that medication-assisted treatment (MAT) without a broader treatment program is generally insufficient to achieve recovery for most opioid-dependent individuals. However, it is also known that MAT has proved to be effective in enabling many individuals to succeed on the long-term path to recovery. The primary agents used in MAT are methadone, buprenorphine hydrochloride (BPN), and naltrexone. Buprenorphine, a partial μ-opioid receptor agonist, is effective and safe (marketed in 34 countries), and has expanded access to treatment for individuals who might otherwise remain untreated. Sublingual (SL) BPN, first approved in 2002, has become widely-available and highly-effective treatment for opioid dependence.

Although daily dosing of SL BPN has proven effective, this route of delivery has several shortcomings. First, SL BPN can easily be diverted for illicit use, injected for greater effect, or accidentally ingested especially by children (Winstock et al., 2008). Second, adherence to daily medication is a challenge, and a conscious decision to discontinue BPN treatment in anticipation of exposure to illicit drugs can also be achieved. Medication non-adherence may lead to relapse, treatment failure, and mortality in the opioid-dependent population. Such limitations are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently), or to those who have difficulty managing the responsibility of daily dosing.

Probuphine® (buprenorphine hydrochloride implant; herein referred to as Probuphine) is a subdermally implantable, abuse- and diversion-deterrent formulation of BPN under development for the maintenance treatment of opioid dependence. Probuphine was developed as an additional therapeutic alternative in maintenance treatment of opioid dependence by providing a long-acting six-month BPN implant that is inherently less susceptible to accidental ingestion (especially by children), abuse and diversion than SL BPN, and is intended to facilitate medication adherence. Probuphine is inserted subdermally in a brief in-office procedure under local anesthetic. Probuphine is designed to provide sustained release of BPN for up to 6 months. At the end of each 6-month treatment, Probuphine is removed in a brief, in-office procedure.
under local anesthetic. Each Probuphine implant consists of 80 mg of BPN that has been blended and extruded with ethylene vinyl acetate (EVA).

5.2. Safety and Efficacy of Buprenorphine

The safety and efficacy of BPN in the treatment of opioid dependence are well-established (Eder et al., 1998; Johnson et al., 1992; Johnson et al., 1995; Johnson et al., 2000; Lopatko et al., 2003; Strain et al., 1994). As a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor, a ceiling or plateauing effect is observed whereby higher doses of BPN are less likely to cause complications of overdose relative to full μ-opioid receptor agonists (Walsh et al., 1994). This results in a safety profile superior to methadone and levo-acetyl-methadol, though efficacy of these treatments for opioid dependence is comparable (Johnson et al., 2000).

In controlled clinical trials with SL BPN, the most common adverse events (AEs) (i.e., those occurring in >10% of subjects) included headache, pain, withdrawal syndrome, asthenia, anxiety, depression, insomnia, rhinitis, nausea, constipation, back pain, infection, and sweating (Reckitt Benckiser Pharmaceuticals, Inc., 2013). From published clinical studies, additional common side effects reported with BPN include drowsiness (increased with alcohol), vomiting, orthostatic hypotension, and sweating. In addition, due to its κ-receptor antagonist activity, BPN can cause withdrawal symptoms if administered with a μ-opioid agonist (such as heroin). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in patients receiving BPN, both in clinical trials and in post-marketing AE reports (Reckitt Benckiser Pharmaceuticals, Inc., 2013). Available data cannot exclude the role of BPN as either causative or contributory in the development of these hepatic abnormalities.

Buprenorphine is metabolized by the 3A4 isoenzyme of cytochrome P450 (CYP3A4). Therefore, concomitant use of CYP 3A4 inhibitors, such asazole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) may increase plasma concentrations of BPN.

Respiratory and central nervous system (CNS) depression can be magnified with concomitant use of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedatives/hypnotics, or other CNS depressants (including alcohol). There have been post-marketing reports of coma and death associated with the concomitant intravenous (IV) misuse of SL BPN and benzodiazepines. In many of these cases, SL BPN was misused by self-injection of crushed SL BPN tablets. In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if
required. Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine.

Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Subjects should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BPN therapy does not adversely affect their ability to engage in such activities. Like other opioids, BPN may produce orthostatic hypotension in ambulatory subjects.

As with other µ-opioid receptor agonists, the administration of BPN may obscure the diagnosis or clinical course of subjects with acute abdominal conditions.

5.3. **Safety and Efficacy of Probuphine**

The safety and efficacy of Probuphine have been studied for the maintenance treatment of opioid dependence in two six-month randomized controlled trials and two six-month, open-label re-treatment trials (Table 1). The pharmacokinetic properties of Probuphine have been evaluated in two relative bioavailability studies, in which plasma concentrations of BPN derived from four 80 mg Probuphine implants were observed to be comparable to the average of those measured in subjects receiving 8 mg or less of SL BPN per day. The subjects in these Phase 3 studies were adults who had not received any MAT for at least 90 days prior to entering the studies, and who underwent a brief induction with SL BPN 12 to 16 mg daily prior to randomization in the controlled trials or continuation in the re-treatment trials.

The medical literature, the completed studies with Probuphine, and an additional pharmacometric analyses performed by the Sponsor demonstrate:

1. Safety and effectiveness of SL BPN in the maintenance treatment of opioid dependence;
2. Effective use of lower SL BPN doses for maintenance treatment of individuals stabilized on daily doses of SL BPN 8 mg or less;
3. Four 80 mg Probuphine implants yield average BPN plasma concentrations of 0.74 to 0.76 ng/mL (average concentration \([C_{avg}]\) over weeks 4 to 24 in subjects who received 4 implants and did not take supplemental SL BPN in PRO-805/PRO-806 studies), which is within a range of approximately 0.5 to 1.0 ng/mL, comparable to the average of those observed following daily doses of 8 mg or less of SL BPN;
4. Probuphine implants provide stable and consistent therapeutic BPN concentrations resulting from continuous delivery of BPN over 6 months, with low intra- and inter-subject variability, and without risk of non-adherence that may be associated with SL BPN;
5. Safety and efficacy of Probuphine in a more difficult-to-treat population of opioid-dependent patients (inducted on 12 to 16 mg/day) (Ling et al., 2010; Rosenthal et al., 2013), allowing a potential downward extrapolation of efficacy to a more stable population of patients on longer-term maintenance treatment with 8 mg SL BPN or less.

In addition to the above, Probuphine may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy. Thus, Probuphine is expected to provide patients and clinicians with an additional treatment option with the potential for more stable plasma concentrations, enhanced adherence and reduced public health consequences of diverted and abused SL BPN.

Table 1: Summary of Previous Data to Support Probuphine Safety and Efficacy

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Study Number</th>
<th>Subjects</th>
<th>Key Findings for Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>TTP-400-02-01</td>
<td>N=12 (N=6 with 4 implants; N=6 with 2 implants)</td>
<td>Four 80 mg Probuphine implants yield BPN plasma concentrations comparable to those observed upon administration of SL doses of 8 mg or less daily.</td>
</tr>
<tr>
<td></td>
<td>PRO-810</td>
<td>N=9</td>
<td>Probuphine implants provide stable BPN concentrations over 6 months, with low intra- and inter-subject variability.</td>
</tr>
<tr>
<td></td>
<td>PRO-805 PRO-806</td>
<td>Population Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>PRO-805 PRO-806</td>
<td>N=262</td>
<td>Statistical significance of pre-specified endpoints met in a population of subjects stabilized for as little as 3 days. Efficacy &gt; Placebo (with SL rescue) on multiple outcome measures. Efficacy similar to SL BPN according to PRO-806 and published data (Rosenthal et al., 2013 In PRO-806, retention rates were 64% for both Probuphine and SL BPN</td>
</tr>
<tr>
<td>Safety</td>
<td>PRO-805 PRO-806 PRO-807 PRO-811</td>
<td>Common adverse events (AEs) and safety issues similar to those seen with SL BPN 2% of subjects discontinued treatment due to implant-related AEs.</td>
<td></td>
</tr>
</tbody>
</table>

Overall, the safety data indicate that Probuphine is well-tolerated over two 24-week implant periods, and exclusive of implant-related treatment emergent AEs, the safety profile is consistent with other marketed buprenorphine-containing products. Including patients receiving Probuphine in safety studies after completing a placebo arm, a total 262 patients have received Probuphine in
the efficacy and safety studies (201 subjects for at least 24 weeks and 82 subjects for at least 48 weeks). With the exception of implant-related AEs, the most common AEs with Probuphine are similar to those observed with SL BPN, and include AEs such as headache, insomnia, nausea, back pain, and diarrhea.

Additional safety information is available in the Probuphine Investigator’s Brochure.

5.4. Study Rationale

Medication-assisted treatment (MAT) is one of the most effective therapies available for opioid dependence and is associated with substantial reductions in illicit opioid use, criminal activity, deaths, and HIV transmission. Because patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, treatment strategies that keep patients in treatment longer may have additional advantages (WHO, 2004). Limitations associated with SL BPN are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently) or to those who have difficulty managing the responsibility of daily dosing. Probuphine offers a valuable opportunity to overcome adherence issues, and to deliver the expected exposure levels that only patients who are compliant with SL BPN may achieve. In addition, although daily dosing of SL BPN has proven effective, SL tablets or even film can easily be diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (Winstock et al., 2008).

Four 80 mg Probuphine implants are expected to approximate the plasma concentrations of BPN observed following daily SL BPN doses of 8 mg or less. Previous clinical trials have demonstrated the efficacy of SL BPN doses of 8 mg/day or less for the maintenance treatment for opioid dependence (Johnson et al, 1992; Johnson et al., 1995; Ling et al., 1998). In addition, post-market studies have shown that clinicians are effectively treating many patients with maintenance BPN doses of 8 mg or less (Apelt et al., 2013; Mattick et al., 2008; Meade et al., 2010). The needs of patients who have been effectively maintained on relatively low SL BPN doses and require less frequent follow-up visits, may be better met by Probuphine than by SL formulations. In addition, Probuphine provides an alternative dosage form that can reduce diversion and enhance abuse deterrence. Therefore, the purpose of this study is to demonstrate the maintenance of the safety and efficacy by an alternate delivery form of BPN, Probuphine, in
the continuing treatment of opioid dependence in clinically stabilized SL BPN* maintenance patients.

6. STUDY OBJECTIVES

6.1. Primary Objective

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN, to 4 Probuphine implants compared to SL BPN.

6.2. Secondary Objective

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a randomized, double-blind, double dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN.

The study will include 3 Phases; Screening, Maintenance and Follow-up. Subjects will participate in this study for up to 29 weeks, including 3 weeks of the Screening Phase, 24 weeks of study drug treatment (Maintenance Phase) and 2 weeks of the Follow-up Phase.

All subjects who have provided written informed consent and have met the other study entry criteria will be enrolled and randomized into the Maintenance Phase. At least 180 subjects will be randomized to one of 2 treatment groups in a 1:1 ratio.

The overall study design is illustrated in Figure 1. Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2).

* Note that throughout this protocol, SL BPN may refer to either sublingual buprenorphine or sublingual buprenorphine/naloxone products, unless otherwise indicated.
All subjects will be seen for a total of approximately 14 visits (total of 10 urine toxicology samples will be collected) as outlined in the Schedule of Assessments:

- 1 Screening visit
- 12 main study visits:
  - 8 Maintenance Phase visits, including 1 Baseline and Initiation of Study Drugs Visit (post-randomization Implant Day [Day 1]), 1 Post-Implant Follow-up Visit, and 6 additional monthly Maintenance Phase visits, including the End of Treatment Visit at Week 24
  - 4 Random urine toxicology visits
- A Post-Treatment Telephone Contact will occur 1 week after the End of Treatment Visit (~1 week prior to the Follow-Up Visit).
- 1 Follow-Up Visit (2 weeks after the End of Treatment Visit)

Additional visits may be scheduled at the discretion of the subject or Investigator.

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects (regardless of randomized group) will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of all study-related medications and counseling will also be covered by the Sponsor.

Section 10 provides additional information on the baseline, efficacy and safety assessments included in the study. Efficacy endpoints and statistical analyses are described in Section 10.6 and Section 12, respectively.

### 7.1.1 Screening Phase (Week -3 to -1)

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history. Data on urine toxicology results for the duration of historical stable maintenance dosing (e.g., at least 90 days at time of randomization) and the treating Health Care Practitioner’s documentation on the patient’s clinical stability (including the length of time that they have judged the patient to be stable) will be obtained via the clinical stability form (provided in the MOP).

Following the Screening Phase, subjects will be eligible for randomization if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.
7.1.2. Maintenance Phase (Month 1 to 6; Week 1 to Week 24)

Eligibility for randomization will be confirmed after the Screening visit and prior to implantation on Day 1 (Baseline and Initiation of Study Drugs Visit). Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Subjects in Treatment Group A will be transitioned to the same dose of SL BPN on which they were previously maintained. Treatment Group B will be transitioned to four Probuphine implants that are expected to yield BPN plasma concentration within a range of approximately 0.5 to 1 ng/mL, comparable to the average of those observed following daily dose of 8 mg or less of SL BPN.

All subjects will be blinded to their treatment group assignment, as will all study staff with the exception of the clinician(s) performing the implant procedure and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets). To maintain blinding, all subjects will receive 4 implants (Probuphine or placebo) and SL tablets (BPN equivalent to their daily dose during the Screening Phase or placebo). Implants will be surgically inserted on Day 1. After Day 1, there will be a Post-Implant Follow-up Visit (to occur within 5 days after implantation) to conduct implant site examination and any additional safety assessments. Further information on implantation procedures can be found in Section 9.1.1.

During the first month, subjects will be required to attend 3 scheduled visits: Baseline and Initiation of Study Drugs Visit (Probuphine/placebo implant insertion and SL BPN/SL placebo administration [Day 1]), Post-Implant Follow-up Visit, and Week 4 first study assessment Visit (evaluation of outcome measures and safety assessments).

During months 2 to 6, subjects will return for monthly study visits for evaluation of outcome measures and safety assessments as described in Table 2. Subjects will be provided with sufficient take home medication for the daily dose of SL BPN or placebo for the subsequent month, as appropriate.

In order to assess number of opioid-free months throughout the 6 months (24 weeks) of treatment, a total of 6 monthly study visits (6 scheduled monthly urine toxicology samples) and 4 random visits (4 random urine samples throughout the 6 months) will be obtained for each subject.

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Each investigator will be instructed to treat additional symptoms (e.g., withdrawal, desire/need to uses, etc.) as they usually would under normal clinical practice, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions (other than those identified as prohibited in Section 9.7). Subjects will be told that their study dose of BPN is comparable to the dose they have been stable on and is expected to be adequate to maintain stability. Therefore, it is generally not anticipated that they will need any additional SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine), but additional counseling and other pharmacological interventions may be available at the discretion of the investigator. Any additional interventions that the subjects receive will be recorded.

Final outcome measures will be collected at the final treatment visit at Week 24 (End of Treatment Visit) and implants will be removed as described in Section 9.1.1

7.1.3. Follow-up Phase

Additional post-implant removal and other assessments will be performed on Week 25 to 26 as outlined in Table 2. Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects, 1 week (± 3 days) after the End of Treatment Visit to capture any AEs that may have occurred. Week 26 (± 3 days) will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).
Figure 1: Overview of Study Design

**Screening**
- Clinically stable, daily ≤ 8 mg SL BPN for at least 90 days, No positive urine toxicology for last 90 days
- Up to 3 Weeks (Weeks 3 to 1)

**Maintenance Phase**
- Group A:
  - Daily SL BPN ≤ 8 mg
  - 4 placebo implants

- Group B:
  - 4 Probuphine implants
  - Daily SL placebo

- 6 Scheduled Urine Toxicology & Other Study Assessments (one per month)
- 4 Random Urine Toxicology

- 24 Weeks (Weeks 1 to 24)
- Monthly Visits

**Follow-up**
- 2 Weeks (23 to 25)

**Randomization**
- Takes place on Day 1 (day of implant)

SL BPN = sublingual buprenorphine or sublingual buprenorphine/naloxone
7.2. Discussion of Overall Study Design

The design selected to meet the objectives of the study is a 24-week randomized double-blind, double-dummy study with SL BPN as an active comparator in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN. Probuphine will be compared to SL BPN using a non-inferiority analysis. Given the pharmacokinetic data showing that four 80 mg Probuphine implants produce BPN plasma concentrations similar to a daily SL BPN dose of 8 mg or less, the proposed design is consistent with other trials evaluating the transfer of subjects to alternative dosage forms, where the overall plasma concentrations have been demonstrated to be similar, such as the transfer from once-daily to weekly dosing of anti-diabetics (Gastaldelli et al., 2013).

Research indicates that for most people with drug dependence, the threshold of significant improvement is reached after about 3 months in treatment, with further gains as treatment is continued (WHO, 2004). Therefore, subjects in maintenance treatment for at least 6 months will be included in the study. Investigators will be required to gain confirmation of clinical stability for subjects according to the clinical judgement of the patients’ treating physician. The clinical judgement should be confirmed by both objective and subjective measures, as described below:

1. According to the results from the Sponsor survey of addiction specialists, clinicians generally consider duration of stability on a given dose to be a proxy for clinical stability. Therefore, one criterion for entry into the study will be a treatment dose of SL BPN (≤8 mg) for at least 90 days.

2. In addition to being on a stable dose for at least 90 days, clinicians will also attest to their patients’ clinical stability as characterized by absence of withdrawal symptoms and no evidence of positive urine toxicology tests for illicit opioids in the previous 90 days. Other elements of clinical stability include, social, emotional and psychological stability (i.e., stable family/home life and employment, treated emotional/psychological issues), compliance to clinic visits, and ongoing counseling.

The current study will enroll patients who have had no evidence of positive urine toxicology results for illicit opioids in the past 90 days. Nevertheless, addiction specialists state that clinically stable patients may have occasional opioid-positive urine toxicology. This is also supported by studies in the literature, that demonstrate subjects undergoing prescribed treatment for at least 3 months report monthly illicit opioid use in the range of 13% to 46.5% (Carrieri et al., 2003; Galanter et al., 2003; Guichard et al., 2003; Jones et al., 2009). While self-reports may
be somewhat less reliable, similar data have been reported using urine toxicology. In these studies, positive opioid urine toxicology screen results in stable subjects maintained on buprenorphine were in the range of 10% up to approximately 25% (Fiellen et al., 2008; Jones et al., 2009; Kakko et al., 2003; Maremmani et al., 2007).

The study will include 24 weeks of study drug treatment (Maintenance Phase). The patient population is clinically stable and accustomed to less frequent visits. Therefore, the study assessment visits will be monthly throughout the 6-month Maintenance Phase of the study starting with Week 4 Visit (Weeks 4 to 24). While previous studies of opioid dependence treatment have required subjects to attend up to thrice weekly visits, the clinically stable subjects under investigation in the current trial do not routinely receive such frequent and intense monitoring for their treatment. The proposed study visit schedule is designed to potentially increase study feasibility as well as improve retention. In addition to the 6 scheduled monthly study assessment visits, subjects will be required to provide 4 random urine toxicology samples throughout the Maintenance Phase of the study, which should be sufficient to detect any abuse of opioids during the 24 weeks of treatment. Subjects will also be encouraged to contact their investigator for unscheduled visits should they experience any signs of inadequate treatment.

8. SELECTION OF STUDY POPULATION

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized into the Maintenance Phase.

This study will enroll adult outpatients with opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR), who have been on a stable dose of 8 mg or less of SL BPN for at least 90 days at time of randomization, and meet their treating healthcare provider’s criteria for clinical stability.

8.1. Inclusion Criteria

Subjects must meet each of the following inclusion criteria at Screening to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for 6 months (at least 24 weeks) at time of randomization.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.
   c. No positive urine toxicology results for illicit opioids in the last 90 days at time of randomization.

5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.

6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

8.2. Exclusion Criteria

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met at Screening:

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.
6. Requires current use of agents metabolized through CYP 3A4 such asazole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.
8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).
9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.
10. Current medical conditions such as severe respiratory insufficiency that may prevent
the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine
aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the
upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening
laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments,
according to the Investigator.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any
time for any reason. A subject’s participation must therefore be terminated immediately upon
his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study for any of the following reasons:

- Evidence of implant removal or attempted removal of the implant
- Safety reasons, including AEs or significant concomitant illness, injury, or urgent
  surgeries/procedures that would, in the judgment of the Investigator, affect assessments of
  clinical status to a significant extent, require discontinuation of study drug, or both
- At the request of the Sponsor, Regulatory, or IRB
  - Subject is lost to follow-up
  - Death of subject

A subject may also be discontinued from the study, at the discretion of the Investigator and/or
Sponsor, for any of the following reasons:

- Subject refusal or unable to adhere to the study protocol
- Protocol violation
- Pregnancy
- Requirement for continual use of opioid analgesics > 7 days or requirement for general
  anesthesia for surgery
The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

For any case of early discontinuation (whether or not the subject is at the clinical site), the subject will be required to return for, at minimum, the End of Treatment Visit to remove the implants. All efforts should be made by the Investigator to continue collection of urine samples at the protocol-defined study visit intervals (monthly and random), concomitant medications, and adverse events in subjects that discontinue study drugs, unless the subject withdraws his/her consent at time of early discontinuation. The Investigator should also ask the subject to return for the Follow-up assessments (i.e., Week 26 assessments), provided that the subject has not withdrawn consent for those assessments. If a subject refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

9. TREATMENTS

9.1. Treatment Administration

Following confirmation of a signed informed consent document, eligibility and randomization:

- Subjects randomized to Treatment Group A will receive daily doses of SL BPN (containing BPN and naloxone) equivalent to their usual single daily dose of BPN ($\leq 8$ mg per day) for 24 weeks. Subjects randomized to this group will also receive 4 placebo implants on Day 1.

- Subjects randomized to Treatment Group B will receive 4 Probuphine implants on Day 1, which are expected to deliver BPN to the subject for at least a period of 24 weeks. Subjects randomized to this group will also receive daily SL placebo tablets.

9.1.1. Implant Insertion and Removal Procedures

All Probuphine and placebo implants will be implanted and removed by trained clinicians. The Sponsor will institute the Probuphine Clinical and Procedure Training and Evaluation program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards. The Sponsor will also provide an Implant Insertion/Removal Instruction
for Use slide deck, training DVD, as well as live training on the instructions for aseptic subdermal insertion and removal of Probuphine or placebo implants.

Prior to randomization and Day 1 (Implant Day), it will be recommended that subjects discontinue SL BPN and have implants inserted subdermally within 12-24 hours after their last SL BPN dose. In addition, it will be recommended that subjects discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to and bathe the day of insertion and removal of implants.

Implantation under the skin of the upper arm will be performed using a specialized applicator provided by the Sponsor. The Probuphine Applicator has been utilized in previous Probuphine studies and is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon®. Additional details on Insertion/Removal procedures and training will be provided in the Study Manual of Procedures (MOP) and the Implant Training DVD. Subjects should be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff. The Implant Clinician will also complete the Implant Insertion Procedure Assessment form provided in the Study MOP.

Subjects will have their implants removed during the End of Treatment Visit. Implant removal procedures are described in detail in the MOP and the Implant Training DVD. If, upon removal, the Implanting Clinician has difficulty locating the implants, ultrasound may be used to facilitate their localization. The Implant Clinician will also complete the Implant Removal Procedure Assessment form provided in the Study MOP.

9.2. Identity of Investigational Products

Probuphine and placebo implants are sterile, approximately 26 mm in length, and 2.5 mm in diameter. The implants are translucent to off-white in appearance. Each Probuphine implant contains 80 mg of BPN HCl, which has been blended and extruded with EVA. Buprenorphine HCl is a Schedule III controlled substance that is chemically derived from thebaine. One milligram of buprenorphine HCl is equal to 0.93 mg of buprenorphine as base. Placebo implants contain only EVA.

Each implant is individually packaged in a foil-lined, heat-sealed pouch. Pouches are then sterilized using gamma radiation. Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants or 4 placebo implants.
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Subjects will be required to take daily SL BPN (BPN/naloxone) during the Maintenance Phase. These products will be supplied by the Sponsor or designee. Matching SL placebo tablets will be provided for each dosage strength. More information regarding the SL BPN and near-matching SL placebo products can be found in the MOP.

For potential supplemental SL BPN needs, a different brand of SL BPN will be utilized to prevent the unblinding of study drug. Information on this brand of SL BPN can be found in the MOP.

All containers/packages/boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

9.2.1. **Handling, Storage, and Accountability**

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

All Patient Kits should be stored at room temperature (15–25°C / 59–77°F) in a secured, double-locked area and in accordance with applicable laws, regulations and institutional requirements. SL BPN should be stored in a secured area and in accordance with the product labeling (a copy is located in the MOP) and all applicable laws, regulations, and local/institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor’s drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site. The Investigator or designee must maintain an inventory record of all SL BPN dispensed to subjects for the purpose of treatment and supplemental use. The drug accountability records for returned SL BPN and placebo tablets will be handled by the unblinded study site personnel. Additional details are provided in the Study MOP.

Following implant removal, appropriate collection and disposal of all implants is outlined in the Study MOP.
Buprenorphine is a Schedule III controlled substance and study drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

9.2.2. Dispensing and Administration Procedures

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects. Subjects will be provided with a monthly supply of study medications.

Subjects will be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, tablets should be placed in different areas under the tongue at the same time.

9.2.3. Supplemental SL BPN

Investigator will be instructed to treat additional symptoms as they would usually, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions. However, subjects will be told that while additional counseling and other pharmacological interventions could be available, their current dose of BPN is expected to be adequate to maintain stability and their physician does not expect that they will need any additional supplemental SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine).

Any supplemental SL BPN, additional counseling, and other pharmacological interventions provided by the Investigator will be recorded, along with the reasons for determining the need for any supplemental interventions.

9.3. Method of Assigning Subjects to Treatment Groups

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.
Subjects who have met the eligibility criteria (Section 8) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group A: Daily SL BPN plus placebo implants or Treatment Group B: four Probuphine implants plus SL placebo tablets). Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2.

### 9.4. Selection of Doses in the Study

The dose of 4 Probuphine implants was selected based on efficacy, safety and pharmacokinetic data from Studies PRO-805, PRO-806, TPP-400, and PRO-810 (Investigator’s Brochure for Probuphine). Four Probuphine implants are expected to yield BPN plasma concentrations comparable to a SL BPN dose of 8 mg or less per day.

### 9.5. Selection and Timing of Dose for Each Subject

Subjects will be randomized to receive either 4 Probuphine implants or SL BPN. The SL BPN will be administered at a dose level equivalent to their usual care/Screening Phase dose.

No fasting or special dietary requirements are required for the study; however, when taking the SL BPN or placebo tablets, subjects should be advised to not eat or drink anything until the tablet(s) are completely dissolved. To ensure consistency in bioavailability, subjects should follow the same manner of dosing for the duration of the study.

### 9.6. Blinding

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets initiated after randomization, subjects will be told that clinical supplies of SL BPN have been specifically developed for this study and may look or taste different than commercially available products they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets. To provide additional
assurance of maintaining the blind, a different brand of SL BPN will be utilized for any potential supplemental SL BPN needs. Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects.

Since the placebo implants have a slightly different appearance than the Probuphine implants, the following will be agreed upon in a signed document by the Implanting Clinician and the Investigator in order to maintain the blind:

- The Implanting Clinician and any other staff involved in the implant insertion and removal procedures must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.
- In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct the subject’s view of the procedure, etc.).
- The study staff must not ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject’s safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

9.7. Prior and Concomitant Therapy

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject’s eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:
- It will be recommended that subjects discontinue NSAID or aspirin-containing medications during the week prior to implant insertion and the week prior to implant removal.

- Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take several days following discontinuation of Probuphine or SL BPN treatment. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.

- Buprenorphine is metabolized via CYP3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of BPN, if CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) are required, the Medical Monitor must be consulted. Interactions with CYP 3A4 inducers have not been investigated; therefore it is recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.

- Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with Probuphine or SL BPN. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in the study. Subjects should be explicitly advised of the danger of IV abuse of benzodiazepines while under treatment with implants or SL BPN.

### 9.8. Subject Study Drug Accountability

Although it is difficult to divert the subdermal Probuphine implants for abuse (removal of implants and extraction of the active BPN HCl from the EVA), diversion can theoretically occur.
10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2); the following sections outline the details and procedures associated with the assessments. Additional details on the assessments, including copies of questionnaires, logs, manuals, and information sheets are provided in the Study MOP.
### Table 2: Schedule of Assessments

<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month:</strong></td>
<td>-</td>
<td>Month 1 Visits</td>
<td>Month 2 to 5 Visits</td>
</tr>
<tr>
<td>Week:*</td>
<td>-3 to 1</td>
<td>Week 1</td>
<td>Week 4</td>
</tr>
<tr>
<td>Day:</td>
<td>-</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Informed Consent&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Eligibility Criteria Review&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical and Medication History / Substance Abuse and Treatment History</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSM-IV-TR, MINI, v 6.0</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbreviated Review of Systems</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs&lt;sup&gt;g&lt;/sup&gt;</td>
<td>X</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistry, Hematology, Urinalysis and Coagulation Profile</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment Visits should be conducted within a window of ±7 days for the monthly visits, except for Post-Implant Visit, which should occur within a window of 1 to 5 days after Day 1. Visits for Weeks 25 and 26 should occur within ±3 days. If a subject misses a visit or completes a visit early or late, the original schedule should be resumed at the subsequent visit such that the ensuing visits occur as originally scheduled, relative to Day 1.

<sup>b</sup> Baseline and Initiation of Study Drugs Visit.

<sup>c</sup> Post-Implant Visit.

<sup>d</sup> Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.

<sup>e</sup> Prior to enrollment in the randomization and Maintenance Phase of this study, all Inclusion and Exclusion criteria must be met.

<sup>f</sup> A complete physical exam of all major body systems will be performed at the Screening Visit.

<sup>g</sup> Includes temperature, blood pressure, pulse rate, respiration rate, and weight. Height will be captured at Screening Visit. BMI will be auto-calculated.

<sup>h</sup> Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implant insertion/removal, and then 15 minutes and 30 minutes after implant insertion/removal.
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<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month:</td>
<td>-</td>
<td>Month 1 Visits</td>
<td>Month 2 to 5 Visits</td>
</tr>
<tr>
<td>Week:*</td>
<td>-3 to -1</td>
<td>Week 1</td>
<td>Week 4</td>
</tr>
<tr>
<td>Day:</td>
<td>-</td>
<td>Day 1(^{b})</td>
<td>Post-Implant(^{a})</td>
</tr>
<tr>
<td>Pregnancy test(^{1})</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis B/C, HIV(^{1})</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant Site Examination(^{b})</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Dispense Treatment Identification Card</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Toxicology</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Random Urine Toxicology</td>
<td></td>
<td>4 Random Urine Toxicology Tests</td>
<td></td>
</tr>
<tr>
<td>Illicit Drug Use Self-Report</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Withdrawal and Desire to Use/Need to Use (SOWS, COWS, VAS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SL BPN or placebo dispensing</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Probuphine or placebo [four (4) implants] Insertion</td>
<td>X(^{1})</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Implant removal procedure</td>
<td>X(^{1})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional interventions(^{n})</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) A serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit (Week 24). An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed prior to start of SL BPN and Probuphine treatment.

\(^{1}\) It is the investigator’s responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood. Hepatitis B/C and HIV testing is required unless a site’s IRB prohibits such testing.

\(^{a}\) The implant site will be visually inspected and palpated.

\(^{b}\) Subjects should be instructed to arrive having bathed with soap and water on Day 1.

\(^{m}\) It is recommended that subjects return 7 days post implant for suture removal.

\(^{n}\) Subjects may receive additional counseling, supplemental SL BPN, or other pharmacological interventions deemed appropriate by the investigator, at any time after implantation, at the investigator’s discretion.
<table>
<thead>
<tr>
<th>Study Period/Phase</th>
<th>Screening</th>
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<tr>
<td><strong>Week:</strong></td>
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<tr>
<td><strong>Day:</strong></td>
<td>-</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Implant Insertion Procedure Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant Removal Procedure Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial Counseling</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events&lt;sup&gt;o&lt;/sup&gt;&lt;sup&gt;p&lt;/sup&gt;&lt;sup&gt;q&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications/Procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wound Care Information Sheet&lt;sup&gt;s&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone Contact</td>
<td></td>
<td></td>
<td>X (As Needed)</td>
</tr>
</tbody>
</table>

<sup>o</sup> AEs that are reported by the subject at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.

<sup>p</sup> Subjects will be monitored for at least 30 minutes after implantation for AEs. AEs will be recorded both prior to and after implant removal at Week 24.

<sup>q</sup> During removal process, careful inspection of the implant site, difficulty of removal and/or fracturing of the implants will be recorded.

<sup>r</sup> If a significant AE is described by the subject and is judged by the Investigator as being possibly related to study treatment, the subject will visit the study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).

<sup>s</sup> A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the participant by the Investigator or designated study personnel. The participant must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject’s medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. Demographics and Psychosocial History

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity. A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.3. Medical History

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

A psychiatric interview will be conducted using the Mini International Neuropsychiatric Interview, Version 6.0 (MINI). The MINI is a valid and reliable structured diagnostic interview for DSM-IV-TR psychiatric disorders.

10.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatments will be collected separately.
10.1.5. Substance Use and Treatment History
A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences and concomitant medications, using a timeline follow-back type of interview (Fals-Stewart, 2000). Validation of historical clinical stability, including duration of treatment and dose at which patient has been stable, and any data available on urine toxicology results, will be captured and reported on the study entry form. Detailed information on substance use and treatment history is provided in the Study MOP.

10.2. Eligibility Review and Randomization
Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of randomization in the Maintenance Phase.

Randomization will be accomplished centrally, using an Interactive Voice Response System and/or by an Interactive Web Response System managed by the Sponsor.

10.3. Efficacy Assessments
Details regarding primary, secondary and exploratory endpoints are provided in Section 10.6 (Efficacy Variables); and discussed further in Section 12.3 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Study MOP.

10.3.1. Urine Toxicology for Opioids
Urine toxicology samples will be collected at each visit (both scheduled and random) using a urine collection cup containing a temperature sensor. Specimen authenticity will be verified at the site using this sensor to measure the urine temperature immediately following collection. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the
subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as 'missing', and should not be sent for analysis (any such samples must be documented in the subject’s records). Direct observation approach to obtaining urine samples may be used if the investigator deem necessary. Urine samples will be logged and numbered and then sent to a central laboratory for analysis for the presence of opioids (e.g., codeine, morphine, hydrocodone, oxymorphone, hydromorphone, oxycodone, methadone, and fentanyl). In addition, it is recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

10.3.2. Self-Reported Illicit Drug Use
Subjects will be questioned about illicit drug use, including illicit or prescription opioids and other drugs of abuse using a timeline follow-back type of interview (Fals-Stewart, 2000). A copy of the Illicit Drug Use Self-Report form is provided in the Study MOP.

10.3.3. Measures of Desire and Need to Use
Desire to Use and Need to Use will be administered using unipolar 100 mm VAS (“Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm= Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively) (Kozlowski et al., 1989).

Copies of these VASs are provided in the Study MOP. **NOTE: Only VAS copies provided by the Sponsor should be used with study subjects; photocopies made locally may result in changes to the length of the scale, leading to inaccurate results.**

* A separate VAS will be provided for each Desire to Use and Need to Use and measurements must be taken separately (i.e., separated in time or by other procedures).

10.3.4. Measures of Withdrawal

10.3.4.1. Subjective Opioid Withdrawal Scale (SOWS)
Subjects will complete a self-assessment of withdrawal symptoms using the SOWS. This form contains 16 questions that rate the intensity of withdrawal from 0 (“Not at all”) to 4 (“Extremely”). A copy of the SOWS is provided in the Study MOP.
10.3.4.2. Clinical Opioid Withdrawal Scale (COWS)

Study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater. A copy of the COWS is provided in the Study MOP.

10.3.5. Urine Toxicology for Other Drugs of Abuse

Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative methods. Positive results will not be confirmed using quantitative methods.

10.3.6. Supplemental Visits, Medication and Counseling

Supplemental SL BPN use will be allowed, as described in Section 9.2.3. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for supplemental visits, supplemental SL BPN needs, phone calls or additional counseling or other pharmacological interventions, will be recorded.

10.4. Safety Assessments and Other Procedures

Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF. Appropriate medical intervention should be provided and, if necessary, implants may be removed or SL BPN treatment discontinued as clinically indicated.

10.4.1. Adverse Events and Serious Adverse Events

The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
10.4.1.1. Adverse Event Reporting

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Relationship to insertion/removal procedure
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the End of Treatment Visit (i.e., implant removal and discontinuation of SL BPN/placebo treatment). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

10.4.1.2. Serious Adverse Event

A serious adverse event (SAE) or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
10.4.1.2.1. Serious Adverse Event Reporting

Serious Adverse Events (SAEs) must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the End of Treatment Visit are reportable within 24 hours. During the follow-up period beyond 14 days from implant removal or discontinuation of SL BPN assigned treatment, only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.
- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.
- The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
  - Subject ID
  - Basic demographic information (age, gender, weight)
o Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)

o Onset date and severity of the event

o Brief description of the event including frequency and severity of symptoms leading to diagnosis, and information on supplemental SL BPN

o List of relevant test results and lab data

o Any other relevant history

o Dates of implantation and removal, if applicable

o Dates and doses of supplemental SL BPN usage

o Whether the study drug was discontinued

o Whether the event abated after implants removed and/or assigned treatment SL BPN discontinued and/or supplemental SL BPN discontinued, as applicable

o Investigator’s assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB / Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

10.4.2. Pregnancy

Pregnancies among trial participants should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant may withdraw their consent and discontinue the study and be referred back to the care of their usual provider. Follow-up information will be obtained where possible (with the consent of the participant or their partner)
regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

### 10.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not clinically significant) or “CS” (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., “CS/mild anemia.” In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 3.
Table 3: Clinical Laboratory Assessments

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Sodium</td>
<td>Color</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Potassium</td>
<td>pH</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Magnesium</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>RBC Morphology</td>
<td>Calcium</td>
<td>Ketones</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Glucose (random)</td>
<td>Protein</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Bicarbonate</td>
<td>Glucose</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Chloride</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>concentration</td>
<td>Creatinine</td>
<td>Nitrite</td>
</tr>
<tr>
<td>Total and differential (absolute)</td>
<td>Total protein</td>
<td>Urobinogen</td>
</tr>
<tr>
<td>white blood cell count</td>
<td>Blood urea nitrogen</td>
<td>Occult blood</td>
</tr>
<tr>
<td>Platelets</td>
<td>Albumin</td>
<td>Microscopic examination of sediment, only if urinalysis dipstick results are abnormal</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Total bilirubin</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (PT), INR</td>
<td>Alanine transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic dehydrogenase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine phosphokinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total cholesterol (non-fasting)</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit. An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of SL BPN and Probuphine treatment.

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed for all subjects, unless a site’s IRB prohibits such testing. It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.
10.4.4. Vital Signs
Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

10.4.5. 12-Lead Electrocardiogram (ECG)
12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

10.4.6. Physical Examination
A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be determined as described in Table 2

10.4.7. Implant Site Examination and Wound Care
Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs. Copies of the wound care information sheets must be reviewed and approved by each site’s IRB, prior to providing them to subjects.

Implant site reactions can occur with the implantation and removal of Probuphine or placebo implants. The most frequently-reported AEs related to the insertion/removal procedure (occurring in greater than 10% of subjects) in previous Phase III clinical studies were erythema, edema, itching, pain, bleeding, bruising, and scarring. The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities, including implant expulsion or implant migration. The implant site should also be palpated to ensure that the four implants have not been removed. If there is any evidence of removal or attempted removal of the implants, or if the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and any remaining implants will be removed.
10.4.8. **Psychosocial Counseling**

All subjects will receive manual-guided drug counseling during the study, as outlined in Table 2 and described in more detail in the Individual Drug Counseling Manual (provided in the Study MOP) (Mercer & Woody). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

10.4.9. **Treatment Identification Card**

Subjects will receive a wallet card indicating that they are receiving BPN as part of the study. This card should be presented to health care providers by the subject in the event of an emergency or if medications such as opioid analgesics are required (see Section 9.7). Sample wallet cards will be provided for IRB submission.

10.4.10. **Other Safety Considerations**

Buprenorphine may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction and after implant insertion, and to exercise caution in performing activities requiring alertness such as driving a car during the first few days after implant insertion, or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

10.5. ** Appropriateness of Measures**

The efficacy outcome measures were selected to provide an efficacy assessment of the study medications with regards to both objective (i.e., urine toxicology results for opioids), and patient-based assessment (i.e., subject-reported desire/need to use and desire/need to use opiates). The most direct method to ascertain the frequency and amount of illicit opiate use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (Zanis et al., 1994). Thus, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. Urine toxicology has been used in many efficacy assessments of buprenorphine and will be used as the primary outcome measure in the definition of responders in this study (Section 10.6). Urine toxicology results will be adjusted for self-reported drug use at each study visit.

Secondary outcome measures were selected as a series of measures and scales to provide a complete assessment of the effectiveness and efficiency of transfer from SL BPN to Probuphine implants with regard to patient-based assessments (i.e., subject-reported desire and need to use...
opioids, withdrawal), as well as measures of the subject’s functional impairment status (Sheehan Disability Scale).

Desire to Use VAS and Need to Use VAS were selected over the typical Craving VAS because the latter term is ambiguous and may have different meaning to different individuals, while the Desire/Need to Use VAS more directly assess the potential behavioral outcome (Kozlowski et al., 1989).

Standard and widely used measures of withdrawal will be included in this study (COWS and SOWS) (Wesson & Ling, 2003; Handelsman et al., 1987) in order to ensure that subject’s withdrawal symptoms are adequately controlled by the Probuphine implants as compared to SL BPN.

In addition, although expected to be relatively rare in this study, supplemental SL BPN use will be evaluated. Finally, to ensure that potential signs of treatment failure are not missed, additional measures of potentially inadequate treatment will include subject- or Investigator-requested additional visits or counseling.

10.6. Efficacy Variables

10.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is a responder analysis. A subject will be designated as a responder (meaning they have maintained stability) if they have no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

10.6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include average scores over 24 weeks of treatment and average change from baseline (Day 1) scores over 24 weeks of treatment for the following outcome measures:

- Measures of desire/need to use:
  - Desire to Use VAS
  - Need to Use VAS

- Measures of withdrawal:
  - Clinical Opiate Withdrawal Scale (COWS)
  - Subjective Opioid Withdrawal Scale (SOWS)
Illicit opioid use:
  o Illicit opioid use by Month (urine toxicology and self-report illicit drug use)
  o Time to first evidence of illicit opioid use

10.6.3. Exploratory Efficacy Variables

Exploratory variables include:

  ▪ Urine toxicology for other drugs of abuse
  ▪ Supplemental SL BPN use, unscheduled visits, phone calls and additional psychosocial counseling and other pharmacological interventions, including reasons for use
  ▪ Treatment discontinuation, including reasons for discontinuation

10.7. Safety Variables

Safety variables include:

  ▪ AEs
  ▪ Clinical laboratory tests
  ▪ ECG
  ▪ Physical and implant site examinations
  ▪ Implant site insertion and removal assessments
  ▪ Concomitant medications
  ▪ Vital signs

11. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and
11.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor’s monitor or designated representative. The Sponsor’s monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

11.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor’s designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to
systematically and independently examine all study-related activities and documents to
determine whether the study-related activities were conducted, and data recorded, analyzed, and
accurately reported according to the protocol, the site’s standard operating procedures, GCP
guidelines of the ICH, and any applicable regulatory requirements. The Investigator should
contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

12. STATISTICAL METHODS AND DETERMINATION OF
SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical
analysis plan (SAP), which will be completed prior to unblinding of the study data. This
document will include more detail of analysis populations, summary strategies, and any
amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be
outlined in the final study report.

12.2. Analysis Populations

The study analysis populations will consist of:

- **Randomized Population**: All subjects who are randomized into the Maintenance Phase
- **Intent-to-Treat (ITT) Population**: All subjects who have been randomized and have
  received an implant and/or received SL BPN/placebo. Analyses based on this population
  will group subjects according to the treatment they were randomized to receive,
  regardless of actual treatment received, and this will be the primary analysis population.
- **Safety Population**: All subjects who are randomized and treated with implants or who
  received any dose of SL BPN/placebo in the Maintenance Phase. Analyses based on this
  population will group subjects according to the treatment they actually received
  regardless of the treatment they were randomized to receive. All safety analyses will use
  the safety population.
- **Per Protocol Population**: All subjects in the ITT population with no major protocol
  violations. Major protocol violation criteria will be established prior to the database lock.
12.3. Planned Analyses

12.3.1. Disposition, Demographics and Other Baseline Characteristics
Disposition for all randomized subjects will be summarized by the randomized treatment group. Reasons for discontinuation will be tabulated for each treatment group and overall.

Demographic data and baseline psychosocial characteristics will be summarized.

Tabular summaries and/or listings will be provided for baseline clinical characteristics such as illicit drug and treatment use history, medical and psychiatric history, inclusion/exclusion criteria, and medication history.

12.3.2. Analysis of Efficacy Measures

12.3.2.1. Primary Endpoint
The primary efficacy variable will be responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

A total of 10 urine toxicology samples will be collected throughout the 6 months of the study treatment period with 6 scheduled visits (1 visit per month) plus 4 random urine toxicology visits.

12.3.2.2. Analysis of Primary Endpoint
A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta=20\%$ will be employed to define non-inferiority. Let $\pi_C$ and $\pi_T$ be the rate of response at 24-weeks on the control arm and experimental treatment arm, respectively. The null hypothesis (of inferiority is

The alternative hypothesis (of non-inferiority is

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).
Rationale for 20% non-inferiority margin: The 20% margin is appropriate from a scientific validity perspective as well as meeting Food and Drug Administration (FDA) guidelines for non-inferiority margin selection (FDA, 2010). In this study with 180 subjects, the observed data that meet the statistical 20% margin will meet scientific face-validity for the equivalency of the treatment arms. The table below (Table 4) summarizes the required Probuphine Treatment Group’s response rate (% of responders) to satisfy non-inferiority based on the 20% margin and the sample size of 90 subjects per group at the two-sided 5% significance level for a range of observed SL BPN arm’s response rate (Note: due to discreteness some percentages are not possible).

<table>
<thead>
<tr>
<th>Observed SL BPN Arm’s Response Rate (% of Responders)</th>
<th>Required Minimum Observed Probuphine Arm’s Response Rate (% of Responders) to Satisfy Non-inferiority (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>81.1</td>
</tr>
<tr>
<td>84.4</td>
<td>76.7</td>
</tr>
<tr>
<td>80</td>
<td>73.3</td>
</tr>
<tr>
<td>74.4</td>
<td>67.8</td>
</tr>
<tr>
<td>70</td>
<td>64.4</td>
</tr>
<tr>
<td>64.4</td>
<td>58.9</td>
</tr>
<tr>
<td>60</td>
<td>54.4</td>
</tr>
</tbody>
</table>

The table demonstrates that utilizing the 20% margin to satisfy non-inferiority, the Probuphine Treatment Group’s response rate should be at least similar to the rate for SL BPN control arm.

Although there is little literature on SL BPN treatment in long-term stabilized maintenance subjects, there is some empirical information available to lend credence to the 20% non-inferiority margin:

1. With patients on longer term BPN or methadone treatment, blinded taper (detoxification) studies indicate rates of continued opioid abstinence following complete withdrawal of about 18 to 31%. Although little data is available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15%. A summary of literature is provided in Section 16.
2. A survey of addiction experts was performed by the Sponsor to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN.

   a. The results demonstrated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability) to illicit opioid use if these patients were taken off their stable dose of 8 mg or less of SL BPN. The FDA Draft Guidance would suggest a 37.5% margin to be appropriate, based on an estimate of 75% effect size (i.e., assuming all patients being stable at study randomization). However, a 37.5% margin, estimating 50% preservation of the effect size may not be clinically acceptable. The proposed 20% margin would estimate preserving >70% of the effect and should be considered clinically acceptable (Section 17).

3. Finally, the FDA Draft Guidance notes that circumstances might support a less conservative choice for the margin, including:
   a) Pharmacologic properties of the test drug that are very similar to those of the active control – Probuphine is an alternative dosage form of the same active entity with the expectation of similar overall plasma concentrations to the SL BPN arm;
   b) Use of a persuasive biomarker – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success;
   c) If the drug has been shown to be effective in closely-related clinical settings – Probuphine has already been shown to be effective relative to placebo in two trials in harder-to-treat populations;
   d) If the test drug were shown to have some important advantage (e.g., on safety or on a secondary endpoint) – The safety issues associated with abuse of SL BPN are well-known; the Drug Abuse Warning Network confirmed an increasing trend to adverse medical outcomes associated with BPN abuse, i.e., a total of 21,483 emergency department visits related to abuse/misuse were reported in 2011 (DAWN, 2013). Probuphine has the potential to reduce misuse/abuse associated with SL BPN and have a significant positive public health impact, in addition to potentially increasing adherence.

Thus, the overall data and circumstances associated with this study support the use of a 20% non-inferiority margin.

Version: Final 3.0, 24-SEPTEMBER-2014
12.3.2.2.1. Handling of Dropouts or Missing Data

Imputation methods to handle dropouts and/or missing data will be detailed in the SAP.

12.3.2.3. Sensitivity Analyses

The following sensitivity analyses will be performed:

- Analysis based on completers (i.e., analysis based on all subjects who provided all required samples);
- Analysis based on missing values replaced with “Opioid-Positive;”
- Per protocol analysis (i.e., analysis based on subjects who do not have major protocol violations).

Additional sensitivity analysis will be conducted as outlined in the SAP for this study.

12.3.2.4. Analysis of Secondary Efficacy Endpoints

The secondary endpoints will include change from baseline (Day 1 prior to implantation) in two measurements of desire/need to use (Desire to Use VAS, Need to Use VAS), two measurements of withdrawal (COWS and SOWS at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.

Details of additional measures of efficacy and their analysis will be described prospectively, prior to final database lock and unblinding, in the SAP for this study.

12.3.3. Analysis of Safety

Exposure will be summarized by treatment group.

AEs will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to study drug or implant insertion/removal, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.
12.4. **Determination of Sample Size**

The sample size of 90 per treatment arm (180 total) was selected to achieve 87.3% power, assuming both arms have a 75% rate of responders. If the true rates are lower, but equal in both arms, with a 65% rate of response, the power of the trial to determine non-inferiority is 80.3%. If each treatment arm has an 85% rate of response, then the trial with 180 subjects would have 96.4% power to determine non-inferiority.
13. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the Sponsor and the investigational site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Study

The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor’s representatives and/or regulatory authority’s representatives at any time.

13.1.2. Ethics Approval

The investigational site’s IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

13.1.3. Subject Informed Consent

The Investigator (or authorized designee) will ensure that the participant (or the participant’s legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided...
in a language understandable to the participant and must not include any language that waives
the participant’s legal rights. Prospective participants must also be informed of their right to
withdraw consent without prejudice at any time during the study. If the participant chooses to
participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the
ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain
the original, signed ICF in the participant’s source documents. A copy of the signed ICF must be
given to the study participant.

13.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her
jurisdiction. Only information identified in this protocol will be collected. The information
collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at
their first assessment. This identifier will be cross-referenced in the participant’s chart. The
identifier will not contain any potentially identifiable information. An identifier log will be
maintained, linking each participant’s name to the corresponding identifier. This log will be
stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor,
representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such
as the United States FDA) may inspect medical records related to the study to check the validity
and accuracy of the data gathered in this study. Participant medical records (with participant’s
initials and/or date of birth) may be copied. Confidentiality of participant records will be
maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be
identifiable in any way. Published reports or presentations will refer to grouped data or coded
individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug
regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or
her information as described in the ICF document. If a participant withdraws consent, some of
the subject’s information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

### 13.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

### 13.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:
Clinical Trial Protocol
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- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator’s portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

13.5. **Delegation of Responsibilities and Adequate Resources**

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.
13.6. Protocol Amendments

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

13.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
14. SPONSOR APPROVAL PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 3.0

Date: 24-SEPTEMBER-2014

Frank E. Young, MD, PhD
Executive Vice President, Clinical and Regulatory Affairs

Date:
24 September 2014
15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 3.0
Date: 24-SEPTEMBER-2014

I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonization/Good Clinical Practice Guidelines.

Investigator’s Name (please print or type)

________________________________________

Signature

________________________________________

Date

Version: Final 3.0, 24-SEPTEMBER-2014

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16. SUMMARY OF LITERATURE TO SUPPORT NON-INFERIORITY MARGIN

A meta-analysis of tapered discontinuation following long-term methadone or BPN treatment found an average abstinence rate of 33% (Korner & Waal, 2005). However, because of the differences in methodology (single or double-blinding, naturalistic, etc.), definitions of abstinence, treatments administered during MAT and durations of follow-up, some studies are more relevant than others. In addition, this article didn’t report on the baseline rates of percentage abstinence or urine toxicology results.

Breen et al., (2003) reported on a study of stable methadone patients (for at least 6 months) to BPN and then gradual reduction to 0 mg BPN (i.e., blinded) over an average duration of 11 weeks showed that subjects at 1 month follow-up after complete BPN discontinuation had 31% negative opioid samples (relative to about 73% negative at baseline, 89% negative during BPN induction, and 91% negative during BPN taper).

One double-blind, double-dummy study in methadone users found 25% abstinence overall during 1 month follow-up after complete discontinuation following gradual taper regimens. Abstinence was 18% in the “rapid” withdrawal group (taper over 10 weeks) (versus 100% negative urine opioid results for 4 weeks preceding study entry and 92% negative for the 6 months prior to the study) (Senay, 1977).

Most of the studies used tapered discontinuation, but in terms of abrupt discontinuation, one survey study in Australia reported that 15% of patients who abruptly discontinued opioid maintenance therapy (BPN or methadone) were abstinent for at least 3 months, while 26-27% were abstinent with either self- or physician-directed taper regimens (Winnstock et al., 2011).
### SUMMARY OF SURVEY RESULTS FROM ADDICTION SPECIALISTS

<table>
<thead>
<tr>
<th>PI #</th>
<th>% Negative UDS Over 6 mths*</th>
<th>% Negative UDS Over Next 6 mths*</th>
<th>% Relapse upon BPN Discontinuation (Over 6 mths)</th>
<th>Maximum Reasonable Change in % UDS positive</th>
<th>% of Patients</th>
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**Mean (Median):** 92 (97) 89 (90) 70 (75) 14 (17) 63 (65)

**Range:** 75-100 65-100 30-95 0-33 10-95

**NOTES:**

- DNAQ = response given did not match question asked and is not useful for the averages; NNR = no numerical response; UDS=urine opioid toxicology
- Some answered as % positive some as % negative, for ease, results have been converted to % negative.
- If range was given; the average of the range has been entered here (i.e., 30-40% = 35% for purposes of these calculations)
- If answer given as < or >, response was entered as the numeric value
- “X of 6 responses were calculated as: 0 of 6 = 0%; 1 of 6 = 17%; 2 of 6 = 33%; 3 of 6 = 50%; 4 of 6 = 67%; 5 of 6 = 83%; 6 of 6 = 100%
18. REFERENCES


Kozlowski LT1, Mann RE, Wilkinson DA, Poulos CX. "Cravings" are ambiguous: ask about urges or desires. Addict Behav. 1989;14(4):443-5.


Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans’ Affairs Medical Center.


Suboxone® (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets) and Subutex® (buprenorphine HCl sublingual tablets) US Prescribing Information. Richmond, VA: Reckitt Benckiser Pharmaceuticals, Inc., November 2013.


World Health Organization, United Nations Office on Drugs and Crime. Substitution maintenance therapy in the management of opioid dependence and HIV/AIDS prevention:

Clinical Trial Protocol
PRO-814

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

PROBUPHINE®
(BUPRENORPHINE HYDROCHLORIDE IMPLANT)

BRAEBURN PHARMACEUTICALS:
47 Hulfish Street, Suite 441
Princeton, NJ 08542

Original Protocol: 1.0, 14-MAY-2014
Amendment No. 1: 2.0, 14-AUGUST-2014
Amendment No. 2: 3.0, 24-SEPTEMBER-2014
Amendment No. 3: 4.0, 30-MARCH-2015

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SUMMARY OF CHANGES

Study Title: A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Original Protocol: Version 1.0, 14-MAY-2014
Amendment No. 1: Version 2.0, 14-AUGUST-2014
Amendment No. 2: Version 3.0, 24-September-2014
Amendment No. 3: Version 4.0, 30-MARCH-2015

AMENDMENT No. 3, DESCRIPTION OF CHANGES

1. Section 2: Protocol Synopsis-Statistical Methods (Data Analysis), Secondary efficacy analysis

   Deleted Text: “The secondary endpoints will include change from baseline (Day 1) in the secondary efficacy variables at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.”

   New Text Added: “All secondary efficacy analysis will be described in detail in the SAP.”

2. Section 10.5: Appropriateness of Measures-Deleted “, as well as measures of the subject’s functional impairment status (Sheehan Disability Scale).” from end of paragraph.

3. Section 10.6.2: Secondary Efficacy Endpoints

   Deleted Text:
   “Secondary efficacy endpoints will include average scores over 24 weeks of treatment and average change from baseline (Day 1) scores over 24 weeks of treatment for the following outcome measures:

   • Measures of desire/need to use:
     o Desire to Use VAS

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Need to Use VAS

- Measures of withdrawal:
  - Clinical Opiate Withdrawal Scale (COWS)
  - Subjective Opioid Withdrawal Scale (SOWS)
- Illicit opioid use:
  - Illicit opioid use by Month (urine toxicology and self-report illicit drug use)
  - Time to first evidence of illicit opioid use

New Text Added:
“Secondary efficacy endpoints will include the following:
- Percent of Subjects with No Illicit Opioid Use by Month;
- Time to First Evidence of Urine Illicit Opioid Use;
- Cumulative Percentage of Evidence of Urine Illicit Opioid Use by Month;
- Percent of Subjects with No Self-Reported Illicit Drug Use by Month;
- Measures of craving: Desire to Use VAS, Need to Use VAS;
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and subjective Opioid Withdrawal Scale (SOWS),”

4. Section 10.6.3: Exploratory Efficacy Variables

Deleted Text:
“Exploratory variables include:
- Urine toxicology for other drugs of abuse
- Supplemental SL BPN use, unscheduled visits, phone calls and additional psychosocial counseling and other pharmacological interventions, including reasons for use
- Treatment discontinuation, including reasons for discontinuation”

New Text Added:
“Exploratory variables include:
- Supplemental SL BPN use
- Additional supplemental counseling
- Additional unscheduled visit to obtain supplemental pharmacological therapies for withdrawal symptoms or desire to use illicit opioids
- Urine toxicology results for other drugs of abuse
- Treatment discontinuation and reasons for discontinuation”

5. Section 12.3.2.4: Analysis of Secondary Efficacy Endpoints

Deleted Text: “The secondary endpoints will include change from baseline (Day 1 prior to implantation) in two measurements of desire/need to use (Desire to Use VAS, Need to Use VAS), two measurements of withdrawal (COWS and SOWS at all post baseline visits where the measurements are assessed. These variables will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment

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differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented.

Next Text Added:
“Secondary efficacy variables will include:
- Percent of Subjects with No Illicit Opioid Use by Month;
- Time to First Evidence of Urine Illicit Opioid Use;
- Cumulative Percentage of Evidence of Urine Illicit Opioid Use by Month;
- Percent of Subjects with No Self-Reported Illicit Drug Use by Month;
- Measures of craving: Desire to Use VAS, Need to Use VAS;
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS).”

“Additional” added to the start of the last sentence “details of measures of efficacy....”

## 1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

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<th>ROLE IN STUDY</th>
<th>NAME</th>
<th>CONTACT INFORMATION</th>
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<tr>
<td>Study Sponsor</td>
<td>Braeburn Pharmaceuticals, Inc.</td>
<td>47 Hulfish Street, Suite 441 Princeton, NJ 08542</td>
</tr>
<tr>
<td>Medical Monitor(s)</td>
<td>PPD, Inc.</td>
<td>PPD, Inc. 929 North Front Street Wilmington, NC 28401 Telephone: 800-201-8725 Fax: 888-488-9697</td>
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<tr>
<td>Sponsor Project Manager</td>
<td>Scott Smith</td>
<td>PPD, Inc. 10476 N. Sugarloaf Dr. Cedar Hills, Utah 84062 Telephone: 512-913-6731 Fax: 512-747-9612 Email: <a href="mailto:Scott.Smith@ppdi.com">Scott.Smith@ppdi.com</a></td>
</tr>
<tr>
<td>Principal Investigators</td>
<td>Frank Vocci, PhD</td>
<td>Friends Research Institute, Inc. 1040 Park Avenue, Suite 103 Baltimore, MD 21201 Phone: 410-837-3977 x 255 Fax: 410-752-4218</td>
</tr>
<tr>
<td></td>
<td>Richard N. Rosenthal, MD</td>
<td>Icahn School of Medicine at Mount Sinai Medical Director of Addiction Psychiatry, Mount Sinai Behavioral Health System 425 West 59th St., Suite 7C New York, NY 10019 Tel: (212) 523-5366 Fax: (212) 523-7720</td>
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</table>
2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Braeburn Pharmaceuticals

Name of Investigational Product: Probuphine® (buprenorphine hydrochloride implant)

Name of Active Ingredient: buprenorphine hydrochloride

Study Title:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Objectives:

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of sublingual (SL) buprenorphine (BPN), to 4 Probuphine implants compared to SL BPN.

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

Methodology:

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN. The study will include 3 Phases; Screening, Maintenance and Follow-up.

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history.

All subjects who have provided written informed consent and have met the other study entry criteria will be eligible for randomization. Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit). On Post-Implant Visit, additional follow-up safety and implant assessment procedures will be conducted. Subjects will return for monthly study visits on Weeks 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). In addition to the monthly scheduled visits, subjects will provide 4 random
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Braeburn Pharmaceuticals
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urine toxicology samples throughout the 24-week treatment period.

A total of 10 urine toxicology samples will be collected; 6 at scheduled visits (1 per month) and 4 at random urine toxicology visits throughout the 24-week treatment period. At the scheduled visits, other assessments of efficacy and safety will be collected. Implants will be removed at the End of Treatment Visit on Week 24.

Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects and Week 26 will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

Number of Subjects (Planned):
An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized in the Maintenance Phase.

Inclusion and Exclusion Criteria

Inclusion Criteria
1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for 6 months (at least 24 weeks) at time of randomization.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.
   c. No positive urine toxicology results for illicit opioids in the last 90 days at time of randomization.
5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.
6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

Exclusion Criteria
2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or
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5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.

6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).

7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.

8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).

9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.

10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥3 X the upper limit of normal, alanine aminotransferase levels ≥3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

Investigational Product, Dosage and Mode of Administration:

All subjects will receive either four 80 mg Probuphine implants or four matching placebo implants for a period of 24 weeks.

Reference Therapy, Dosage and Mode of Administration:

Buprenorphine will be administered as 2 mg or 8 mg SL BPN tablets at doses of ≤8 mg (the same dose subjects had been previously stable on) per day or matching placebo SL tablets for a period of 24 weeks.

Duration of Study:

Subjects will participate in this study for up to 29 weeks, including Screening (up to 3 weeks), Maintenance/active study drug treatment (24 weeks), and Follow-up (2 weeks).
Criteria for Evaluation:

Primary Efficacy Endpoint: The primary efficacy endpoint is a responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

Secondary Efficacy Endpoints
Secondary efficacy endpoints will include measures of desire/need to use (Desire to Use VAS, Need to Use VAS) and measures of withdrawal (Clinical Opiate Withdrawal Scale [COWS] and Subjective Opioid Withdrawal Scale [SOWS]), illicit opioid use by month by opioid urine toxicology and self-reported illicit drug use, and time to first evidence of illicit opioid use.

Exploratory Efficacy Variables:
Exploratory variables include: Urine toxicology for other drugs of abuse, supplemental SL BPN use, unscheduled visits, phone calls, additional psychosocial counseling, other pharmacological interventions, and treatment discontinuation, including reasons for discontinuation.

Safety Variables
Safety endpoints include: adverse events (AEs), clinical laboratory tests, electrocardiogram, physical and implant site examinations, implant site insertion and removal assessments, concomitant medications and vital signs.

Statistical Methods (Data Analysis):
Primary efficacy analysis:
A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta = 20\%$ will be employed to define non-inferiority. Let $\pi_1$ and $\pi_2$ be the rate of response at 24-weeks on the control arm (SL BPN) and experimental treatment arm (Probuphine), respectively. The null hypothesis ($H_0$) of inferiority is $H_0: \pi_1 \leq \pi_2 - 0.20$.

The alternative hypothesis ($H_a$) of non-inferiority is $H_a: \pi_1 > \pi_2 - 0.20$.

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).

Secondary efficacy analysis:
All secondary efficacy analysis will be described in detail in the SAP.
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<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPN</td>
<td>Buprenorphine (may refer to buprenorphine/naloxone or buprenorphine alone)</td>
</tr>
<tr>
<td>Cavg</td>
<td>Average plasma concentration</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COWS</td>
<td>Clinical Opioid Withdrawal Scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (may include electronic data capture systems or paper forms)</td>
</tr>
<tr>
<td>CS</td>
<td>Clinically significant</td>
</tr>
<tr>
<td>CSA</td>
<td>Clinical Study Agreement</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic data capture</td>
</tr>
<tr>
<td>EE</td>
<td>Efficacy Evaluable</td>
</tr>
<tr>
<td>EVA</td>
<td>Ethylene vinyl acetate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>Clinical Trial Protocol</td>
<td>Braeburn Pharmaceuticals</td>
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</tbody>
</table>

ICH | International Conference on Harmonization  
IRB | Institutional Review Board  
ITT | Intent-to-Treat  
IV | Intravenous  
MAT | Medication-assisted treatment  
MINI | Mini International Neuropsychiatric Interview  
MOP | Manual of Procedures  
NCS | Not clinically significant  
NSAID | Non-steroidal anti-inflammatory  
SAE | Serious adverse event  
SL | Sublingual  
SOC | System Organ Class  
SOWS | Subjective Opioid Withdrawal Scale  
RBC | Red blood cell  
SAP | Statistical Analysis Plan  
THC | Tetrahydrocannabinol  
US | United States  
VAS | Visual analogue scale
5. **INTRODUCTION**

5.1. **Background**

Opioid dependence is a serious chronic, debilitating, and sometimes fatal disorder. The process of recovery from opioid dependence is, for most individuals, a long-term and non-linear endeavor that is subject to recurrent relapse. It is well understood that medication-assisted treatment (MAT) without a broader treatment program is generally insufficient to achieve recovery for most opioid-dependent individuals. However, it is also known that MAT has proved to be effective in enabling many individuals to succeed on the long-term path to recovery. The primary agents used in MAT are methadone, buprenorphine hydrochloride (BPN), and naltrexone. Buprenorphine, a partial μ-opioid receptor agonist, is effective and safe (marketed in 34 countries), and has expanded access to treatment for individuals who might otherwise remain untreated. Sublingual (SL) BPN, first approved in 2002, has become widely-available and highly-effective treatment for opioid dependence.

Although daily dosing of SL BPN has proven effective, this route of delivery has several shortcomings. First, SL BPN can easily be diverted for illicit use, injected for greater effect, or accidentally ingested especially by children (Winstock et al., 2008). Second, adherence to daily medication is a challenge, and a conscious decision to discontinue BPN treatment in anticipation of exposure to illicit drugs can also be achieved. Medication non-adherence may lead to relapse, treatment failure, and mortality in the opioid-dependent population. Such limitations are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently), or to those who have difficulty managing the responsibility of daily dosing.

Probuphine® (buprenorphine hydrochloride implant; herein referred to as Probuphine) is a subdermally implantable, abuse- and diversion-deterrent formulation of BPN under development for the maintenance treatment of opioid dependence. Probuphine was developed as an additional therapeutic alternative in maintenance treatment of opioid dependence by providing a long-acting six-month BPN implant that is inherently less susceptible to accidental ingestion (especially by children), abuse and diversion than SL BPN, and is intended to facilitate medication adherence. Probuphine is inserted subdermally in a brief in-office procedure under local anesthetic. Probuphine is designed to provide sustained release of BPN for up to 6 months. At the end of each 6-month treatment, Probuphine is removed in a brief, in-office procedure.
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under local anesthetic. Each Probuphine implant consists of 80 mg of BPN that has been blended and extruded with ethylene vinyl acetate (EVA).

5.2. Safety and Efficacy of Buprenorphine

The safety and efficacy of BPN in the treatment of opioid dependence are well-established (Eder et al., 1998; Johnson et al., 1992; Johnson et al., 1995; Johnson et al., 2000; Lopatko et al., 2003; Strain et al., 1994). As a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor, a ceiling or plateauing effect is observed whereby higher doses of BPN are less likely to cause complications of overdose relative to full μ-opioid receptor agonists (Walsh et al., 1994). This results in a safety profile superior to methadone and levo-acetyl-methadol, though efficacy of these treatments for opioid dependence is comparable (Johnson et al., 2000).

In controlled clinical trials with SL BPN, the most common adverse events (AEs) (i.e., those occurring in >10% of subjects) included headache, pain, withdrawal syndrome, asthenia, anxiety, depression, insomnia, rhinitis, nausea, constipation, back pain, infection, and sweating (Reckitt Benckiser Pharmaceuticals, Inc., 2013). From published clinical studies, additional common side effects reported with BPN include drowsiness (increased with alcohol), vomiting, orthostatic hypotension, and sweating. In addition, due to its κ-receptor antagonist activity, BPN can cause withdrawal symptoms if administered with a μ-opioid agonist (such as heroin). Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in patients receiving BPN, both in clinical trials and in post-marketing AE reports (Reckitt Benckiser Pharmaceuticals, Inc., 2013). Available data cannot exclude the role of BPN as either causative or contributory in the development of these hepatic abnormalities.

Buprenorphine is metabolized by the 3A4 isoenzyme of cytochrome P450 (CYP3A4). Therefore, concomitant use of CYP 3A4 inhibitors, such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) may increase plasma concentrations of BPN.

Respiratory and central nervous system (CNS) depression can be magnified with concomitant use of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedatives/hypnotics, or other CNS depressants (including alcohol). There have been post-marketing reports of coma and death associated with the concomitant intravenous (IV) misuse of SL BPN and benzodiazepines. In many of these cases, SL BPN was misused by self-injection of crushed SL BPN tablets. In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if
required. Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine.

Buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Subjects should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that BPN therapy does not adversely affect their ability to engage in such activities. Like other opioids, BPN may produce orthostatic hypotension in ambulatory subjects.

As with other µ-opioid receptor agonists, the administration of BPN may obscure the diagnosis or clinical course of subjects with acute abdominal conditions.

### 5.3. Safety and Efficacy of Probuphine

The safety and efficacy of Probuphine have been studied for the maintenance treatment of opioid dependence in two six-month randomized controlled trials and two six-month, open-label re-treatment trials (Table 1). The pharmacokinetic properties of Probuphine have been evaluated in two relative bioavailability studies, in which plasma concentrations of BPN derived from four 80 mg Probuphine implants were observed to be comparable to the average of those measured in subjects receiving 8 mg or less of SL BPN per day. The subjects in these Phase 3 studies were adults who had not received any MAT for at least 90 days prior to entering the studies, and who underwent a brief induction with SL BPN 12 to 16 mg daily prior to randomization in the controlled trials or continuation in the re-treatment trials.

The medical literature, the completed studies with Probuphine, and an additional pharmacometric analyses performed by the Sponsor demonstrate:

1. Safety and effectiveness of SL BPN in the maintenance treatment of opioid dependence;
2. Effective use of lower SL BPN doses for maintenance treatment of individuals stabilized on daily doses of SL BPN 8 mg or less;
3. Four 80 mg Probuphine implants yield average BPN plasma concentrations of 0.74 to 0.76 ng/mL (average concentration [C_{avg}] over weeks 4 to 24 in subjects who received 4 implants and did not take supplemental SL BPN in PRO-805/PRO-806 studies), which is within a range of approximately 0.5 to 1.0 ng/mL, comparable to the average of those observed following daily doses of 8 mg or less of SL BPN;
4. Probuphine implants provide stable and consistent therapeutic BPN concentrations resulting from continuous delivery of BPN over 6 months, with low intra- and inter-subject variability, and without risk of non-adherence that may be associated with SL BPN;
5. Safety and efficacy of Probuphine in a more difficult-to-treat population of opioid-dependent patients (inducted on 12 to 16 mg/day) (Ling et al., 2010; Rosenthal et al., 2013), allowing a potential downward extrapolation of efficacy to a more stable population of patients on longer-term maintenance treatment with 8 mg SL BPN or less.

In addition to the above, Probuphine may provide significant potential for reducing risks of diversion, abuse, and accidental pediatric exposure, which continue to be important public health consequences of SL BPN therapy. Thus, Probuphine is expected to provide patients and clinicians with an additional treatment option with the potential for more stable plasma concentrations, enhanced adherence and reduced public health consequences of diverted and abused SL BPN.

### Table 1: Summary of Previous Data to Support Probuphine Safety and Efficacy

<table>
<thead>
<tr>
<th>Type of Data</th>
<th>Study Number</th>
<th>Subjects</th>
<th>Key Findings for Current Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>TTP-400-02-01</td>
<td>N=12</td>
<td>Four 80 mg Probuphine implants yield BPN plasma concentrations comparable to those observed upon administration of SL doses of 8 mg or less daily.</td>
</tr>
<tr>
<td></td>
<td>PRO-810</td>
<td>N=9</td>
<td>Probuphine implants provide stable BPN concentrations over 6 months, with low intra and inter-subject variability.</td>
</tr>
<tr>
<td></td>
<td>PRO-805</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-806</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Population Pharmacokinetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>PRO-805</td>
<td>N=262</td>
<td>Statistical significance of pre-specified endpoints met in a population of subjects stabilized for at least 3 days. Efficacy &gt; Placebo (with SL rescue) on multiple outcome measures. Efficacy similar to SL BPN according to PRO-806 and published data (Rosenthal et al., 2013). In PRO-806, retention rates were 64% for both Probuphine and SL BPN.</td>
</tr>
<tr>
<td>Safety</td>
<td>PRO-805</td>
<td></td>
<td>Common adverse events (AEs) and safety issues similar to those seen with SL BPN. 2% of subjects discontinued treatment due to implant-related AEs.</td>
</tr>
<tr>
<td></td>
<td>PRO-806</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-807</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRO-811</td>
<td></td>
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</tr>
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</table>

Overall, the safety data indicate that Probuphine is well-tolerated over two 24-week implant periods, and exclusive of implant-related treatment emergent AEs, the safety profile is consistent with other marketed buprenorphine-containing products. Including patients receiving Probuphine in safety studies after completing a placebo arm, a total 262 patients have received Probuphine in...
the efficacy and safety studies (201 subjects for at least 24 weeks and 82 subjects for at least 48 weeks). With the exception of implant-related AEs, the most common AEs with Probuphine are similar to those observed with SL BPN, and include AEs such as headache, insomnia, nausea, back pain, and diarrhea.

Additional safety information is available in the Probuphine Investigator’s Brochure.

5.4. Study Rationale

Medication-assisted treatment (MAT) is one of the most effective therapies available for opioid dependence and is associated with substantial reductions in illicit opioid use, criminal activity, deaths, and HIV transmission. Because patients often discontinue treatment prematurely, an outcome associated with higher rates of relapse to drug use, treatment strategies that keep patients in treatment longer may have additional advantages (WHO, 2004). Limitations associated with SL BPN are of particular importance to patients with children in the home, to those who have difficulty making frequent visits to the physician’s office (e.g., patients in remote locations, those with limited mobility, or those who travel frequently) or to those who have difficulty managing the responsibility of daily dosing. Probuphine offers a valuable opportunity to overcome adherence issues, and to deliver the expected exposure levels that only patients who are compliant with SL BPN may achieve. In addition, although daily dosing of SL BPN has proven effective, SL tablets or even film can easily be diverted for illicit use, injected for greater effect, or accidentally ingested, especially by children (Winstock et al., 2008).

Four 80 mg Probuphine implants are expected to approximate the plasma concentrations of BPN observed following daily SL BPN doses of 8 mg or less. Previous clinical trials have demonstrated the efficacy of SL BPN doses of 8 mg/day or less for the maintenance treatment for opioid dependence (Johnson et al, 1992; Johnson et al., 1995; Ling et al., 1998). In addition, post-market studies have shown that clinicians are effectively treating many patients with maintenance BPN doses of 8 mg or less (Apelt et al., 2013; Mattick et al., 2008; Meade et al., 2010). The needs of patients who have been effectively maintained on relatively low SL BPN doses and require less frequent follow-up visits, may be better met by Probuphine than by SL formulations. In addition, Probuphine provides an alternative dosage form that can reduce diversion and enhance abuse deterrence. Therefore, the purpose of this study is to demonstrate the maintenance of the safety and efficacy by an alternate delivery form of BPN, Probuphine, in
the continuing treatment of opioid dependence in clinically stabilized SL BPN\textsuperscript{*} maintenance patients.

6. **STUDY OBJECTIVES**

6.1. **Primary Objective**

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN, to 4 Probuphine implants compared to SL BPN.

6.2. **Secondary Objective**

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

7. **INVESTIGATIONAL PLAN**

7.1. **Overall Study Design and Plan**

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN.

The study will include 3 Phases; Screening, Maintenance and Follow-up. Subjects will participate in this study for up to 29 weeks, including 3 weeks of the Screening Phase, 24 weeks of study drug treatment (Maintenance Phase) and 2 weeks of the Follow-up Phase.

All subjects who have provided written informed consent and have met the other study entry criteria will be enrolled and randomized into the Maintenance Phase. At least 180 subjects will be randomized to one of 2 treatment groups in a 1:1 ratio.

The overall study design is illustrated in Figure 1. Study assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2).

\* Note that throughout this protocol, SL BPN may refer to either sublingual buprenorphine or sublingual buprenorphine/naloxone products, unless otherwise indicated.
All subjects will be seen for a total of approximately 14 visits (total of 10 urine toxicology samples will be collected) as outlined in the Schedule of Assessments:

- 1 Screening visit
- 12 main study visits:
  - 8 Maintenance Phase visits, including 1 Baseline and Initiation of Study Drugs Visit (post-randomization Implant Day [Day 1]), 1 Post-Implant Follow-up Visit, and 6 additional monthly Maintenance Phase visits, including the End of Treatment Visit at Week 24
  - 4 Random urine toxicology visits
- A Post-Treatment Telephone Contact will occur 1 week after the End of Treatment Visit (~1 week prior to the Follow-Up Visit).
- 1 Follow-Up Visit (2 weeks after the End of Treatment Visit)

Additional visits may be scheduled at the discretion of the subject or Investigator.

To ensure adequate enrollment and address potential inconvenience to subjects, all subjects (regardless of randomized group) will receive appropriate compensation for time and travel expenses related to attendance at study visits. All costs of all study-related medications and counseling will also be covered by the Sponsor.

Section 10 provides additional information on the baseline, efficacy and safety assessments included in the study. Efficacy endpoints and statistical analyses are described in Section 10.6 and Section 12, respectively.

7.1.1. Screening Phase (Week -3 to -1)

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history. Data on urine toxicology results for the duration of historical stable maintenance dosing (e.g., at least 90 days at time of randomization) and the treating Health Care Practitioner’s documentation on the patient’s clinical stability (including the length of time that they have judged the patient to be stable) will be obtained via the clinical stability form (provided in the MOP).

Following the Screening Phase, subjects will be eligible for randomization if they meet all of the inclusion criteria and do not meet any of the exclusion criteria.
7.1.2. Maintenance Phase (Month 1 to 6; Week 1 to Week 24)

Eligibility for randomization will be confirmed after the Screening visit and prior to implantation on Day 1 (Baseline and Initiation of Study Drugs Visit). Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Subjects in Treatment Group A will be transitioned to the same dose of SL BPN on which they were previously maintained. Treatment Group B will be transitioned to four Probuphine implants that are expected to yield BPN plasma concentration within a range of approximately 0.5 to 1 ng/mL, comparable to the average of those observed following daily dose of 8 mg or less of SL BPN.

All subjects will be blinded to their treatment group assignment, as will all study staff with the exception of the clinician(s) performing the implant procedure and designated personnel who will be responsible for drug accountability (i.e., counting the active and placebo SL BPN returned tablets). To maintain blinding, all subjects will receive 4 implants (Probuphine or placebo) and SL tablets (BPN equivalent to their daily dose during the Screening Phase or placebo). Implants will be surgically inserted on Day 1. After Day 1, there will be a Post-Implant Follow-up Visit (to occur within 5 days after implantation) to conduct implant site examination and any additional safety assessments. Further information on implantation procedures can be found in Section 9.1.1.

During the first month, subjects will be required to attend 3 scheduled visits: Baseline and Initiation of Study Drugs Visit (Probuphine/placebo implant insertion and SL BPN/SL placebo administration [Day 1]), Post-Implant Follow-up Visit, and Week 4 first study assessment Visit (evaluation of outcome measures and safety assessments).

During months 2 to 6, subjects will return for monthly study visits for evaluation of outcome measures and safety assessments as described in Table 2. Subjects will be provided with sufficient take home medication for the daily dose of SL BPN or placebo for the subsequent month, as appropriate.

In order to assess number of opioid-free months throughout the 6 months (24 weeks) of treatment, a total of 6 monthly study visits (6 scheduled monthly urine toxicology samples) and 4 random visits (4 random urine samples throughout the 6 months) will be obtained for each subject.
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Each investigator will be instructed to treat additional symptoms (e.g., withdrawal, desire/need to
uses, etc.) as they usually would under normal clinical practice, including additional counseling
sessions, supplemental SL BPN, or other pharmacological interventions (other than those
identified as prohibited in Section 9.7). Subjects will be told that their study dose of BPN is
comparable to the dose they have been stable on and is expected to be adequate to maintain
stability. Therefore, it is generally not anticipated that they will need any additional SL BPN (the
Sponsor proposes such language to be included in the final approved labeling for Probuphine),
but additional counseling and other pharmacological interventions may be available at the
discretion of the investigator. Any additional interventions that the subjects receive will be
recorded.

Final outcome measures will be collected at the final treatment visit at Week 24 (End of
Treatment Visit) and implants will be removed as described in Section 9.1.1

7.1.3. Follow-up Phase
Additional post-implant removal and other assessments will be performed on Week 25 to 26 as
outlined in Table 2. Following Week 24, subjects will be re-transitioned back to usual care (pre­
trial), as needed. During Week 25, telephone contact will be made with all subjects, 1 week (± 3
days) after the End of Treatment Visit to capture any AEs that may have occurred. Week 26 (± 3
days) will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).
Figure 1: Overview of Study Design

Screening

Clinically stable, Daily ≤ 8 mg SL BPN for at least 90 days, No positive urine toxicology for last 90 days
Up to 3 Weeks (Weeks -3 to -1)

Maintenance Phase

Group A:
Daily SL BPN ≤ 8 mg
4 placebo implants

Group B:
4 Probuphine implants
Daily SL placebo

6 Scheduled Urine Toxicology & Other Study Assessments (one per month)
4 Random Urine Toxicology

Follow-up

24 Weeks (Weeks 1 to 24)
Monthly Visits

24 Weeks (6 months) on Treatment

Randomization takes place on Day 1 (day of implant)

SL BPN = sublingual buprenorphine or sublingual buprenorphine/naloxone
7.2. Discussion of Overall Study Design

The design selected to meet the objectives of the study is a 24-week randomized double-blind, double-dummy study with SL BPN as an active comparator in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN. Probuphine will be compared to SL BPN using a non-inferiority analysis. Given the pharmacokinetic data showing that four 80 mg Probuphine implants produce BPN plasma concentrations similar to a daily SL BPN dose of 8 mg or less, the proposed design is consistent with other trials evaluating the transfer of subjects to alternative dosage forms, where the overall plasma concentrations have been demonstrated to be similar, such as the transfer from once-daily to weekly dosing of antidiabetics (Gastaldelli et al., 2013).

Research indicates that for most people with drug dependence, the threshold of significant improvement is reached after about 3 months in treatment, with further gains as treatment is continued (WHO, 2004). Therefore, subjects in maintenance treatment for at least 6 months will be included in the study. Investigators will be required to gain confirmation of clinical stability for subjects according to the clinical judgement of the patients’ treating physician. The clinical judgement should be confirmed by both objective and subjective measures, as described below:

1. According to the results from the Sponsor survey of addiction specialists, clinicians generally consider duration of stability on a given dose to be a proxy for clinical stability. Therefore, one criterion for entry into the study will be a treatment dose of SL BPN (≤8 mg) for at least 90 days.

2. In addition to being on a stable dose for at least 90 days, clinicians will also attest to their patients’ clinical stability as characterized by absence of withdrawal symptoms and no evidence of positive urine toxicology tests for illicit opioids in the previous 90 days. Other elements of clinical stability include, social, emotional and psychological stability (i.e., stable family/home life and employment, treated emotional/psychological issues), compliance to clinic visits, and ongoing counseling.

The current study will enroll patients who have had no evidence of positive urine toxicology results for illicit opioids in the past 90 days. Nevertheless, addiction specialists state that clinically stable patients may have occasional opioid-positive urine toxicology. This is also supported by studies in the literature, that demonstrate subjects undergoing prescribed treatment for at least 3 months report monthly illicit opioid use in the range of 13% to 46.5% (Carrieri et al., 2003; Galanter et al., 2003; Guichard et al., 2003; Jones et al., 2009). While self-reports may
be somewhat less reliable, similar data have been reported using urine toxicology. In these studies, positive opioid urine toxicology screen results in stable subjects maintained on buprenorphine were in the range of 10% up to approximately 25% (Fiellen et al., 2008; Jones et al., 2009; Kakko et al., 2003; Maremmmani et al., 2007).

The study will include 24 weeks of study drug treatment (Maintenance Phase). The patient population is clinically stable and accustomed to less frequent visits. Therefore, the study assessment visits will be monthly throughout the 6-month Maintenance Phase of the study starting with Week 4 Visit (Weeks 4 to 24). While previous studies of opioid dependence treatment have required subjects to attend up to thrice weekly visits, the clinically stable subjects under investigation in the current trial do not routinely receive such frequent and intense monitoring for their treatment. The proposed study visit schedule is designed to potentially increase study feasibility as well as improve retention. In addition to the 6 scheduled monthly study assessment visits, subjects will be required to provide 4 random urine toxicology samples throughout the Maintenance Phase of the study, which should be sufficient to detect any abuse of opioids during the 24 weeks of treatment. Subjects will also be encouraged to contact their investigator for unscheduled visits should they experience any signs of inadequate treatment.

8. SELECTION OF STUDY POPULATION

An appropriate number of subjects will be screened in order to ensure that at least 180 subjects are randomized into the Maintenance Phase.

This study will enroll adult outpatients with opioid dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR), who have been on a stable dose of 8 mg or less of SL BPN for at least 90 days at time of randomization, and meet their treating healthcare provider’s criteria for clinical stability.

8.1. Inclusion Criteria

Subjects must meet each of the following inclusion criteria at Screening to be eligible for participation in the study:

1. Subject must provide written informed consent prior to the conduct of any study-related procedures.
2. Male or female, 18-65 years of age, inclusive.
4. Subject is considered clinically stable by their treating healthcare provider and confirmed by the following:
   a. Subject must be on SL BPN treatment for 6 months (at least 24 weeks) at time of randomization.
   b. Subject must have been on a SL BPN dose of 8 mg or less daily for at least the last 90 days at time of randomization.
   c. No positive urine toxicology results for illicit opioids in the last 90 days at time of randomization.

5. Free from significant withdrawal symptoms (score of ≤ 5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at the Screening Visit.

6. Female subjects of childbearing potential must be willing to use a reliable method of contraception during the entire study (Screening Visit to Follow-Up Visit).

**8.2. Exclusion Criteria**

Subjects will not be eligible to participate in this study if any one of the following exclusion criteria is met at Screening:

2. Current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that require opioid treatment.
3. Pregnant or lactating or planning to become pregnant during the study.
4. Hypersensitivity or allergy to ethylene vinyl acetate (EVA)-containing substances or naloxone.
5. Recent scarring or tattoos on their upper arms, or a history of keloid scarring.
6. Requires current use of agents metabolized through CYP 3A4 such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors (e.g., ritonavir, indinavir, and saquinavir).
7. History of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.
8. Current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).
9. Significant symptoms or other factors which in the opinion of the Investigator would preclude compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.
10. Current medical conditions such as severe respiratory insufficiency that may prevent the subject from safely participating in study.

11. Any pending legal action that could prohibit participation or compliance in the study.

12. Exposure to any investigational drug within the 8 weeks prior to Screening.

13. Aspartate aminotransferase levels ≥ 3 X the upper limit of normal, alanine aminotransferase levels ≥ 3 X the upper limit of normal, total bilirubin ≥ 1.5 X the upper limit of normal, or creatinine ≥ 1.5 X upper limit of normal on the Screening laboratory assessments.

14. Clinically significant low platelet count on the Screening laboratory assessments, according to the Investigator.

8.3. Removal of Subjects from Therapy or Assessment

A subject is free to withdraw his/her consent and discontinue participation in the study at any time for any reason. A subject’s participation must therefore be terminated immediately upon his/her request, and the reason(s) for discontinuation appropriately documented.

A subject must be discontinued from the study for any of the following reasons:

- Evidence of implant removal or attempted removal of the implant
- Safety reasons, including AEs or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the judgment of the Investigator, affect assessments of clinical status to a significant extent, require discontinuation of study drug, or both
- At the request of the Sponsor, Regulatory, or IRB
  - Subject is lost to follow-up
  - Death of subject

A subject may also be discontinued from the study, at the discretion of the Investigator and/or Sponsor, for any of the following reasons:

- Subject refusal or unable to adhere to the study protocol
- Protocol violation
- Pregnancy
- Requirement for continual use of opioid analgesics > 7 days or requirement for general anesthesia for surgery
The Investigator must maintain a record of all subjects who discontinue from the study prior to completion; the reason(s) for study discontinuation will be documented. In the event that a subject chooses to withdraw from the study, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the subject is not obligated to provide such a reason.

For any case of early discontinuation (whether or not the subject is at the clinical site), the subject will be required to return for, at minimum, the End of Treatment Visit to remove the implants. All efforts should be made by the Investigator to continue collection of urine samples at the protocol-defined study visit intervals (monthly and random), concomitant medications, and adverse events in subjects that discontinue study drugs, unless the subject withdraws his/her consent at time of early discontinuation. The Investigator should also ask the subject to return for the Follow-up assessments (i.e., Week 26 assessments), provided that the subject has not withdrawn consent for those assessments. If a subject refuses to complete early termination procedures and/or Follow-up, this information will be recorded.

9. TREATMENTS

9.1. Treatment Administration

Following confirmation of a signed informed consent document, eligibility and randomization:

- Subjects randomized to Treatment Group A will receive daily doses of SL BPN (containing BPN and naloxone) equivalent to their usual single daily dose of BPN (≤8 mg per day) for 24 weeks. Subjects randomized to this group will also receive 4 placebo implants on Day 1.
- Subjects randomized to Treatment Group B will receive 4 Probuphine implants on Day 1, which are expected to deliver BPN to the subject for at least a period of 24 weeks. Subjects randomized to this group will also receive daily SL placebo tablets.

9.1.1. Implant Insertion and Removal Procedures

All Probuphine and placebo implants will be implanted and removed by trained clinicians. The Sponsor will institute the Probuphine Clinical and Procedure Training and Evaluation program to ensure that clinicians who perform the implant insertion and removal procedures meet competency standards. The Sponsor will also provide an Implant Insertion/Removal Instruction
for Use slide deck, training DVD, as well as live training on the instructions for aseptic subdermal insertion and removal of Probuphine or placebo implants.

Prior to randomization and Day 1 (Implant Day), it will be recommended that subjects discontinue SL BPN and have implants inserted subdermally within 12-24 hours after their last SL BPN dose. In addition, it will be recommended that subjects discontinue any non-steroidal anti-inflammatory (NSAID) or aspirin-containing medications one week prior to and bathe the day of insertion and removal of implants.

Implantation under the skin of the upper arm will be performed using a specialized applicator provided by the Sponsor. The Probuphine Applicator has been utilized in previous Probuphine studies and is similar in design to the commercially-approved applicators currently used for the insertion of other implantable drugs, such as Implanon®. Additional details on Insertion/Removal procedures and training will be provided in the Study Manual of Procedures (MOP) and the Implant Training DVD. Subjects should be monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified study staff. The Implant Clinician will also complete the Implant Insertion Procedure Assessment form provided in the Study MOP.

Subjects will have their implants removed during the End of Treatment Visit. Implant removal procedures are described in detail in the MOP and the Implant Training DVD. If, upon removal, the Implanting Clinician has difficulty locating the implants, ultrasound may be used to facilitate their localization. The Implant Clinician will also complete the Implant Removal Procedure Assessment form provided in the Study MOP.

### 9.2. Identity of Investigational Products

Probuphine and placebo implants are sterile, approximately 26 mm in length, and 2.5 mm in diameter. The implants are translucent to off-white in appearance. Each Probuphine implant contains 80 mg of BPN HCl, which has been blended and extruded with EVA. Buprenorphine HCl is a Schedule III controlled substance that is chemically derived from thebaine. One milligram of buprenorphine HCl is equal to 0.93 mg of buprenorphine as base. Placebo implants contain only EVA.

Each implant is individually packaged in a foil-lined, heat-sealed pouch. Pouches are then sterilized using gamma radiation. Pouched implants are labeled and packaged into an individual Patient Kit (Box). All Initial Implant Kits contain 4 Probuphine implants or 4 placebo implants.
Subjects will be required to take daily SL BPN (BPN/naloxone) during the Maintenance Phase. These products will be supplied by the Sponsor or designee. Matching SL placebo tablets will be provided for each dosage strength. More information regarding the SL BPN and near-matching SL placebo products can be found in the MOP.

For potential supplemental SL BPN needs, a different brand of SL BPN will be utilized to prevent the unblinding of study drug. Information on this brand of SL BPN can be found in the MOP.

All containers/packages/boxes of study drug will be clearly labeled with study-specific information meeting all the applicable regulatory/institutional requirements.

9.2.1. Handling, Storage, and Accountability

All study drugs will be transported, received, stored, and handled strictly in accordance with the container or product label, the instructions provided to the research site, and applicable regulations.

All Patient Kits should be stored at room temperature (15–25°C / 59–77°F) in a secured, double-locked area and in accordance with applicable laws, regulations and institutional requirements. SL BPN should be stored in a secured area and in accordance with the product labeling (a copy is located in the MOP) and all applicable laws, regulations, and local/institutional requirements.

Detailed drug accountability records must be maintained, including the dates shipments are received, the quantity of material received, the dates dispensed, the running inventory, and the unused quantities returned to the Sponsor’s drug supply vendor at the end of the trial. All unused supplies will be checked against the drug accountability records during the study and/or at the end of the study. Subjects will be instructed to return all unused study drugs to the clinical site. The Investigator or designee must maintain an inventory record of all SL BPN dispensed to subjects for the purpose of treatment and supplemental use. The drug accountability records for returned SL BPN and placebo tablets will be handled by the unblinded study site personnel. Additional details are provided in the Study MOP.

Following implant removal, appropriate collection and disposal of all implants is outlined in the Study MOP.
Buprenorphine is a Schedule III controlled substance and study drugs must be handled and stored strictly in accordance with restrictions related to controlled substances. Study drugs must be kept securely locked with access limited to appropriate study personnel, according to applicable regulations.

9.2.2. Dispensing and Administration Procedures

Only eligible subjects participating in the study will receive the study drug. Only authorized research site staff may supply or administer the study drugs. Once dispensed, study drug may not be relabeled or reassigned for use by other subjects. Subjects will be provided with a monthly supply of study medications.

Subjects will be instructed to place SL BPN or placebo tablets under the tongue until dissolved. For dosages requiring more than one SL tablet, tablets should be placed in different areas under the tongue at the same time.

9.2.3. Supplemental SL BPN

Investigator will be instructed to treat additional symptoms as they would usually, including additional counseling sessions, supplemental SL BPN, or other pharmacological interventions. However, subjects will be told that while additional counseling and other pharmacological interventions could be available, their current dose of BPN is expected to be adequate to maintain stability and their physician does not expect that they will need any additional supplemental SL BPN (the Sponsor proposes such language to be included in the final approved labeling for Probuphine).

Any supplemental SL BPN, additional counseling, and other pharmacological interventions provided by the Investigator will be recorded, along with the reasons for determining the need for any supplemental interventions.

9.3. Method of Assigning Subjects to Treatment Groups

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.
Subjects who have met the eligibility criteria (Section 8) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group A: Daily SL BPN plus placebo implants or Treatment Group B: four Probuphine implants plus SL placebo tablets). Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2.

9.4. Selection of Doses in the Study

The dose of 4 Probuphine implants was selected based on efficacy, safety and pharmacokinetic data from Studies PRO-805, PRO-806, TPP-400, and PRO-810 (Investigator’s Brochure for Probuphine). Four Probuphine implants are expected to yield BPN plasma concentrations comparable to a SL BPN dose of 8 mg or less per day.

9.5. Selection and Timing of Dose for Each Subject

Subjects will be randomized to receive either 4 Probuphine implants or SL BPN. The SL BPN will be administered at a dose level equivalent to their usual care/Screening Phase dose.

No fasting or special dietary requirements are required for the study; however, when taking the SL BPN or placebo tablets, subjects should be advised to not eat or drink anything until the tablet(s) are completely dissolved. To ensure consistency in bioavailability, subjects should follow the same manner of dosing for the duration of the study.

9.6. Blinding

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded. The subject, investigational site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets initiated after randomization, subjects will be told that clinical supplies of SL BPN have been specifically developed for this study and may look or taste different than commercially available products they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets. To provide additional
assurance of maintaining the blind, a different brand of SL BPN will be utilized for any potential supplemental SL BPN needs. Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects.

Since the placebo implants have a slightly different appearance than the Probuphine implants, the following will be agreed upon in a signed document by the Implanting Clinician and the Investigator in order to maintain the blind:

- The Implanting Clinician and any other staff involved in the implant insertion and removal procedures must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.
- In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct the subject’s view of the procedure, etc.).
- The study staff must not ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject’s safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

9.7. **Prior and Concomitant Therapy**

All non-study medications, including prescription, over-the-counter, or herbal therapies, used by the subject will be documented for the 30 days prior to Screening and throughout the study. The Investigator will determine if the prior/concomitant medication(s) affect the subject’s eligibility to participate or continue to participate in the study. The following restrictions on concomitant medications will be in place during the study:
• It will be recommended that subjects discontinue NSAID or aspirin-containing medications during the week prior to implant insertion and the week prior to implant removal.

• Opioid receptors are likely to be occupied by BPN, which may reduce the analgesic effects of an opioid. The dissociation of BPN from the receptors may take several days following discontinuation of Probuphine or SL BPN treatment. Therefore, subjects requiring analgesic emergency treatment or anesthesia for surgery should ideally be treated with a non-opioid analgesic. Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration. The clinical course should be fully documented for subjects who have a requirement for any opioid analgesic for >7 days continually or general anesthesia for surgery.

• Buprenorphine is metabolized via CYP3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of BPN, if CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir) are required, the Medical Monitor must be consulted. Interactions with CYP 3A4 inducers have not been investigated; therefore it is recommended that the use of agents such as phenobarbital, carbamazepine, phenytoin and rifampicin be avoided in subjects receiving study treatment. The Medical Monitor must be consulted prior to starting subjects on any of these agents.

• Concomitant use of other narcotic anesthetics, benzodiazepines, phenothiazines, other tranquilizers, or other CNS depressants (including alcohol and sedative/hypnotics) may cause respiratory and CNS depression. Use of these substances should be minimized during treatment with Probuphine or SL BPN. If these sedatives are required during the study, the Medical Monitor must be consulted. Subjects should be advised of the danger of concomitant use of sedatives while participating in the study. Subjects should be explicitly advised of the danger of IV abuse of benzodiazepines while under treatment with implants or SL BPN.

9.8. Subject Study Drug Accountability

Although it is difficult to divert the subdermal Probuphine implants for abuse (removal of implants and extraction of the active BPN HCl from the EVA), diversion can theoretically occur.
Subjects must therefore be carefully monitored for such diversion. The implant site will be visually inspected and palpated (for accountability of the implants) at each visit, and, if there is any evidence of removal of the implants by the subject, the subject will be withdrawn from study. If there is evidence of attempted removal, the subject will be withdrawn from the study and all implants will be removed (Section 9.1.1). Due to the non-biodegradable nature of the Probuphine and placebo implants, it is vital that no subject is lost to follow-up to ensure proper implant removal, and that the End of Treatment Visit is completed as outlined in this protocol.

Subjects will be reminded to bring any remaining unused dispensed SL tablets to every visit.

10. STUDY PROCEDURES AND ASSESSMENTS

All study assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 2); the following sections outline the details and procedures associated with the assessments. Additional details on the assessments, including copies of questionnaires, logs, manuals, and information sheets are provided in the Study MOP.
### Table 2: Schedule of Assessments

<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Month 1 Visits</th>
<th>Month 2 to 5 Visits</th>
<th>Month 6/End of Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month:</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Week:</td>
<td>-3 to -1</td>
<td>Week 1</td>
<td>Week 4</td>
<td>Week 8, 12, 16, 20</td>
<td>Week 24</td>
</tr>
<tr>
<td>Day:</td>
<td>-</td>
<td>Day 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Informed Consent<sup>d</sup>  
- Eligibility Criteria Review<sup>e</sup>  
- Medical and Medication History / Substance Abuse and Treatment History  
- DSM-IV-TR, MINI, v 6.0  
- Physical Examination<sup>f</sup>  
- Abbreviated Review of Systems  
- Vital Signs<sup>g</sup>  
- ECG  
- Chemistry, Hematology, Urinalysis and Coagulation Profile

<sup>a</sup> Treatment Visits should be conducted within a window of ±7 days for the monthly visits, except for Post-Implant Visit, which should occur within a window of 1 to 5 days after Day 1. Visits for Weeks 25 and 26 should occur within ±3 days. If a subject misses a visit or completes a visit early or late, the original schedule should be resumed at the subsequent visit such that the ensuing visits occur as originally scheduled, relative to Day 1.

<sup>b</sup> Baseline and Initiation of Study Drugs Visit.

<sup>c</sup> Post-Implant Visit.

<sup>d</sup> Subjects must voluntarily provide written informed consent prior to any study-related procedures being performed.

<sup>e</sup> Prior to enrollment in the randomization and Maintenance Phase of this study, all Inclusion and Exclusion criteria must be met.

<sup>f</sup> A complete physical exam of all major body systems will be performed at the Screening Visit.

<sup>g</sup> Includes temperature, blood pressure, pulse rate, respiration rate, and weight. Height will be captured at Screening Visit. BMI will be auto-calculated.

<sup>h</sup> Vital signs (temperature, blood pressure, pulse rate, and respiration rate) will be measured just prior to implant insertion/removal, and then 15 minutes and 30 minutes after implant insertion/removal.
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#### Study Period/Phase:

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>Month 1 Visits</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month:</strong></td>
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<td>Month 1 Visits</td>
<td>Month 2 to 5 Visits</td>
<td>Month 6/End of Treatment Visit</td>
</tr>
<tr>
<td><strong>Week:</strong></td>
<td>-3 to -1</td>
<td>Week 1</td>
<td>Week 8, 12, 16, 20</td>
<td>Week 24</td>
</tr>
<tr>
<td><strong>Day:</strong></td>
<td>Day 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Post-Implant&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Hepatitis B/C, HIV&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Implant Site Examination&lt;sup&gt;e&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
</tr>
<tr>
<td>Dispense Treatment Identification Card</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>-</td>
</tr>
<tr>
<td>Urine Toxicology</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>Random Urine Toxicology</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 Random Urine Toxicology Tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illicit Drug Use Self-Report</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>Withdrawal and Desire to Use/Need to Use (SOWS, COWS, VAS)</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>SL BPN or placebo dispensing</td>
<td>X</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>Probuphine or placebo [four (4) implants] Insertion</td>
<td>X&lt;sup&gt;f&lt;/sup&gt;</td>
<td>X&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Monthly</td>
<td>X&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Implant removal procedure</td>
<td>X</td>
<td>X</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Additional interventions&lt;sup&gt;j&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> A serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit (Week 24). An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed prior to start of SL BPN and Probuphine treatment.

<sup>b</sup> It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to HIV, Hepatitis B, and Hepatitis C and testing of blood.

<sup>c</sup> Hepatitis B/C and HIV testing is required unless a site’s IRB prohibits such testing.

<sup>d</sup> The implant site will be visually inspected and palpated.

<sup>e</sup> Subjects should be instructed to arrive having bathed with soap and water on Day 1.

<sup>f</sup> It is recommended that subjects return 7 days post implant for suture removal.

<sup>g</sup> Subjects may receive additional counseling, supplemental SL BPN, or other pharmacological interventions deemed appropriate by the investigator, at any time after implantation, at the investigator’s discretion.

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<table>
<thead>
<tr>
<th>Study Period/Phase:</th>
<th>Screening</th>
<th>Maintenance Phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month:</strong></td>
<td>-</td>
<td>Month 1 Visits</td>
<td>Month 6/End of Treatment Visit</td>
</tr>
<tr>
<td><strong>Week:</strong></td>
<td>-3 to -1</td>
<td>Week 1</td>
<td>Week 4</td>
</tr>
<tr>
<td><strong>Day:</strong></td>
<td>-</td>
<td>Day 1³</td>
<td></td>
</tr>
<tr>
<td>Implant Insertion Procedure Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implant Removal Procedure Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosocial Counseling</td>
<td>X</td>
<td>Monthly</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events⁴⁵⁶⁷⁸</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications/Procedures</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wound Care Information Sheet ¹</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone Contact</td>
<td>X (As Needed)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁹ AEs that are reported by the subject at times during the study other than during the visits as specified above (i.e., at any clinic visit) must be recorded.

³ During removal process, careful inspection of the implant site, difficulty of removal and/or fracturing of the implants will be recorded.

⁴ If a significant AE is described by the subject and is judged by the Investigator as being possibly related to study treatment, the subject will visit the study site for an unscheduled follow-up assessment (separate from the Week 26 Follow-Up Visit).

¹ A Wound Care Information Sheet will be given to the subject after each insertion/removal procedure.
10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the study and its risks and benefits will be explained to the participant by the Investigator or designated study personnel. The participant must voluntarily provide written informed consent on an ethics-approved informed consent form (ICF), prior to performing any study-related procedures. The subject’s medical records must document that the consent process has been completed and that written informed consent has been obtained from the subject prior to the initiation of any study-specific procedures. Documentation that the subject was given adequate time to ask the Investigator (or designee) questions about their participation in the study and that a signed and dated copy of the ICF was provided to the subject should also be included in the medical records or clinical chart.

10.1.2. Demographics and Psychosocial History

The following demographics will be recorded: age (birthdate), sex, race, and ethnicity. A complete psychosocial history will be obtained including education, employment status, marital/significant other status, residential status and legal status/arrest history.

10.1.3. Medical History

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. All findings on medical history will be evaluated by the Investigator for clinical significance.

A psychiatric interview will be conducted using the Mini International Neuropsychiatric Interview, Version 6.0 (MINI). The MINI is a valid and reliable structured diagnostic interview for DSM-IV-TR psychiatric disorders.

10.1.4. Medication History

All medications (prescription and non-prescription, herbal medications/natural health products, or investigational drugs) taken by the subjects during the 30 days prior to Screening will be recorded in the source documentation as medication history. Substance Abuse History and Treatments will be collected separately.
10.1.5. Substance Use and Treatment History

A complete history of previous and current illicit drug use, substance abuse/dependence, and treatments for any substance use disorders (pharmacologic as well as non-pharmacologic) will be obtained. This will include drugs used, type, frequency and patterns of abuse, routes, doses, drug preferences and concomitant medications, using a timeline follow-back type of interview (Fals-Stewart, 2000). Validation of historical clinical stability, including duration of treatment and dose at which patient has been stable, and any data available on urine toxicology results, will be captured and reported on the study entry form. Detailed information on substance use and treatment history is provided in the Study MOP.

10.2. Eligibility Review and Randomization

Prior to randomization, subjects must meet all inclusion and not meet any exclusion criteria as outlined in Section 8.1 and 8.2.

The Investigator or designee must document that the subjects meet each individual criterion via a signed note or eligibility and clinical stability checklist during Screening. Signatures on these documents must be dated on or before the date of randomization in the Maintenance Phase.

Randomization will be accomplished centrally, using an Interactive Voice Response System and/or by an Interactive Web Response System managed by the Sponsor.

10.3. Efficacy Assessments

Details regarding primary, secondary and exploratory endpoints are provided in Section 10.6 (Efficacy Variables); and discussed further in Section 12.3 (Statistical Analysis). The following sections provide an overview of the efficacy assessments included in the study. Additional details, such as the questionnaire items/scale text and additional instructions (where applicable) are provided in the Study MOP.

10.3.1. Urine Toxicology for Opioids

Urine toxicology samples will be collected at each visit (both scheduled and random) using a urine collection cup containing a temperature sensor. Specimen authenticity will be verified at the site using this sensor to measure the urine temperature immediately following collection. The temperature of a urine sample within 4 minutes of voiding should fall within the range of 32.2 to 37.7 degrees Celsius (90 to 100 degrees Fahrenheit). If test results are outside these ranges, the
subject will be asked to immediately provide another urine sample. If this second sample is outside of the temperature range, the sample will be counted as ‘missing’, and should not be sent for analysis (any such samples must be documented in the subject’s records). Direct observation approach to obtaining urine samples may be used if the investigator deem necessary. Urine samples will be logged and numbered and then sent to a central laboratory for analysis for the presence of opioids (e.g., codeine, morphine, hydrocodone, oxymorphone, hydromorphone, oxycodone, methadone, and fentanyl). In addition, it is recommended that the scheduled assessment visits take place on Mondays to potentially improve detection of illicit opioid use that may have occurred over the weekend.

10.3.2. Self-Reported Illicit Drug Use
Subjects will be questioned about illicit drug use, including illicit or prescription opioids and other drugs of abuse using a timeline follow-back type of interview (Fals-Stewart, 2000). A copy of the Illicit Drug Use Self-Report form is provided in the Study MOP.

10.3.3. Measures of Desire and Need to Use
Desire to Use and Need to Use will be administered using unipolar 100 mm VAS (“Since your last scheduled assessment visit, indicate your worst or strongest desire/need to use opioids, where 0 = No desire to use and 100 mm = Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively) (Kozlowski et al., 1989).

Copies of these VASs are provided in the Study MOP. NOTE: Only VAS copies provided by the Sponsor should be used with study subjects; photocopies made locally may result in changes to the length of the scale, leading to inaccurate results.

A separate VAS will be provided for each Desire to Use and Need to Use and measurements must be taken separately (i.e., separated in time or by other procedures).

10.3.4. Measures of Withdrawal

10.3.4.1. Subjective Opioid Withdrawal Scale (SOWS)
Subjects will complete a self-assessment of withdrawal symptoms using the SOWS. This form contains 16 questions that rate the intensity of withdrawal from 0 (“Not at all”) to 4 (“Extremely”). A copy of the SOWS is provided in the Study MOP.
10.3.4.2. Clinical Opioid Withdrawal Scale (COWS)
Study personnel will assess clinical observations indicative of withdrawal using the COWS. This scale consists of 11 common opiate withdrawal signs or symptoms, rated on a numeric scale and based on a timed period of observation of the subject by the rater. A copy of the COWS is provided in the Study MOP.

10.3.5. Urine Toxicology for Other Drugs of Abuse
Urine will be tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine and cannabinoids [THC]) using qualitative methods. Positive results will not be confirmed using quantitative methods.

10.3.6. Supplemental Visits, Medication and Counseling
Supplemental SL BPN use will be allowed, as described in Section 9.2.3. Subject-requested or physician-directed supplemental visits, phone calls or additional counseling, or other pharmacological interventions, along with the reason(s) for supplemental visits, supplemental SL BPN needs, phone calls or additional counseling or other pharmacological interventions, will be recorded.

10.4. Safety Assessments and Other Procedures
Safety monitoring will be performed throughout the study for all subjects. All AEs, regardless of causality or severity, will be recorded on the AE CRF. Appropriate medical intervention should be provided and, if necessary, implants may be removed or SL BPN treatment discontinued as clinically indicated.

10.4.1. Adverse Events and Serious Adverse Events
The following definitions, developed in accordance with the United States (US) Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Clinical Safety Data Management Guidance for Industry, E2A, will be used for the purpose of identifying AEs in this clinical study.

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or increase in severity of a preexisting abnormality, temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.
10.4.1.1. **Adverse Event Reporting**

All AEs (except for withdrawal symptoms, see below) must be entered on the AE CRF, regardless of causality or severity. AEs include new AEs, worsening baseline conditions, clinically significant laboratory findings, disease-related signs and symptoms that were not present at baseline, and any events or findings that the Investigator feels are clinically significant. Withdrawal symptoms will be captured via specified assessments and should not be recorded as AEs.

Disease-related signs and symptoms that are present at baseline should not be recorded as AEs unless they worsen in severity or increase in frequency.

Information collected concerning AEs will include the following:

- Name of the event
- Onset date
- Resolution date
- Severity (i.e., mild, moderate, or severe)
- Relationship to study drug
- Action and outcome
- Relationship to insertion / removal procedure
- Seriousness of event

All AEs will be documented and followed from the time the subject has signed the ICF until 14 days after the End of Treatment Visit (i.e., implant removal and discontinuation of SL BPN/placebo treatment). Serious AEs and AEs that have been designated as possibly related to study drug will be followed until resolution or stabilization.

10.4.1.2. **Serious Adverse Event**

A serious adverse event (SAE) or reaction is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect (in an offspring)

An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All AEs requiring hospitalization or prolongation of a pre-existing hospitalization should be reported as SAEs unless they occur greater than 14 days after the End of Treatment Visit AND are not considered to be drug-related by the Investigator.

Hospitalizations meeting the following criteria will not be reported as an SAE but must be recorded on the appropriate CRF: study specified hospitalization, short-term administrative hospitalization for procedures, tests or treatments of conditions that would not otherwise constitute an SAE, elective hospitalizations.

10.4.1.2.1. Serious Adverse Event Reporting

Serious Adverse Events (SAEs) must be reported to the Sponsor or designee within 24 hours of knowledge of the event. All SAEs that occur while a subject is receiving study drug and within 14 days following the End of Treatment Visit are reportable within 24 hours. During the follow-up period beyond 14 days from implant removal or discontinuation of SL BPN assigned treatment, only those SAEs that are considered to be possibly related to study drug should be reported within 24 hours.

The procedure for reporting an SAE is as follows:

- Within 24 hours of knowledge of the event, the site must contact the Sponsor (or designee) by telephone or facsimile to report the event.

- The initial report should include all information known at the time of the report (additional information can be reported as discovered). Do not delay the initial reporting in order to obtain resolution or follow-up information.

- The site will enter into the electronic database (or fax, if the database cannot be accessed for any reason) an SAE report, or similar form, that includes the following information, as available:
  - Subject ID
  - Basic demographic information (age, gender, weight)
Outcomes attributed to the event (death, life-threatening hospitalization [new or prolonged], disability, congenital anomaly, required medical intervention to prevent permanent impairment/damage, etc.)

- Onset date and severity of the event
- Brief description of the event including frequency and severity of symptoms leading to diagnosis, and information on supplemental SL BPN
- List of relevant test results and lab data
- Any other relevant history
- Dates of implantation and removal, if applicable
- Dates and doses of supplemental SL BPN usage
- Whether the study drug was discontinued
- Whether the event abated after implants removed and/or assigned treatment SL BPN discontinued and/or supplemental SL BPN discontinued, as applicable
- Investigator's assessment of causality

The Medical Monitor or another representative of the Sponsor may contact the Investigator to request additional information regarding the event or to confirm information. All SAEs will be entered on the AE CRF. The same nomenclature should be used on both the SAE report and the AE CRF.

Specific instructions for SAE reporting and a copy of an SAE report form are provided in the MOP.

The Investigator is responsible for the complete and timely reporting of all SAEs to the Sponsor (or designee), reporting pertinent follow-up information on the SAE, and notifying the appropriate IRB / Independent Ethics Committee (IEC) of the occurrence of and details surrounding the event. In the event there is a question as to whether the AE is serious, the event should be reported.

10.4.2. Pregnancy

Pregnancies among trial participants should be reported to the Sponsor or designee as soon as possible after learning of the event. Subjects who become pregnant may withdraw their consent and discontinue the study and be referred back to the care of their usual provider. Follow-up information will be obtained where possible (with the consent of the participant or their partner).
regarding the course and outcome of the pregnancy, including any post-natal sequelae in the infant.

10.4.3. Clinical Laboratory Assessments

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests that are conducted at the study site. The central lab will generate laboratory reports and forward them to the clinical site in a timely manner. It is the responsibility of the Investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of study subjects. The Investigator should sign and date each lab report concurrent with her or his review, and should indicate the clinical significance of each abnormal/flagged value by noting “NCS” (not clinically significant) or “CS” (clinically significant), for example. Notations indicating that a value is clinically significant should also include a brief description of the underlying disease or condition that is associated with the value, e.g., “CS/mild anemia.” In general, abnormal, clinically significant laboratory values are expected to be associated with an item recorded in medical history or with an AE.

Blood and urine samples will be collected, processed, and shipped according to instructions from the safety laboratory. Additional laboratory samples may be taken at the discretion of the Investigator if the results of any tests fall outside reference ranges or clinical symptoms necessitate testing to ensure safety. Specific hematology, coagulation, biochemistry, and urinalysis assessments are listed in Table 3.
Table 3: Clinical Laboratory Assessments

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Biochemistry</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Sodium</td>
<td>Color</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Potassium</td>
<td>pH</td>
</tr>
<tr>
<td>Red blood cell (RBC) count</td>
<td>Magnesium</td>
<td>Specific gravity</td>
</tr>
<tr>
<td>RBC Morphology</td>
<td>Calcium</td>
<td>Ketones</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>Glucose (random)</td>
<td>Protein</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Bicarbonate</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin</td>
<td>Chloride</td>
<td>Nitrite</td>
</tr>
<tr>
<td>concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total and differential (absolute)</td>
<td></td>
<td>Urobilinogen</td>
</tr>
<tr>
<td>white blood cell count</td>
<td></td>
<td>Occult blood</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td>Microscopic examination of sediment, only if urinalysis dipstick results are abnormal</td>
</tr>
<tr>
<td>Prothrombin time (PT), INR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aspartate transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic dehydrogenase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lipase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gamma-glutamyl transferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine phosphokinase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total cholesterol (non-fasting)</td>
<td></td>
</tr>
</tbody>
</table>

In addition to the clinical laboratory tests, a serum pregnancy test will be performed at the Screening Visit and the End of Treatment Visit. An “in-office” urine pregnancy test will be required at Day 1 PRIOR to randomization, and then monthly thereafter (for women of childbearing potential). Results must be reviewed and confirmed to be negative prior to start of SL BPN and Probuphine treatment.

A blood sample for a serology panel testing for hepatitis B surface antigen, anti-hepatitis C antibodies, and HIV will be performed for all subjects, unless a site’s IRB prohibits such testing. It is the Investigator’s responsibility to understand and comply with all laws and regulations that apply to the testing of blood for HIV and hepatitis B and C. These laws and regulations may include state laws related to written consent, separate from the ICF for this study, and pre- and post-test counseling.
10.4.4. **Vital Signs**

Vital signs will consist of temperature, blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min) collected while sitting, following a rest period of at least 3 minutes.

10.4.5. **12-Lead Electrocardiogram (ECG)**

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant. In general, abnormal, clinically significant ECGs are expected to be associated with an item recorded in medical history or with an AE.

10.4.6. **Physical Examination**

A complete physical examination including all major body systems will be performed at Screening. At select subsequent study visits, an abbreviated review of systems will be performed to capture changes since Screening.

Height, weight and BMI will be determined as described in Table 2

10.4.7. **Implant Site Examination and Wound Care**

Subjects will receive written instructions that explain how to care for the surgical site after implant insertion and removal. Subjects should be informed about care of the implant site and implant site safety, educated about situations where they should seek medical attention, and queried about implant-related AEs. Copies of the wound care information sheets must be reviewed and approved by each site’s IRB, prior to providing them to subjects.

Implant site reactions can occur with the implantation and removal of Probuphine or placebo implants. The most frequently-reported AEs related to the insertion/removal procedure (occurring in greater than 10% of subjects) in previous Phase III clinical studies were erythema, edema, itching, pain, bleeding, bruising, and scarring. The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities, including implant expulsion or implant migration. The implant site should also be palpated to ensure that the four implants have not been removed. If there is any evidence of removal or attempted removal of the implants, or if the subject confirms the removal of some or all of the implants, the subject will be withdrawn from study and any remaining implants will be removed.

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10.4.8. Psychosocial Counseling
All subjects will receive manual-guided drug counseling during the study, as outlined in Table 2 and described in more detail in the Individual Drug Counseling Manual (provided in the Study MOP) (Mercer & Woody). Additional counseling can be provided as clinically indicated; however, all additional counseling, visits or phone calls must be recorded.

10.4.9. Treatment Identification Card
Subjects will receive a wallet card indicating that they are receiving BPN as part of the study. This card should be presented to health care providers by the subject in the event of an emergency or if medications such as opioid analgesics are required (see Section 9.7). Sample wallet cards will be provided for IRB submission.

10.4.10. Other Safety Considerations
Buprenorphine may impair the mental and physical abilities required for performance of potentially dangerous tasks. Subjects will be instructed to avoid operating heavy machinery during induction and after implant insertion, and to exercise caution in performing activities requiring alertness such as driving a car during the first few days after implant insertion, or until such time that they are reasonably certain that their ability to engage in such activities is not adversely affected.

10.5. Appropriateness of Measures
The efficacy outcome measures were selected to provide an efficacy assessment of the study medications with regards to both objective (i.e., urine toxicology results for opioids), and patient-based assessment (i.e., subject-reported desire/need to use and desire/need to use opiates). The most direct method to ascertain the frequency and amount of illicit opiate use would be through the use of patient self-reports. However, these reports may not always be reliable or accurate (Zanis et al., 1994). Thus, the analysis of urine samples for specific drugs or drug metabolites is typically used as an objective criterion for assessing illicit drug use. Urine toxicology has been used in many efficacy assessments of buprenorphine and will be used as the primary outcome measure in the definition of responders in this study (Section 10.6). Urine toxicology results will be adjusted for self-reported drug use at each study visit.

Secondary outcome measures were selected as a series of measures and scales to provide a complete assessment of the effectiveness and efficiency of transfer from SL BPN to Probuphine...
implants with regard to patient-based assessments (i.e., subject-reported desire and need to use opioids).

Desire to Use VAS and Need to Use VAS were selected over the typical Craving VAS because the latter term is ambiguous and may have different meaning to different individuals, while the Desire/Need to Use VAS more directly assess the potential behavioral outcome (Kozlowski et al., 1989).

Standard and widely used measures of withdrawal will be included in this study (COWS and SOWS) (Wesson & Ling, 2003; Handelsman et al., 1987) in order to ensure that subject’s withdrawal symptoms are adequately controlled by the Probuphine implants as compared to SL BPN.

In addition, although expected to be relatively rare in this study, supplemental SL BPN use will be evaluated. Finally, to ensure that potential signs of treatment failure are not missed, additional measures of potentially inadequate treatment will include subject- or Investigator-requested additional visits or counseling.

10.6. Efficacy Variables

10.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is a responder analysis. A subject will be designated as a responder (meaning they have maintained stability) if they have no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

10.6.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints will include the following:

- Percent of Subjects with No Illicit Opioid Use by Month
- Time to First Evidence of Urine Illicit Opioid Use
- Cumulative Percentage of Evidence of Urine Illicit Opioid Use by Month
- Percent of Subjects with No Self-Reported Illicit Drug Use by Month
- Measures of craving: Desire to Use VAS, Need to Use VAS
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS)

10.6.3. Exploratory Efficacy Variables

Exploratory variables include:
10.7. Safety Variables

Safety variables include:

- AEs
- Clinical laboratory tests
- ECG
- Physical and implant site examinations
- Implant site insertion and removal assessments
- Concomitant medications
- Vital signs

11. DATA QUALITY ASSURANCE

This study will be conducted under Good Clinical Practice (GCP) and all applicable regulatory requirements. To ensure compliance, the Sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; the review of protocol procedures with the Investigator and study personnel prior to study start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the Sponsor. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. The Sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator, as appropriate.
11.1. Data Collection

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, participant diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This study will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system.

All CRFs will be completed by the site staff prior to review by the Sponsor’s monitor or designated representative. The Sponsor’s monitor or designated representative will review all source records on-site and compare them to the data collected on the CRF. All entries, corrections, and alterations will be made by the Investigator or other authorized study personnel. All data entries will be verified for accuracy and correctness by independent monitors. The electronic data capture system maintains a full audit trail.

11.2. Study Auditing and Monitoring

Monitoring of the study site (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the Sponsor’s designated monitor(s). The extent, nature, and frequency of on-site visits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. By signing the protocol, the Investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the Sponsor, a regulatory authority, and/or an IRB may visit the site to perform audits or inspections, including the drug storage area, study drug stocks, drug accountability records, participant charts and source documents, and other records related to study conduct. The purpose of the Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether the study-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site’s standard operating procedures, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.
12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the study data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final study report.

12.2. Analysis Populations

The study analysis populations will consist of:

- **Randomized Population**: All subjects who are randomized into the Maintenance Phase
- **Intent-to-Treat (ITT) Population**: All subjects who have been randomized and have received an implant and/or received SL BPN/placebo. Analyses based on this population will group subjects according to the treatment they were randomized to receive, regardless of actual treatment received, and this will be the primary analysis population.
- **Safety Population**: All subjects who are randomized and treated with implants or who received any dose of SL BPN/placebo in the Maintenance Phase. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.
- **Per Protocol Population**: All subjects in the ITT population with no major protocol violations. Major protocol violation criteria will be established prior to the database lock.

12.3. Planned Analyses

12.3.1. Disposition, Demographics and Other Baseline Characteristics

Disposition for all randomized subjects will be summarized by the randomized treatment group. Reasons for discontinuation will be tabulated for each treatment group and overall.

Demographic data and baseline psychosocial characteristics will be summarized.
Tabular summaries and/or listings will be provided for baseline clinical characteristics such as illicit drug and treatment use history, medical and psychiatric history, inclusion/exclusion criteria, and medication history.

12.3.2. Analysis of Efficacy Measures

12.3.2.1. Primary Endpoint

The primary efficacy variable will be responder rate analysis, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use is defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

A total of 10 urine toxicology samples will be collected throughout the 6 months of the study treatment period with 6 scheduled visits (1 visit per month) plus 4 random urine toxicology visits.

12.3.2.2. Analysis of Primary Endpoint

A test of non-inferiority in the rate of responders between the two treatments arms will be conducted. A non-inferiority of $\delta = 20\%$ will be employed to define non-inferiority. Let $\pi_c$ and $\pi_e$ be the rate of response at 24-weeks on the control arm and experimental treatment arm, respectively. The null hypothesis ($H_0$) of inferiority is

$$H_0: \pi_e \leq \pi_c - 0.20.$$ 

The alternative hypothesis ($H_a$) of non-inferiority is

$$H_a: \pi_e > \pi_c - 0.20.$$ 

The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above $-0.20$).

**Rationale for 20% non-inferiority margin:** The 20% margin is appropriate from a scientific validity perspective as well as meeting Food and Drug Administration (FDA) guidelines for non-inferiority margin selection (FDA, 2010). In this study with 180 subjects, the observed data that meet the statistical 20% margin will meet scientific face-validity for the equivalency of the treatment arms. The table below (Table 4) summarizes the required Probuphine Treatment Group's response rate (% of responders) to satisfy non-inferiority based on the 20% margin and the sample size of 90 subjects per group at the two-sided 5% significance level for a range of
observed SL BPN arm’s response rate (Note: due to discreteness some percentages are not possible).

Table 4: Response Rates and Non-InferiorityMargins

<table>
<thead>
<tr>
<th>Observed SL BPN Arm’s Response Rate (% of Responders)</th>
<th>Required Minimum Observed Probuphine Arm’s Response Rate (% of Responders) to Satisfy Non-Inferiority (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>81.1</td>
</tr>
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<td>84.4</td>
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<tr>
<td>64.4</td>
<td>58.9</td>
</tr>
<tr>
<td>60</td>
<td>54.4</td>
</tr>
</tbody>
</table>

The table demonstrates that utilizing the 20% margin to satisfy non-inferiority, the Probuphine Treatment Group’s response rate should be at least similar to the rate for SL BPN control arm.

Although there is little literature on SL BPN treatment in long-term stabilized maintenance subjects, there is some empirical information available to lend credence to the 20% non-inferiority margin:

1. With patients on longer term BPN or methadone treatment, blinded taper (detoxification) studies indicate rates of continued opioid abstinence following complete withdrawal of about 18 to 31%. Although little data is available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15%. A summary of literature is provided in Section 16.

2. A survey of addiction experts was performed by the Sponsor to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN.

   a. The results demonstrated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability) to illicit opioid use if these patients were taken off their stable dose of 8 mg or less of SL BPN. The FDA Draft Guidance would suggest a 37.5% margin to be
appropriate, based on an estimate of 75% effect size (i.e., assuming all patients being stable at study randomization). However, a 37.5% margin, estimating 50% preservation of the effect size may not be clinically acceptable. The proposed 20% margin would estimate preserving >70% of the effect and should be considered clinically acceptable (Section 17).

3. Finally, the FDA Draft Guidance notes that circumstances might support a less conservative choice for the margin, including:

a) *Pharmacologic properties of the test drug that are very similar to those of the active control* – Probuphine is an alternative dosage form of the same active entity with the expectation of similar overall plasma concentrations to the SL BPN arm;

b) *Use of a persuasive biomarker* – responder definition in this trial will include the standard and well-accepted objective urine toxicology results to confirm treatment success;

c) *If the drug has been shown to be effective in closely-related clinical settings* – Probuphine has already been shown to be effective relative to placebo in two trials in harder-to-treat populations;

d) *If the test drug were shown to have some important advantage (e.g., on safety or on a secondary endpoint)* – The safety issues associated with abuse of SL BPN are well-known; the Drug Abuse Warning Network confirmed an increasing trend to adverse medical outcomes associated with BPN abuse, i.e., a total of 21,483 emergency department visits related to abuse/misuse were reported in 2011 (DAWN, 2013). Probuphine has the potential to reduce misuse/abuse associated with SL BPN and have a significant positive public health impact, in addition to potentially increasing adherence.

Thus, the overall data and circumstances associated with this study support the use of a 20% non-inferiority margin.

12.3.2.2.1. Handling of Dropouts or Missing Data

Imputation methods to handle dropouts and/or missing data will be detailed in the SAP.

12.3.2.3. Sensitivity Analyses

The following sensitivity analyses will be performed:
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- Analysis based on completers (i.e., analysis based on all subjects who provided all required samples);
- Analysis based on missing values replaced with “Opioid-Positive;”
- Per protocol analysis (i.e., analysis based on subjects who do not have major protocol violations).

Additional sensitivity analysis will be conducted as outlined in the SAP for this study

12.3.2.4. Analysis of Secondary Efficacy Endpoints

Secondary efficacy variables will include:

- Percent of Subjects with No Illicit Opioid Use by Month
- Time to First Evidence of Urine Illicit Opioid Use
- Cumulative Percentage of Evidence of Urine Illicit Opioid Use by Month
- Percent of Subjects with No Self-Reported Illicit Drug Use by Month
- Measures of craving: Desire to Use VAS, Need to Use VAS
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS)

Additional details of measures of efficacy and their analysis will be described prospectively, prior to final database lock and unblinding, in the SAP for this study.

12.3.3. Analysis of Safety

Exposure will be summarized by treatment group.

AEs will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by number and percent of subjects in each primary SOC and preferred term. Summaries of these AE subsets will be presented for relationship to study drug or implant insertion/removal, intensity, seriousness, AEs or SAEs leading to discontinuation and AEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Data for clinical laboratory tests, ECG, vital signs, and physical and implant examinations will be summarized using standard descriptive and change from baseline statistics. Shift tables and tabular summaries of abnormalities will be provided, where appropriate.

Medications will be coded using the World Health Organization Drug dictionary and summarized using descriptive statistics.

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By-subject listings will be provided for all safety data.

12.4. Determination of Sample Size

The sample size of 90 per treatment arm (180 total) was selected to achieve 87.3% power, assuming both arms have a 75% rate of responders. If the true rates are lower, but equal in both arms, with a 65% rate of response, the power of the trial to determine non-inferiority is 80.3%. If each treatment arm has an 85% rate of response, then the trial with 180 subjects would have 96.4% power to determine non-inferiority.
13. STUDY ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Study Agreement (CSA) between the Sponsor and the investigational site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Study
The Investigator will conduct the study in accordance with GCP and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor’s representatives and/or regulatory authority’s representatives at any time.

13.1.2. Ethics Approval
The investigational site’s IRB must meet all relevant regulatory requirements. The study protocol and ICF will be reviewed by the IRB prior to enrolling participants into the study; written approval from the committee must be received by the sponsor before drug will be released to the Investigator. The Investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new drug safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the Investigator may be obligated to provide periodic safety updates on the conduct of the study at his or her research site and notification of study closure to the IRB. Such periodic safety updates and notifications are the responsibility of the Investigator and not of the Sponsor. The Sponsor will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective study site to the Sponsor in a timely fashion.

13.1.3. Subject Informed Consent
The Investigator (or authorized designee) will ensure that the participant (or the participant’s legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the study. Each prospective subject will receive an IRB-approved ICF that summarizes the pertinent study information and will be given ample time to read the form and ask questions about the study. All information is to be provided
in a language understandable to the participant and must not include any language that waives
the participant’s legal rights. Prospective participants must also be informed of their right to
withdraw consent without prejudice at any time during the study. If the participant chooses to
participate, he/she must sign the ICF before any study-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the
ICF, which must be reviewed and signed by all applicable study participants.

The time that informed consent is obtained must be documented. The Investigator must maintain
the original, signed ICF in the participant’s source documents. A copy of the signed ICF must be
given to the study participant.

13.2. Privacy and Confidentiality

The Investigator is responsible for complying with applicable privacy regulations, per his or her
jurisdiction. Only information identified in this protocol will be collected. The information
collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, participants will be assigned a unique identifier at
their first assessment. This identifier will be cross-referenced in the participant’s chart. The
identifier will not contain any potentially identifiable information. An identifier log will be
maintained, linking each participant’s name to the corresponding identifier. This log will be
stored at the research site in a secure location.

The knowledge gained through this study is the property of the Sponsor. The Sponsor,
representatives and affiliated companies of the Sponsor, the IRB, and regulatory agencies (such
as the United States FDA) may inspect medical records related to the study to check the validity
and accuracy of the data gathered in this study. Participant medical records (with participant’s
initials and/or date of birth) may be copied. Confidentiality of participant records will be
maintained except where release of information is required by law.

The results of this study will be reported in such a manner that participants will not be
identifiable in any way. Published reports or presentations will refer to grouped data or coded
individual data and not to any identifiable individuals. Study reports sent to the Sponsor or drug
regulatory agencies will not include participant names.

By signing the ICF, the participant consents to the collection, access, use, and disclosure of his or
her information as described in the ICF document. If a participant withdraws consent, some of
the subject’s information may still be collected, used, and disclosed by those involved in this study, per applicable laws.

By signing this protocol, the Investigator affirms that he or she will maintain in confidence information furnished to him or her by the Sponsor and will divulge such information to his or her respective IRB or IEC under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the Sponsor. Please refer to the Clinical Study Agreement (CSA) for details.

13.3. Study and Site Closure

Upon completion of the study, all study data will be provided to the Sponsor following review of site study records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused study drugs, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time and for any reason. If such action is taken, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. The Sponsor will promptly inform any other investigators and/or institutions conducting the study, if the study is suspended or terminated for safety reasons and will inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator will inform the IRB promptly and provide the study participants with the reason for the suspension or termination. If the study is prematurely discontinued, all study data will be returned to the Sponsor.

13.4. Regulatory Documents and Records Retention

The Investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or CSA. The Investigator must provide key documents to the Sponsor prior to the start of the study. A complete list of required regulatory documents will be supplied by the Sponsor or its representative.

Federal and local regulations require that the Investigator retain a copy of all regulatory documents and records that support the data for this study for whichever of the following is the longest period of time:
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- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

The Sponsor will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the Sponsor that the entire clinical investigation (not merely the Investigator’s portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with the Sponsor.

13.5. Delegation of Responsibilities and Adequate Resources

The Investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study.

The term “Investigator” used throughout this protocol refers to the principal investigator and/or qualified sub-investigators. However, the Investigator may delegate responsibilities to other investigational site personnel. The Investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The Investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The Investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the investigational site.
13.6. Protocol Amendments

Approval of a protocol amendment by the Investigator’s IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the participant or when the change involves logistical or administrative aspects of the study. The protocol amendment must be signed and dated by both the Sponsor and the Investigator. The Sponsor or designee will submit protocol amendments to the appropriate regulatory authorities, if required.

13.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of research participants. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
14. SPONSOR APPROVAL PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 4.0

Date: 30-MARCH-2015

Braeburn Pharmaceuticals

Frank E. Young, MD, PhD
Executive Vice President, Clinical and Regulatory Affairs

Date 30-March-2015
15. INVESTIGATOR PROTOCOL AGREEMENT PAGE

A RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE-CONTROLLED MULTICENTER STUDY OF ADULT OUTPATIENTS WITH OPIOID DEPENDENCE TRANSITIONED FROM A DAILY MAINTENANCE DOSE OF 8 MG OR LESS OF SUBLINGUAL BUPRENORPHINE OR BUPRENORPHINE/NALOXONE TO FOUR PROBUPHINE® SUBDERMAL IMPLANTS

Version: 4.0

Date: 30-MARCH-2015

I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonization/Good Clinical Practice Guidances.

Investigator’s Name 

(please print or type)

Signature ________________________

Date ________________________
16. SUMMARY OF LITERATURE TO SUPPORT NON-INFERIORITY MARGIN

A meta-analysis of tapered discontinuation following long-term methadone or BPN treatment found an average abstinence rate of 33% (Kornr & Waal, 2005). However, because of the differences in methodology (single or double-blinding, naturalistic, etc.), definitions of abstinence, treatments administered during MAT and durations of follow-up, some studies are more relevant than others. In addition, this article didn’t report on the baseline rates of percentage abstinence or urine toxicology results.

Breen et al. (2003) reported on a study of stable methadone patients (for at least 6 months) to BPN and then gradual reduction to 0 mg BPN (i.e., blinded) over an average duration of 11 weeks showed that subjects at 1 month follow-up after complete BPN discontinuation had 31% negative opioid samples (relative to about 73% negative at baseline, 89% negative during BPN induction, and 91% negative during BPN taper).

One double-blind, double-dummy study in methadone users found 25% abstinence overall during 1 month follow-up after complete discontinuation following gradual taper regimens. Abstinence was 18% in the "rapid" withdrawal group (taper over 10 weeks) (versus 100% negative urine opioid results for 4 weeks preceding study entry and 92% negative for the 6 months prior to the study) (Senay, 1977).

Most of the studies used tapered discontinuation, but in terms of abrupt discontinuation, one survey study in Australia reported that 15% of patients who abruptly discontinued opioid maintenance therapy (BPN or methadone) were abstinent for at least 3 months, while 26-27% were abstinent with either self- or physician-directed taper regimens (Winnstock et al., 2011).
## 17. SUMMARY OF SURVEY RESULTS FROM ADDICTION SPECIALISTS

<table>
<thead>
<tr>
<th>PI #</th>
<th>% Negative UDS Over 6 mths*</th>
<th>% Negative UDS Over Next 6 mths*</th>
<th>% Relapse upon BPN Discontinuation (Over 6 mths)</th>
<th>Maximum Reasonable Change in % UDS positive</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>83</td>
<td>85</td>
<td>0</td>
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<tr>
<td>2</td>
<td>75</td>
<td>80</td>
<td>75</td>
<td>17</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>NNR</td>
<td>DNAQ</td>
<td>NNR</td>
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<td>55</td>
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<td>100</td>
<td>60</td>
<td>8.5</td>
<td>NNR</td>
</tr>
</tbody>
</table>

**Mean (Median):** 92 (97) 89 (90) 70 (75) 14 (17) 63 (65)

**Range:** 75-100 65-100 30-95 0-33 10-95

**NOTES:**
- DNAQ = response given did not match question asked and is not useful for the averages; NNR = no numerical response; UDS = urine opioid toxicology
- Some answered as % positive some as % negative, for ease, results have been converted to % negative.
- If range was given, the average of the range has been entered here (i.e., 30-40% = 35% for purposes of these calculations)
- If answer given as < or >, response was entered as the numeric value
- *X of 6 responses were calculated as: 0 of 6 = 0%; 1 of 6 = 17%; 2 of 6 = 33%; 3 of 6 = 50%; 4 of 6 = 67%; 5 of 6 = 83%; 6 of 6 = 100%
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18. REFERENCES


Kozlowski LT1, Mann RE, Wilkinson DA, Poulos CX. "Cravings" are ambiguous: ask about urges or desires. Addict Behav. 1989;14(4):443-5.


Mercer D, Woody G. Individual Drug Counseling: adapted from the Naltrexone and Fluoxetine for Heroin Addiction Study; Philadelphia Veterans' Affairs Medical Center.


Suboxone® (buprenorphine HCl and naloxone HCl dihydrate sublingual tablets) and Subutex® (buprenorphine HCl sublingual tablets) US Prescribing Information. Richmond, VA: Reckitt Benckiser Pharmaceuticals, Inc., November 2013.


A Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients with Opioid Dependence Transitioned from a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Probuphine® Subdermal Implants

Statistical Analysis Plan (SAP)

Sponsor
BRAEBURN PHARMACEUTICALS
47 Hulfish Street, Suite 441
Princeton, NJ 08542
Tel: (609) 751-5375
Fax: (609) 921-2156

Version 1.01 16 November, 2014
The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the PRO-814 data.

**SPONSOR APPROVAL**

BRAEBURN PHARMACEUTICALS

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<tr>
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<tr>
<td>Sonnie Kim, Pharm.D.</td>
<td>[Signature]</td>
<td>Nov 16, 2014</td>
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**STATISTICIAN**

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<tr>
<td>Michael Chen</td>
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1.0 DOCUMENT HISTORY

<table>
<thead>
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<tr>
<td>Final 1.00</td>
<td>29 Sept, 2014</td>
<td>Incorporate reviewers’ comments with particular emphasis on imputation of missing Urine samples</td>
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<tr>
<td>Final 1.01</td>
<td>16 November, 2014</td>
<td>Revising missing value imputation method section to incorporate FDA’s recommendation dated on November 13, 2014</td>
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2.0 LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
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<th>Definition</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>COWS</td>
<td>Clinical Opioid Withdrawal Scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (may include electronic data capture systems or paper forms)</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
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<td>Informed consent form</td>
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<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>ITT</td>
<td>Intent-to-Treat</td>
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<tr>
<td>IVRS</td>
<td>Interactive Voice Response System</td>
</tr>
<tr>
<td>IWRS</td>
<td>Interactive Web Response System</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PT</td>
<td>MedDRA Preferred Term</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SL BPN</td>
<td>Sublingual Buprenorphine or Buprenorphine/Naloxone</td>
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<td>SOC</td>
<td>MedDRA System Organ Class</td>
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<td>Treatment-Emergent Adverse Event</td>
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<td>VAS</td>
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3.0 INTRODUCTION

This statistical analysis plan (SAP) is based on Protocol PRO-814, Version 3.0, dated 24-SEPTEMBER-2014.

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the safety and efficacy data from the study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before database is locked and treatment codes are unblinded. Deviations from the approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

The primary objective of the study is to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of sublingual (SL) buprenorphine (BPN), to 4 Probuphine implants compared to SL BPN.

The secondary objective of the study is to confirm the safety of 4 Probuphine implants in adult outpatients with opioid dependence who are clinically stabilized on 8 mg or less of SL BPN.

4.2 STUDY TREATMENTS

In this double blind double dummy study, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit).

4.3 STUDY DESIGN

This is a randomized, double-blind, double-dummy, active-controlled multi-center study to evaluate the efficacy of transition to four 80 mg Probuphine implants in adult outpatients with opioid dependence, who are clinically stabilized on 8 mg or less of SL BPN. The study will include 3 Phases; Screening, Maintenance and Follow-up.

Medical and eligibility screening should occur within 3 weeks of the first Maintenance Phase visit. The Screening Visit will include standard medical screening procedures, complete medical/psychosocial history, urine toxicology and detailed substance use and treatment history.

All subjects who have provided written informed consent and have met the other study entry criteria will be eligible for randomization. Following confirmation of eligibility, subjects will be randomized to one of two treatment groups in a 1:1 ratio:

- Treatment Group A: Daily SL BPN tablets (≤8 mg/daily) + four placebo implants
- Treatment Group B: Four 80 mg Probuphine implants + daily SL placebo tablets

Implants will be surgically inserted on Day 1 (Baseline and Initiation of Study Drugs Visit). On Post-Implant Visit, additional follow-up safety and implant assessment procedures will be conducted. Subjects will return for monthly study visits on Weeks 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). In addition to the monthly scheduled visits, subjects will provide 4 random urine toxicology samples throughout the 24-week treatment period.

A total of 10 urine toxicology samples will be collected; 6 at scheduled visits (1 per month) and 4 at random urine toxicology visits throughout the 24-week treatment period. At the scheduled visits, other assessments of efficacy and safety will be collected. Implants will be removed at the End of Treatment Visit on Week 24.

Following Week 24, subjects will be re-transitioned back to usual care (pre-trial), as needed. During Week 25, telephone contact will be made with all subjects and Week 26 will include an on-site visit to the clinic for final follow-up assessments (Follow-up Visit).

4.4 RANDOMIZATION AND BLINDING

Randomization will be used to avoid bias in the assignment of subjects to treatment sequences, to increase the likelihood that known and unknown subject attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Subjects who have provided written informed consent will be assigned a unique number in the screening process. This number will be used to identify the subject throughout the study.

Subjects who have met the eligibility criteria (Section 8) will be randomized to one of the 2 treatment groups in a 1:1 ratio (Treatment Group A: Daily SL BPN plus placebo implants or Treatment Group B: four Probuphine implants plus SL placebo tablets). Due to the size of the study, it is expected that subjects will be balanced for various other baseline factors, including age.

Once any subject number or randomization number is assigned, it cannot be reassigned to any other subject. This study will use central randomization, as described in Section 10.2 of the protocol.

In order to reduce the potential for bias in the study, treatment group assignments will be double-blinded. The subject, investigative site personnel, Sponsor, and Sponsor designees directly involved in the conduct and/or monitoring of this study will not be aware of the treatment group assignments. Sublingual BPN tablets used during the study will have a nearly-matching placebo. Due to minor potential differences between active and placebo SL tablets initiated after randomization, subjects will be told that clinical supplies of SL BPN have been specifically developed for this study and may look or taste different than commercially available products they may have been treated with previously. Subjects should not interpret these differences as indicative of whether they are receiving SL active or placebo tablets. To provide additional assurance of maintaining the blind, a different brand of SL BPN will be utilized for any potential supplemental SL BPN needs. Designated site personnel will remain unblinded to maintain drug accountability records for all dispensed and returned SL BPN or SL placebo tablets. This unblinded site personnel must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the SL tablets in reference to the subjects.
Since the placebo implants have a slightly different appearance than the Probuphine implants, the following will be agreed upon in a signed document by the Implanting Clinician and the Investigator in order to maintain the blind:

- The Implanting Clinician and any other staff involved in the implant insertion and removal procedures must not participate in subject efficacy evaluations nor discuss with other study staff any information regarding the implants in reference to the subjects.

- In order to keep the subjects blinded, appropriate steps must be taken to ensure that the subject is unable to view the implant insertion or removal procedures at any time (e.g., by draping the surgery table to obstruct the subject’s view of the procedure, etc.).

- The study staff must not ask the Implanting Clinician or any other staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently unblind the study staff.

Under normal circumstances, the blind will not be broken until all participants have completed treatment. In case of emergency, and only if the information is required by the Investigator to ensure subject’s safety in managing a medical condition, the treatment may be unblinded at the site by using a code break module. The code break module will be provided by the Sponsor or designee. If possible, the Investigator should contact the Sponsor prior to unblinding and after any actions have been taken. Whenever a treatment sequence is prematurely unblinded, the reason, date and time of the unblinding, and the individual who broke the blind must be documented. Individual code breaks will result in withdrawal of the participant from the study.

### 5.0 ANALYSIS POPULATIONS

#### 5.1 RANDOMIZED POPULATION

The randomized population will consist of all subjects who complete the Screening Phase and are randomized to a treatment arm.

#### 5.2 SAFETY POPULATION

The safety population will include all subjects who have received study medication. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.

#### 5.3 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) population will consist of all randomized subjects who have received study medication and provided some efficacy data. The primary efficacy analyses will be based on the ITT population.

#### 5.4 PER PROTOCOL POPULATION

The Per Protocol population will include all subjects in the ITT population with no major protocol violations. Major protocol violation criteria will be established prior to the data base lock. Protocol deviations will be presented in the clinical study report. Efficacy analyses may also be performed based on the per protocol population.
6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed using SAS Version 9 and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous (non survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on CRFs by study drug, center, and subject number. Unless otherwise stated data will be presented by treatment and overall.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement on the date of randomization will be considered the baseline measurement. If multiple observations are made during baseline, the baseline will be defined as average of the observations obtained during the baseline phase.

6.2 SOFTWARE

Most analyses will be conducted using SAS Version 9.2 or higher.

6.3 CHANGES TO PLANNED ANALYSES

Draft versions of the SAP will be numbered sequentially as Version 0.0. The final approved version will be numbered as Version 1.00. Revisions after the “Final” version will be numbered as Version 1.0x. The Clinical Study Report will document any changes made after the final version approved before unblinding.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., ITT, safety or Per Protocol) in the title.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm and will include the number of subjects randomized, the number and percentage of randomized subjects in the safety, ITT, and per protocol (if applicable) populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

Disposition summaries will be presented for safety, intent-to-treat, and per protocol populations (if applicable) separately.
7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS
A summary of demographics and baseline characteristics will be presented by treatment arm and overall for the ITT and safety populations. The demographic characteristics will consist of age, sex, ethnicity, and race using descriptive statistics.

Demographic data including age, race, ethnicity, and gender, as well as baseline clinical characteristics will be summarized. Age will be calculated based on the following conditional algorithm:

- Has the patient had his/her birthday this year?
  - Yes, then \( AGE = (year \text{ of informed consent}) - (year \text{ of birth}) \).
  - No, then \( AGE = (year \text{ of informed consent}) - (year \text{ of birth}) - 1 \).

Clinical baseline characteristics summarized will include BMI, type of primary opioid use (heroin, prescription opioid pain relievers, other), years of drug use, when first diagnosed with opioid dependence, proportion of patients previously treated for opioid dependence, duration of buprenorphine treatment, duration of 8 mg or less buprenorphine treatment, and dose of buprenorphine treatment prior to randomization. Clinical baseline characteristics will summarized by treatment group and overall.

7.3 MEDICAL HISTORY
Medical history will be coded using MedDRA dictionary Version 17.0. A medical history listing will be presented.

8.0 PRIOR AND CONCOMITANT MEDICATIONS
All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary Enhanced March 2014. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment component and no more than 30 days after the last administration of any study treatment component. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

Medications that clearly stopped prior to date of first administration of any study treatment component will be included in the prior medications table, and medications that clearly started on or after date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

Prior and Concomitant medication will be summarized for the safety population.
9.0 EFFICACY ANALYSES

9.1 PRIMARY EFFICACY OUTCOME – RESPONDER RATE

The primary efficacy variable will be responder rate, where a responder is defined as a patient with no more than 2 of 6 months with any evidence of illicit opioid use. A total of 10 urine toxicology samples will be collected throughout the 6 months of the study treatment period with 6 scheduled visits (1 visit per month) plus 4 random urine toxicology visits. The investigators have been instructed to schedule the monthly scheduled visits on Mondays to the greatest extent possible.

9.1.1 DERIVATION OF RESPONSE RATE

For the purpose of deriving the responder rate, the following rules will be used:

**Monthly Window for Illicit Opioid Use Assessment**

The monthly window will be defined as the time window from previous scheduled visit window date to current window date. For example, the first monthly Illicit Opioid Use Assessment window is the time between randomization date and Week 4 visit date; the second monthly Illicit Opioid Use Assessment window is the time between Week 4 visit date +1 and Week 8 visit date. Based on this definition, the monthly window may not be exact 4 weeks for all subjects or for all monthly assessment windows within the same subject.

**Evidence of Illicit Opioid Use within a Monthly Window**

Evidence of illicit opioid use within a monthly window is defined as a positive opioid urine toxicology result or self-reported illicit opioid use within that monthly window, including the results from random urine toxicology samples obtained within that monthly window. Therefore, there is evidence of illicit opioid use, if self-reported illicit opioid use is present; regardless of the opioid urine toxicology result is positive or negative. If urine toxicology results are missing, for example, due to missing scheduled visit, corruption of the sample or early discontinuation of the study, the results will be imputed according to the Missing Value Imputation rules discussed in Section 9.1.3 of the SAP.

A responder is defined as a subject with no more than 2 of 6 months with evidence of illicit opioid use. The responder rate for a treatment group is the percentage of the responder for that group.

9.1.2 PRIMARY ANALYSIS

The primary analysis of response rate will be performed using the ITT population.

A test of non-inferiority in the primary efficacy variable between the two treatments arms will be conducted. A non-inferiority margin of 20% will be employed to define non-inferiority. Let \( \pi_C \) and \( \pi_T \) be the response rate for the control arm and experimental treatment arm, respectively. The null hypothesis \( (H_0) \) of inferiority is

\[
H_0: \pi_T \leq \pi_C - 0.20.
\]

The alternative hypothesis \( (H_A) \) of non-inferiority is

\[
H_A: \pi_T > \pi_C - 0.20.
\]
The hypothesis of non-inferiority will be concluded if the null hypothesis can be rejected at the 5% level (if the two-sided 95% confidence interval for the difference between the probabilities of response is above –0.20). The 95% confidence interval, (LB, UB), will be derived using normal approximation:

\[
LB = (P_T - P_C) - 1.96*(1/N_T*P_T*(1-P_T) + 1/N_C*P_C*(1-P_C))^{0.5}, \text{ and }
UB = (P_T - P_C) + 1.96*(1/N_T*P_T*(1-P_T) + 1/N_C*P_C*(1-P_C))^{0.5},
\]

where \(P_T\) and \(P_C\) are observed proportions of the responders for the treatment and the control, respectively, and \(N_T\) and \(N_C\) are the sample sizes for the treatment and the control, respectively.

### 9.1.3 MISSING VALUE IMPUTATION

Unless otherwise stated the following procedures will be used to handle missing values for urine toxicology.

If all missing values (e.g., unavailable or unanalyzable) for laboratory outcomes of the urine toxicology results for illicit opioids are replaced with extreme values (i.e., either all replaced with “negative” or all replaced with “positive”), biases will be introduced. For example, if all missing values are replaced with “positive,” the results will be biased in favor of the group with smaller dropout rate.

To avoid such biases, in the primary analyses, missing values will be replaced by randomly generated binary indicator (1=“Opioid-Positive” and 0=“Opioid-Negative”) using seed=1374809352 in SAS. The probability of having 1 for each treatment group will be in the following manner per FDA’s recommendation dated on November 13, 2014.

**Primary Imputation** - Imputation with 20% (NI Margin) relative penalty: In this imputation missing values in the sublingual buprenorphine arm will be imputed based on the proportion of “Opioid-Positive” samples within its treatment arm. This proportion will be the average of the within subject proportion of “Opioid-Positive” sample. Missing values in Probuphine arm will be imputed based on the proportion that is equal to 1.2 times of the maximum proportion of the two proportions from the two treatment groups. As an example, the proportion of “Opioid-Positive” samples is 14% for Probuphine arm and 15% for sublingual buprenorphine arm. The imputation for sublingual buprenorphine arm will be based on 15% and the imputation for Probuphine arm will be base based on 18%.

This primary imputation method increases, relative to complete data (with no missing data), the likelihood of response (primary endpoint responder definition of no more than 2 months with opioid-positive samples) rate. This is demonstrated through a simulation to provide sample calculation of discordance.

In the simulation study, we generated a dataset for 100 subjects within each of the two treatment arms in each simulation. For each subject we randomly generated 6 binary opioid urine toxicology result outcomes. Each outcome is equal to 1 or 0, where 1=“Opioid-Positive” and 0=“Opioid-Negative”, with probability of 0.2 being positive. Based on the results of the 6 samples we can determine the response rate outcome for the subject. The subject is a responder (indicator=1), if the number of opioid-positive samples <=2 and is a non-responder (indicator=0) if number of opioid-positive samples >2.
We randomly selected 10% of subjects to have 3 missing opioid urine toxicology results from the above complete data set. We then imputed the missing values from SAS binary outcome generator Ranbin based on within treatment proportion of Opioid-Positive (primary imputation methodology). After applying the primary imputation method, we had 6 opioid-urine toxicology result outcomes for all subjects. Based on this, we determined the responder status for each subject. The imputation could change the responder status in the following manners (discordance) vs. the first dataset (complete data set):

- Change from a non-responder status (indicator=0) based on all data known (complete data set) to a responder status (indicator=1) after applying the imputation – Bias in favor of the imputation, or
- Change from a responder status (indicator=1) based on all data known (complete data set) to a non-responder (indicator=0) after applying the imputation – Bias against the imputation

The direction of the bias can be determined based on the difference between the two probabilities below:

1. Probability of bias in favor of the imputation and
2. Probability of bias against the imputation.

We ran this simulation 10,000 times. Simulation of this primary imputation methodology with relative 20% penalty would change a non-responder (with no missing values) to a responder (missing values imputed) 38.5% of the time, but it would change a responder (with no missing values) to a non-responder (missing values imputed) 61.5% of the time. Therefore, in net, the relative 20% penalty method would reduce the chance to be a responder by more than 23%, relative to the complete data method (no missing values).

The missing value imputation process will be carried out after missing value data set is sorted by site, subject identification, and time point.

For sensitivity analysis, a imputation method based on 10% relative penalty will also be applied.
9.1.4 SENSITIVITY ANALYSES
Sensitivity analyses will be performed to further support the primary analyses. The following sensitivity analyses may be performed using the same methodologies for the primary analyses:

- Analysis based Imputation 2 - Imputation with 10% relative penalty
- Analysis based on the monthly windows defined as below:

<table>
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<th>Monthly Window (Scheduled Day)</th>
<th>Start Day</th>
<th>End Day</th>
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<td>1 (28)</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>2 (56)</td>
<td>42</td>
<td>69</td>
</tr>
<tr>
<td>3 (84)</td>
<td>70</td>
<td>97</td>
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<tr>
<td>4 (112)</td>
<td>98</td>
<td>125</td>
</tr>
<tr>
<td>5 (140)</td>
<td>126</td>
<td>153</td>
</tr>
<tr>
<td>6 (168)</td>
<td>154</td>
<td>End of study</td>
</tr>
</tbody>
</table>

The days are relative to the randomization date (Day 1). In general, a month window starts 14 days before the scheduled day and ends 13 days after the scheduled day. The only exceptions are Month 1 Window, where the start day is 1, and the end day of Month 6 Window, where the end day is last day of the study.

- Analysis based on completers (i.e., analysis based on all subjects who provided all required samples);
- Per protocol analysis (i.e., analysis based on subjects who do not have major protocol violations) may also be performed.

Depending on the results of the study, additional sensitivity analyses may be performed.

9.2 SECONDARY EFFICACY OUTCOMES
Secondary efficacy variables will include:
- Percent of Subjects with No Illicit Opioid Use by Month;
- Time to First Evidence of Urine Illicit Opioid Use;
- Cumulative Percentage of Evidence of Urine Illicit Opioid Use by Month;
- Percent of Subjects with No Self-Reported Illicit Drug Use by Month
- Measures of craving: Desire to Use VAS, Need to Use VAS, and Craving VAS;
- Measures of withdrawal: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS);

9.2.1 PERCENT OF SUBJECTS WITH NO ILLICIT OPIOID USE BY MONTH
For the purpose of deriving percent of Subjects with No Illicit Opioid Use by Month, the same definitions for monthly window and evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation.

The treatment differences in these by month variables will be analyzes using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented.
9.2.2 TIME TO FIRST EVIDENCE OF URINE ILLICIT OPIOID USE
For the purpose of deriving Time to First Evidence of Urine Illicit Opioid Use, the time will be defined as:

- If the evidence is obtained during the scheduled visit, the time is the number of days between the randomization day to the scheduled visit day. For example, if first evidence is obtained on Week 8 visit, the time would be 56.
- If the evidence is obtained during random test, time is the number of days between randomization day to the day that random sample is obtained (Random Sample Date – Randomization Date).

The same definition for evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation.

Time to First Evidence of Urine Illicit Opioid Use will be analyzed via log-rank model with treatment effects. Time to event “Survival” curve will be presented using Kaplan-Meier method. Median time to event and the 95% confidence interval of the median times will be presented, if estimable. In this time to event analyses, subjects who do not have any opioid-positive results during the entire study and who do not have any opioid-positive results before discontinuing from the study will be censored at the day when the last sample was obtained.

9.2.3 CUMULATIVE PERCENTAGE OF EVIDENCE OF URINE ILLICIT OPIOID USE BY MONTH
The Cumulative Percentage of Evidence of Urine Illicit Opioid Use will be calculated for all post baseline scheduled visits (for Week 4 through Week 24). The same definition for evidence of illicit opioid use (see Section 9.1.1) and the same rules for missing value imputation (see Section 9.1.3) will be used in the calculation. As the percentage is derived on a cumulative basis, subject will be included in the numerator (i.e., users) at a given scheduled visit, if the subjects have evidence of use at any prior visits or at the current visit.

The cumulative percentages by month will be analyzes using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented.

9.2.4 PERCENT OF SUBJECTS WITH NO SELF-REPORTED ILLICIT DRUG USE BY MONTH
Percent of Subjects with No Self-Reported Illicit Drug Use by Month (by scheduled post baseline visit) will be analyzes using chi square tests. The percentages for each treatment and between treatment percentage differences will be estimated. The 95% confidence intervals of the estimates will be presented.

9.2.5 MEASURES OF CRAVING (VAS)
Measures of craving include Desire to Use VAS and Need to Use VAS, will be administered using unipolar 100 mm VAS (“In the past week/month, how intense has been your average desire/need to use “drug name?”, where 0 = No desire to use and 100 mm= Strongest possible desire, and from 0=No need to use and 100 mm=Strongest possible need, respectively). They will be measured at baseline and monthly (every 4 weeks) thereafter from Week 4 to Week 24.

Changes from baseline in the above VASs will be derived by subtracting the baseline values from the post-baseline values, thus, negative changes are indicative of improvement. Changes from baseline in
measurements of craving will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented. In this primary analysis, missing values will be imputed using Last Observation Carried Forward (LOCF) method.

As a supportive analysis, these variables will also be analyzed via Mixed Model Repeated Measures (MMRM) methods. These analyses will accommodate the non-independence of repeated measurements on individuals. An auto-regressive correlation structure will be specified, which assumes that observations within a subject are correlated and that this correlation decreases with increasing time between observations. Month and treatment will be included in the model as fixed effects. Subject will be included in the model as a random effect and the baseline as covariate. A month-by-treatment interaction term will be included in the model.

9.2.6 MEASURES OF WITHDRAWAL

Measures of withdrawal include Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS). The COWS is comprised of 11 items each with a score of 0 through 4. Higher scores are associated with greater withdrawal symptoms. The items are meant to be objective (e.g., resting pulse rate) measures of patient’s withdrawal symptoms. The SOWS is comprised of 16 items each with a score of 0 through 4. Higher scores are associated with greater withdrawal symptoms. The items are statements which are evaluated by the patient and are there for subjective (e.g., I feel anxious, 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). Both COWS and SOWS will be measured at baseline and monthly (every 4 weeks) thereafter from Week 4 to Week 24.

If there are >=3 (i.e., >=20%) missing items in the COWS scale at a given visit or >=4 (i.e., >20%) missing items in the SOWS scale at a given visit, the COWS/SOWS score for that visit will be missing. If there are 1 or 2 missing items for the COWS assessment then the total of the non-missing items will be calculated and the product of the calculated total and 11/(11- # missing) will be used for the COWS score for that visit. If 3 or fewer items are missing for the SOWS score then the total of the non-missing items will be calculated and the product of the calculated total and 16/(16 - # missing) will be used for the SOWS score. Missing total scores or scores with more than two missing components in COWS, or more than 3 missing components in SOWS, will be imputed using LOCF method.

Changes from baseline in COWS and SOWS will be derived by subtracting the baseline values from the post-baseline values, thus, negative changes are indicative of improvement. Changes from baseline in measurements of withdrawal will be analyzed via Analysis of Covariance (ANCOVA) model with treatment and baseline effects. Treatment effects and treatment differences will be estimated. The two-sided 95% confidence intervals of the between- and within-treatment differences will be presented. In this primary analysis, missing values will be imputed using LOCF method.

As a supportive analysis, these variables will also be analyzed via Mixed Model Repeated Measures (MMRM) methods. These analyses will accommodate the non-independence of repeated measurements on individuals. An auto-regressive correlation structure will be specified, which assumes that observations within a subject are correlated and that this correlation decreases with increasing time between observations. Month and treatment will be included in the model as fixed effects. Subject will be included in the model as a random effect and the baseline as covariate. A month-by-treatment interaction term will be included in the model.
9.3 EXPLORATORY ANALYSES OF ADDITION EFFICACY ENDPOINTS

Exploratory variables include:
- Supplemental SL BPN use
- Additional supplemental counseling
- Additional unscheduled visit to obtain supplemental pharmacological therapies for withdrawal symptoms or desire to use illicit opioids
- Urine toxicology results for other drugs of abuse
- Treatment discontinuation and reasons for discontinuation

As these variables are for exploratory purpose, no missing value imputation will be performed in the analyses. The primary interests for these variables are the outcomes during the entire 24 weeks of post-baseline assessment period. However, unless otherwise stated, for completeness the outcomes for the monthly intervals (4-week intervals) will also be presented.

Urine Toxicology for Other Drugs of Abuse
Percentages of subjects using the illicit drugs (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phenycyclidine, and THC) during Weeks 1-24 will be summarized.

Supplemental SL BPN Use
Percentages of subjects who require supplemental SL BPN, total number of supplemental SL BPN dispensing episodes and average supplemental SL BPN mg dose dispensed per episode.

Additional Unscheduled Visit to Obtain Other Pharmacological Therapies for Withdrawal Symptoms or Desire to Use Illicit Opioids
Percentages of subjects who required additional unscheduled visit to obtain supplemental pharmacological therapies for withdrawal symptoms or desire to use illicit opioids during Weeks 1-24 will be summarized. In addition, number of unscheduled visit to obtain such therapies will also be summarized.

Additional Unscheduled Visit to Obtain Counseling to Manage Withdrawal Symptoms or Desire to Use Illicit Opioids
Percentages of subjects who required additional unscheduled visit to obtain counseling to manage withdrawal symptoms or desire to use illicit opioids during Weeks 1-24 will be summarized. In addition, number of unscheduled visit to obtain such counseling will also be summarized.

Treatment Discontinuation
Percentage of subjects who discontinued study early for each treatment arm and the reason for early discontinuation will be summarized.

9.4 INTERIM ANALYSES

No interim analyses will be performed.

9.5 ADJUSTMENTS FOR MULTIPlicity

Since there will be one primary efficacy variable, no multiple endpoints adjustment is required.
### 9.6 Power and Sample Size Justification

The sample size of 90 per treatment arm (180 total) was selected to achieve 87.3% power, assuming both arms have a 75% rate of responders. If the true rates are lower, but equal in both arms, with a 65% rate of response, the power of the trial to determine non-inferiority is 80.3%. If each treatment arm has an 85% rate of response, then the trial with 180 subjects would have 96.4% power to determine non-inferiority.

### 10.0 Summaries of Measures of Safety

Safety analyses will be performed for the safety population. Safety evaluations will be based on the incidence, intensity, and type of adverse events, as well as on clinically significant changes in the subject’s physical examination, vital signs, and clinical laboratory results, implant site examination and wound care. Safety variables will be tabulated and presented by study drug actually received.

Because there is no pre-specified safety outcome defined in terms of AEs, clinically relevant laboratory parameters, or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

### 10.1 Extent of Exposure

Summary statistics (number and percentage) of weeks of exposure to study drug (i.e. from date of removal to date of initial insertion of the implants in Treatment Group B and date of last dose to date of first dose for subjects in Treatment Group A) will be tabulated by treatment group.

### 10.2 Adverse Events

Each AE and SAE term recorded on the case report forms (CRFs) by primary system organ class (SOC) and will be mapped to a preferred term using the MedDRA dictionary. The investigator will assess AE severity and relationship to the study treatment.

A treatment emergent adverse event (TEAE) is defined as any AE with an onset date on or after date of randomization, or any ongoing event on the date of first dose that worsens in severity after date of randomization. Only TEAEs with an onset date prior to date of last dose + 30 days will be tabulated in summary tables. For the purpose calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix B.

AEs will be summarized by the number and percent of subjects in each primary SOC and preferred term. Patients will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and intensity will be provided. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest intensity. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest intensity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the most related event. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that primary SOC category by using the most related event. In addition, serious adverse events (SAE) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per patient.
Implant related AEs, Other (non-implant related) AEs as well as all AEs will be presented by treatment group and overall. Summaries of these AE subsets will be presented for the following categories:

- Study drug related
- Intensity
- Relationship to implant insertion/removal
- Possibly study drug related by intensity
- Reasonably insertion/removal related by intensity
- Serious
- AEs which led to discontinuation
- SAEs which led to discontinuation
- AEs occurring in 5% or greater of any treatment group (by preferred term)

In the AE summary, preferred terms within each SOC will appear in alphabetical order as well as in decreasing order of total incidence.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

To assess the AE profile during the first week of treatment (first week after the randomization), AEs that occur within the first week of treatment will be presented.

Other safety analyses will be performed as appropriate

10.3 LABORATORY ASSESSMENTS

Chemistry, Hematology, Urinalysis and Coagulation Profile will be assessed at baseline and Week 24 (see Section 10.4.3 for a complete list of parameters to be assessed). Summary statistics for these parameters will be presented by visit for the actual value and change from baseline for each test in each laboratory category (Hematology, Chemistry, Urinalysis, and Coagulation Profile). Shift tables will be presented for shifts from baseline lab categories to end of study laboratory category. The three laboratory categories will be: L (below lower bound of normal range), N (within normal range), and H (above higher bound of normal range).

If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the first evaluation at that time point will be used for summarization purposes. For the purpose of determining baseline, the last nonmissing observation on or prior to randomization will be used. The Week 24 values will be the last post-baseline value on or prior to Week 24.

10.4 VITAL SIGNS

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min), and oxygen saturation (%) collected while sitting, following a rest period of at least 3 minutes. Vital sign values and change from baseline in the vital signs will be summarized for each treatment group.

10.5 PHYSICAL EXAM
Number and percent of subjects with abnormal physical exam findings at Screening will be summarized by body system for each treatment group and overall. Physical Exam data for each subject will also be presented in a listing.

### 10.6 12-LEAD ELECTROCARDIOGRAM (ECG)

12-Lead ECGs will be performed at screening and at Week 24 after the subject has been resting in a recumbent/supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and the PR, QRS, QT, QTcB and QTcF intervals. The ECGs will be signed and dated by a medically-qualified individual to confirm review of the ECG and verify whether any abnormalities are clinically significant.

Number and percent of subjects in each ECG finding category (normal, abnormal not clinically significant, and abnormal and clinically significant), will be summarized for each visit by each treatment group and overall. Summary statistics will be presented for the actual value and change for each ECG parameter.

### 10.7 IMPLANT SITE EXAMINATION AND WOUND CARE

Implant site reactions can occur with the implantation and removal of Probuphine or placebo implants. The implant site will be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing and any other abnormalities, including implant expulsion or implant migration.

AEs that believed to be associated with implant procedures will be summarized similarly to the summaries for other AEs (not associated with implant procedures).

### 11.0 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

### 12.0 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the CRFs against the investigator’s records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

### 13.0 REFERENCES
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### 14.1 APPENDIX A - LIST OF TABLES, LISTINGS, AND FIGURES

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14.2 APPENDIX B - IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of randomization.
If (year is present and month and day are missing) or (year and day are present and month is missing):
  • If year = year of randomization, then set month and day to month and day of randomization
  • If year < year of randomization, then set month and day to December 31.
  • If year > year of randomization, then set month and day to January 1.
If month and year are present and day is missing:
  • If year=year of randomization and
    • If month = month of randomization then set day to day of first dose
    • If month < month of first dose then set day to last day of month
    • If month > month of first dose then set day to first day of month
  • If year < year of randomization then set day to last day of month
  • If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.