

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204442Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	2/13/2016
<b>From</b>	Celia Winchell, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA</b>	204442
<b>Applicant</b>	Braeburn Pharmaceuticals on behalf of Titan Pharmaceuticals
<b>Date of Submission</b>	8/27/2015
<b>PDUFA Goal Date</b>	2/27/2016
<b>Proprietary Name / Established (USAN) names</b>	Probuphine (buprenorphine hydrochloride) Implant for Subdermal Use
<b>Dosage forms / Strength</b>	EVA implants, 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride). Recommended dose: 4 implants every 6 months
<b>Proposed Indication(s)</b>	“For the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg/day of Subutex or Suboxone sublingual tablet or generic equivalent).  PROBUPHINE should be used as part of a complete treatment program to include counseling and psychosocial support. Prescription use of this product is limited under the Drug Addiction Treatment Act.”
<b>Recommended:</b>	<i>Approval</i>

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## 1. Introduction

Probuphine is a rod-shaped implant designed to provide sustained delivery of buprenorphine, a partial agonist at the  $\mu$ -opiate receptor, for up to six months when 4 rods are implanted subdermally. Probuphine is intended as a maintenance treatment for opioid-dependent patients who have been clinically stable for a sustained period of time on low to moderate doses of transmucosal buprenorphine (e.g., 8 mg/day or less of buprenorphine sublingual tablet<sup>1</sup>). The application references both NDA 20732, Subutex (buprenorphine sublingual tablets) and NDA 20733, Suboxone (buprenorphine/naloxone combination tablets), which are approved for the treatment of opioid dependence<sup>2</sup>.

Because of the potential for an implantable product to mitigate risks of abuse, diversion, and accidental pediatric exposure, the application was granted a priority review.

This is the second review cycle for this application. Initially, in 2012, the Applicant provided efficacy data from two placebo-controlled trials in patients newly-entering treatment for opioid dependence. As explained in detail in my Cross-Discipline Team Leader (CDTL) review of the original application, I concluded that the dose tested was inadequate, and I did not believe that the results achieved outweighed the risks of treatment in that population. This finding was unsurprising, given that the steady-state plasma level of buprenorphine achieved by Probuphine is approximately half the trough level associated with the recommended dose of the reference product (16 mg/day), and less than one-third the area under the curve (AUC) for buprenorphine exposure at that dose. The initial application received a Complete Response letter on April 30, 2013, calling for study of higher doses and/or data to support the clinical benefit of the results observed in the clinical trials.

In subsequent discussions, the Applicant (previously Titan, now represented by a marketing partner, Braeburn), elected to study the product in a sub-population of opioid-dependent patients for whom the dose might be adequate; namely, patients who had already attained and sustained clinical stability and had been tapered to doses which more closely approximate the plasma levels achieved by Probuphine.

In this resubmission, the Applicant has provided efficacy data from a single, double-blind, double-dummy, active-controlled trial which is relied on in conjunction with reference to previous Agency findings of efficacy for Subutex and Suboxone. The study design includes a number of novel features not seen in prior studies of drugs used to treat opioid dependence.

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<sup>1</sup> Equivalent doses include Subutex buprenorphine tablets 8 mg; Suboxone buprenorphine/naloxone tablet; 8 mg/2 mg; Suboxone buprenorphine/naloxone sublingual film 8 mg/2 mg; Zubsolv buprenorphine/naloxone sublingual tablet 5.7 mg/1.4 mg; Bunavail buprenorphine/naloxone buccal film 4.2 mg/0.7 mg; and corresponding generics.

<sup>2</sup> Suboxone tablets and Subutex tablets are no longer marketed, but generic equivalents are available.

These include:

- Enrollment of clinically-stable patients
- Infrequent verification of abstinence from illicit drug use, consistent with the frequency of clinical monitoring of stable patients
- Use of an active-control design with the objective of demonstrating non-inferiority of the treatment under evaluation to an active control

The Applicant's submission includes safety data from 370 unique patients who were treated with Probupine in clinical trials and clinical pharmacology studies, most of whom received one course of treatment (up to 24 weeks) with 107 receiving a second course of treatment. The Sponsor tabulates that 151 patients were exposed for 6 months or more and 85 patients were exposed for a year.

The overall safety experience is consistent with the known safety profile of buprenorphine, which includes risks of hepatic effects, possible effects on cardiac conduction, and allergic reactions, as well as the possibility of overdose particularly when combined with other depressants. However, the product presents a novel safety concern due to the need for surgical implantation.

The procedure is similar in many respects to Norplant, an implantable, progestin-releasing contraceptive which is no longer marketed in the US. Norplant's safety experience identified the potential for various implantation and removal-related complications, some of them with disabling consequences. These occurred despite the fact that insertion and removal of Norplant were performed by providers trained in surgical procedures. Probupine is somewhat more complicated to insert and to remove, because it requires placement of four rods (b) (4) and additional incisions are needed for removal. Moreover, Probupine must be replaced much more frequently than Norplant.

Physicians currently providing buprenorphine treatment are primarily from non-surgical specialties. The Applicant has proposed a training program for providers, and a closed distribution system to ensure the product is implanted only by trained providers, to address this concern. At the time of this writing, details of this program, proposed as a Risk Mitigation and Evaluation Strategy (REMS) are under review, because the proposal has been revised during the review cycle. This review will document only the concerns raised by the Division of Risk Management (DRISK) on the last-reviewed version.

## 2. Background

Buprenorphine is a partial agonist at the  $\mu$ -opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, and two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence<sup>3</sup>. Three other transmucosal formulations have subsequently been approved for opioid dependence, as well as two transdermal products and one transmucosal product for pain. Approximately 10.6 million prescriptions were dispensed from outpatient retail pharmacies and approximately 1.3 million patients received a dispensed prescription for buprenorphine tablets or films during 2014.<sup>4</sup>

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the  $\mu$ -opioid receptor. First, buprenorphine had been shown to have a ceiling effect for respiratory depression, suggesting that it would be “impossible to overdose” on buprenorphine. Second, initial clinical evaluations of buprenorphine’s ability to produce physical dependence led to the conclusion that physical dependence to buprenorphine, if it developed, was associated with a mild withdrawal syndrome. Third, it was expected to have limited attractiveness as a drug of abuse relative to full agonists.<sup>5</sup>

Buprenorphine was expected to have limited abuse potential for two reasons. First, due to its partial agonist properties, the euphorogenic effects of buprenorphine were understood to reach a “ceiling” at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. Second, when a partial agonist displaces a full agonist at the receptor, the relative reduction in receptor activation can produce withdrawal effects. Individuals dependent on full agonists may therefore experience sudden and severe symptoms of withdrawal if they use buprenorphine. These features were expected to limit its attractiveness as a drug of abuse for patients and for illicit use.

In addition to the improved safety profile, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, deterring abuse of opioids by buprenorphine-maintained patients.

Unfortunately, despite these features, buprenorphine sublingual products have been increasingly identified in the illicit drug market, and it is known that they are diverted, abused, and misused. Additionally, they have been implicated in a number of cases of

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<sup>3</sup> Subutex, buprenorphine sublingual tablets (Reckitt Benckiser NDA 20732) and Suboxone, buprenorphine/naloxone sublingual tablets (Reckitt Benckiser NDA 20733). Naloxone is intended to further deter abuse by the intravenous route by precipitating withdrawal if the product is injected by persons dependent on full agonists.

<sup>4</sup> IMS National Prescription Audit and Total Patient Tracker, Year 2014, extracted 12/15

<sup>5</sup> Many of these beliefs have subsequently been found to have been erroneous, or at least overstated, but these were the generally-held views about buprenorphine’s pharmacology at the time it was being developed.

accidental poisonings of small children. Therefore, a depot injection or an implantable product which would be difficult to divert or abuse, and would be less likely to be accidentally ingested by small children, offers potential advantages. In addition, if a depot or implantable product provided a sufficient plasma level of buprenorphine to block the effects of exogenous opioids, the nature of the product would enforce compliance so that patients could not periodically discontinue use to allow the blocking effect to dissipate in order to experience the effects of their opioids of choice. (This last feature is not provided by Probuphine.)

The recommended dose of sublingual buprenorphine is in the range of 12 mg to 16 mg daily. Pharmacokinetic comparisons of Probuphine to sublingual buprenorphine demonstrate that the relative bioavailability of four Probuphine implants (320 mg total buprenorphine) based on the mean  $AUC_{0-24}$  values at steady state compared with sublingual buprenorphine (16 mg once daily) is 31.3%. The trough concentrations of buprenorphine at steady-state obtained with Probuphine were approximately 0.72 to 0.83 ng/mL, approximately half the trough concentrations observed with 16 mg daily of sublingual buprenorphine at steady state ( $1.6 \pm 0.6$  ng/mL).

## **2.1 Clinical Development of Probuphine**

### **2.1.1 Original NDA Submission**

Titan initially envisioned Probuphine as a product which could be provided to patients at the outset of their treatment—after just a few days of titration on a sublingual formulation. To support this indication, the Applicant was asked to provide evidence from replicated trials showing that Probuphine was appropriate treatment for patients who might not yet be stabilized on buprenorphine. The appropriate approach to take in designing clinical trials to evaluate treatments for opioid addiction continues to evolve and so there is no standard approach to the clinical trial design of studies that evaluate treatment of opioid dependence. The original development program undertaken by Titan included two placebo-controlled trials that enrolled new entrants to buprenorphine treatment. The results of these studies, although meeting the pre-specified endpoints, pointed to a conclusion that the dose provided was too low to provide effective treatment for patients new to buprenorphine treatment.

Ultimately, the Application was not approved. APPENDIX A, page 52 provides, in detail, information about the original clinical trials and the Division's interpretation of the results.

### **2.1.2 Post-Action Discussions and Development Activities**

As the Division concluded, on review of the data, that the dose of Probuphine was too low to be effective, the Applicant was encouraged to study a higher dose of Probuphine. Although the Applicant disagreed with the Division's conclusions regarding the efficacy findings, they did acknowledge that four Probuphine implants yield buprenorphine concentrations similar to those observed with 4 to 8 mg sublingual buprenorphine based on average exposure (e.g., mean  $AUC$  values) or concentration. It was noted that, when

the study results were discussed at a meeting of the Psychiatric Drugs Advisory Committee on March 21, 2013, experts on the panel commented that there could be a subset of long-term, patients stable on lower doses of buprenorphine who could benefit from the product. In accordance with this finding, the Applicant proposed a revised indication for Probupine of *for the treatment of patients stabilized on sublingual buprenorphine at doses of 8 mg or less*. The Division agreed that, with adequate support, the revised indication may be suitable for a subset of patients given the public health benefit that Probupine could potentially offer related to decreased misuse, abuse, and accidental pediatric exposure.

## **2.2 Background Related to Efficacy Endpoints and Study Design**

Ultimately, to support the revised indication, Study PRO-814 was designed and conducted by the Applicant to assess the efficacy of Probupine in this new population. Certain aspects of the study design were novel. Customarily, studies of drugs to treat opioid addiction have featured frequent visits for collection of urine toxicology tests to ascertain abstinence from illicit drug use. However, because stable patients already in established buprenorphine treatment would not ordinarily be seen thrice-weekly, or even weekly, the burden on participants was seen as a barrier to participation and likely to lead to discontinuations and missing data. Additionally, there was discomfort with the idea of any design that withdrew stable patients from an effective treatment, putting them at risk for relapse which might not be readily reversed. Therefore, the Division and the Applicant jointly agreed that a double-blind, double-dummy non-inferiority study with sublingual buprenorphine in patients already stable on buprenorphine treatment could be conducted. Although it might be argued that a passive-compliance formulation such as Probupine should be superior to a formulation that relies upon patients to adhere to a medication regimen, the regulations do not require that a new medication be shown to be superior to an approved medication. Moreover, continued treatment success was expected to be the rule, rather than the exception, in this population of patients, so it would be difficult to show that a new treatment could improve upon the existing treatment.

Customarily, non-inferiority studies require that a treatment have a known and consistent effect in order to support the assumptions used to choose the non-inferiority margin. Therefore, historically, the Division has been reluctant to agree to non-inferiority designs for trials of drugs intended to treat opioid dependence because of the lack of consistent information about the expected response rate, related to the heterogeneity of response definitions, study designs, populations, and treatments. However, some flexibility was deemed appropriate because the Division recognized the potential public health benefit of an implantable formulation of buprenorphine in light of a growing problem of misuse, abuse, and accidental exposure of buprenorphine. The Division encouraged the Applicant to seek various sources of information about the expected rate of non-relapse in stable, successfully-treated patients who continue on buprenorphine over a six-month period. The sources of information used to establish the protocol-specified responder definition are outlined in detail in Dr. Skeete's Medical Officer review and described briefly below in Section 7.3. Ultimately, a number of assumptions used to establish the approach to determining response (e.g., how to impute values for missing urine

toxicology samples, how to account for patients who required supplemental dosing with sublingual buprenorphine, how to set the margin for non-inferiority determination) were not borne out by the observed data, and the Division's approach to re-analysis based on the observed data, supported by the comments of the Advisory Committee, are detailed below.

In pre-submission interactions, the Division informed the Applicant that because of the uncertainties regarding a non-inferiority design in this setting, the Division planned to quantitatively and qualitatively assess the analysis of the primary endpoint and the clinical meaningfulness of the trial findings to determine whether the study would provide the adequate evidence necessary to support a conclusion of efficacy for Probuphine in the treatment of patients stabilized on sublingual buprenorphine at doses 8 mg or less.

### **2.3 Safety Concerns Related to Surgically Implantable Drugs**

The Agency's previous experience with surgically implantable products, specifically contraceptive implants, was used to identify potential concerns that could arise in the use of Probuphine, as well as upon the experience in the development program itself.

Implantable methods of contraception consist of devices that can be placed subcutaneously to provide long-acting, readily-reversible contraception. Four iterations of contraceptive implants have been approved for marketing in the United States, with each new generation featuring product designs aimed at improving tolerability. Norplant, the first generation of contraceptive implant, consisted of six levonorgestrel-containing capsules and was approved in 1990. Subsequent versions of implants include Jadelle (a two-capsule, levonorgestrel-containing implant), Implanon (a single-capsule, etonogestrel-containing implant), and Nexplanon (similar to Implanon, but is radio-opaque and detectable by X-ray). Currently, only Nexplanon is marketed in the U.S. It is distributed only to providers who have completed a Sponsor-provided training program. It is a single implant, pre-loaded into an applicator that has been developed to facilitate one-handed insertion. The procedures involved are considerably simpler than those required for Norplant, and similarly, simpler than those required for Probuphine.

While implantable contraceptive methods are generally well-tolerated, notable procedure-related adverse events include pain, infection, numbness, and scarring at the implant site. Complications such as bleeding or hematoma have also been reported. The most significant safety concerns include injuries related to damage of the ulnar or medial cutaneous nerve, which have resulted in permanent disability. These risks may be mitigated by adequate provider training in the procedures of both insertion and removal, and by providers developing and maintaining familiarity with the procedures, ideally achieved through frequent performance.

Insertion and removal procedures for Probuphine are shown in APPENDIX B: Insertion and Removal Procedures, page 75.

Notably, implantable contraceptive products are inserted and removed by obstetrician/gynecologists, who are surgically trained. Their medical offices are suitably equipped for the performance of minor surgical procedures; they have access to imaging modalities (such as ultrasound) for localizing implants that cannot be palpated, and to operating suites if a more extensive surgical procedure is required to manage a complication. In contrast, buprenorphine treatment is currently provided by physicians who may not have suitable training and may not practice in suitable environments to permit them to perform the insertion or removal procedures, or to manage complications.

Drug utilization data in 2012 indicated that 32% of prescriptions for buprenorphine/naloxone sublingual tablets are written by physicians whose specialty is identified as General Practitioner/Family Medicine/Doctor of Osteopathy. While some of these individuals may perform minor surgical procedures, others may not be prepared to do so. Fully 22% of prescriptions were written by psychiatrists, who are not routinely trained to perform surgical procedures, and whose office environments are not generally unsuitable for managing procedural complications associated with insertion and removal of the implants. The Applicant has proposed that only clinicians with current familiarity with performing procedures would be eligible to be certified to insert and remove Probupine. Other clinicians could be certified to prescribe, but not to insert/remove. In order to be certified to insert/remove, clinicians will need to demonstrate procedural competency in a simulated procedure. Other details of the program to ensure that only appropriately-qualified personnel will perform insertions and removals are detailed in Section 16.2, on page 46, below.

## ***2.4 Legal and Regulatory Issues Constraining Buprenorphine Treatment***

Buprenorphine is a Schedule III Controlled Substance and physicians prescribing Probupine must comply with the relevant aspects of the Controlled Substances Act. In addition, the provision of agonist treatment of opioid addiction is governed by certain legal requirements. Unlike methadone, buprenorphine may be prescribed by physicians meeting certain requirements.

Methadone treatment of opioid addiction is delivered in a closed distribution system (opioid treatment programs, OTPs) that originally required special licensing by both Federal and State authorities, under the Narcotic Addict Treatment Act of 1974. The current regulatory system is accreditation-based, but OTPs must still comply with specific regulations that pertain to the way clinics are run, the credentials of staff, and the delivery of care. To receive methadone maintenance, patients are required to attend an OTP, usually on a daily basis, with the possibility of earning the privilege of taking home doses as their treatment stability increases. Buprenorphine may also be administered to patients at OTPs.

Buprenorphine treatment is covered Title XXXV of the Children's Health Act of 2000 (P.L. 106-310), which provides a "Waiver Authority for Physicians Who Dispense or

Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients.” This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000). Under the provisions of DATA 2000, qualifying physicians may obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. At present, the only products covered by DATA 2000 (i.e., Schedule III-IV, approved for the indication) are buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and films.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. The 8 hour training courses are provided by various physician organizations (e.g. APA) and delivered in-person, in web-based formats, or through other mechanisms. Physicians who obtain DATA 2000 waivers may treat opioid addiction with products covered by the law in any appropriate clinical settings in which they are credentialed to practice medicine.

The Applicant has been advised by DEA that both the physician who prescribes Probuphine and, if different, the physician who implants Probuphine must be DATA-waived.

### **3. CMC/Device**

Probuphine is a combination product comprising drug and device components. The drug component is the individual implant or rod that contains buprenorphine and ethylene vinyl acetate (EVA). The device component is the applicator which consists of an obturator and cannula. The CMC review of the drug component in the first review cycle was performed by Edwin Jao, Ph.D., supervised by Prasad Peri, Ph.D., and the review of the device component was performed by Jacqueline Ryan, CDRH. In the second review cycle, the CMC review of the drug component was performed by Xiaobin Shen, Ph.D., supervised by Julia Pinto, Ph.D. and the review of the device component was performed by John McMichael, in the Office of Device Evaluation in CDRH.

Text below is primarily excerpted from Dr. Shen’s review.

- General product quality considerations

The drug substance is Buprenorphine Hydrochloride (BPN). It is not a NME. The characterization of this compound has been well documented in the literature, and the applicant has adequately confirmed the structure of the drug substance they produced. The drug substance does not contain structural alert moieties. Only one crystal form of

BPN was observed. Neither polymorphism nor (b) (4) was observed.

BPN is manufactured through multiple steps of synthesis. The detailed CMC information is incorporated by reference to DMF 16419. This DMF is considered adequate to support this NDA. The proposed drug substance specification meets and exceeds that required by the USP monograph for BPN. The quality and stability of the registration batches of the drug substance BPN are adequately demonstrated by release and stability data. The drug substance is packaged (b) (4). There are no safety concerns for the container/closure system. The proposed retest period of (b) (4) months is supported by real time stability data.

The drug product Probuphine® (buprenorphine HCl implant) is a subdermal implant containing 80 mg buprenorphine hydrochloride USP (BPN) coextruded with (b) (4) mg of ethylene vinyl acetate copolymer (EVA, the only excipient) as a matrix (b) (4). Each implant measures 26 mm in length and 2.5 mm in diameter. The implants are individually packaged into laminated foil pouches. The pouches are terminally sterilized using gamma irradiation. (b) (4)

(b) (4)  
The release profile consists of an initial burst followed by a slow steady state drug release over a period of 6 months.

Ethylene vinyl acetate is listed in the inactive ingredient database for several approved applications with similar dosage forms. The quantity of (b) (4) mg used in this formulation is well below the largest amount used in the listed applications. The EVA used in this drug product contains (b) (4)% of vinyl acetate. It is biocompatible, but not biodegradable.

The commercial batch size for the drug product will be (b) (4) kg. The manufacturing process of the drug product involves (b) (4) packaging, and terminal sterilization. Adequate in-process and material controls are in place. One batch of EVA (from (b) (4)) is used in the manufacturing of the development, clinical, registration, and immediate commercial batches. This batch is well characterized and controlled, including extractables.

The proposed drug product specification is acceptable from a safety perspective and supported by release and stability data. The sterilization process and sterility controls have been evaluated by the microbiology team and are considered acceptable. Release data from eight batches (four commercial scale of (b) (4) kg, and four (b) (4) g to (b) (4) g scale) are provided. Release batch data are acceptable per specification. Up to 48 months of stability data are provided from the four (b) (4) g to (b) (4) g scale batches. No significant trend is observed for assay and impurity levels. The requested shelf life of 36 months is supported by stability data and therefore granted.

The Probuphine implants are packaged in a laminated foil pouch (b) (4). No safety issues associated with the container/closure system are identified. Extractable study was conducted, and no evidence of leachables in the drug product is observed.

- Facilities review/inspection

The current supplier of buprenorphine drug substance is Teva. The establishment has been determined to be acceptable by the Office of Compliance for this NDA.

The drug product is manufactured by DPT of Texas. The recommendation from the Office of Compliance for this establishment is approval.

The device for delivery of the implants was reviewed by Jacqueline Ryan, CDRH in the first review cycle and in the second cycle by John McMichael. The text below describing the product is primarily from the most recent review.

The Probuphine Applicator consists of three parts: (1) an insertable obturator (stylet rod), (2) a cannula needle, and (3) a needle guard which covers the entire cannula from hub to tip. Further descriptions of the device parts are below.

1. Obturator

Medical grade 304 stainless steel rod (Obturator) used to advance the Probuphine implants to the proper subdermal position. The Stylet wire has a diameter of 0.110 in (2.79 mm), and a length of 3.5 mm  $\pm$  0.79 mm with a blunt tip that can be easily inserted into the Cannula without catching or obstruction. The fit between the stylet wire and the cannula ensures that Probuphine will not remain in the barrel of the cannula if the stylet is inserted to the stop marker. There is a stop marker line 26 mm  $\pm$  0.79 mm from the hub on the Stylet.

2. Cannula

Thin walled piercing needle, made of medical grade 304 stainless steel with a smooth inner surface, 10 gauge internal diameter and 60 mm length, in order to allow the passage of Probuphine (2.5 mm + 2.5 mm diameter) without impediment. The needle has two depth orientation markers are 60 mm  $\pm$  0.79 mm from the hub on the Cannula and 40 mm  $\pm$  0.79 mm from tip of Cannula.

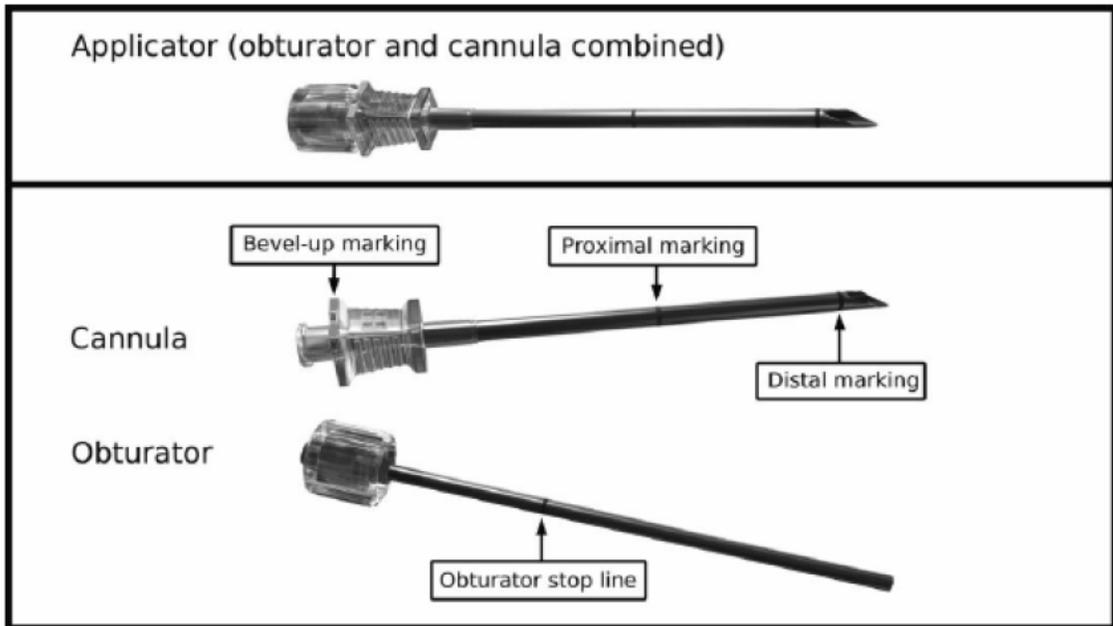
3. Needle Guard

The Needle Guard for the Applicator consisting of an LDPE sleeve which covers the entire Cannula from the hub to the tip. The Needle Guard protects the Applicator tip during transport and handling and as a safety measure during user handling (removal of the Applicator from packaging). The components of the Applicator are shown in (excluding the Cover). The Cannula and Stylet have interlocking hubs (referred to as Swivel Nuts) manufactured from biocompatible polymeric materials. The Applicator design includes guide and orientation marker visual aids to assist healthcare providers with the proper placement of the Probuphine implants. These markers include orientation

markings on both the Cannula and Stylet to facilitate the proper depth of implant placement, and a foil stamp marking on the hub of the Cannula showing the correct "bevel up" position for the cannula which facilitates the correct subdermal insertion of Probupine.

Packaging of Probupine Applicator:

The Probupine Applicator is packaged in a (b) (4) pouch (b) (4)  
The material has been verified to maintain sterility for up to (u) (4) months.



**Figure 1: Probupine Applicator Components**

During insertion, the cannula is subdermally inserted through a small incision in the inner side of the non-dominant upper arm, to the 40 mm mark. A sterile Probupine implant is inserted into the cannula and the stylet is used to advance the implant to the correct position under the skin. The cannula is withdrawn to the 60 mm mark to allow insertion of the next implant. This process is repeated until the 4 Probupine implants are inserted at which time the cannula is removed.

CDRH's review of the device constituent for this Combination Product consisted of a review of device performance, biocompatibility, and sterility. The reviewer noted concerns with performance testing, and confirmed that no performance testing had been performed on aged devices. The Sponsor updated their protocol for design verification testing after aging according to the comments made by the Agency. The updated version was found to be adequate. The Sponsor also agreed to present the results of the verification testing of the aged samples at the same time as the stability data of the drug product, which was determined to be an adequate approach.

- Purported Abuse-Deterrent Features

(b) (4) Braeburn has claimed that Probuphine is an abuse-deterrent formulation because it is not to be distributed to patients and will be implanted in the patient's arm. However, the product itself, before insertion and after removal, does not include any physical or chemical properties to deter abuse. In the original review cycle, Stephen Sun, M.D. of the Controlled Substances Staff, reviewed the application to evaluate the potential for abuse of Probuphine. He noted that while no formal extraction studies were performed, *in vitro* dissolution studies showed that 90-95% of buprenorphine is released within 4 to 5 days in water and 15 mg of buprenorphine can be washed off after 30 minutes using ethanol. An implant placed in 900 mL of purified water at 37°C for 4-hours would release between 4.2 mg and 6.2 mg buprenorphine. Because even used implants at the end of the six month implantation period contain 40% of the original amount of buprenorphine, implants that are removed or accidentally expelled could be subject to abuse and the product itself cannot be described as abuse-deterrent.

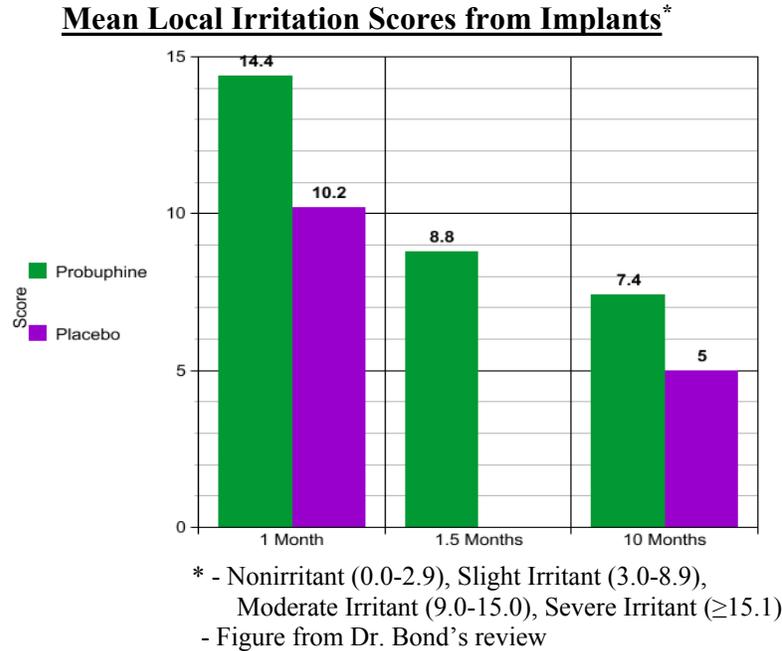
## 4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology portion of the application was reviewed by Gary Bond, Ph.D., supervised in the original review cycle by Adam Wasserman, Ph.D., and in the second review cycle by Jay Chang, Ph.D. and R. Daniel Mellon, Ph.D. Text below is taken primarily from Dr. Wasserman's memo from the first review cycle and from Dr. Bond's review of the current submission. Much of the pharmacology/toxicology information supporting this application is included by reference to previous Agency findings.

Titan submitted chronic studies of a Probuphine development product (BDDS) in dogs, as well as evaluations of local tolerance in rabbits up to 26 weeks duration, and sensitization and intracutaneous reactivity studies in guinea pigs and rabbits. Titan additionally submitted a number of genotoxicity studies, an acute systemic toxicity test in mice, and an evaluation of pyrogenicity and intracutaneous local toxicity of BDDS extracts in rabbits order to define the potential toxicities of extractable/leachable compounds from the implant.

The reviewers concluded that the information provided support the approval of the application. Only local toxicity associated with the BDDS implant was identified and this was slightly more pronounced than observed with the negative/EVA placebo implant. In the major NDA-supportive 10-month toxicity study in the dog, both BDDS and placebo implants demonstrated evidence of "moderate irritation" at the one month interim time-point which on microscopic examination was further described as an inflammatory response characterized principally by increased infiltrating lymphocytes, macrophages, occasional giant cells and fibrosis. The inflammatory response was reduced in severity, scoring as "slight irritation", when evaluated at 6 weeks and 10 months post-implant placement.

The mean local irritation scores in dogs over 10 months are illustrated in the following graph.



There were no other notable toxicologic findings with the BDDS implant, EVA implant, or extracts in the remainder of the nonclinical package.

The systemic level of buprenorphine produced by the intended usage of Probuphine rods is well within that of approved sublingual buprenorphine; therefore, the systemic safety of buprenorphine as released by the drug product is not at issue.

Dr. Wasserman noted that the team faced challenges in determining the appropriate wording in the non-clinical sections of labeling because of the uncertainty in converting the exposures to terms of "human equivalent dose." The Complete Response letter included a request for bridging toxicokinetic data to allow the nonclinical studies cited in the labels to be related to clinical exposures with Probuphine.

In this submission, the Applicant provided the requested bridging toxicokinetic studies which were reviewed by Dr. Bond in support of newly-calculated exposure margins for labeling. The pharmacology-toxicology review team also provided recommendations to ensure that the labeling conformed with the requirements of the Pregnancy and Lactation Labeling Rule (PLLR).

The submitted studies included

- a. A 28 Day Pharmacokinetic Study of Buprenorphine in Sprague-Dawley Rats – Study Number 2335-001.

- b. A 28 Day Pharmacokinetic Study of Buprenorphine in CD1 Mice – Study Number 2335-002.
- c. A 12 to 14-Day Pharmacokinetic Study of Buprenorphine in Gravid and Non-Gravid Sprague-Dawley Rats – Study Number 2335-003.
- d. A 12-Day Pharmacokinetic Study of Buprenorphine in Gravid New Zealand White Rabbits– Study Number 2335-004.5.

Dr. Bond noted that

...the labels of the listed drugs (LDs) Suboxone (buprenorphine and naloxone) sublingual film and Subutex (buprenorphine) sublingual tablet each describe virtually identical nonclinical findings from reproductive and developmental toxicology studies, carcinogenicity studies, and mutagenicity studies conducted with buprenorphine. The Suboxone label also describes findings from nonclinical studies conducted with buprenorphine and naloxone. Notably, the nonclinical information described in Section 8.1 *Pregnancy* of these labels describe findings derived from reproductive and developmental toxicology studies performed in animals using a variety of routes of administration including oral, intravenous, intramuscular, and subcutaneous. Also of note, the carcinogenicity information described Section 13.1 *Carcinogenesis, Mutagenesis, Impairment of Fertility* in those labels were derived from rodent feeding studies. As such, the Sponsor conducted and submitted nonclinical TK studies employing the subcutaneous route, which is the clinically relevant route for Probupine, to bridge to the reproductive and developmental information in the LD labels and studies employing dietary administration of buprenorphine to bridge to the carcinogenesis information.

Because of differences in the approach taken in calculating exposure margins, Dr. Bond's calculations differ from that of the Applicant. The Agency uses the mean values when making exposure comparisons for labeling purposes, as the overall toxicology findings are based on the totality of the data, rather than the one animal with the highest exposure, which was the Applicant's approach for some of the studies. Elsewhere, the Applicant used the (b) (4) in some calculations instead of the steady state level, which the review team believed to be more appropriate for a carcinogenicity endpoint. The review team's calculations were incorporated into the labeling.

In the post-action discussions of the approach to toxicokinetic bridging, the review team informed the sponsor that if the exposure data obtained in the SC bridging TK study would provide for a safety margin for human exposure to be expressed in the label, the inclusion of nonclinical findings from the other exposure routes would be unnecessary. However, upon formal review of the submitted PK data and the referenced drug product labels, the review concluded that it would be inappropriate to limit the labeling to only the data derived from SC dosing studies, noting:

...the toxicological characterization of buprenorphine is based on the entirety of the data from the referenced product labels. Removal of the studies that were not

completed by the SC route of administration minimizes the overall risk summary message and there is no reason to believe that this drug product is any safer than the other buprenorphine drug products that would be used by the patients who are stabilized on not more than 8 mg of buprenorphine via the sublingual route.

The team recommended retaining the animal data sections from the referenced products in Probuphine labeling with the exposure margins updated to reflect actual exposure data, where available. Additionally, in the Pregnancy section, the team recommended that risk summary should also be reproduced from the referenced Subutex labeling with the statements regarding human exposure relevance updated based on the limited new PK data. They noted:

Ideally, exposure data would have been provided for all of the studies, to put the findings into context, since the limited exposure data submitted suggest a larger safety margin than predicted by the body surface area comparison in the referenced product labeling. However, since we do not have AUC data for all of these studies, the label can only reflect the data we have and the relative risk suggested by the data in the referenced product labels.

## 5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was performed by David Lee, Ph.D., supervised by Yun Xu, Ph.D. Two clinical pharmacology studies were submitted in support of the Probuphine NDA, and were reviewed in detail by the Clinical Pharmacology Team during the first review cycle. No new clinical pharmacology information was submitted in support of the resubmission. Both studies compared Probuphine (4 implants) to 16 mg/day sublingual buprenorphine; there has been no direct comparison of Probuphine, 4 implants, to 8 mg/day sublingual buprenorphine.

The two clinical pharmacology studies [PRO-TTP-400-02-01 and PRO-810] demonstrated that steady-state buprenorphine exposures obtained with four implants (80 mg of buprenorphine each, 320-mg total) were approximately 0.72 to 0.83 ng/mL, which is approximately half the trough concentrations observed with 16 mg/day SL buprenorphine at steady state ( $1.6 \pm 0.6$  ng/mL), and approximates the trough concentrations observed with 8 mg/day SL buprenorphine.

The relative bioavailability of Probuphine implants (320 mg total buprenorphine) based on the mean  $AUC_{0-24}$  values at steady state (Day 28) compared with SL buprenorphine (16 mg once daily for 5 Days) was 31.3%. The average steady-state buprenorphine concentration of Probuphine on Day 28 is approximately 0.82 ng/mL, 8% of the peak concentration ( $10.4 \pm 13.4$  ng/mL), and 52% of the trough concentration ( $1.58 \pm 0.60$  ng/mL) of 16 mg/day sublingual buprenorphine at steady state.

The pharmacokinetic parameters of Probuphine, compared to 16 mg/day sublingual buprenorphine tablet, are shown in the table below (Table 12 from Dr. Lee's first-cycle review).

Pharmacokinetic Parameter	Sublingual Buprenorphine		Probuphine Implants		
	Day -2 n=9	Day -1 n=9	Day 1 n=9	Day 28 n=8	Day 57 <sup>a</sup> n=6
C <sub>max</sub> (ng/mL)	8.61 (6.900)	10.40 (13.400)	4.89 (1.110)	0.91 (0.157)	0.78 (0.128)
T <sub>max</sub> <sup>b</sup> (hr)	1.5 (0.50, 2.5)	1.5 (1.0, 2.0)	12 (9.0, 36)	10 (0.00, 24)	0.00 (0.00, 12)
AUC <sub>0-t</sub> <sup>c</sup> (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	113.13 (27.737)	19.60 (3.372)	10.23 (2.264)
AUC <sub>0-24</sub> (ng•hr/mL)	66.25 (35.878)	62.67 (36.397)	75.191 (24.443)	19.60 (3.372)	10.23 (2.264)
t <sub>1/2</sub> <sup>b</sup> (hr)	11.42 (11.04, 12.09)	7.63	--	--	--
λ <sub>z</sub> (hr <sup>-1</sup> )	0.0604 (0.00231)	0.0908	--	--	--

λ<sub>z</sub> = apparent elimination rate constant; AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; AUC<sub>0-t</sub> = area under the plasma concentration-time curve from time 0 to t, where t is the last measurable plasma concentration; C<sub>max</sub> = maximum observed plasma concentration; t<sub>1/2</sub> = apparent terminal elimination half-life; T<sub>max</sub> = time of maximum plasma concentration; SL buprenorphine = 16 mg once per day for 5 consecutive days; Probuphine Implants = 4 Probuphine Implants (80 mg buprenorphine hydrochloride per implant).

<sup>a</sup> Day 57 represents parameters after removal of the Probuphine implants.

<sup>b</sup> Median (minimum, maximum) reported for T<sub>max</sub> and t<sub>1/2</sub>.

<sup>c</sup> On Days -1 and -2, AUC<sub>0-t</sub> represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12. On Day 1, AUC<sub>0-t</sub> represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of insertion.

After six months of implantation, approximately 40% of the buprenorphine remains in the implant. Thus, 192 mg of buprenorphine is delivered over a six-month period.

Buprenorphine distribution, metabolism, and elimination considerations include the following, taken primarily from the referenced labels.

*Distribution:*

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

*Metabolism:*

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in-vitro; however, it has not been studied clinically for opioid-like activity.

*Elimination:*

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual tablet and film buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours.

**Drug-Drug Interactions:**

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when buprenorphine is given concurrently with agents that affect CYP3A4 activity. Drug-drug interaction considerations are complicated because it is anticipated that the greater role of first-pass metabolism in disposition of sublingual products as compared to subdermal products could result in a different impact of metabolic inhibitors or inducers on buprenorphine clearance. The effects of co-administered inducers or inhibitors have been established in studies using transmucosal buprenorphine; study of transdermal buprenorphine suggests it is not affected by ketoconazole, suggesting that the effects may be dependent on the route of administration.

For this reason, considerations are different for various clinical scenarios:

1. Patients transferring from transmucosal buprenorphine taken concomitantly with inhibitors:

In these patients, the plasma exposure of their maintenance transmucosal dose is likely to be higher than in patients not on concomitant inhibitors. When switching to Probupine, which could be less impacted by inhibitors, the result would be that the dose provided by Probupine would be relatively lower and may not be adequate.

2. Patients initiating inhibitors for the first time while maintained on Probupine: In these patients, there is a possibility that the exposure to Probupine could be increased. These patients should be monitored for over-medication and if the inhibitor cannot be discontinued, they should have Probupine removed and be treated with a product that allows for dose adjustment. Although a higher-than-intended exposure is a possibility, the relatively low dose provided by Probupine is unlikely to present significant safety concerns even if the exposure is increased by the addition of inhibitors. (The maximum labeled dose of sublingual buprenorphine is 24 mg/day, and doses as high as 32 mg/day have been studied.)

3. Patients who are already on inhibitors while taking Probupine but discontinue them:

In this situation, the plasma level before *might* fall (although this is unknown). These patients should to be monitored for withdrawal/lack of efficacy and could need

supplementation through the end of the dosing cycle and then could need to be treated with other options.

4. Patients transferring from transmucosal buprenorphine taken concomitantly with inducers:

There is no information to inform this situation because the effects of inducers have not been studied even in sublingual buprenorphine. Hypothetically, if inducers have a greater effect on the sublingual route, a patient transferring from 8 mg taken with a concomitant inducer could experience a higher-than-anticipated plasma level (although, again, not so high as to present a significant safety concern).

5. Patients initiating inducers for the first time while maintained on Probuphine: Hypothetically, these patients might experience a drop in exposure and should be monitored for withdrawal.

6. Patients who are on inducers while taking Probuphine but discontinue them: Hypothetically, these patients might experience an increase in exposure and should be monitored for over-medication.

It is difficult to envision how further light can be shed on this issue because studies would need to be conducted in patients transitioning from transmucosal buprenorphine to Probuphine, and it may be infeasible to conduct appropriate drug-drug interaction studies using such agents as ketoconazole. It is also noted that drug-drug interaction studies with sublingual buprenorphine conducted with various anti-retrovirals have shown that it is difficult to generalize about the effects of concomitant medications based simply on CYP3A4 inhibitory activity. Therefore, at this time, labeling will provide guidance on monitoring of patients when transferring from one route of administration to another in the presence of various concomitant medications, and when initiating or discontinuing a concomitant medication during treatment with Probuphine.

#### Effects of Hepatic Impairment:

In a pharmacokinetic study with sublingual buprenorphine, buprenorphine plasma levels were found to be higher and the half-life was found to be longer in subjects with moderate and severe hepatic impairment, but not in subjects with mild hepatic impairment. Similar to the issues outlined above, it is not known whether these effects are dependent on the route of administration. Because the effects are not known, and Probuphine cannot be titrated, it seems prudent to recommend that patients with pre-existing moderate to severe hepatic impairment would not be candidates for treatment with Probuphine, and that patients who develop moderate to severe hepatic impairment while being treated with Probuphine should be monitored for signs and symptoms increased levels of buprenorphine, and may require of the implants.

#### QT Prolongation:

There have been no thorough QT (TQT) studies of buprenorphine at the doses used in addiction treatment. In a TQT study of transdermal buprenorphine, a dose of 40 mcg/hour prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. The steady state plasma levels associated with this finding are similar to those produced by 4-5 implants of Probuphine. This information came to light

after products for addiction treatment dosed at substantially higher exposures were already on the market; post-marketing studies were required of the Sponsors of these applications and Braeburn will also be required to evaluate the effect of Probuphine on cardiac conduction.

## **6. Clinical Microbiology**

*Not applicable*

## **7. Clinical/Statistical- Efficacy**

The original development program undertaken by the Applicant included two placebo-controlled trials that enrolled new entrants to buprenorphine treatment. The appropriate approach to take in designing clinical trials to evaluate treatments for opioid addiction continues to evolve and so there is no standard approach to the clinical trial design of studies that evaluate treatment of opioid dependence. The Applicant conducted the original development program for this indication with advice from the Agency on the trial design and analytic approach.

The Applicant initially envisioned Probuphine as a product which could be provided to patients at the outset of their treatment—after just a few days of titration on a sublingual formulation. To support this indication, the Applicant was asked to provide evidence from replicated trials showing that Probuphine was appropriate treatment for patients who might not yet be stabilized on buprenorphine. The results of these studies, although meeting the pre-specified endpoints, pointed to a conclusion that the dose provided was too low to provide effective treatment for patients new to buprenorphine treatment.

Appendix A, page 51, provides, in detail, information about the original clinical trials and the Division's interpretation of the results.

For the new, proposed indication, the efficacy data were reviewed by Rachel Skeete, M.D., M.H.S., medical officer, and James Travis, Ph.D., biostatistics reviewer. Dr. Travis was supervised by David Petullo, M.S. Both reviewers concluded that non-inferiority of Probuphine to treatment-as-usual was demonstrated, providing evidence in support of Probuphine's efficacy, although Dr. Travis expressed concern that some analyses did not support a conclusion that 70% of the effect of sublingual buprenorphine would be preserved.

My own conclusions is that the data, taken together with previous Agency findings of efficacy for buprenorphine, support the conclusion that Probuphine is not unacceptably less effective to standard-of-care, and is very comparable under conditions of regular clinical supervision (as will be advised in labeling. These conclusions are explained in detail below.

## **7.1 Study Design and Endpoints**

Clinical trial evidence of efficacy is provided from Study PRO-814, a randomized, double-blind, double-dummy, active-controlled, multicenter, non-inferiority study conducted to evaluate the safety and efficacy of four 80 mg Probuphine implants in adult outpatients with opioid dependence who were clinically stabilized on no more than 8 mg of sublingual buprenorphine.

The primary objective for this study was to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence that were clinically stabilized on 8 mg or less of sublingual buprenorphine to 4 Probuphine implants compared to treatment as usual with sublingual buprenorphine.

This study consisted of three phases: a Screening Phase (Weeks -2 to -1), a 24-week Maintenance Phase, and a 2-week Follow-Up Phase.

Subjects were randomized equally to the following two treatment groups:

- Treatment Group A: Treatment as usual with daily sublingual buprenorphine tablets ( $\leq 8$  mg/daily) + four placebo implants.
- Treatment Group B: Four 80 mg Probuphine implants + daily sublingual placebo tablets.

The subject's sublingual buprenorphine/placebo dosage was matched to their prior stable maintenance dose, using a generic brand of sublingual buprenorphine tablets or "nearly-matching" placebo.

Subjects returned for monthly study visits during Week 4, 8, 12, 16, 20, and 24 (End of Treatment Visit). During each of these six visits, subjects were to provide urine toxicology samples. Subjects were also required to provide four random urine toxicology samples throughout the 24-week treatment period. At the end of the study implants were to be removed and subjects were to be transitioned back to their pre-trial care as needed.

The Applicant's primary efficacy endpoint for this study was the proportion of responders for each treatment group, where a responder was defined as a subject with no more than 2 out of 6 months with any evidence of illicit opioid use. Illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use. The responder definition did not address use of supplemental buprenorphine, and included optimistic assumptions about missing urine toxicology samples, as described below.

A number of aspects of the study design were novel. Customarily, studies of drugs to treat opioid addiction have featured frequent visits for collection of urine toxicology tests to ascertain abstinence from illicit drug use. However, because stable patients already in established buprenorphine treatment would not ordinarily be seen thrice-weekly, or even weekly, the burden on participants was seen as a barrier to participation and likely to lead to discontinuations and missing data. Although the Sponsor used a low limit of detection

for the toxicology tests, it is acknowledged that this frequency of sample collection has a lower sensitivity to detection of illicit use than the customary thrice-weekly collection.

Additionally, there was discomfort with the idea of any design that withdrew stable patients from an effective treatment, putting them at risk for relapse which might not be readily reversed. Therefore, the Division and the Applicant jointly agreed that a double-blind, double-dummy non-inferiority study with sublingual buprenorphine in patients already stable on buprenorphine treatment could be conducted. Although it might be argued that a passive-compliance formulation such as Probupine should be superior to a formulation that relies upon patients to adhere to a medication regimen, the regulations do not require that a new medication be shown to be superior to an approved medication. Based on the Sponsor's assumptions that non-relapse would be the rule among stable patients continued on usual treatment, there would also be little room to demonstrate non-inferiority. Therefore, a non-inferiority analysis was agreed upon. Considerations in the analysis are further discussed below.

## **7.2 Population**

In order to be eligible for the study, subjects were required to be between 18 and 65 years of age, have a primary diagnosis of opioid dependence (Diagnostic and Statistical Manual – 4<sup>th</sup> Edition – Text Revision [DSM-IV-TR]), and be considered clinically stable by their treating healthcare provider. Indicators of treatment stability were documented on a stability checklist which included parameters such as stable living environment, participation in job or structured activity, participation in behavioral therapy or peer support program, compliance with treatment visits, and an absence of withdrawal, desire to use opioids, hospitalizations or emergency visits for addiction or mental health issues. Subjects were also required to meet the following criteria:

8. Had been on sublingual buprenorphine treatment for at least 6 months.
9. Had been on a sublingual buprenorphine dose of no more than 8 mg/day for at least the last 90 days.
10. Had no positive urine toxicology results for illicit opioids in the last 90 days.

A total of 211 subjects were screened and 177 were enrolled and randomized into the study at 21 sites in the U.S. from June 2014 to May 2015. This high rate of enrollment of potential subjects is in contrast to the original studies in which fewer than 60% of screened subjects were randomized. Braeburn explained (at the Advisory Committee meeting) that the majority of subjects were established patients at the participating clinical sites. Several sites enrolled very few subjects (<10), with some enrolling as few as a single subject; only three sites contributed 20 or more. This seems consistent with sites recruiting known patients to participate.

The enrolled population was predominantly (60%) male, almost exclusively white, non-Hispanic/non-Latino, about 40 years of age, on average, and all under 65 years of age. Prescription opioids were the primary drug of abuse for about three-quarters of the patients in both treatment arms, with heroin reported as the primary drug in 17% of the Probupine arm and 25% of the SL buprenorphine arm, with a small number (6% vs 2%)

reporting that they used both. This is in contrast to the primarily heroin-using population studied in the previous trials. The average time since diagnosis was 6 years and the the average duration of buprenorphine treatment prior to study entry was two consecutive years, although the Sponsor did not clearly capture the duration of treatment immediately prior to study entry for all patients. At study entry, the majority (70-75%) of patients were on a dose of 8 mg/day sublingual buprenorphine, primarily Suboxone tablets (or generic) but some on Suboxone film.

Patient disposition is shown in the table below. The high rate of completion in this study is in contrast to the experience in the prior studies (in which 35% of the Probuphine-treated patients and 72% of the placebo-treated patients in the controlled trials did not complete the full 24 weeks of treatment), reflecting both the greater stability of the population and the lack of protocol-specified “failure” criteria based on rescue medication use, which resulted in the removal of a substantial number of placebo-treated patients in the earlier studies.

**Patient Disposition**

	Probuphine	SL Buprenorphine
Randomized	87	90
Safety Population	87	89
Completed, n (%)	81 (93%)	84 (94%)
Discontinued	6 (7%)	5 (6%)
Adverse Event	1 (1%)	0
Sponsor Request	0	1 (1%)
Lost to follow-up	4 (5%)	2 (2%)
Other (incarcerated)	1 (1%)	0
Subject request	0	2 (2%)

Source: Table 4 from Sponsor’s Study Report

The Applicant excluded four randomized subjects from the Intent-to-Treat (ITT) population used for the primary efficacy analysis. One subject in the sublingual buprenorphine treatment group was removed from the study after randomization but before receiving any study drug because of scheduled surgery. In the Probuphine treatment group one subject was incarcerated and two subjects were lost to follow-up immediately after being randomized and receiving the implants. The review team disagrees with omitting these three patients from the analysis as both loss to follow-up (particularly in patients previously stable and presumably engaged in treatment) and incarceration are almost always regarded as negative outcomes in treatment of addiction. In the analyses presented below, the reviewers have included these patients as non-responders.

**7.3 Statistical Methodologies**

The efficacy analysis was conducted by Biostatistics Reviewer, James Travis, Ph.D. The primary efficacy endpoint for this study was the proportion of responders for each treatment group. The protocol specified that a responder would be defined as a subject

with no more than 2 out of 6 months with any evidence of illicit opioid use. Illicit opioid use was defined as either a positive opioid urine toxicology result or self-reported illicit opioid use.

The Applicant conducted a test of non-inferiority for the rate of responders between the two treatment arms utilizing a non-inferiority margin of 20%. If  $\pi_c$  and  $\pi_t$  equal the proportion of responders for the control arm and the experimental treatment arm, respectively, then the null hypothesis of inferiority can be stated as:

$$H_0: \pi_t \leq \pi_c - 0.20.$$

The alternative hypothesis of non-inferiority can then be stated as:

$$H_A: \pi_t > \pi_c - 0.20.$$

The hypothesis of non-inferiority would be concluded if the null hypothesis can be rejected at the 5% level. In order to test this hypothesis the Applicant computed the standard Wald confidence interval for the risk difference. If the lower bound of the 95% confidence interval for the difference between Probuphine and sublingual buprenorphine was greater than -0.20 then non-inferiority would be established.

Dr. Skeete's medical review provides considerable detail concerning how the Sponsor determined the definition of responder and the appropriate non-inferiority margin to test. Briefly, based on (limited) published information on the expected rate of non-relapse after discontinuation of long-term methadone or buprenorphine treatment, and a (small) survey of a convenience sample of addiction treatment providers, Braeburn concluded that the expected rate of non-relapse in patients discontinued from treatment would be in the range of 25%. Assuming that stable patients remaining on their prior treatment would continue to be stable, a non-inferiority margin of 20% was selected as it would preserve greater than 70% of the estimated effect size. This was considered clinically significant by the Sponsor. Notably, the assumption of 100% response in patients continued on treatment-as-usual was not consistent with the observed data, so these assumptions required examination as discussed below.

The number of "allowable" positive urine toxicology results was derived primarily from the clinician survey. As discussed in detail in Dr. Skeete's review, 18 clinicians were surveyed and asked how often they expected the average stable patient in their practice to test positive for opioids over a 6-month period and what they would consider maximum reasonable change in a stable patient's test results for the patient to still be considered stable (presented as multiple choice). Ten endorsed that a maximum of 1 of 6 positives over a six-month period would be acceptable but six endorsed lower limits. Braeburn calculated a mean recommendation for the number of acceptable positives and for the maximum allowable change and concluded that two positives within six months should be considered consistent with ongoing stability. This was operationalized as two *months* with positive tests or self-reports, so four tests were possible if a patient presented a positive test at a scheduled visit and a random visit in the same month. Generally speaking, the experts at the Advisory Committee meeting did not dispute the possibility

that a stable patient might, from time to time, present a positive sample; however, they were not comfortable with applying this definition and thought that it set a precedent of defining a responder too loosely. Particularly considering the infrequency of the sample collection and their scheduled nature, the sensitivity of the sampling scheme was a concern. In the analyses below, other definitions were applied.

Regarding imputation of results for missing urine toxicology samples, Braeburn argued that the customary approach of assuming that missing samples would be positive would be inappropriate for this study. First, because stable patients might miss visits for reasons other than relapse, and second, because that approach would tend to bias the results in favor of the group with the smaller dropout rate (which, indeed, did occur in the original studies in which placebo patients were discontinued per protocol). Therefore Braeburn proposed imputing missing urines using the average of the within-subject proportion of opioid positive samples. The primary analysis was then made more conservative by applying a 20% relative penalty to the higher of the two positive rates to impute missing data in the Probuphine treatment arm. For example, if the imputation for sublingual buprenorphine used a 15% positive rate then the rate for Probuphine would be 18%. Random samples were assumed to be negative if the patient had provided a negative sample in the same month. In discussions at the Advisory Committee meeting, however, the addiction treatment experts were in general agreement that (particularly with once-monthly, scheduled sampling), a patient failing to present for a urine toxicology test – particularly a random visit—should be regarded as a “red flag,” and that the assumption of a positive test was, if not statistically conservative, clinically realistic. Furthermore, the observed data confirmed that even in this population of presumably stable patients, 20% of the submitted samples were positive.

The use of supplemental doses of sublingual buprenorphine was not addressed at all in the protocol-specified responder definition. In the analyses below, the review team took the position that Probuphine, which cannot be titrated, might provide too low a dose of buprenorphine for some patients. Therefore, the need for supplemental buprenorphine in Probuphine treated patients could be seen as an indicator that the dose was not adequate for that patient. Notwithstanding the actual clinical outcome for the patient, who may have been held in a state of clinical stability through the provision of supplemental doses, any patient needing more than minimal supplemental doses could not be viewed as responding to Probuphine, per se. Therefore, such patients are adjudicated as non-responders in the reviewer’s analyses, and various approaches to this issue were taken on an exploratory basis. On the other hand, treatment as usual with sublingual buprenorphine includes dose adjustments as clinically-indicated, so use of supplemental doses would not be considered an indicator of lack of treatment response in patients treated with sublingual buprenorphine.

The protocol defined several secondary efficacy endpoints, including VAS measures of desire/need to use and Clinical Opiate Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS) measures of withdrawal. However, since no adjustments for multiplicity were considered, Dr. Travis did not evaluate these endpoints in his review and recommended they not be described in labeling.

It should be noted that, customarily, non-inferiority studies require that a treatment have a known and consistent effect in order to support the assumptions used to choose the non-inferiority margin. Therefore, historically, the Division has been reluctant to agree to non-inferiority designs for trials of drugs intended to treat opioid dependence because of the lack of consistent information about the expected response rate, related to the heterogeneity of response definitions, study designs, populations, and treatments. However, some flexibility was deemed appropriate because the Division recognized the potential public health benefit of an implantable formulation of buprenorphine in light of a growing problem of misuse, abuse, and accidental exposure of buprenorphine.

Because of these uncertainties regarding a non-inferiority design in this setting, the Division declined, when asked, to confirm that a finding that the study met its proposed primary endpoint, augmented by the secondary endpoints, would necessarily provide the adequate evidence necessary to support a label for “the treatment of patients stabilized on sublingual buprenorphine at doses 8 mg or less with four Probuphine subdermal implants.” The Sponsor was informed that this would be a matter for review, and that the reviewers would quantitatively and qualitatively assess the analysis of the primary endpoint and the clinical meaningfulness of the trial findings to make such a determination.

## 7.4 Results

The results of the Applicant’s primary analysis are shown in the table below from Dr. Travis’ review. The Applicant found that the lower bound of the 95% confidence interval of the difference in the proportion of responders was greater than -0.20 and hence concluded that Probuphine was non-inferior to sublingual buprenorphine. The Applicant also found a p-value for superiority of 0.03 and so concluded that Probuphine was superior to sublingual buprenorphine. However, there were several issues with the primary analysis which led to the reviewers disagreeing with this analysis and the conclusion of superiority.

### Applicant's Primary Analysis

Category	Probuphine n (%)	SL BPN n (%)	Proportion Difference (95% CI) Probuphine – SL BPN	Superiority P-Value (2-Sided)
N	84	89		
Responder	81 (96%)	78 (88%)	0.09 ( <b>0.01</b> , 0.17)	0.03
Non-Responder	3 (4%)	11 (12%)		

Source: Statistics Review, Table 4

The reviewer’s concerns included issues related to the analysis population, the procedure for making assumptions about missing urine test results, the interpretation of the implications of supplemental sublingual buprenorphine use, and the number of positive tests that defined a responder. These are discussed in depth in the statistical and clinical

reviews and are summarized here. The impact of different approaches to these issues is then illustrated in a series of response rate calculations undertaken by Dr. Travis.

#### *Analysis Population*

The first concern noted was the exclusion of four subjects who were randomized into the study but excluded from the analysis population (one subject randomized to sublingual buprenorphine and three subjects randomized to Probuphine). The subject that was randomized to sublingual buprenorphine did not receive study medication; therefore, as noted above, the team agreed that it is appropriate to exclude this subject from the analysis population. However, as discussed above, the three subjects that were excluded from the Probuphine arm did receive study medication and should not have been excluded from the analysis population; it is clinically reasonable to assume they are non-responders.

#### *Missing Urine Toxicology Results*

There were approximately twice as many positive samples provided by subjects in the sublingual buprenorphine treatment as for those in the Probuphine treatment arm. There were however, approximately twice as many samples that were either missed or were not conclusively analyzed for the Probuphine arm compared to the sublingual buprenorphine arm. Therefore, the procedures for imputing missing data are important to examine.

Dr. Travis noted concerns about the protocol's missing data handling procedures. First, missing data was only imputed if all samples were missing for a particular month. For example, if a random sample was scheduled and missed for a particular month and the sample collected during their monthly visit was found to be negative then no imputation was performed. Second, illicit opioid usage was assumed to be equally likely for missing and observed data. As the experts in attendance at the Advisory Committee meeting confirmed, patients have often become adept at concealing use by avoiding urine testing when testing might detect illicit use; consequently, the fact of missing a test has clinical relevance and it is not reasonable to assume that missing and collected tests have an equal probability of being positive. Dr. Travis observed that the missing data imputation scheme allowed for the possibility of classifying a subject who provided absolutely no efficacy data in the study as a responder. For example, the primary analysis used a positive rate of approximately 13% which gives a 97% probability that someone who provided absolutely no efficacy data would be classified as a responder. This does not seem clinically reasonable, and the review team applied a more common approach, endorsed by the Advisory Committee, of imputing a positive result when a test was missing.

Additionally, there were a number of issues with inconclusive urine samples that were collected but could not be completely analyzed for various issues, such as the site not submitting them to the lab promptly. The Advisory Committee felt it was appropriate to adjudicate samples that were provided, but not completely analyzed, as negative if all analytes that could be analyzed were negative and the patient provided a negative self-report.

The table below from Dr. Travis' review summarizes the frequency of missing, inconclusive, and positive tests. Approximately half of the randomized subjects completed the study and provided ten negative urine samples.

**Summary of Urine Toxicology Samples**

Issue	Probupine n (%)	SL BPN n (%)	Total n (%)
N	87	89	176
No Issues	46 (53%)	49 (55%)	95 (54%)
Missing Data	31 (36%)	22 (25%)	53 (30%)
Missed Sample	11 (13%)	11 (12%)	22 (13%)
Incomplete Result	22 (25%)	16 (18%)	38 (22%)
Rescue Use	15 (17%)	13 (15%)	28 (16%)
Positive Test	10 (12%)	25 (28%)	35 (20%)

Source: Statistical Review, Table 7

The graphic below, created by Dr. Travis, illustrates the pattern of test results over time for each patient. Each row in the figure shows the results for a single subject. The green crosses represent negative tests, the orange squares represent positive tests, and the blue circles represent either samples that were not provided or were not completely analyzable. Black squares mark the final visit for subjects who were non-completers. Subjects above the black horizontal line provided at least three positive samples.

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*Use of Supplemental Sublingual Buprenorphine*

It was anticipated that since the subjects who were to be enrolled in this study were clinically stable and on a stable dose of sublingual buprenorphine with no dose adjustments for at least the last three months prior to randomization the need for supplemental buprenorphine would be minimal. However, supplemental buprenorphine was required by approximately 16% of the subjects in the study. Similar numbers of subjects in both treatment arms received supplemental buprenorphine. However, when considering number of tablets dispensed, subjects in the Probupine arm were dispensed approximately 70% more supplemental tablets during the study than subjects in the sublingual buprenorphine arm. Dr. Travis constructed the graphic below which shows how long the patient could have been using supplemental doses across the study. Each row in the figure shows the results for a single subject; only subjects who used supplemental doses are shown. The green crosses represent negative toxicology test results, the orange squares represent positive or missing tests, and the blue circles represent days when supplemental medication was dispensed. The length of the line or duration was calculated by assuming that a subject required a single additional sublingual buprenorphine tablet per day unless otherwise specified.

## Supplemental Buprenorphine Use

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Note: Black squares indicate subjects who did not provide all ten urine samples.  
Source: Statistics Review, Figure 2

This shows that there were a number of subjects who received supplemental medication for the majority of the study. This level of use was not anticipated and hence was not considered by the protocol definition of a responder. Additional analyses were conducted where subjects who required any supplemental medication were considered to be non-responders. The graphic below, constructed by Dr. Travis, illustrates the effect of considering supplemental medication in the responder definition. Patients above the horizontal line would be considered non-responders if missing tests are imputed as positive and supplemental medication use is considered non-response.

## Missing Urine Tests Imputed as Positive and Use of Rescue Considered Non-Response

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Black squares indicate subjects who did not provide all ten urine samples  
Source: Statistical Review, Figure 3

Additionally, in response to suggestions from the Advisory Committee, analyses were conducted in which some minimal use could be permitted shortly after Probupine was inserted or at the end of the dosing period, to reflect possible individual differences in attaining or maintaining steady state levels. Results are shown below.

As noted above, the need for supplemental buprenorphine in Probupine treated patients could be seen as an indicator that the dose was not adequate for that patient. On the other hand, treatment as usual with sublingual buprenorphine includes dose adjustments as clinically-indicated, so use of supplemental doses would not be considered an indicator of lack of treatment response in patients treated with sublingual buprenorphine who otherwise gave no evidence of relapse. Therefore, analyses were conducted in which supplemental use was taken into consideration in the response definition only for the Probupine arm. Results are shown below.

### ***Reviewers' Analyses***

To explore the effects of the above issues on the relative response rates, Dr. Travis conducted a number of sensitivity analyses. The results of all the analyses conducted are displayed in the table below. All but the first (the Applicant's) use the revised analysis

population, which includes the three patients who received Probuphine but provided no efficacy data. They are counted as non-responders.

All but one of these analyses found Probuphine to be non-inferior to sublingual buprenorphine with the Applicant’s pre-specified margin of -20%. Superiority of Probuphine to sublingual buprenorphine was not demonstrated. Moreover, the claimed response rate of 96% for Probuphine over-estimates the efficacy of the product—so too does the 88% response rate for treatment as usual over-estimate the treatment response for usual care. The most reasonable scenario, based on Advisory Committee input, seems to be the last row of the table, in which patients are counted as treatment responders if they have no completely missing samples or positive tests, and, for Probuphine-treated patients, if they did not require supplemental medication outside of the first and last months.

### Results of Additional Analyses

Analysis Population	Number of Allowed Positive Months	Value Imputed for Missing Data	Value Imputed for Incomplete Samples	Rescue Use Permitted		PRO n (%)	SL BPN n (%)	Lower Bound (95% CI)
				PRO	SL BPN			
Applicant’s	2	Applicant’s	Negative	Yes	Yes	81 (96%)	78 (88%)	0.01
Revised	2	Applicant’s	Negative	Yes	Yes	81 (93%)	78 (88%)	-0.03
Revised	2	Positive	Negative	Yes	Yes	78 (90%)	76 (85%)	-0.06
Revised	2	Positive	Positive	Yes	Yes	73 (84%)	70 (79%)	-0.06
Revised	2	Positive	Negative	No	No	63 (72%)	65 (73%)	-0.14
Revised	2	Positive	Positive	No	No	58 (67%)	59 (66%)	-0.14
Revised	2	Positive	Negative	No	Yes	63 (72%)	76 (85%)	-0.25
Revised	2	Positive	Negative	Month 1 & 6	Yes	66 (76%)	76 (85%)	-0.21
Revised	0	Positive	Negative	Month 1 & 6	Month 1 & 6	57 (66%)	48 (54%)	-0.03
Revised	0	Positive	Negative	Month 1 & 6	Yes	57 (66%)	57 (64%)	-0.13

Abbreviations: PRO, Probuphine

Source: Statistical Review, Table 13

### Explorations of Subgroups

Dr. Travis also explored whether the response to treatment varied based on the patient’s pre-study medication (e.g., tablet or film—because the plasma level from 8 mg/day film is actually higher than from 8 mg/day tablet), pre-study dose, weight, BMI, and sex. Not all of these analyses are included in his review, but no consistent differences in response

to treatment were noted. Patients on higher doses had an overall lower response rate than those on lower doses, but there was no differential effect of treatment.

*Additional Analyses*

In addition to the above analyses, I asked Dr. Travis to undertake some additional analyses to better understand the impact of some of the assumptions in the analyses. In each of the analyses below, the analysis population is the review team’s preferred, the imputation strategy assumes that a completely missing sample is positive but an incompletely analyzed or inconclusive sample is negative (if otherwise negative).

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Additional Efficacy Explorations

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Number of Allowed Positive Months	Rescue Use Permitted		PRO n (%)	SL BPN n (%)	Lower Bound (95% CI)
	PRO	SL BPN			
0	Yes	Yes	66 (76%)	57 (64%)	-0.02
2	Yes	Yes	78 (90%)	76 (85%)	-0.06
0	Month 1 & 6	Yes	57 (66%)	57 (64%)	-0.13
2	Month 1 & 6	Yes	66 (76%)	76 (85%)	-0.21
0	No	Yes	55 (63%)	57 (64%)	-0.15
2	No	Yes	63 (72%)	76 (85%)	-0.25

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Source: Prepared by author from analyses performed by statistical reviewer

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To address the possibility that the “no positives” responder definition is “too stringent,” I juxtaposed the analytic approaches allowing either zero or two positives. While the responder rate for both arms is understandably higher in the “two positives allowed” analyses, this approach does not seem to be a better way to elucidate the treatment effect.

I also thought it would be helpful to examine the scenario in which supplemental buprenorphine was not considered indicative of non-response unless there were other indicators (positive or missing samples or self-report). This represents the best-case scenario, when Probuphine-treated patients are appropriately monitored by careful clinicians who provide supplemental medication when clinically-indicated. This type of

clinical care was provided in the trial and the label will state that it *should* be provided after approval. It is reasonable to assume that the convenience of a six-month implant could result in less careful monitoring on the part of the clinician or less adherence with monthly visits on the part of the patient. However, if this type of care is provided, we can see that Probuphine with careful monitoring and as-needed rescue is *clearly* no less effective than treatment as usual. The first line of the table below illustrates the responder rates and shows that the lower bound of the 95% confidence interval is -0.02, indicating that we can be confident these treatments differ very little.

In the worst case scenario, a patient would not be seen between insertions and removals, and no rescue could be provided. The scenario in which all rescue is counted as non-response for Probuphine patients (but not for treatment as usual) yields lower responder rate for Probuphine but the lower bound of the confidence interval is -0.15, still meeting the non-inferiority criteria, although we are less confident of the fraction of effect size preserved. Dr. Travis pointed out that for the scenario between the best and worst cases, the lower bound of the 95% confidence interval was 12.6%, which based on his calculations using the assumptions about the active and placebo effect sizes, would not allow us to conclude non-inferiority if preservation of 70% is of clinical importance. He notes that “if the requirement were relaxed to around 60% then non-inferiority could be concluded.”

Given that the intention is for patients to receive care much closer to the best case than to the worst case, these analyses support the conclusion that Probuphine is not unacceptably less effective than usual care when patients are appropriately monitored and supported. This underscores that Probuphine is not a stand-alone treatment and that it should be offered in conjunction with the same clinical supervision and behavioral support as usual treatment.

## **7.5 Discussion/Conclusion**

This study enrolled a specific subset of patients in buprenorphine maintenance treatment for opioid dependence—those who are, essentially, in remission and require relatively low doses of medication to maintain this status. Among these patients are some who would prefer the convenience and privacy of an implantable form of medication. Although Probuphine matches only the *trough* buprenorphine blood levels provided by 8 mg/day sublingual buprenorphine tablets (specifically Suboxone or Subutex; there are now other tablets with different bioavailability), it appears that for many patients, this is adequate to meet their requirements. There was no clear indication that it was less effective for patients on higher doses or on more bioavailable products. Some patients do require supplemental dosing and therefore the promise of Probuphine as a way to overcome geographical and logistical barriers to treatment access seems limited; patients will still require regular clinical monitoring.

Taken together with previous Agency findings of efficacy for sublingual buprenorphine, this study provides evidence of efficacy for Probuphine in this limited population already responsive to buprenorphine.

## 11. Safety

Safety data derive from three controlled clinical trials, two open-label extensions, and two clinical pharmacology studies. Overall, 370 individuals were exposed to Probuphine treatment in clinical pharmacology studies (21), controlled trials (309) and direct-enrollment into open-label extensions (40). Of these most received one course of treatment (up to 24 weeks) and 107 received a second course of treatment (up to a total of 48 weeks). The Sponsor tabulates that 151 patients were exposed for 6 months or more and 85 patients were exposed for a year. The basic design of the studies included in the safety database are summarized in the table below.

**Table of Probupine Studies/Clinical Trials**

Study No. & Design	Study Treatments	Population	Duration	Location/ # of Centers
<p>PRO-814  P3, DB, double-dummy, active-controlled (SL buprenorphine tablets), non-inferiority trial</p> <p>First subject enrolled: June 26, 2014  Last subject completed: May 18, 2015</p>	<p><u>Group A:</u>  SL buprenorphine tablets 8 mg/day or less &amp; 4 placebo implants</p> <p><u>Group B:</u>  4 Probuphine subdermal implants &amp; placebo SL tablets</p> <p><u>All:</u> supplemental SL BPN as needed</p>	<p>N=177 opioid-dependent subjects who were clinically stable on 8 mg/day or less of a buprenorphine-containing transmucosal products</p> <ul style="list-style-type: none"> <li>• SL BPN n = 89</li> <li>• Probuphine n=87</li> </ul>	24 weeks	US 21 centers
<p>PRO-805  P3, DB, R, PC trial with 2:1 randomization Probuphine to placebo</p> <p>Initiated: Apr 2, 2007  Completed: Jun 19, 2008</p>	<p>4 Probuphine subdermal implants (80 mg buprenorphine per implant) (5 if protocol-specified criteria met)</p> <p>4 Placebo subdermal implants (5 if protocol-specified criteria met)</p> <p>All: supplemental SL BPN as needed</p>	<p>N = 163 opioid-dependent subjects</p> <ul style="list-style-type: none"> <li>• Probuphine: n= 108</li> <li>• Placebo: n=55</li> </ul>	Single dose; 24 weeks	US 23 centers
<p>PRO-806  P3, DB, R, PC and OL AC trial with 2:1:2 randomization Probuphine, placebo, SL BPN</p> <p>Initiated: Apr 22, 2010  Completed: May 12, 2011</p>	<p>4 Probuphine subdermal implants (5 if protocol-specified criteria met)</p> <p>4 Placebo subdermal implants (5 if protocol-specified criteria met)</p> <p>SL BPN 12–16 mg once daily</p> <p>All: SL BPN as needed</p>	<p>N = 301 opioid-dependent subjects (301 enrolled; 287 received study drug)</p> <ul style="list-style-type: none"> <li>• Probuphine: n= 114</li> <li>• Placebo 4 implants: n=54</li> <li>• SL BPN n=119</li> </ul>	Single dose; 24 weeks	US 20 centers
<p>PRO-807  (PRO-805 extension) Open-label;</p>	<p>4 Probuphine subdermal implants (5 if protocol-specified criteria met)</p>	<p>N = 62 opioid-dependent subjects</p> <p>Median age: 37 range (20 – 62)  Gender: 71% male</p>	Single dose; 24 weeks	US 15 centers

<b>Study No. &amp; Design</b>	<b>Study Treatments</b>	<b>Population</b>	<b>Duration</b>	<b>Location/ # of Centers</b>
Initiated: Mar 20, 2008 Completed: Feb 19, 2009	All: SL BPN as needed			
PRO-811 (PRO-806 extension) Open-label;  Initiated: Nov 29, 2010 Completed: Nov 30, 2011	4 Probuphine subdermal implants (5 if protocol-specified criteria met)  All: SL BPN as needed	N = 85 opioid-dependent subjects	Single dose; 24 weeks	US 18 centers
TTP-400-02-01 Open label, pharmacokinetic study  Initiated: Jun 3, 2003 Completed: Apr 29, 2004	2 Probuphine subdermal implants (83 mg buprenorphine per implant)	N = 12 opioid-dependent subjects who were in a maintenance pgm with SL BPN <ul style="list-style-type: none"> <li>• 2 Probuphine implants n=6</li> <li>• 4 Probuphine implants n=6</li> </ul> All: SL BPN as needed  Median age: 35 (23 – 48) Gender: 92% male	Single dose; 24 weeks	AU 3 centers
PRO-810 Open-label, single crossover assessing bioavailability of Probuphine implants versus sublingual buprenorphine tablet  Initiated: Sep 29, 2008 Completed: Dec 23, 2008	16 mg SL buprenorphine; cross-over to 4 Probuphine implants (80 mg buprenorphine per implant, single dose, subdermal insertion)  All subjects: sublingual buprenorphine as needed	N = 9 opioid-dependent subjects  Median age: 44 (25 – 63) Gender: 67% male	Single dose 8 weeks	US 1 center

Because the systemic safety of buprenorphine is fairly well-characterized, the size of the safety database seems adequate to identify systemic safety concerns related to Probuphine and to provide a characterization of the local tolerability of the implant.

The safety database informing an understanding of the risks of the insertion and removal procedures also includes patients who underwent the procedures for insertion and removal of placebo implants. A total of 654 patients underwent at least one insertion procedure. The safety experience in the initial trials in the program indicated that modifications to the procedures were needed to improve procedural safety. Therefore, the size of the safety database collected before modifications to the equipment and procedures do not provide insight into the risks of the current procedures; unfortunately, the Sponsor did not carefully capture the numbers of patients enrolled before and after these changes. Suffice it to say, the numbers of patients who underwent insertions and removals according to the current procedures is not extensive and the understanding of the potential risks of the procedures must be based, in part, on the risks that emerged with Norplant. Further post-marketing collection of information on the procedures and outcomes will be helpful to augment understanding of the risks.

The major safety findings are summarized below. In comparing rates across arms, it is important to note that patients designated as being in a “placebo” arm often received sublingual buprenorphine for part of the time they were participating, making a true placebo comparison difficult. Additionally, in the original clinical trials, many placebo patients discontinued early in the trials, giving less opportunity to report adverse events. Patients designated as “SL buprenorphine” were enrolled in the open-label comparator arm in Study 806 (no implants) or the double-dummy arm in Study 814 (placebo implants). Patients in the Probuphine arms of the controlled trials were treated with 4 implants initially; some patients in Studies 805 and 806 had a 5<sup>th</sup> implant added.

There were no deaths that occurred among subjects on Probuphine in any trial in the clinical development program. One death occurred in a patient in the open-label sublingual buprenorphine arm in PRO-806, attributed to accidental heroin overdose, three days after the subject discontinued study participation at her own request.

Nonfatal serious adverse events occurred in ten subjects on Probuphine (3%), 7 subjects on placebo (6%), and nine subjects on sublingual buprenorphine (4%) in the pooled double-blind studies. Four SAEs were reported in the open-label extension studies, and one in a clinical pharmacology study.

The SAEs primarily included complications of drug addiction (hospitalization for relapse, complicated opiate withdrawal, abscesses and other infections). Depression and suicidal thoughts and actions were also reported in both Probuphine-treated and placebo-treated patients.

One SAE related to the implant site was reported in a patient who received a placebo implant. However, because the risks of implantation are likely to be related to the procedure, and not to the drug, this event is of concern even in a placebo-treated patient. It occurred in the first clinical trial, before improvements were made to the equipment and procedures.

Discontinuations that were reported as being due to adverse events were infrequent across all the treatment arms in the studies. In the double-blind studies, adverse events leading to discontinuation of treatment and withdrawal from the trial occurred in 7 subjects on Probuphine (3%), 2 subjects on placebo (2%), and five subjects on open-label sublingual buprenorphine (4%).

In the pooled open-label extension studies, these occurred among three subjects, all of whom were on Probuphine in the double-blind studies and continued on Probuphine in the open-label studies. A single subject among the participants in the clinical pharmacology studies discontinued due to adverse events.

Discontinuations due to implant-site related AEs occurred in 3 patients in Study PRO-805 (all on Probuphine), and two in PRO-807 (the follow-on to PRO-805). These studies predate the improvements to the equipment and techniques. No placebo-treated patients discontinued due to implant-site AEs. Discontinuations due to hepatic enzyme abnormalities occurred in 3 patients treated with Probuphine (pooled) and one patient treated with sublingual buprenorphine. The reason for discontinuation for one placebo-treated patient was “worsening Hepatitis C.”

## **7.1 Significant Adverse Events**

### **7.1.1 Implant Site Adverse Effects and Complications of Insertion and Removal**

Because the systemic safety profile of buprenorphine has been characterized, one of the most important issues in the review of this application was to gain an understanding of the risks of the surgical procedures for insertion and removal of the Probuphine implants, and any risks associated with having the implants indwelling in the patient's arm for six months. Diagrams illustrating the procedures are shown in Appendix A. The procedure illustrated employs the final version of the equipment and the technique Braeburn recommends for use with Probuphine. However, this version of the equipment and technique were used only in the latter half of the development program.

For Studies PRO-805, the first Phase 3 double-blind trial, and PRO-807, the follow-on extension, a blunt applicator was used for insertion. The standard removal technique used for Norplant removals, and a straight removal clamp, were employed in the removal procedures. This procedure involves attempting to remove the implants by pulling on the proximal end through an incision made at the insertion site. This technique reportedly was difficult to accomplish and implant breakage was a frequent issue. The Probuphine implants are evidently less flexible than Norplant implants. One of the implanting clinicians proposed modifications to the equipment and procedures that were implemented in the later studies.

For Studies PRO-806 and PRO-811, a beveled applicator was used for the insertion, and the "U" technique and a modified vasectomy clamp were used for implant removal. This procedure involves making an incision between the implants, parallel to their course, performing blunt dissection with an instrument, pushing the implants into the incision, and removing them by grasping them in the middle. This technique was reportedly proposed for use with Norplant by some clinicians shortly before Norplant was removed from the U.S. market, and is therefore not familiar to most individuals working with implantable contraceptives. Removal is reportedly the more difficult procedure to perform with implantable contraceptives, although the difficulties in removal are often attributable to errors in insertion, with implants being placed too deeply. Twenty-two different implanting physicians participated in Study PRO-806, and 20 (many of them the same individuals) performed insertions and removals in Study 814, so experience with the techniques and equipment now recommended is limited to this small sample of providers (and any additional individuals, if any, who may have provided the service in the open-label follow-on studies).

Another aspect contributing to improvement in technique was the training method. In Studies PRO-805 and PRO-807, implanting physicians were provided with an instructional DVD, self-guided written instructions, with on-site training by the implant medical monitor provided if needed. For Studies 806 and 811, training components included a training manual, a training video, a half-day training class, and a hands-on training using a "meat model."

In the efficacy studies and open-label extensions, 654 patients underwent the surgical procedure to have Probuphine or placebo implants inserted. The vast majority, though not all, of these patients also had removal procedures performed at the end of the treatment cycle to have the implants removed. The majority of procedures were performed by Family Medicine physicians and OB/Gyns.

During the Probuphine clinical trials, the implant site was to be evaluated at each clinic visit. The implant site was to be visually inspected for evidence of erythema, edema, itching, pain, infection, bleeding, abnormal healing, and any other abnormalities. According to information obtained during OSI inspection of the initial studies, “normal edema or other conditions after a surgical incision are expected and they were instructed by the Sponsor to report these only if the conditions were excessive and not a normal result of a surgical incision.” This implies that a higher rate of edema, pain, or redness may actually have occurred, and that the events in the table represent only those which struck the investigator as “excessive.” Treatment-emergent implant-site AEs were tabulated by treatment arm, although it may be noted that even events occurring at similar rates between the Probuphine group and the placebo group are of interest in identifying procedure-related complaints.

Surgically-trained obstetrician/gynecologists from the Division of Bone, Reproductive, and Urologic Products (DBRUP) were consulted to provide an expert assessment of the safety data on the insertion and removal procedures and to help inform aspects of the training and certification program to be required under the REMS.

To assess procedure-related safety, DBRUP pooled procedures performed across five trials – three efficacy trials (805, 806, 814) and two extension trials (807 and 811) in which subjects received a second treatment cycle. Cumulative exposure to the insertion/removal procedures among subjects who participated in these five trials is shown in the table below:

**Pooled Extent of Exposure to Procedures**

Number of subjects	Probuphine implants	Placebo implants	Total
Study 805	108	55	163
Study 806	114	54	168
Study 814	87	89	176
Study 807	62	N/A	62
Study 811	85	N/A	85
	456	198	654

Source: Extracted from Table 5, disposition of Subjects by Study, pages 31-32 of 153, ISS Addendum, Module 5.3.5.3; NDA 204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body PRO-807, Module 5.3.5.2; 204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body, Module 5.3.5.2204442/0000: Table 10-1Disposition of Subjects (safety population) Clinical Study Report, page 65, Study Report Body PRO-811, Module 5.3.5.2, page 65.

As expected, commonly reported procedure-related adverse events (AEs) were mild and self-limiting, such as pain, pruritis, erythema at the incision/implant site. Procedure-related AEs of special interest are summarized below. Compared to contraceptive implants, higher incidences of bleeding (10.9%), complicated removals (3.2%), and implant site infection (4.0%) were noted in the Probuphine trials.

Of note, DBRUP disagreed with the Applicant’s categorization of AEs associated with “complication of device removal.” In the Applicant’s individual study reports and the integrated safety summary, subjects who required a second attempt to remove all implants were not deemed to have “complicated removal.” DBRUP considered a failure to remove all implants during the first attempt – thus necessitating imaging studies to locate all implants and a second removal attempt – to be a complication of the initial implant removal attempt.

**Key Procedure-Related Adverse Events by Trial**

	Efficacy Studies			Extension Studies		Total # Events of Special Interest	AE incidence (% of Total # Procedures Performed, 654)
	Study 805 (N = 163)	Study 806 (N = 168)	Study 814 (N = 176)	Study 807 (N = 62)	Study 811 (N = 85)		
Implant expulsion <sup>‡</sup>	4 (2.5%)	1 (0.6%)	1 (0.6%)	2 (4.8%)	0	8	1.2%
Implant site infection*	9 (5.5%)	3 (1.8%)	6 (3.4%)	4 (6.4%)	4 (4.7%)	26	4.0%
Wound complications <sup>∞</sup>	4 (2.5%)	2 (1.2%)	2 (1.1%)	1 (1.6%)	1 (1.1%)	10	1.5%
Complicated removal or requiring 2 <sup>nd</sup> attempt	15 (9.2%)	0	7 (4%)	3 (4.8%)	2 (2.3%)	27	4.1%
Bleeding**	30 (18.4%)	19 (11.3%)	1 (0.6%)	16 (25.8%)	5 (5.9%)	71	10.9%

Source: DBRUP consult

- For Study 805: extracted from Table 15/page 78 of Study Report, Table 2 and written response to Information Request dated 2/28/13
- For Study 806: extracted from Table 14.3.1.2 of Study Report, response to Information Request dated 2/28/13
- For Study 814: extracted from Table 30 of Study Report
- For Study 807: extracted from Table 14.3.1.2.1 of Study Report, response to Information Request dated 2/28/13
- For Study 811: extracted from Table 14.3.1.2 of Study Report, response to Information Request dated 2/28/13
- For Study 814: extracted from Table 30 of Study Report

<sup>‡</sup> including implant expulsion and implant protrusion

\*including AE terms of cellulitis, purulent discharge, implant site pruritus, incision site infection, and wound infection, implant site abscess, and subcutaneous abscess

<sup>∞</sup> including AE terms of incision site necrosis, wound dehiscence, incision site complication, postoperative wound complication, suture-related complication, wound complication, impaired healing

\*\*including AE terms of implant site bleeding/hematoma/hemorrhage, and incision site hemorrhage

DBRUP's review did not identify any long-term complications such as permanent disability due to nerve damage; it would be unlikely for such events to be observed in a clinical program of this size.

There were more difficulties with the removals than with the insertions. A second attempt was required to remove the implants in a relatively high number of patients, given the small numbers of procedures performed. Although most of these complications occurred in studies using the original insertion tool and removal procedures, difficulties were also encountered in Studies 811 and 814. Ultrasound was required for many of these cases, and it is noted that a specialized ultrasound not available in physicians' offices must be used for location of Probupine implants. They are not radio-opaque. One patient required general anesthesia to complete removal.

There is a potential for the buprenorphine in Probupine to be a target of abuse, misuse, or diversion or to accidentally come into contact with non-tolerant individuals if the implants come out of the skin. In some patients, the Probupine rods worked their way through the skin and either protruded partially (extrusion) or fell out (or were pulled out) altogether (expulsion). Seven patients (six Probupine, one placebo) had events of this nature. One patient (Probupine) had multiple events of implant extrusion and expulsion and had to have her implants replaced on four occasions. All but two of these events occurred in studies using the original insertion tool and training procedures. One patient in the most recent trial developed cellulitis at the implant site on Day 5, which was treated with oral antibiotics and reported as resolved on Day 18. On Day 30, protrusion of 1 rod without complete expulsion was observed; the following day, the subject had his 4 implants removed from the left arm and 4 new placebo implants were inserted in his right arm. Although these events are not common, they did occur and are thought to be more likely in the setting of improper insertion technique.

The overall experience with insertion and removal of Probupine using the current equipment and procedures is limited to roughly 400 insertions and removals, by a few dozen practitioners. The OB/Gyn participants in the 2013 Advisory Committee meeting stressed the importance of proper training, and the importance of providers performing procedures frequently and regularly to maintain their skills.

### **7.1.2 Hepatic Effects**

As noted in labeling for Suboxone and Subutex, buprenorphine has been associated with hepatic adverse events, ranging from "transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in

amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary.”

Hepatic enzymes were monitored in the Probuphine clinical program, and the Sponsor identified a number of patients who experienced elevations of ALT and/or ALT to >3x the upper limit of normal and patients who had elevations in total bilirubin. No cases met the “Hy’s Law” criteria. Adverse events of liver injury included cases coded to the term “Hepatitis C.”

### **7.1.3 Cardiac Conduction Effects**

Careful evaluation of the effects of buprenorphine on cardiac conduction was not performed during the development programs for Suboxone or Subutex. Based on *in vitro* binding studies, buprenorphine was not expected to have cardiac conduction effects. However, a thorough QT (TQT) study was performed in a more-recent development program for a transdermal buprenorphine product used for analgesia. This study identified a signal for QT prolongation that was considered to meet the threshold for regulatory concern, but that was not of clear clinical significance. The dose studied was significantly lower than the labeled dose used for sublingual buprenorphine products for treating drug addiction; however, the potential for doses of buprenorphine used for the treatment of opioid dependence to prolong the QT interval has not yet been evaluated in formal thorough QT studies. Such studies have been requested as post-marketing requirements, but have not yet been completed. At the time that the Probuphine trials were being designed, this signal had not been identified and Titan was not asked to include formal evaluation of ECG effects in their program. ECGs were collected in the studies, but were performed at research sites and interpreted on-site by “medically qualified individuals,” and the timing of ECGs relative to the dosing of any supplemental sublingual buprenorphine was not standardized.

QT interval prolongation was observed across all treatment arms in the clinical trial database, suggesting that this is not a phenomenon specific to Probuphine. There was some indication that larger shifts, i.e., changes relative to baseline > 60 msec, were more common with Probuphine. Detailed tables may be found in Dr. Skeete’s review.

## 7.2 Common AEs

The table below, adapted from Dr. Skeete’s review, illustrates common adverse events in the Probuphine studies, which are consistent with the common adverse events seen in current labeling for the sublingual formulations. The table includes any High Level Group Term which was reported in 5% or more of the Probuphine-treated patients and more commonly than in the comparator arm. Preferred terms within that HLGTT reported in at least 1% are shown below the HLGTT. Because the comparator arm includes patients from Study PRO-806 who did not receive implants at all, comparisons of implant-site related observations are not possible and these types of events were omitted from the table. Nausea, vomiting, constipation, headache, fatigue, and depression were somewhat more common in Probuphine-treated patients.

	Probuphine N = 309		Placebo/SL BPN N = 317	
	N	%	N	%
<b>SOC</b>				
HLGT				
<i>PT</i>				
<b>GASTROINTESTINAL DISORDERS</b>				
DENTAL AND GINGIVAL CONDITIONS	16	5%	12	4%
<i>Toothache</i>	14	5%	10	3%
GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	27	9%	23	7%
<i>Constipation</i>	20	6%	9	3%
<i>Diarrhoea</i>	10	3%	13	4%
GASTROINTESTINAL SIGNS AND SYMPTOMS	42	14%	39	12%
<i>Abdominal discomfort</i>	6	2%	6	2%
<i>Abdominal pain upper</i>	10	3%	7	2%
<i>Nausea</i>	20	6%	15	5%
<i>Vomiting</i>	17	6%	11	3%
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>				
GENERAL SYSTEM DISORDERS NEC	40	13%	25	8%
<i>Asthenia</i>	5	2%	1	0%
<i>Fatigue</i>	9	3%	4	1%
<i>Influenza like illness</i>	1	0%	4	1%
<i>Oedema peripheral</i>	6	2%	5	2%
<i>Pain</i>	12	4%	9	3%

	Probuphine N = 309		Placebo/SL BPN N = 317	
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>				
INJURIES NEC	26	8%	24	8%
<i>Contusion</i>	6	2%	9	3%
<i>Excoriation</i>	7	2%	3	1%
<i>Laceration</i>	8	3%	4	1%
<i>Muscle strain</i>	1	0%	4	1%
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>				
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	27	9%	23	7%
<i>Back pain</i>	18	6%	15	5%
<i>Neck pain</i>	4	1%	3	1%
<i>Pain in extremity</i>	9	3%	3	1%
<b>NERVOUS SYSTEM DISORDERS</b>				
HEADACHES	42	14%	35	11%
<i>Headache</i>	39	13%	32	10%
<i>Migraine</i>	5	2%	3	1%
NEUROLOGICAL DISORDERS NEC	26	8%	16	5%
<i>Dizziness</i>	11	4%	7	2%
<i>Somnolence</i>	9	3%	1	0%
<b>PSYCHIATRIC DISORDERS</b>				
DEPRESSED MOOD DISORDERS AND DISTURBANCES	20	6%	13	4%
<i>Depression</i>	20	6%	10	3%
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>				
RESPIRATORY DISORDERS NEC	31	10%	19	6%
<i>Cough</i>	10	3%	4	1%
<i>Oropharyngeal pain</i>	14	5%	10	3%
<i>Rhinorrhoea</i>	4	1%	4	1%
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>				
EPIDERMAL AND DERMAL CONDITIONS	19	6%	10	3%
<i>Rash</i>	6	2%	2	1%

## 12. Advisory Committee Meetings

The original submission of this application was discussed at a meeting of the Psychiatric Drugs Advisory Committee (PDAC) on March 22, 2013. Because of the specific concerns to be discussed, SGEs with a variety of backgrounds were added as voting members for this meeting. These included two Obstetrician/Gynecologists with expertise in the use of implantable contraceptives, three experts with expertise in REMS who serve as members or SGE consultants to the Drug Safety and Risk Management Advisory Committee, a statistician, a patient representative, and four physicians with addiction medicine experience.

Although the majority of the committee voted that efficacy had been demonstrated, that safety had been adequately characterized, and that the risk/benefit ratio favored approval, the comments during the discussion and the breakdown of votes reveal considerable ambivalence about the application. Regarding safety, the discussion focused primarily on issues related to the implantation and removal procedures. The obstetrics/gynecology experts emphasized that removal is the more difficult of the two procedures, but that complications of removal are often attributable to errors in insertion. They observed that the “U-technique” that is to be used in Probuphine removal is not the procedure that was used to remove Norplant; therefore, there is little experience with this procedure even among Norplant-experienced providers. The experts noted that “with the correct training that this is something that you can teach any provider to know how to do....It is really important that the training be adequate and appropriate.” Several commenters noted that “high volume” is important in developing and maintaining expertise in any procedure, and recommended that certification should be reviewed if providers do not do the procedures regularly.

A second PDAC meeting was held on January 12, 2016 to discuss the resubmitted Probuphine application. Two members of the PDAC, both psychiatrists, attended, as well as two additional psychiatrists slated to join the PDAC who were temporary voting members at the time of the meeting. Because of the specific concerns to be discussed, SGEs with a variety of backgrounds were added as voting members for this meeting. These included two statisticians, a patient representative, a consumer representative, an internist, and eight clinicians with addiction medicine experience. Most participants who had attended the meeting to discuss the original application were invited; many were not available. The issues related to understanding the procedures for insertion and removal were not re-visited; therefore, the obstetrics/gynecology experts did not participate in the second meeting.

Key issues to be discussed at the meeting included the Committee’s opinion on

- Whether the target population—stable patients on lower doses of buprenorphine—is a realistic target that would benefit from Probuphine, and how such patients should be selected.
- What the most clinically-relevant considerations would be in defining a responder to treatment, including what conclusions should be drawn when urine

toxicology samples were not provided, when supplemental buprenorphine doses were required, or when patients were lost to follow-up.

- What guidance should be given to the prescriber regarding the use of supplemental buprenorphine doses.
- Whether the proposed training program appeared adequate to ensure the safe insertion and removal of the implants

The Committee, in general, agreed that there were some patients who might be sufficiently stable to benefit from Probuphine, but felt that it would be important to emphasize in labeling that patients should be quite stable clinically. Members agreed that mere time in treatment or time on a particular dose would be insufficient to identify suitable patients, and noted that six months of stability would be a minimum time.

The Applicant and the Agency presented analyses involving a number of different approaches to handling issues that arose in the trial, including patients who were lost to follow-up, use of supplemental doses of buprenorphine, missing or mis-handled urine toxicology samples, and positive urine toxicology findings.

The Committee generally agreed that the consistent finding of non-inferiority across a variety of analyses supported a conclusion that Probuphine was effective in the intended population.

The Committee also generally agreed that the protocol-specified responder definition was not appropriate. They noted that patients who were lost to follow-up should be considered non-responders. They also agreed that use of supplemental buprenorphine in the Probuphine arm on more than one or two occasions could be construed as an indicator that Probuphine was not adequately treating the patient; therefore patients who required ongoing rescue should be adjudicated as non-responders. They recommended that urine samples that were not collected should be assumed to be positive; urine samples that were collected but not analyzed appropriately could be treated as negative if no other indicators of drug use were present. Finally, they generally agreed that, in a stable population, it would be appropriate to adjudicate patients with any evidence of drug use as non-responders.

Regarding the proposed REMS, the Committee expressed some reservations about the adequacy of the training program using a meat model to simulate the insertion procedures, with several participants noting that this might not be sufficient for them as psychiatrists who are not adept at procedures. Some participants advocated for the availability of additional training opportunities or supervised procedures.

In the Open Public Hearing, several patients and family members made general statements about the tragic impacts of opioid addiction and the need for treatments, but, in addition, some patients who participated in the Probuphine studies made remarks specifically supporting the benefit of the treatment paradigm for them, personally. Benefits included reduced concern about small children in the household accidentally ingesting buprenorphine tablets, reduced potential for embarrassment and stigma from

having medication bottles observed, convenience when traveling and reduced burden of having prescriptions filled regularly.

Some other speakers touted the potential for Probuphine to overcome logistical challenges for patients who are geographically remote from treatment providers or who otherwise find it difficult to come for treatment visits. The Committee members, however, specifically objected to the concept of Probuphine reducing the need for regular clinical visits. They stressed that patients treated with Probuphine would still require regular follow-up and office visits to ensure stability and progress towards goals.

The Committee voted 12-5 in favor of approval. Those voting against included one statistician and the patient representative who identified concerns with the wording of the question, and the consumer representative who provided no comment. The acting chairman of the committee voted against approval noting concerns with the Applicant's approach to analyzing the data, and one addiction expert voted against approval noting her concerns about the Applicant's responder definition, the use of rescue medication, and the lack of information about how to continue dosing past four treatment cycles. Those voting yes emphasized the need to clearly define the patient population in terms of stability and to make it clear that regular follow-up visits would still be required; they also supported the Division's approach to revising the responder definition.

### 13. Pediatrics

In the original application, Titan requested a partial waiver for patients ages (b) (4) years of age only, and a deferral for studies in pediatrics ages (b) (4) years. (b) (4)

(b) (4)

DAAAP believed that a full waiver would be more appropriate as the population of treatment-seeking, opioid-dependent adolescents appropriate for maintenance therapy is too low for studies to be feasible. The prevalence of opioid addiction in younger children is not even captured in surveys and is considered to be very low. The exception is that infants exposed to opioids prenatally may be born with a physiologic dependence to opioids. Some medications useful for the treatment of opioid dependence, including buprenorphine, may have utility in this condition. However, Probuphine is not considered an appropriate therapy for infants born with drug dependence due to *in utero* exposure to opioids due to the invasive nature and the inflexibility of dosing.

PeRC agreed to the waiver on 4/3/13.

(b) (4)

## 14. Other Relevant Regulatory Issues

Financial disclosures and DSI audits are described in Dr. Skeete’s review and did not identify barriers to approval.

## 15. Labeling

There were substantial differences between the Sponsor’s proposed labeling and the review team’s recommendations in many sections of labeling. Labeling is still under discussion at this time.

The most significant differences were found in the Indications and Clinical Trials sections. The Sponsor’s proposed labeling (b) (4)

(b) (4) The Sponsor proposed a broadly-worded indication and description of (b) (4) in the clinical trials section (b) (4)

The proposed indication was “PROBUPHINE is indicated for the maintenance treatment of opioid dependence and should be used as part of a complete treatment program to include counseling and psychosocial support. The label did not identify the intended population in the indication section. The Dosage and Administration section noted that Probuphine should only be used in “patients who are opioid tolerant and are currently on a maintenance dose of 8 mg or less of sublingual Subutex or Suboxone equivalent,” which implies that the limitation of use is a safety, rather than efficacy concern. No guidance on patient selection was provided. The review team revised the indications statement, created a section on patient selection, and revised the clinical management section to emphasize the need for ongoing monitoring and a judicious approach to providing supplemental doses.

The Clinical Trials section stated that the (b) (4)  
(b) (4) The Division does not agree that (b) (4)  
and deleted them from the section. (b) (4)

This was also deleted.

Another major difference is that, in several places, the label (b) (4)

Other issues identified include, but are not limited to, the following:

1. The instructions for use stated that Probuphine [REDACTED] his has not been established.
2. A section describing the REMS, including a boxed warning (included when a REMS with ETASU is required) needed to be added.
3. Information taken from the referenced labels and not directly relevant to Probuphine needed to be modified in several parts of labeling, including, e.g., the drug-drug interaction section (as discussed above).
4. The pharmacology-toxicology team, as noted above, determined that additional information from other routes of administration as depicted in the referenced product labels should be included.
5. To conform with ONDQA policy, the implants previously described as 80 mg need to be described as 74.2 mg buprenorphine, equivalent to 80 mg buprenorphine hydrochloride.
6. The pharmacokinetic section required revision to convey clinically relevant comparisons to transmucosal buprenorphine.

## 16. Recommendations/Risk Benefit Assessment

I recommend this application be approved for the indication described above.

### 16.1 Risk Benefit Assessment

Medication-assisted treatment with methadone and buprenorphine are well-established paradigms for the treatment of opioid addiction. Since approval of the first sublingual buprenorphine products in 2002, millions of patients have received treatment with buprenorphine. Clearly, it is not universally effective, but there exists a population of patients who have been successfully-treated and who have attained clinical stability on buprenorphine, and have been tapered to daily doses that are well below the 16 mg/day target dose recommended in the referenced product labeling. These patients may have achieved sufficient stability that they no longer require a dose high enough to block the effects of illicitly-administered opioids, because they are no longer using illicit opioids.

From an efficacy standpoint, the data support the conclusion that Probuphine is not unacceptably less effective in maintaining established stability than treatment-as-usual for this population. The dose will not be sufficient for all patients, but if they are appropriately monitored and provided with supplemental doses judiciously at clinic visits, stability can be maintained roughly as well with Probuphine as with clinically-titrated transmucosal buprenorphine.

For this patient population, Probuphine offers the prospect of increased convenience and discreetness, as well as reduced concerns about the potential for their medication to be lost, stolen, or accidentally ingested. These benefits, which have been articulated as being important to patients, will need to be weighed against the risk of procedural complications based on how salient the benefits are to the individual.

From a public health standpoint, while Probuphine itself is not an abuse-deterrent formulation, the treatment paradigm, in which the product is distributed to the treatment provider and then inserted into the patient's arm, is one that has the potential to reduce abuse, misuse, diversion, and accidental pediatric exposure.

I continue to believe that efficacy was not convincingly demonstrated in the population of new entrants to treatment studied in the original trials and do not believe the product would be effective in those patients.

## **16.2 Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Details of the REMS and the specific materials are still under review by the Division of Risk Management. At this time, the proposed REMS includes a Medication Guide (MG) and elements to assure safe use (ETASU), which include prescriber certification and certification of HCP who dispense (i.e. HCP who Insert/Remove Probuphine).

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse by:

- a) Ensuring that healthcare providers are educated on the following:
  - proper insertion and removal of Probuphine
  - risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of Probuphine
  - risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin
- b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.
- c) Ensuring that Probuphine is administered only to patients informed about the risks of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

This REMS has different goals and features from those in the program for the transmucosal buprenorphine products because the goals of that REMS are to mitigate risks of misuse, abuse, overdose, and accidental exposure primarily via education of patients and providers. Because the risks of misuse, abuse, and accidental exposure with Probuphine are limited to the circumstance when the implant comes out of the skin, the two programs are not parallel.

The REMS creates two possible roles for clinicians—prescribers and inserters/removers. Clinicians could play both roles, but this approach allows for the possibility that an addiction treatment specialist without the necessary experience or expertise in performing sterile procedures could nevertheless prescribe Probuphine and provide the ongoing supervision and treatment to patients who have undergone the insertion procedures provided by a different (certified) clinician. This may allow for greater access to treatment. However, realizing that the ability to recognize and appropriately address insertion-site complications (if only via referral) would be part of the prescriber’s role, the REMS requires that even prescribers who do not intend to perform the procedures must take the live training program in order to gain an understanding of the procedures and their risks. [REDACTED] (b) (4)

[REDACTED]. The live training program includes didactic components and a practicum using a meat model to demonstrate the procedures. Clinicians must demonstrate competency in the live practicum to become certified to perform the procedures.

### **Closed Distribution System**

Under the REMS proposal, only the certified prescriber is able to order and stock Probuphine. A certified HCP who inserts/removes cannot order or stock Probuphine unless they are also a certified prescriber. However, healthcare providers have the option to become dually certified, that is they are able to certify as both a prescriber and a HCP who inserts/removes. It is important to keep in mind that while the REMS does not specifically require a DATA-2000 waiver to become certified, Probuphine will only be shipped to certified prescribers after verifying that the healthcare provider is DATA-2000 waived.

At the time of this writing, it appears that the closed distribution system would need to be accomplished through adding an additional element to assure safe use (ETASU C) to the REMS requiring Probuphine to be inserted or removed only in certain healthcare facilities, specifically facilities in which a REMS certified prescriber is practicing. This additional requirement will minimally impact how the REMS is operationalized while complying with regulations.

### **Certification of HCP who Prescribe**

Healthcare providers (HCP) who prescribe Probuphine will need to be specially certified in the Probuphine REMS. Certification will include completion of Didactic and Live Practicum Training, as well as, passing the Probuphine REMS Program Knowledge Assessment Test. As a condition of certification, prescribers must counsel patients using the Patient Counseling Tool, ensure that the procedure is only performed under their supervision by a HCP who is certified to insert/remove Probuphine and maintain a copy of the completed Probuphine Insertion/Removal Log in the patient’s medical record.

### **Certification of HCP who Dispense (i.e. HCP who Insert/Remove Probuphine)**

To be specially certified to insert/remove Probuphine, HCP must complete both the Didactic and Live Practicum Training, as well as, pass the Probuphine REMS Program Knowledge Assessment Test. Additionally, these providers must pass the Assessment of Procedural Competency (i.e., a live practicum training assessment). As a condition of certification, HCPs who insert/remove Probuphine must ensure that the facility where the

procedure is being conducted has the appropriate equipment to safely insert/remove Probuphine and that the procedure will take place only in the presence of a certified Probuphine prescriber. Counseling patients using the MG, and also documenting the procedure on the Insertion/Removal Log is also required of these practitioners.

***Prerequisite for HCPs who Insert/Remove<sup>6</sup>***

Based on the Human Factors evaluation, the Sponsor had concluded that it could be too difficult to teach clinicians without procedure experience to do the task in the context of the proposed training. The original proposal was to limit eligibility for undertaking the training to clinicians whose specialty training included routine performance of procedures. The original proposal also did not include a requirement to demonstrate procedural competency. Instead, DRISK felt it would be more appropriate, based on previous REMS, to allow clinicians with any specialty background to attempt the training, on the understanding that the assessment of procedural competency would be sufficient to identify those who were unable to acquire the skill in the course of the training session. However, after further consultation with the DBRUP clinical team, the review team determined that the REMS should include a requirement of having performed a sterile procedure in the last 3 months, which includes (but is not limited to) using aseptic technique, injecting local anesthetic, making skin incisions, placing sutures, and removing foreign objects as a prerequisite for HCP to attend the training to certify as an Inserter/Remover of Probuphine. In addition, HCP who Insert/Remove must attest to having met this prerequisite at the time of enrollment in the Probuphine REMS Program. This should ensure that clinicians have the appropriate basic skills without arbitrarily assuming that those from one or another specialty do or do not have the skills.

***Recertification requirements<sup>7</sup>***

At the original PDAC meeting in 2013, the obstetrics/gynecology experts who participated stressed that procedure volume was the critical aspect of maintaining competence with a particular procedure. They proposed that there be provisions for recertification of clinicians who did not maintain a minimum procedure volume. The DBRUP staff provided a recommendation for recertification requirements that has been proposed to Braeburn and is under consideration at this time. In this scenario, the main branch point is whether or not the provider currently holds operating privileges at a hospital or an outpatient surgical center. The team felt it would be appropriate to assume that a clinician with such privileges was performing a variety of procedures and could maintain familiarity with the specifics of the Probuphine techniques through review of instructional materials every two years. Because operating privileges are, in turn, based on volume of procedures and other assessments of competence and would not require enforcement via the REMS, this seems a very reasonable branch point to sort out clinicians who regularly perform sterile procedures from those who do not.

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<sup>6</sup> Still under negotiation

<sup>7</sup> Still under negotiation

Clinicians without operating privileges would be held to a standard of needing to perform 5 insertions and 5 removals *successfully* (without assistance of other surgical specialists) in the prior 12 months. Those with a procedure volume at that level could review instructional materials yearly to maintain certification. Those without would need to undertake yearly certification with live training.

### **Medication Guide**

A Medication Guide (MG) will be provided to each patient prior to the insertion procedure to ensure the patient has been provided adequate information about the potential complications that can arise from the procedure and appropriate wound care. The MG can be used by healthcare providers who insert or remove Probuphine to counsel their patients prior to the procedure.

The Human Factors evaluation of the proposed training materials and methods was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and by the OB/Gyn consultants in DBRUP. Their comments are summarized in Dr. Skeete's review and may be found in detail in their own reviews. Briefly, the Sponsor identified the key tasks, risks, and subtasks to mitigate risk, but the assessment demonstrated important gaps in the participants' responses. The results suggested that an assessment of knowledge, without an assessment of procedural competence, would not be sufficient to ensure that the individuals undertaking the training would be able to appropriately complete the procedures. For this reason, the requirement for an assessment of procedural competence was included in the REMS program.

The specific content of the training materials, REMS documents, and MedGuide are under review at this writing.

## **16.3 Recommendation for other Postmarketing Requirements and Commitments**

### 1. Active Surveillance of Experience with Insertion and Removal Procedures:

To further characterize the risks of procedural complications and to identify any gaps in the training and certification program, Braeburn should undertake a post-marketing study collecting information on a large number of insertions and removals. This could parallel similar studies that have been undertaken to monitor for procedural complications with implantable contraceptives.

### 2. Re-use of previously used implant sites/ alternate sites

Because opioid addiction is a chronic, relapsing disorder, it is conceivable that long-term or even life-long pharmacologic treatment will be required by some patients. Probuphine has never been administered in an implant site that was previously-used. Scarring or other local changes may have an impact on drug delivery, or on the feasibility of re-implantation. The presence of scarring could increase the risks of implants being placed at an improper depth, which, in turn, increases the risks of serious complications from device migration. Braeburn should study the feasibility of implantation of Probuphine into previously-implanted sites and determine whether the PK is affected by scarring. Similarly, Braeburn should study whether insertion of

Probuphine into other anatomical sites can be performed safely and reliably and whether the PK is affected.

3. TQT study

Titan should be required to evaluate the effect of Probuphine on cardiac conduction. However, this may be performed as a post-marketing commitment consistent with our approach to already-marketed buprenorphine products.

4. Modification of the implant to include a radio-opaque marker

Braeburn should pursue efforts to add a radio-opaque marker to the implants to facilitate removal when the implants cannot be palpated, or migrate from the implantation site.

The review team continues to discuss whether studies of drug-drug interactions or effects of hepatic impairment are required to delineate effects on buprenorphine delivered by the subdermal route, or if the information available from the sublingual route is adequate.

## **APPENDIX A: Efficacy Results from Original NDA Submission**

### ***Background***

A key issue in this application is the matter of “clinical significance” of the efficacy results. Addiction is a chronic, relapsing disorder in which patients self-administer drugs despite harmful consequences. There has been considerable debate about the proper endpoints to measure in clinical trials for addiction treatments, most of which have focused on attempts to quantify the use of the patients “drug-of-choice” and the effects that medications have on modifying that use.

However, ultimately, the goal of treatment is to produce a clinical benefit—a health benefit, or a benefit in terms of psychosocial or occupational functioning, or a mortality benefit—through suppression (or elimination) of drug use. Drug-taking behavior itself, observed during the brief window of a clinical trial, is a surrogate endpoint. Trials intended to show effects on physical or psychosocial consequences of drug use would need to be very long and very large, and may be impractical. However, when drug-taking behavior is used as a surrogate endpoint, there should be a demonstration of change in behavior that can be reasonably predictive of improvement, such as avoidance of drug-related health and social consequences. Trials demonstrating that patients attain and sustain abstinence from drug use have always been considered to provide compelling evidence of efficacy, without requiring direct measure of clinical benefit (e.g., without validation of abstinence as a surrogate for clinical benefit). Validation of other patterns of behavior as surrogates for clinical benefit can be accomplished by examination of data on long-term functioning of treated individuals comparing use patterns with outcomes—this has been accomplished to validate an endpoint short of abstinence for alcoholism treatment, for example. However, no such validation of other patterns of behavior as predictors of clinical benefit has been undertaken for opiate addiction.

Previous trials for medications to treat opiate addiction have used a variety of measures, including group mean proportion of opioid-negative urine samples, retention in treatment, longest period of abstinence, or other measures. There has not been a consensus on how to approach this problem.

In the development program for Probuphine, the Applicant was advised that analyses focused on group means (such as mean percent of weeks abstinent) were difficult to interpret, because they do not reflect the experience of individual patients, who might range from complete responders to non-responders. In light of this ambiguity, the appropriate endpoints and analytic approach were the subject of considerable debate over the course of the development program.

The emphasis was on trying to define a successful patient in such a way that patients who were clearly clinically successful would not be misclassified as unsuccessful due to a too-stringent definition, such as complete abstinence and attendance at all visits. It is understood that some patients might be fully successful and yet miss some treatment

visits, or might achieve full abstinence, but not by the end of a protocol-specified month or two of grace, or even that a fully-successful patient might “slip up” on occasion. The discussions did not contemplate that patients who achieved only minimal reductions in their drug use could or should be classified as successful.

## **Efficacy Studies**

The original NDA included two placebo-controlled clinical trials, PRO-805 and PRO-806. Both were randomized, double-blind, parallel-group, multi-center studies involving efficacy ascertainment over 24 weeks after insertion of Probuphine or placebo implants. The study designs were essentially identical, except that PRO-806 also included a treatment group in which patients were treated with open-label sublingual buprenorphine.

Eligible participants included patients 18 to 65 years of age who met DSM-IV criteria for current opioid dependence and had not received treatment in the past 90 days. Patients were to undergo initiation of buprenorphine treatment (induction) using sublingual tablets. In order to be randomized to treatment with Probuphine or placebo implant, patients had to meet the following criteria<sup>8</sup> after the induction phase:

- Completed induction with sublingual buprenorphine to a dose of 12–16 mg/day as clinically appropriate within 10 days. Patients requiring <12 mg/day or >16 mg/day were ineligible.
- No significant withdrawal symptoms (defined as a score  $\leq$  12 on the Clinical Opiate Withdrawal Scale [COWS])
- No significant cravings for opioids (defined as a score  $\leq$  20-mm on the 100-mm Opioid Craving Visual Analog Scale [VAS])

Insertion of Probuphine occurred within 12 to 24 hours after the last dose of sublingual buprenorphine. Patients were treated for 24 weeks on study. Following the randomization visit, there were approximately 88 scheduled visits: 16 study visits and 72 urine collection visits.

The protocols allowed for administration of supplemental sublingual buprenorphine during the study for symptoms of withdrawal or “craving” or on request at the discretion of the investigator<sup>9</sup>. Investigators were blind to the urine toxicology results; therefore, *supplemental buprenorphine was not provided on the basis of ongoing illicit drug use.*

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<sup>8</sup> A substantial number of patients screened for inclusion failed to meet these criteria. Waivers were granted for some patients who needed additional time to stabilize or when implantation could not be scheduled in the designated window for logistical reasons. However, for a significant number of screen failures, the reason cited was that the patient was not able to be stabilized on a dose of 12-16 mg over three consecutive days within the specified window.

<sup>9</sup> Criteria for supplemental sublingual buprenorphine were:

- Withdrawal symptoms scoring >12 on COWS
- Request for dose increase by subject that was considered appropriate by investigator
- Cravings >20 mm on the Opioid Craving VAS

In Study 805, patients needed to meet only one criterion to receive rescue medication; in Study 806, patients needed to meet *all three* criteria.

Each dose of supplemental sublingual buprenorphine could only be obtained by patients at their clinic or pharmacy. Take-home sublingual buprenorphine was allowed for weekends, holidays, or other circumstances at the discretion of the investigator. Subjects in the open-label sublingual buprenorphine arm in Study PRO-806 could be provided up to seven days' supply of sublingual buprenorphine at a time.

Treatment failure was defined as

- Requiring supplemental sublingual buprenorphine exceeding the following limits, after having received the optional 5<sup>th</sup> implant<sup>10</sup>:
  - $\geq 3$  days per week for 2 consecutive weeks
  - $\geq 8$  days over 4 consecutive weeks at any time after the implant dose increase
- Requiring  $>1$  additional day per week of counseling for 4 consecutive weeks (i.e.,  $>3$  sessions per week during Weeks 1 through 12 and  $>2$  sessions per week during Weeks 13 through 24)

(Note: results of urine testing for opioid use were not included in criteria for treatment failure or in the criteria for rescue use. Therefore, patients could engage in ongoing illicit drug use without being adjudicated as treatment failures if they did not manifest signs of withdrawal, report craving, or request rescue.)

Any subject who requested, or who met one or more of the following criteria was withdrawn from the study:

- Subject non-compliance, defined as refusal or inability to adhere to the study protocol
  - missing 9 consecutive urine collections after the baseline visit
  - missing 6 consecutive counseling sessions after the baseline visit
  - refusal or inability to adhere to the study protocol, as determined by the principal investigator
- Evidence of implant removal or attempted implant removal
- Unacceptable or intolerable treatment-related AE
- Pregnancy
- Use of other treatments for opioid dependence
- Use of any investigational treatment
- Intercurrent illness or circumstances (e.g., incarceration  $\geq 7$  days) that, in the judgment of the investigator, affected assessments of clinical status to a significant extent
- Requirement for continual use of opioid analgesics  $>7$  days or general anesthesia for surgery
- Lost to follow-up
- Treatment failure, as defined above

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<sup>10</sup> After the first two weeks, if a subject met criteria for supplemental sublingual buprenorphine dosing on 3 or more days per week for 2 consecutive weeks or on 8 or more days total over 4 consecutive weeks, the subject received an implant dose increase.

Any subject who met the above criteria was seen for an end of treatment visit (unless lost to follow-up), during which implants were removed and clinical evaluations performed.

The insertion procedure was performed by a health care provider who had received training from the Applicant on the technique. For Study PRO-805, the training consisted of a DVD and self-teaching materials. New training procedures and a new insertion device was developed after completion of Study 805, and for Study PRO-806, in-person training using an improved device was instituted. Additionally, a somewhat novel approach to removing the implants was employed, using an incision that ran parallel to the implants rather than a perpendicular incision near the insertion incision. New pieces of equipment were provided to facilitate removal via this alternate method. Insertion and removal procedures were typically provided by a specific “implanting physician” at each site. At some sites, the general management of the patient’s addiction problem was handled by one individual (e.g., in the Department of Psychiatry) and arrangements were made for a physician with surgical experience (e.g., in the Department of Gynecology) to perform the insertion and removal procedures.

The primary efficacy outcome for both studies was the cumulative distribution function (CDF) of the percent of urine samples negative for opioids.<sup>11</sup> The endpoint of interest for both studies was the CDF of the percentage of negative urines for Weeks 1 – 24 with self-report imputation. This endpoint was based on urine toxicology findings. Urine samples were taken three times per week during the studies, and tested for opioids with the exception of buprenorphine, as well as other illicit drugs.

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<sup>11</sup> Study PRO-805 was the first Phase 3 trial in the clinical development program, and the CDFs were based on negative urine samples during Weeks 1 through 16. When the Applicant entered Phase 3 of the development program, the Applicant still had some uncertainty about the full duration of therapy with the implant. While the Applicant was operating under the theory that the implant provided buprenorphine for a total of six months, they acknowledged that it was conceivable that it only delivered active drug for four months. For statistical reasons, the four-month window was designated the primary analysis and the six-month window, secondary. Since they judged that the implant lasts for six months, it renders the fourth month evaluations irrelevant, notwithstanding its identification as “primary” in the protocol.

A total of 331 patients were randomized to treatment with Probuphine (n = 222) or placebo (n = 109) in Studies PRO-805 and PRO-806.

- In Study PRO-805, 348 patients were screened and 163 were randomized in a 2:1 ratio to either Probuphine or placebo. This study was conducted at 23 sites in the United States. The first patient was enrolled on April 2, 2007, and the study was completed on June 19, 2008.
- Study PRO-806, 480 patients were screened and 287 were randomized in a 2:2:1 ratio to either Probuphine, open-label sublingual buprenorphine 12-16 mg per day, or placebo. The study was conducted at 20 sites in the United States. The first patient was enrolled on April 22, 2010, and the study was completed on May 12, 2011.

In general, the subject population across the two trials primarily consisted of White, non-Hispanic males in their mid-thirties who used heroin as their primary opioid of abuse and had received treatment for opioid abuse in the past. Most patients had been diagnosed within the five years preceding entry into the study. In PRO-806, a slightly higher proportion of females were enrolled, and the percentage of subjects with previous treatment history was smaller.

Patient disposition is illustrated below. Overall, 35% of the Probuphine-treated patients and 72% of the placebo-treated patients in the controlled trials did not complete the full 24 weeks of treatment. In the placebo arms, the most common reason for premature discontinuation was “treatment failure,” which, again, was defined as requiring more than the protocol-specified limit of supplemental sublingual buprenorphine. Continued use of illicit substances was not considered in the definition of treatment failure, nor was continued use of illicit substances a criterion for receiving rescue medication. Based on the criteria for rescue medication, “treatment failure” refers specifically to inadequacy of treatment of patient-reported symptoms of withdrawal and “craving.” The differences in the protocols with respect to providing rescue (one criteria needed to be met in PRO-805 while all three criteria for rescue had to be met to receive rescue in PRO-806) are reflected in the different rates of “treatment failure” in the placebo group between the two studies. Higher rates of “subject non-compliance” may have reflected dissatisfaction with placebo treatment with strict rescue criteria. High rates of loss to follow-up in the open-label sublingual buprenorphine arm may have reflected the fact that patients could access buprenorphine treatment with a less burdensome visit schedule outside of the study.

The table below includes both PRO-805 and PRO-806, and their respective open-label extensions, PRO-807 and PRO-811.

### Patient Disposition Phase 3 Efficacy Studies and Safety Extensions

Disposition	Double-Blind Studies					Open-Label Studies	
	Study PRO-805		Study PRO-806			Study PRO-807	Study PRO-811
	Probuphine N=108 n (%)	Placebo N=55 n (%)	Probuphine N=114 n (%)	Placebo N=54 n (%)	SL BPN N=119 n (%)	Probuphine N=62 n (%)	Probuphine N=85 n (%)
Subject Completed Study	71 (65.7)	17 (30.9)	73 (64.0)	14 (25.9)	76 (63.9)	46 (74.2)	67 (78.8)
Subject Withdrew Early	37 (34.3)	38 (69.1)	41 (36.0)	40 (74.1)	43 (36.1)	16 (25.8)	18 (21.2)
Most Common Reasons for Early Withdrawal							
Subject Request	8 (7.4)	9 (16.4)	5 (4.4)	9 (16.7)	4 (3.4)	5 (8.1)	7 (8.2)
Subject Non-Compliance	12 (11.1)	7 (12.7)	10 (8.8)	9 (16.7)	8 (6.7)	5 (8.1)	0 (0.0)
Treatment Failure	0 (0.0)	17 (30.9)	6 (5.3)	9 (16.7)	0 (0.0)	0 (0.0)	1 (1.2)
Unacceptable or intolerable treatment-related adverse event	4 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (3.2)	0 (0.0)
Intercurrent illness or circumstance that affected assessments of clinical status or required discontinuation of drug or both	1 (0.9)	0 (0.0)	8 (7.0)	4 (7.4)	8 (6.7)	0 (0.0)	3 (3.5)
Lost to Follow-Up	10 (9.3)	4 (7.3)	9 (7.9)	3 (5.6)	17 (14.3)	4 (6.5)	6 (7.1)

Abbreviations BPN = buprenorphine; SL = sublingual

Note: Percent for each reason for early withdrawal is based on the total number of subjects in the population.

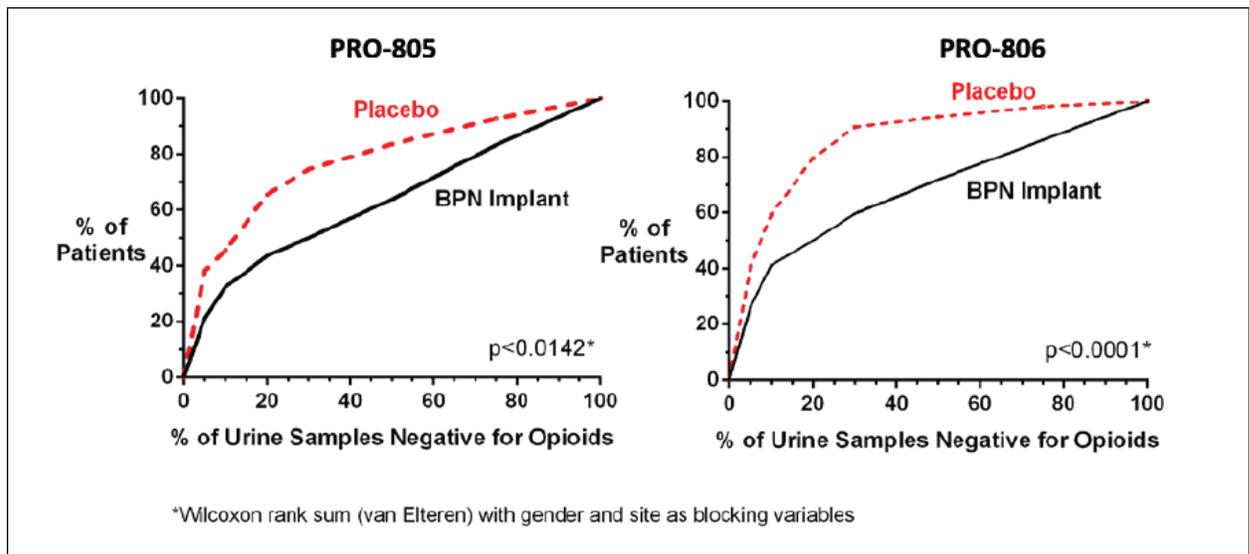
Source: Summary of Clinical Safety, Table 7, page 48.

The primary efficacy analysis compared the cumulative distribution function (CDF) of the percentage of urine samples negative for opioids in the two treatment groups using a stratified Wilcoxon rank sum test with pooled site and gender as stratification variables.

The primary analysis for both studies was conducted by Biostatistics Reviewer, David Petullo, M.S., on the intent-to-treat population, defined as all randomized patients who received an implant. The percentage of negative urines was derived for each patient by summing the total number of negative urine samples and dividing by all possible samples. For weeks 1-24, the denominator was 72. For some patients, the denominator was greater as they had unscheduled urine test results. Missing samples were considered positive. If a patient reported illicit use of opioids during a specific week, urine samples collected during that timeframe were considered positive even if a urine sample tested negative. All results presented below were obtained by incorporating self-reported use.

The Applicant's graphic representations of the study results are presented in the following two figures.

**Cumulative Distribution Function of the Percentage of Urine Samples Negative for Opioids in Weeks 1–24, with Imputation for Patient Illicit Opioid Self-Report: Studies PRO-805 and PRO-806**



**Source:** Figure 15, Applicant's Advisory Committee Backgrounder

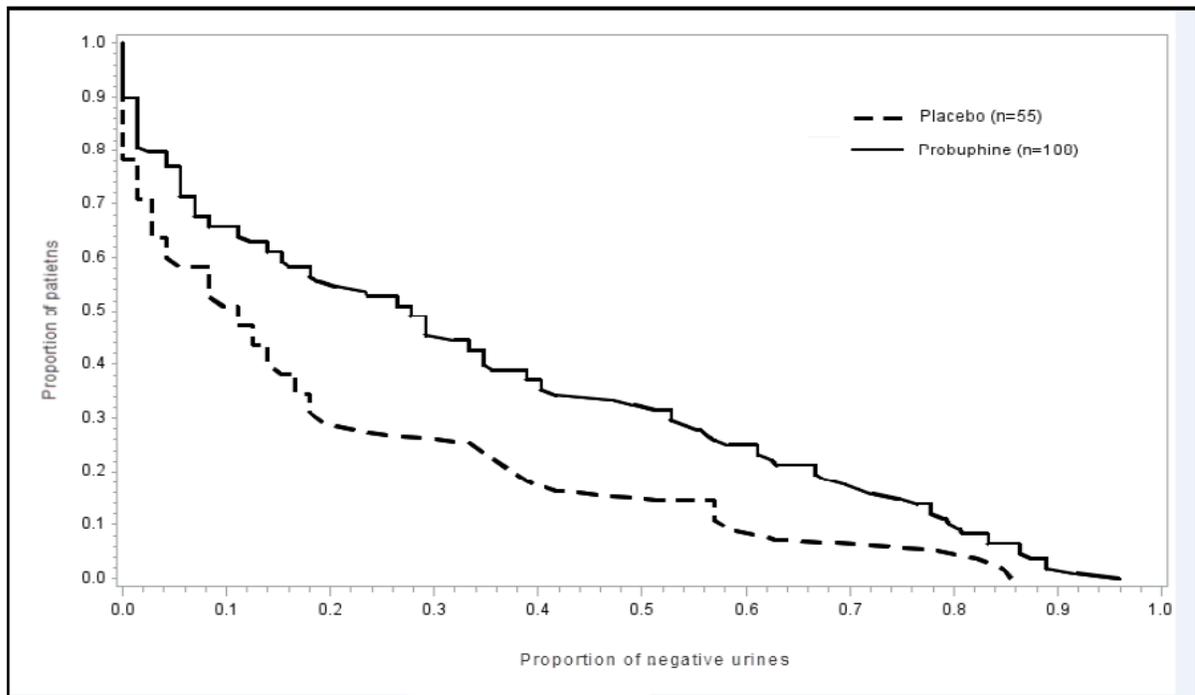
In the Applicant's presentations, the data are shown in graphs that illustrate the proportion of patients who submitted a particular percentage of opioid-negative tests *or fewer*. Although there is nothing technically or statistically wrong with these presentations, they are difficult to interpret intuitively. They can be compared to a survival curve that graphs how many patients died on a particular day *or sooner*. Like the Applicant's data presentations, the curve would rise from the bottom left to the top right, instead of falling from the top left to the bottom right.

To provide a more intuitive presentation of the study results, Mr. Petullo graphed the data to illustrate the proportion of patients who submitted a particular percentage of negative tests *or better*. Thus, for any individual cutoff value (30%, 50%, 70%, etc., chosen for expedience and not because they are known to have any particular significance), there are fewer patients meeting each threshold. To facilitate comparisons at specific cutoffs, Mr. Petullo also provided tabulations of the proportion of patients meeting each cutoff.

For the Statistics Reviewer’s analyses, the conventions used for urine sample and self-report data differed somewhat from the rules used by the Applicant’. Urine samples that the Applicant deemed non-missing and non-analyzable were included and considered positive for the purposes of the Statistics review. If a subject reported opioid use for the past two weeks, any negative urine tests were considered to be positive for those two weeks. Subjects were asked “have you used illicit opioids?” and “what was the duration of use?”

The figure below displays the CDF of percent negative urine samples for Weeks 1–24 with self-reported use incorporated generated by the Statistics Reviewer. The curves fall from 0% at the left to 100% at the right. For example, approximately 45% of the patients in the Probuphine group had at least 30% of urines samples negative for opioids. In comparison, approximately 27% of patients in the placebo group had at least 30% of urine samples negative for opioids.

**PRO-805: CDF of the Percentage of Urine Samples Negative for Opioids in Weeks 1 – 24 with Incorporation of Subject Illicit Opioid Self-Report (ITT Population)**



The CDF was statistically significantly different (p-value of 0.01) in PRO-805. In addition, there were more patients in the Probuphine arm that achieved at least 30%, 50%, or 80% negative urines. This information is provided in tabular format in the following table.

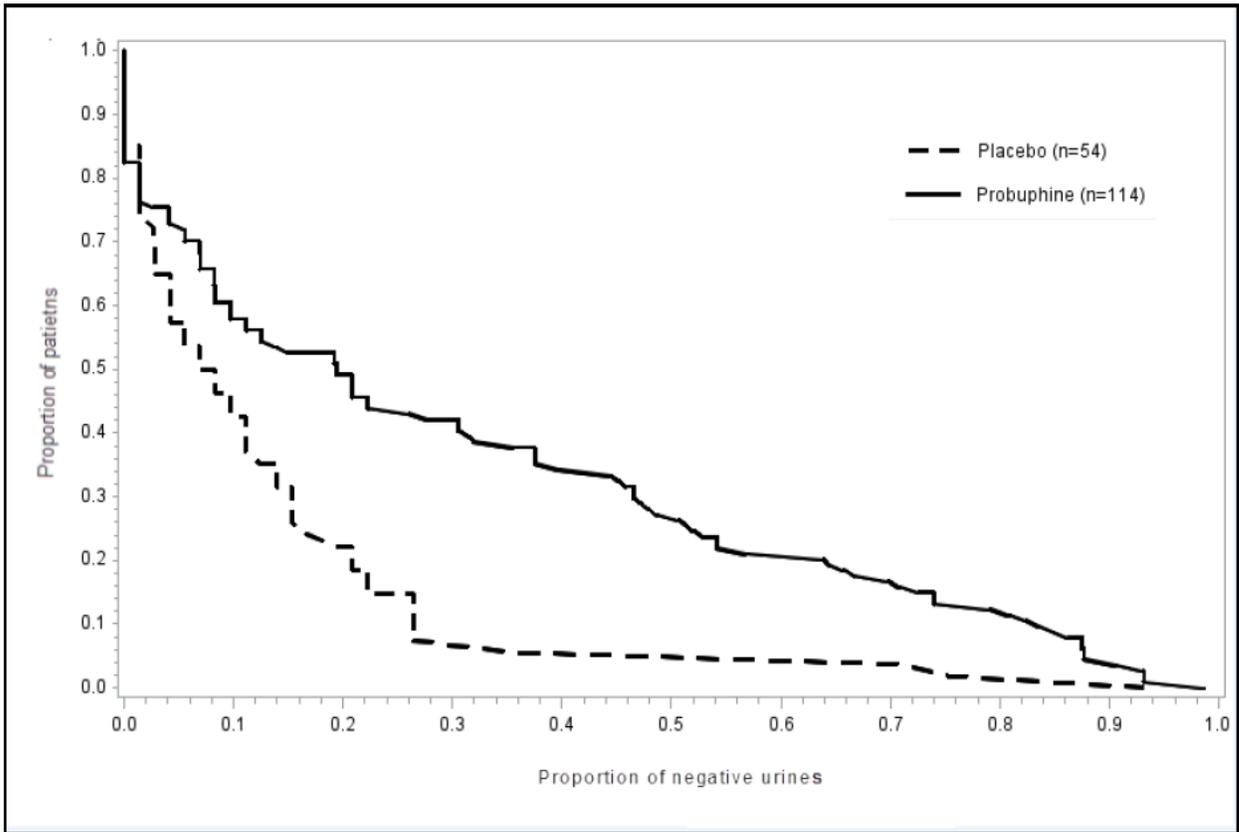
**Study PRO-805: Percentage of negative urines, Weeks 1-24**

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-805	≥ 30	45	27
	≥ 50	32	16
	≥ 75	15	7
	≥ 80	10	5
	≥ 85	6	2
	≥ 90	2	-
	≥ 95	1	-
	100	-	-

The cumulative distribution function and the tabular summary demonstrate that at each given level of percentage of opioid-negative urines, patients on Probuphine were more likely to submit opioid-negative urines. However, there were no patients in either treatment arm that achieved complete abstinence and few whose samples were opioid-negative more than half the time.

The CDF of percent negative urine samples for Weeks 1–24 for Study PRO-806 with self-reported use incorporated is shown in the figure below.

**Study PRO-806: CDF of the Percentage of Urine Samples Negative for Opioids in Weeks 1 – 24 with Incorporation of Subject Illicit Opioid Self-Report (ITT Population)**



The CDF was again statistically significantly different (p-value of <0.001) in PRO-806. In addition, there were again more patients in the Probuphine arm that achieved at least 30%, 50%, or 80% negative urines. This information is provided in tabular format in the following table.

**Study PRO-806: Percentage of negative urines Weeks 1-24**

Study	% Negative Urines	% of subjects	
		Probuphine	Placebo
PRO-806	≥ 30	42	7
	≥ 50	27	6
	≥ 75	13	4
	≥ 80	12	2
	≥ 85	9	2
	≥ 90	4	2
	≥ 95	1	-
	100	-	-

As observed in the PRO-805, the cumulative distribution function and the tabular summary demonstrate that at each given level of the percentage of negative urines, patients on

Probuphine in Study PRO-806 were more likely to submit opioid-negative urines. The efficacy findings observed in PRO-805 were, in fact, replicated in Study PRO-806. However, again, there were no patients in either study that achieved complete abstinence and few whose samples were opioid-negative more than half the time.

In addition to the primary efficacy analyses for the time period of Weeks 1–24, the Applicant was encouraged to also look at the analyses of the endpoint allowing for a suitable “grace period.” Recognizing that patients require some time for engagement in treatment, a grace period during which drug use is not counted in the assessment of response is permissible for the purposes of efficacy ascertainment. The Applicant chose two grace periods of four and eight weeks, reported a summary of the significance testing for each of the analyses for the pooled double-blind studies and the studies individually, and found statistically significant results across both timeframes. It is noteworthy, though, that no patients achieved complete abstinence when these grace periods of four and eight weeks were considered.

Mr. Petullo conducted analyses allowing for four months of grace (evaluating results based only on urine samples during Weeks 17-24), providing even more leniency with respect to allowing for engagement in treatment in order to assess for better outcomes.

In Study PRO-805, there was one patient in the Probuphine arm who had no positive or missing urine samples in the final eight weeks, and in Study PRO-806, there were two. However, there was little indication that allowing four months for engagement in treatment produced a better picture of the results. This is in contrast to general clinical expectations that patients improve over time.

The review team also considered the possibility that three times a week urine testing may have been too burdensome. Patients who are successfully achieving abstinence from illicit drugs may well experience improvements in their social and occupational functioning that provide them with very legitimate reasons to miss study visits. To explore this, Mr. Petullo reanalyzed the data to determine the percentage of subjects who self-reported abstinence, and had negative results for all urine samples collected during each of the last 8 weeks of treatment. For example, if a subject provided a negative urine sample during Visit 1 but missed Visits 2 and 3 of the same week, the subject was considered opioid-free for that week, unless the subject self-reported drug use. Results are shown below in Mr. Petullo’s table.

**Percent of Subjects With Self-Reported Abstinence and No Positive Samples, Weeks 17-24**

Study	% Subjects	
	Placebo	Probuphine
PRO-805	0	6
PRO-806	2	4

Source: Statistics Reviewer

Although this analysis provides a more encouraging picture than the analyses which impute opioid-positive results to missing samples, it is nevertheless dismaying. Even using this most generous approach defining abstinence, and despite over 60% of Probuphine-treated subjects continuing to the end of the study with *ensured compliance with medication* due to the delivery system, only a very small fraction were able to attain abstinence after four months of grace and sustain it for two months of additional observation.

### Use of Rescue Medication

As noted above, rescue medication could be provided at clinic visits when patients met protocol-specified criteria on the basis of withdrawal or craving scores. The table below illustrates the effect of different protocol-specified criteria for providing rescue. A markedly reduced proportion of patients received rescue in PRO-806, compared to PRO-805. Because the populations, procedures, and study medications were identical, it seems logical to conclude that this difference is attributable to the more stringent criteria for rescue applied in PRO-805.

### Summary of Supplemental Buprenorphine Use (Intent-to-Treat Population)

Study	Treatment Group	Number(%) Subjects Requiring Supplemental SL	Number(%) Subjects Requiring Fifth Implant
PRO-805	Probuphine	67 (62.0)	22 (20.4)
	Placebo	50 (90.9)	32 (58.2)
PRO-806	Probuphine	45 (39.5)	25 (21.9)
	Placebo	36 (66.7)	21 (38.9)
	SL buprenorphine	7 (5.9)	Not allowed

SL = sublingual.

Notably, over half of the patients who qualified for a fifth implant in the two studies pooled continued to require rescue medication, although their mean days of rescue use per week and mean milligrams used per week declined.

The Applicant interpreted the use of rescue medication in these studies as an efficacy indicator, pointing out that more patients in the placebo-group required rescue medication than patients in the Probuphine group. However, this is certainly to be expected. All patients were physically dependent on opioids and those in the placebo arm had opioids abruptly discontinued. Indeed, the use of rescue for the placebo-treated patients was, to some extent, necessary for an ethical trial design, because patients seeking treatment for opioid addiction are almost always offered some pharmacologic treatment of their withdrawal symptoms. Not surprisingly, some placebo-treated patients required regular doses of rescue medication at each treatment visit, and quickly met criteria for “treatment failure.” If the objective were to establish efficacy in treating symptoms of withdrawal, this finding would be encouraging. However, the objective was to demonstrate efficacy in maintenance treatment of opiate addiction, which implies that an effect on illicit drug use will be accomplished.

The Applicant also interpreted the frequency of rescue use in the clinical trials as support for their claim that Probuphine treatment would reduce the need for patients to have a supply of buprenorphine tablets or films in the home, which could translate to reductions in abuse, misuse, diversion, and accidental pediatric exposure. However, it must be stressed that the criteria for provision of rescue and the circumstances under which rescue doses were provided in the clinical trials bore very little relationship to the real-world scenario.

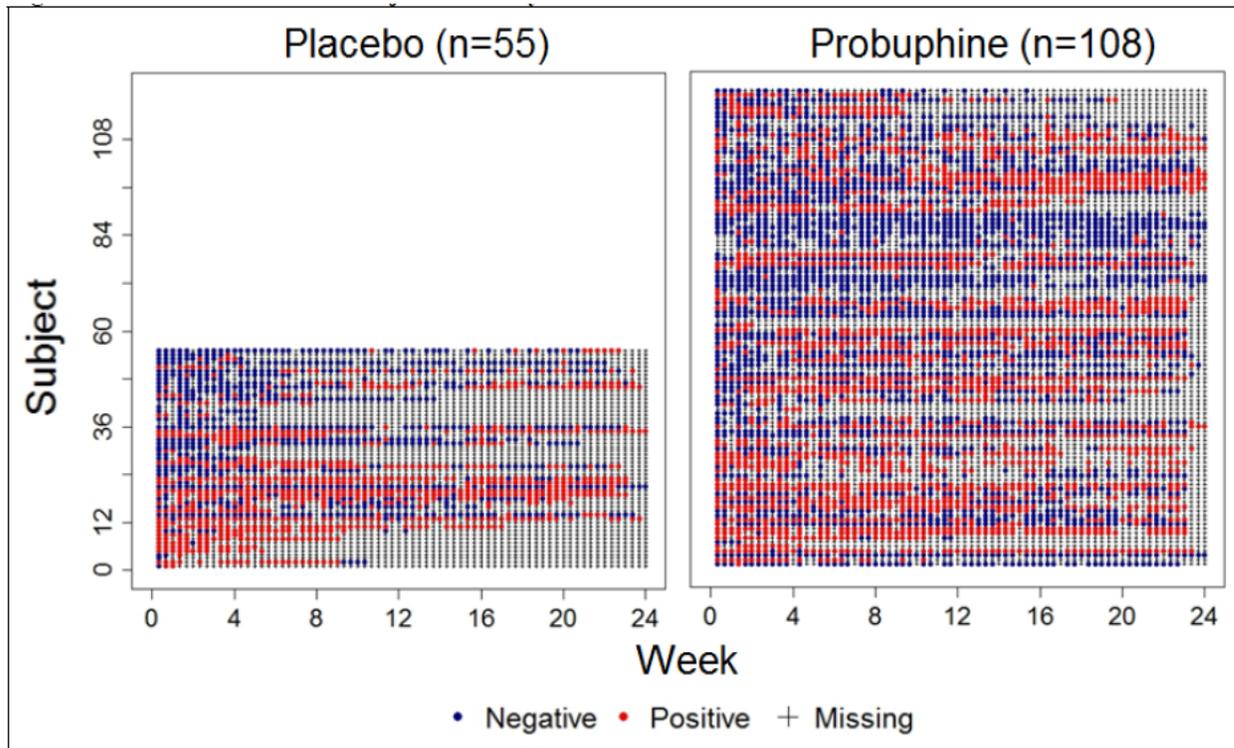
### **Graphic Depiction of Individual Patient Results**

To allow an appreciation of the temporal sequence of patients' test results, Mr. Petullo prepared graphic depictions that show the results of each test for each patient. The overall percent of negative tests does not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for half the study and then stops completely, and a patient who uses intermittently, half the days throughout the study. All of these patients might have 50% of their tests negative. The graphic depictions distinguish among these patterns. They also distinguish between tests that were imputed as positive because they were missing, or because a patient self-reported drug use, and actual positive tests. Mr. Petullo also provided a graphic display of the use of rescue medication over time for each patient.

### **Urine Test Results**

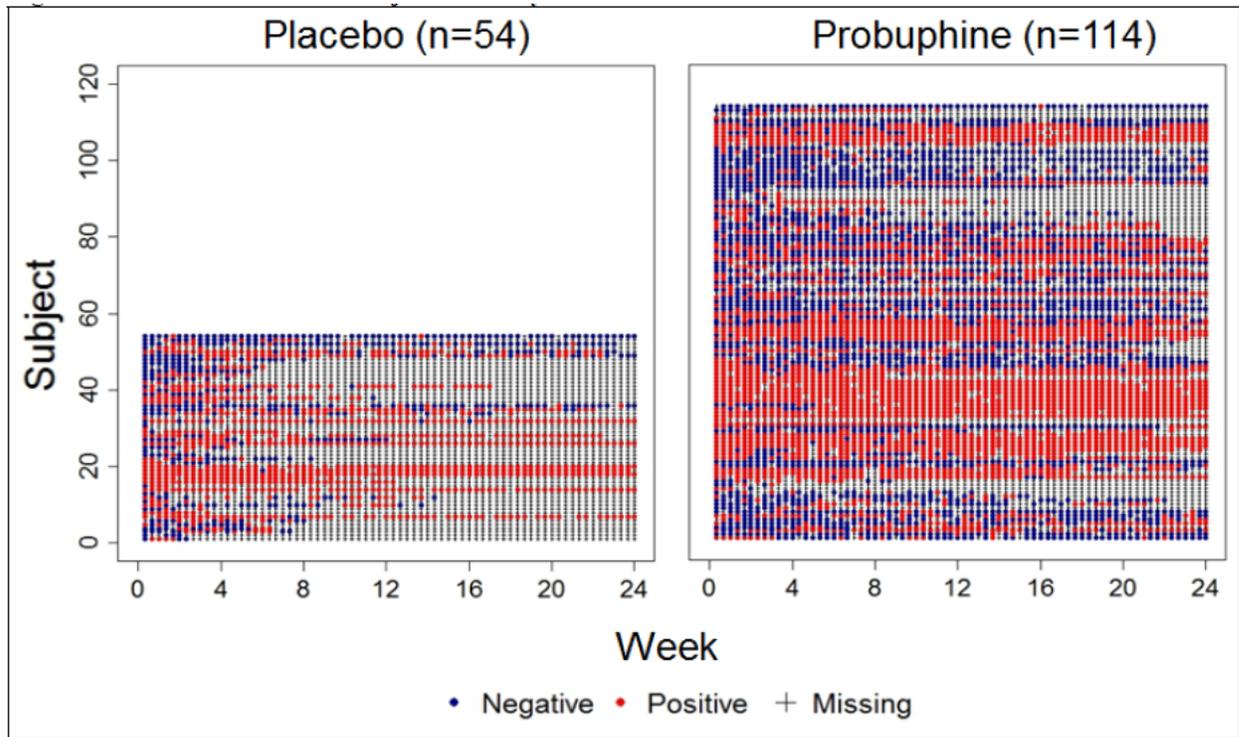
These subject-level analyses are shown below. In these presentations, each individual subject is represented along the y-axis. On the x-axis are the time points during which urine samples were collected. (In these studies, urine samples were collected three times per week). Blue dots are used to represent submission of opioid- negative urine samples at any timepoint, while red dots are used to represent opioid-positive urine submissions. Ideally, a patient achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents longer periods of time on treatment. The data points that appear gray in these presentations are '+' symbols and denote missing urine data.

### PRO-805 Subject-level Urine Sample Results



Source: Statistics Review

**PRO-806 Subject-level Urine Sample Results**



**Source:** Statistics Review

These figures illustrate a surprising result. The clinical expectation in a six-month period of addiction treatment, or a six-month study, is that the patient will probably either improve over time, or drop out of treatment. Completers are expected to be more successful than early dropouts, at least if the end of the study period is the time window of interest. In these studies, however, many patients remained in the study throughout the study period, consistently submitting opioid-positive urine samples over time. There do not seem to be many examples of patient gradually attaining greater periods of abstinence, or patients who have an early response but regrettably relapse.

In many addiction treatment studies, retention in treatment is one of the efficacy outcomes, based on an assumption that retention in treatment is a predictor of good outcome. These assumptions are derived from studies of patients on methadone treatment. These patients came to the clinic daily to receive their methadone dose, with visits potentially decreasing over time as the patients attained greater stability and time refraining from illicit drugs. Attendance at clinic also entailed participation in other aspects of addiction treatment apart from the pharmacological. It is reasonable to believe that there is some therapeutic benefit to coming to treatment visits.

Studies in patients on buprenorphine, too, also initially required daily supervised administration and regular clinic visits. Only since 2002 have patients treated with buprenorphine been able to receive treatment without very frequent clinic visits. However, studies buprenorphine-treated patients that evaluate retention in treatment also pertain to patients coming back to the study site, and participating in treatment visits that may involve

the provision of non-pharmacologic therapy, or may simply have the known therapeutic benefits of being in a treatment setting.

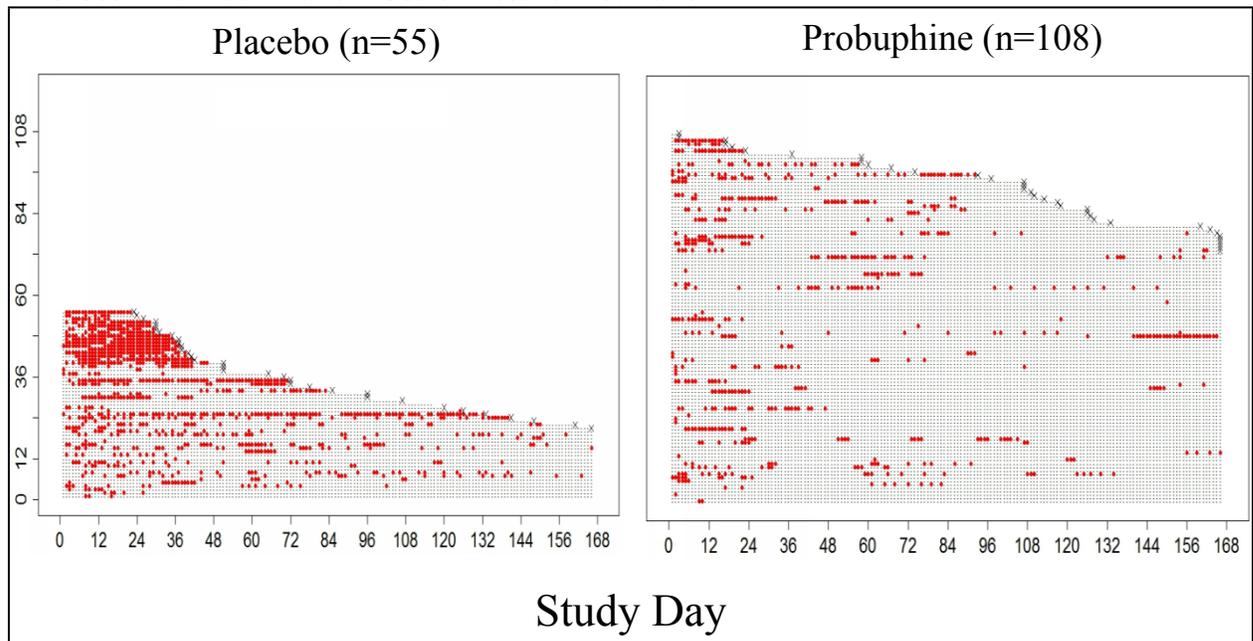
It is striking that patients in the Probuphine studies complied with regular clinic visits over six months, but the protocols may have provided some incentives for them to do so. For example, patients had the prospect of receiving rescue medication at any time and in fact continued to do so sporadically throughout the treatment period.

Conversely, in clinical practice, patients with Probuphine implants may not be retained in treatment. They will be *on treatment*, in the sense that they have circulating blood levels of buprenorphine, but they will not necessarily be *in treatment*. They may have no incentive at all to come to counseling visits or checkups with their treatment provider—and in fact, will be battling a disincentive in the form of charges for office visits. With no reinforcement, in the form of receiving their next monthly prescription, patients may not be seen at all. This called into question whether the benefits of “retention in treatment” would to accrue to these patients.

### Use of Rescue Medication

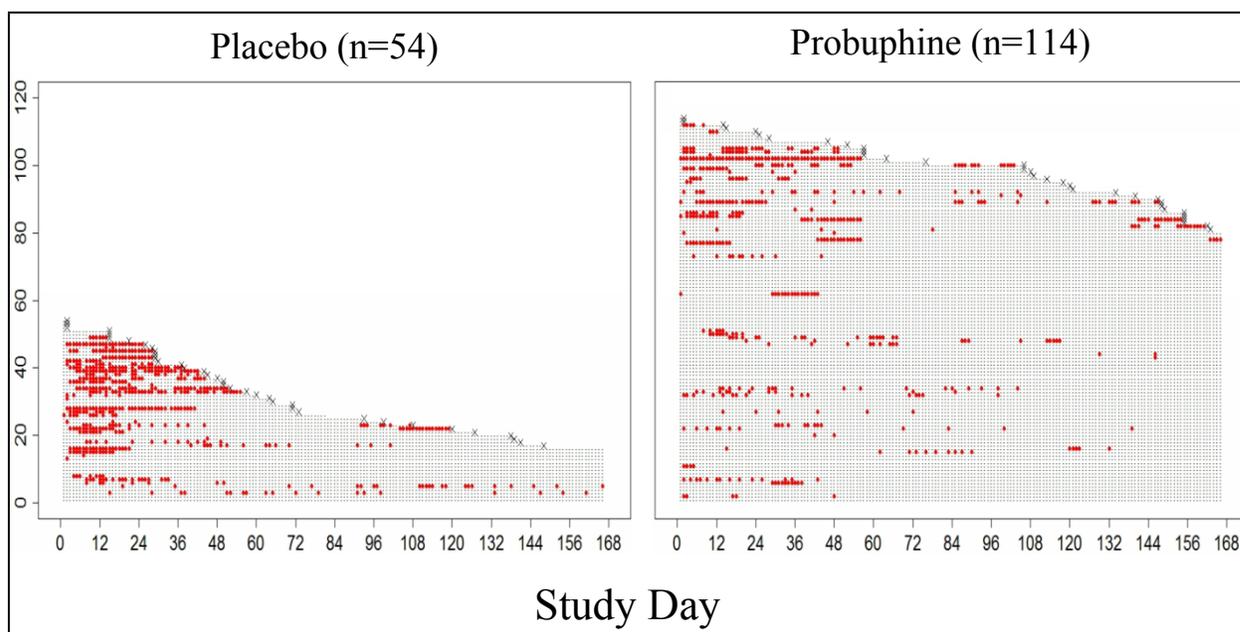
Graphic depictions of the use of rescue medication over time for individual patients are shown in Mr. Petullo’s figures, below. On the y-axis, individual patients are represented. Patients are sorted by date of discontinuation. On the x-axis are the number of days in the trial. The red dots denote any use of sublingual buprenorphine on a particular day.

PRO-805: Individual Patient Use of Rescue Medication



Source: Statistics Reviewer-generated graphical displays

PRO-805: Individual Patient Use of Rescue Medication



**Source:** Statistics Reviewer-generated graphical displays

These figures show that rescue medication use was not limited to the early treatment period where dose titration would be expected to take place. It would not be surprising to see that a subset of patients might require rescue, indicating a need for a fifth implant, get the fifth implant, and require no more rescue. However, sporadic use of rescue medication continued throughout the study. As noted above, over half of patients who met criteria for up-titration with a fifth implant required rescue even after the additional implant was placed.

## Discussion

In the end, the results of the controlled studies revealed that there were vanishingly few patients who attained a pattern of drug use that can convincingly be called successful treatment. Fully 64% of Probuphine-treated patients in Study 805 and 70% in Study 806 submitted opioid-negative urine samples on fewer than 30% of occasions in Weeks 17-24. Albeit, the numbers were even worse for placebo, and the imputation of positive samples for study dropouts inflates these numbers, but with a completion rate of ~65% for Probuphine-treated patients, data imputation is not the explanation. Parameters of drug use were similar between the Probuphine and open-label sublingual buprenorphine-treated arms in Study PRO-806—which is a disappointing result, because passive compliance formulations are expected to perform better than dosage forms that must be, but may not be, self-administered daily. If Probuphine overcomes the limitations of sublingual buprenorphine by ensuring compliance, one would expect it to be *better*. Our statute does not require superiority to a comparator, but a passive compliance delivery system makes the implicit claim that compliance, and therefore, efficacy, will be superior to daily dosing of the same drug. However, if the dose chosen is inadequate, then this promise is not delivered upon. It is difficult to make comparisons between treatments for several reasons. First, patients volunteering for a clinical trial of a new, implantable formulation may, understandably, have been dismayed to an open-label arm in

which they received a medication already available—potentially, one they'd already tried. Some patients may not have had access to buprenorphine treatment, or may have had difficulty paying for it, but, for others, there were certainly other less burdensome and less intrusive ways to receive treatment with sublingual buprenorphine tablets than participation in a clinical trial that required multiple weekly visits. Furthermore, the protocol permitted only doses between 12 and 16 mg/day. Patients could not have dose escalations above 16 mg, and if the dose was decreased at any point, it could not be increased again. Therefore, the dosing was not individualized or titrated to effect, as patients would experience in the normal course of clinical practice. (It is acknowledged that a clinical trial does, customarily, provide dosing flexibility than “real-world” practice, but to the extent that we wish to know how Probuphine compares to “usual care,” this becomes a relevant issue.) Although only 2% are described as discontinuing early to obtain other treatment for opioid dependence, the number of patients lost to follow-up was higher in this arm than in either of the other arms of the study. Nevertheless, overall retention was essentially identical to the Probuphine arm. Compliance with medication was not ensured (medication was given in 7-day take-home supplies).

It should be noted that in “real-world” practice, physicians are not blind to the results of their patients' toxicology screens, and can titrate the medication to effect or refer patients to more structured treatment if necessary. One of the selling points of a six-month implant is that patients need not be followed closely, monitored carefully, or have individually-titrated treatment. However, if these are not provided, then results may not be improved.

In trying to understand whether the results meet clinical expectations of “success,” various sources in literature were reviewed. The treatment guidelines provided by SAMHSA provide a flow chart that includes dose increases when a patient continues to use illicit drugs; this would imply that ongoing drug use is not an expected, acceptable, and routine issue to be overlooked. But this may reflect an aspirational approach to treatment. Looking at how success and failure are defined in clinical trials, Weiss et al analyzed both a “good outcome” definition (abstinent during the final week of a 12-week treatment, and in at least two of the previous three weeks) and complete abstinence in a trial of buprenorphine vs. placebo in patients addicted to prescription opiates. (In this study, 34-39% were completely abstinent for the last four weeks.) On the opposite side of the coin, Fiellin et al conducted two 24-week studies comparing buprenorphine treatment under different conditions of ancillary behavioral therapy. In these protocols, dose increases were allowed for patients with “evidence of ongoing (for 3 consecutive weeks) illicit opioid use,” and the protocols stipulated that “patients with unremitting illicit drug use (3 consecutive weeks of urine specimens positive for opioids after the buprenorphine dose had been increased to 24 mg) met criteria for protective transfer.” Protective transfer refers to discontinuation from the protocol and referral to more structured and intensive treatment. This indicates that ongoing use of illicit drugs was not an expected outcome of treatment. As 30% of participants met criteria for protective transfer in one study (2013), and 11% in the other (2006), this suggests that 70-89% of participants did *not* have ongoing illicit opioid use. Mitchell, et al reported outcomes for 300 patients entering community-based buprenorphine treatment and followed over 6 months. At six months, 56% in a standard outpatient treatment group and 49% in an intensive outpatient treatment group had opioid-positive urine tests. However, days of heroin use in the past 30 days declined from 22 to 3-4. Thus, even in a community treatment setting (not a clinical trial), while abstinence is

less common than one would hope, it is certainly higher than in the Probuphine study and patients who continue to use on 3-4 days/month would be likely to submit negative urine samples about  $\frac{3}{4}$  of the time.

Comparisons to the historical data on the efficacy of buprenorphine are very challenging. Those studies were performed under very different conditions, and the data are not available to subject to analysis of the cumulative distribution functions. One of the trials compared 8 mg sublingual solution (considered roughly equivalent to a 12 mg tablet dose) to two doses of methadone, 20 mg (likely sub-therapeutic) and 60 mg (considered to be the low end of the therapeutic range). The other study compared sublingual buprenorphine solution at 1 mg, 4 mg, 8 mg, and 16 mg (considered roughly equivalent to <2 mg, 6 mg, 12 mg, and 24 mg as tablet doses). Patients were new entrants to treatment, and all were heroin users. Studies involved titration, 4 months of maintenance, and then either taper or open-label follow-on. The results of these studies, in terms of measures of retention and group mean percent opioid-negative urine samples, were not even as encouraging as the results in the open-label arm of Study PRO-806. The populations may have differed (100% heroin-dependent vs. ~60%), and the registration studies for Subutex required daily clinic visits for supervised administration, which is a burdensome feature. The studies were nevertheless accepted as substantial evidence of efficacy; however, it must be noted that the intention was that the medication would be titrated to effect and that patients who did not cease illicit drug use might need higher doses, more structured treatment, or different treatment altogether.

### **Dose-Response Issues**

As noted above, the clinical experience with buprenorphine as it is currently used yields a higher expectation of efficacy. It is not very surprising that the efficacy results for Probuphine are discouraging compared to the expected efficacy of buprenorphine, based on various sources of information. To begin with, the plasma level of buprenorphine in patients treated with Probuphine is half the trough level associated with a 16 mg/day dose of buprenorphine sublingual tablets, which is the target dose recommended in labeling of Subutex and Suboxone. Based on AUC, the level is only 31% that of 16 mg/day dosing. One might wonder why this dose was sufficient to hold patients in treatment, and why there was as little use of supplemental buprenorphine as was observed (about half the patients). This may be explained in two ways.

First, the dose of buprenorphine necessary to allay opioid withdrawal symptoms is very low. Before Suboxone and Subutex were approved, Buprenex (parenteral buprenorphine) was fairly widely used off-label for treatment of withdrawal, at doses of 0.1-0.2 mg i.m. Other data (discussed in Section 3, above) suggest that there is a substantial difference between the level of mu opioid receptor occupancy associated with blockade of exogenous opioids and that associated with withdrawal, confirming that the pharmacokinetic/pharmacodynamic relationships are different for these two effects of buprenorphine.

On the other hand, one reason patients drop out of treatment is that they would like to take a “vacation” from buprenorphine in order to experience the effects of their drug of choice. Buprenorphine, given at the doses recommended as the target dose in labeling, is intended to block the effects of exogenous opioids. The dose needed to accomplish this effect is much

higher than the dose needed to treat withdrawal. It is widely accepted that effectively-blocked patients may “test the blockade” but do not typically engage in regular illicit drug use, because it is “a waste of money.” The dose of buprenorphine provided by Probuphine appears to have allowed a substantial fraction of the patients to continue using illicit opioids occasionally, or even regularly, without needing to discontinue treatment.

### **Clinical Interpretation of Results**

As to the reason for the relatively low use of rescue buprenorphine, it must be noted that the rescue doses were available only at clinic visits, and only when patients met specific criteria, which were related to withdrawal and “craving.” Patients may well have been without measurable symptoms on these instruments, but control of subjective symptoms of withdrawal and “craving” is of uncertain relevance if it does not translate to drug use behavior. One can assume, additionally, that clinicians monitoring their patients’ urine toxicology results (unlike the site investigators, who were blind to the results), would have concluded that the great majority of patients needed rescue medication due to ongoing illicit substance use.

To understand how is this different from other conditions, in which we sometimes accept any difference between the drug-treated patients and the placebo-treated patients as beneficial, it must be reiterated that opioid addiction is a complex of behavioral experiences, in which patients are compelled to use opioids despite ongoing harm, experience preoccupation with thinking about obtaining, using, and recovering from opioid use, and give priority to opioid use over other life activities, to the detriment of their health, psychosocial wellbeing, and occupational functioning. In an analgesic trial, the problem is pain. The symptom that is being measured is pain. If pain is reduced from baseline by the test drug more than the control drug, we can conclude that pain—the problem—is being treated. Patients using the medication and their physicians can readily ascertain whether the problem is being treated well enough to continue on that medication or not. In the Probuphine studies, we were looking at a surrogate endpoint of uncertain predictive value. The data provide little insight into what level of ongoing drug use could be used to conclude that the patient’s opioid addiction was responding or not responding to treatment.

### **Enrichment Strategy**

It should also be noted that these studies employed an enrichment design. Only patients who could tolerate buprenorphine, and who could be stabilized on a dose of 12 mg-16 mg of buprenorphine within about 10 – 16 days could be enrolled. If anything, this design should give a more optimistic picture of the product’s efficacy (and safety) than use in a general population. A significant number of patients (e.g., 84 of 115 screen failures in PRO-805) were screened out based on this criterion, suggesting that many patients will not meet the criteria that will be described in labeling. In the clinical trials, a significant number of waivers were granted to allow patients not meeting the run-in dose criterion to enroll (e.g., 72 of 83 waivers granted in PRO-805), but it is not clear whether these patients required additional time, less time, lower doses, or higher doses than the target.

## **Conclusion**

In summary, despite an enrichment strategy which enrolled patients considered responsive to buprenorphine, only a very small minority of patients treated with Probuphine at the recommended dose seem to have accomplished substantial improvements in their drug-use behavior, even over six to twelve months of treatment.

Taken together, concerns about the clinical significance of the primary analysis, pharmacological reasons to doubt the dose would be effective in blocking exogenous opioids, and the expectation that in the “real world” clinical setting, almost every patient will require ongoing sublingual buprenorphine to supplement Probuphine treatment, led the review team to the conclusion that the benefits of Probuphine, at the dose tested, did not outweigh the risks for the population studied.

## ***Advisory Committee Meeting***

In order to gain a better understanding of the risk/benefit balance for Probuphine, a meeting of the Psychiatric Drugs Advisory Committee was held on 3/22/13 to discuss the Probuphine application. Although the majority of the committee voted that efficacy had been demonstrated, that safety had been adequately characterized, and that the risk/benefit ratio favored approval, the comments during the discussion and the breakdown of votes revealed considerable ambivalence about the application.

Many participants, even some who voted that efficacy had been demonstrated, expressed that their vote reflected the fact that, on the primary endpoint, the drug had out-performed placebo. Several did note concerns about the adequacy of the dose, and five voted that efficacy had not been demonstrated. Panel members noted difficulty reconciling Applicant’s claim that the steady-state blood levels were maintained in an efficacious range with the pattern of urine toxicology results, asking “How can I make the claims of robust efficacy jive with the very disappointing results in terms of negative urines?” and “I’m not sure that we’re doing anyone a service if we put something on the market that’s not the right dose, that doesn’t actually optimally achieve what we’re trying to accomplish...,” and “if there’s tons of positives at the 24th week, did that medicine do the right thing, or ... what’s the purpose of that drug?” One panelist noted that, if he treats a patient with buprenorphine “And if they’ve got a few months of dirty urine, I’m going to say treatment failed” and refer the patient for other treatment.

Although addiction medicine providers on the panel observed that it was not a requirement or expectation for a patient in treatment to have “totally clean urines,” one provider noted that “when we have people who give us urines that are positive for illicit or unauthorized use, it’s a signal to us that we need to reevaluate the patient and make some changes in whatever therapy that we’re providing.” He expressed some concern about the use of supplemental buprenorphine as an indication that the dose was inadequate, and concern that providers would be “stuck with” a dose that would leave providers with “difficulty meeting our patients’ needs.” Another addiction medicine expert noted that the REMS would need to address the use of supplemental sublingual buprenorphine and that physicians would need to be educated to minimize its use.

An expert appearing on behalf of the Applicant noted that “In thinking about the individuals who were stabilized on 12 to 16 milligrams and then transferred over to the rods, I would look at them as very early responders to the treatment. So they're in the phase 1 and 2, at most, in the six months of study. Her further comments seemed to indicate that patients need to be titrated to the dose of medication that is necessary to help them discontinue illicit drug use, which may be higher than 12-16 mg, and certainly higher than the dose provided by Probuphine (which is 1/3 the AUC of 16 mg/day), noting, “people with mild to moderate disease, being those that you want to capture in the 12 to 16 range. I think that's where we want to induce people, and we want to increase them...until we get them at a place where we can reliably support their desire not to use heroin or prescription drugs while they're on this medication.”

One addiction medicine specialist noted, “One of the populations that it has been suggested by several people, and I think it's an appropriate suggestion, is for the patient who's already stable. Half of my stable patients are on less than 12 milligrams. Most of them are on 4 or 8...I frankly think that this is an extremely important product concept, to be able to give a patient six months of medication that will keep them stable and that we would have limited oral or sublingual supplementation on that would decrease that issue with diversion...I've got patients who have been on buprenorphine sublingually now for five to eight years. None of them are on 16. My new patients are generally on 16, but they back off within six months, nine months to a lower dose.

Several participants in the open public hearing were investigators in the clinical trials or individuals with expertise in addiction treatment. Their comments reflected an expectation that the product would be efficacious enough to bring patients' addiction into remission, emphasizing that the benefit of the product was the six month duration of action, so that treatment would be ensured over a time sufficient to accomplish this goal. The comments did not address the clinical significance of the results in patients who continued to use illicit drugs persistently throughout the six months. One site investigator felt that the product would be appropriate for patients who were already engaged in treatment, stabilized, and no longer using illicit drugs for a year or more. Several commenters noted that Probuphine would facilitate treatment in patients who could not come to office visits—citing the possibility of telemedicine in rural communities, benefits for patients who travel, obviation of transportation problems. These commenters saw an advantage in the fact that Probuphine-treated patients would need to be seen only infrequently. Conversely, other commenters emphasized the importance of treatment visits—noting that a medication that did not have to be taken daily would (paraphrasing) “help patients take steps toward focusing not on taking medication but on recovery; they can focus on remaining in treatment,” and “allowing patients to dedicate time and attention to the psychosocial aspects of treatment,” and that medication and therapy are both necessary, with medication helping the patient to refrain from illicit drugs, “the longer time away from the drug of choice, the more available the patient is for treatment.”

Regarding safety, the discussion focused primarily on issues related to the insertion and removal procedures. The obstetrician/gynecology experts, Drs. Espy and Hewitt, emphasized that removal is the more difficult of the two procedures, but that complications of removal are often attributable to errors in insertion. They observed that the “U-technique” that is to be used

in Probuphine removal is not the procedure that was used to remove Norplant; therefore, there is little experience with this procedure even among Norplant-experienced providers. The Applicant's expert on the insertion and removal procedures, Dr. Chavoustie, explained that the Probuphine implant is less "forgiving" (understood to mean more friable) than the Norplant implants, and therefore the alternate technique facilitates removal. Dr. Hewitt noted that "While I do think it's an easier skill for people to acquire that are comfortable doing surgical interventions, I feel really strongly that with the correct training that this is something that you can teach any provider to know how to do....It is really important that the training be adequate and appropriate." Several commenters noted that "high volume" is important in developing and maintaining expertise in any procedure, and noted that certification should be reviewed if providers do not do the procedures regularly. The OB/Gyn experts also observed that providers should be required to have the ability to refer to someone who can do removals of deep implants, which, it was noted, is a specialized skill typically provided at a limited number of facilities.

## **APPENDIX B: Insertion and Removal Procedures**

The insertion and removal procedures as described in the Sponsor's proposed labeling are as follows. **Note that changes to this labeling have been recommended by the review team and this section is included only to provide a general description of the procedures.**

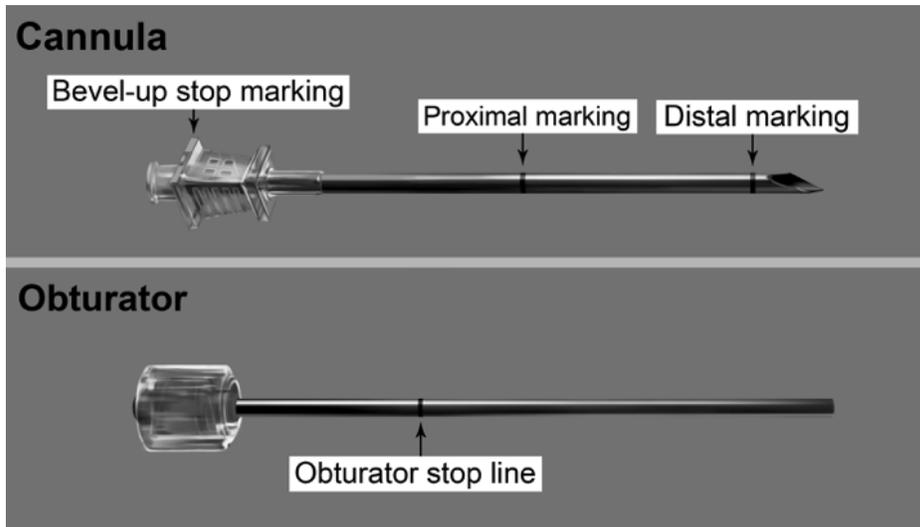
**INSERT PROBUPHINE UNDER ASEPTIC CONDITIONS.**

**THE FOLLOWING EQUIPMENT IS RECOMMENDED FOR IMPLANT INSERTION:**

- An examination table for the patient to lie on
- Mayo instrument stand, sterile tray
- Adequate lighting ( e.g. headlamp)
- Sterile fenestrated drape
- Latex and talc-free sterile gloves
- Chlorhexidine (ChloroPrep®)
- Local anesthetic (1% lidocaine with epinephrine 1:100,000)
- 5 mL syringe with 1.5 inch 25g needle
- Adson single tooth tissue forceps
- #15 blade scalpel
- ¼ inch thin adhesive strip (butterfly strip) (e.g. Steri-strip skin closures)
- 4x4 sterile gauze
- Adhesive bandages
- 3 inch pressure bandages
- Liquid adhesive (e.g. Mastisol)
- 4 PROBUPHINE implants
- 1 PROBUPHINE disposable applicator (Figure 1)

The applicator and its parts are shown in Figure 1.

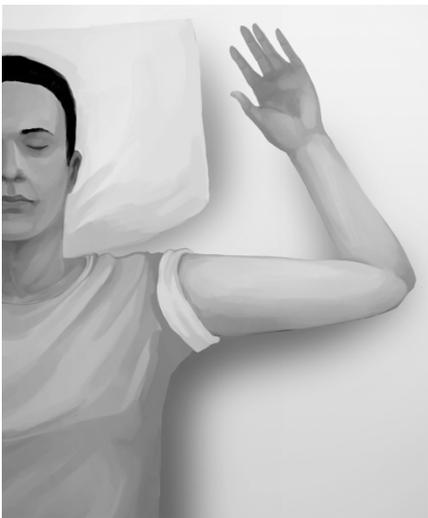
Figure 1



### Insertion Procedure

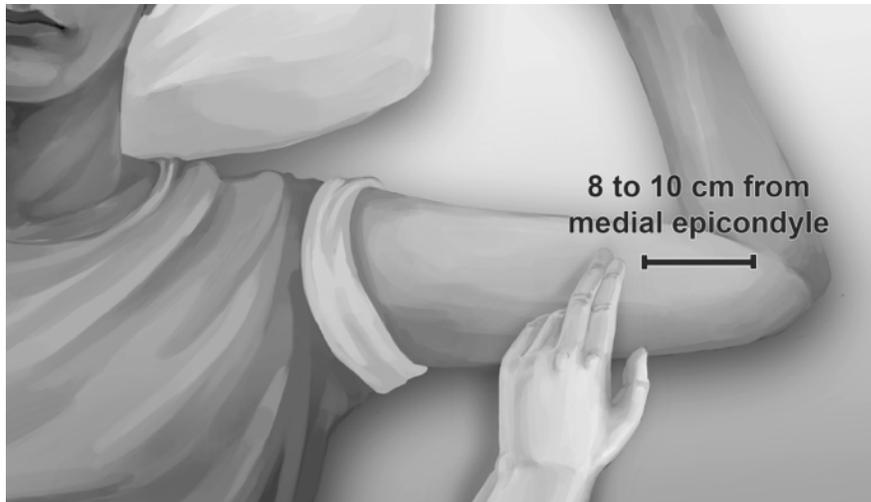
Step 1. Have the patient lie on his/her back, with his/her arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head (Figure 2).

Figure 2



Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site (Figure 3).

Figure 3

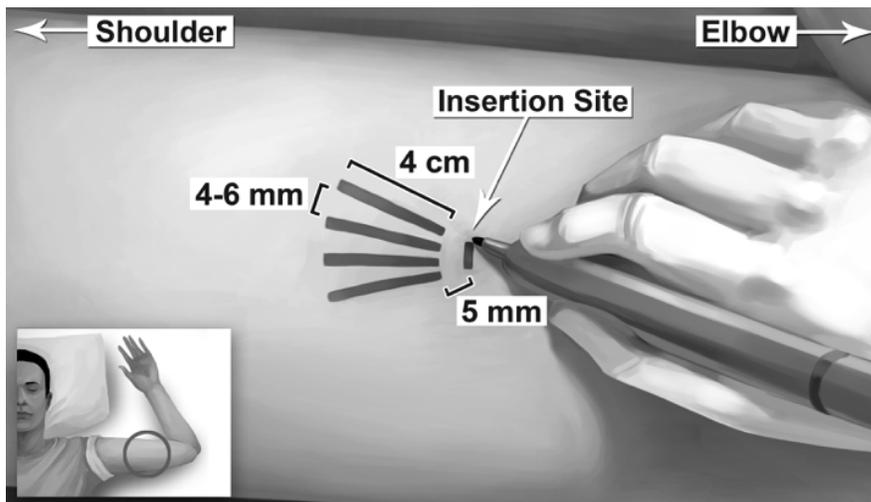


Step 3. Clean insertion site with alcohol prep pad prior to marking the skin.

Step 4. Mark the insertion site with a sterile marker. The implants will be inserted through a small 2.5 mm-3mm subdermal incision.

Step 5. Using a marker, mark the channel tracks where each implant will be inserted by drawing 4 lines with each line 4 cm in length. The implants will be positioned in a close fan-shaped distribution 4-6 mm apart with the fan opening towards the shoulder (Figure 4). The closer the implants lie to each other at time of insertion, the more easily they can be removed. There should be at least 5 mm between the incision and the implant when the implant is properly positioned.

Figure 4



Step 6. Using aseptic technique, place the sterile equipment, PROBUPHINE implants and the applicator on the sterile field of the mayo instrument stand. One applicator is used to insert all four implants.

Step 7. Clean the insertion site with an antiseptic solution (Chlorhexidine ChloroPrep®) using gentle repeated back-and-forth strokes for 30 seconds. When using the triple swabstick applicators, use each swabstick sequentially within the 30 seconds. Allow the area to air dry for approximately 30 seconds and do not blot or wipe away.

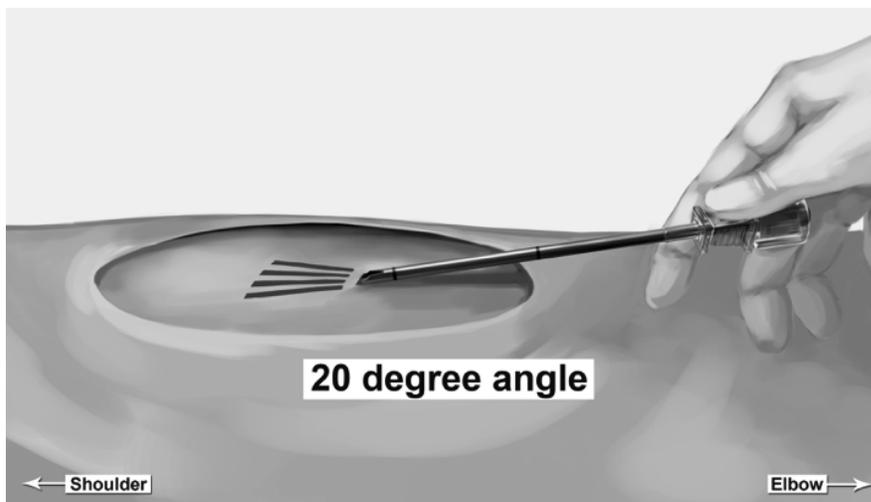
Step 8. Apply the sterile drape to the arm of the patient.

Step 9. Anesthetize the insertion area at the incision site and just under the skin along the planned insertion channels using local anesthetic (for example, by injecting 5 mL lidocaine 1% with epinephrine 1:100,000).

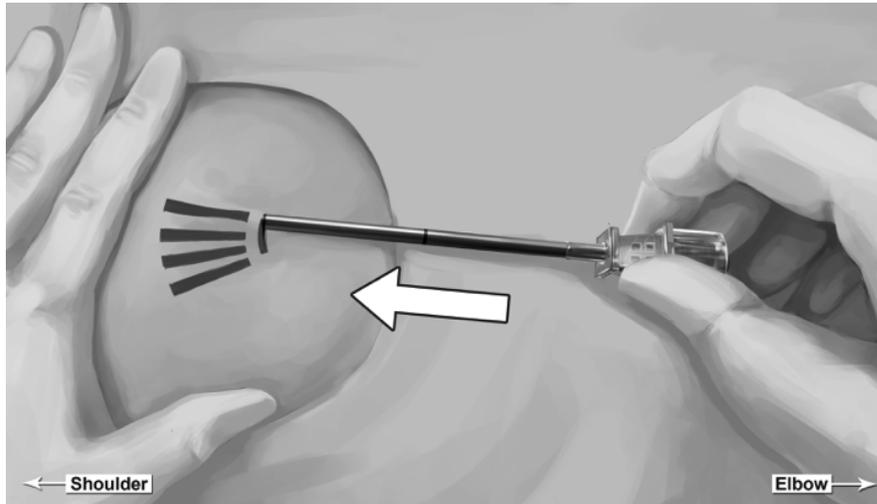
Step 10. After determining that anesthesia is adequate and effective, make a shallow incision that is 2.5-3 mm in length.

Step 11. Lift the edge of the incision opening with a toothed forceps. While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees), into the subdermal space, with the **bevel-up stop marking** on the cannula facing upwards and visible with the obturator locked fully into the cannula (Figure 5). Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue (Figure 6). While tenting (lifting), gently advance the applicator subdermally along the channel marking on the skin until the **proximal marking** on the cannula just disappears into the incision (Figure 7).

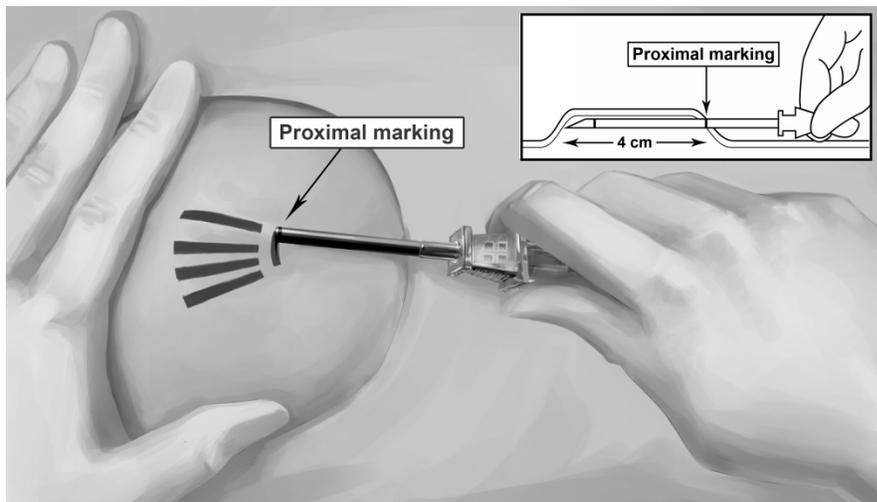
**Figure 5**



**Figure 6**



**Figure 7**

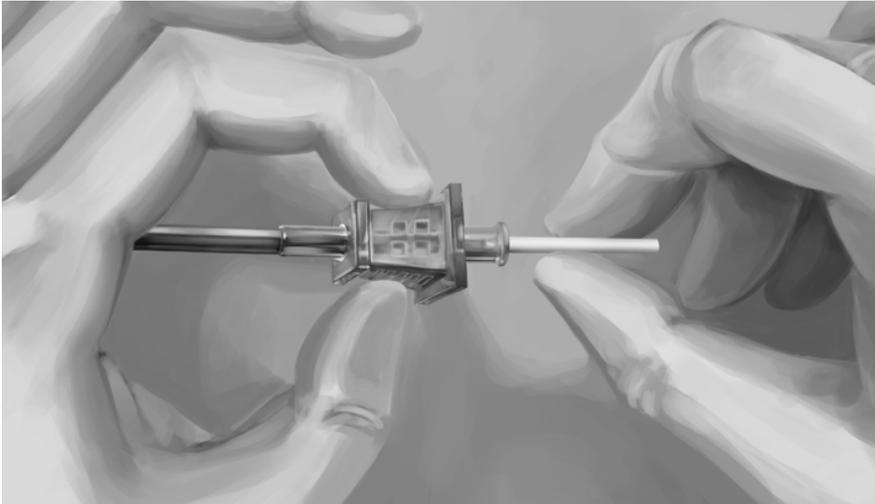


Step 12. Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissues.

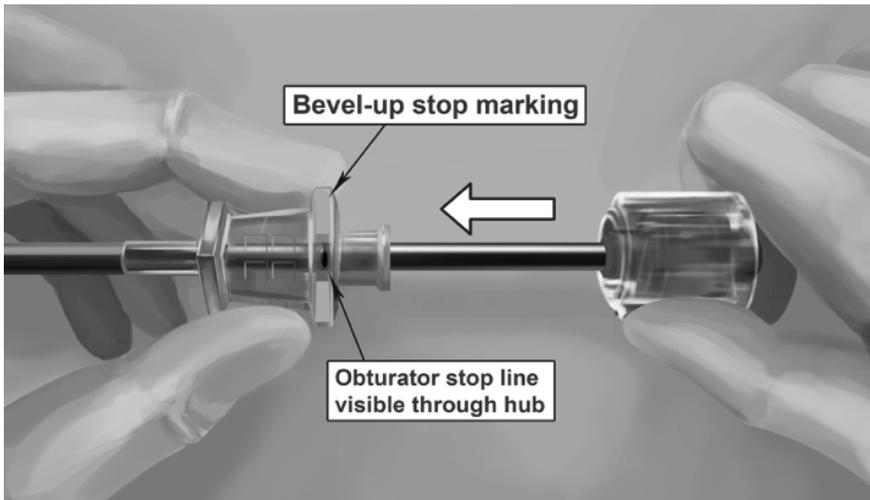
Step 13. While holding the cannula in place, unlock the obturator and remove the obturator.

Step 14. Insert one implant into the cannula (Figure 8), re-insert the obturator, and gently push the obturator forward (mild resistance should be felt) until the obturator **stop line** is level with the **bevel-up stop marking**, which indicates the implant is positioned at the tip of the cannula (Figure 9). **Do not force the implant beyond the end of the cannula with the obturator.** There should be at least 5 mm between the incision and the implant when the implant is properly positioned.

**Figure 8**

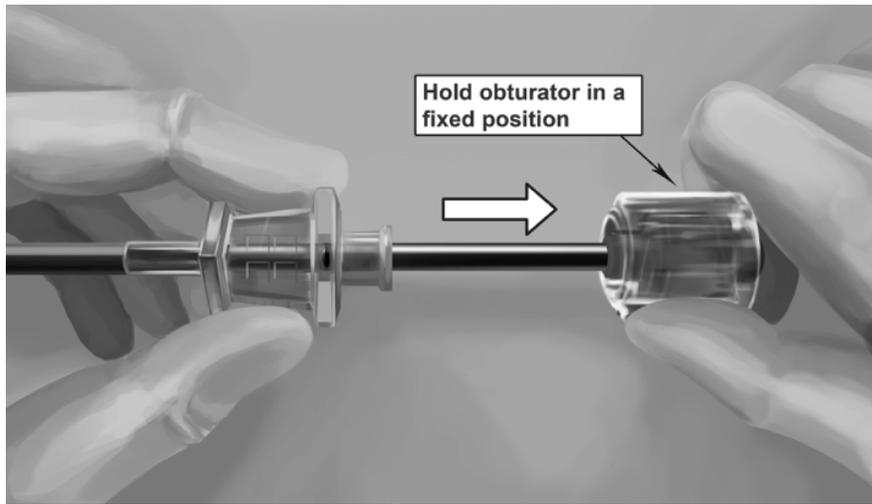


**Figure 9**



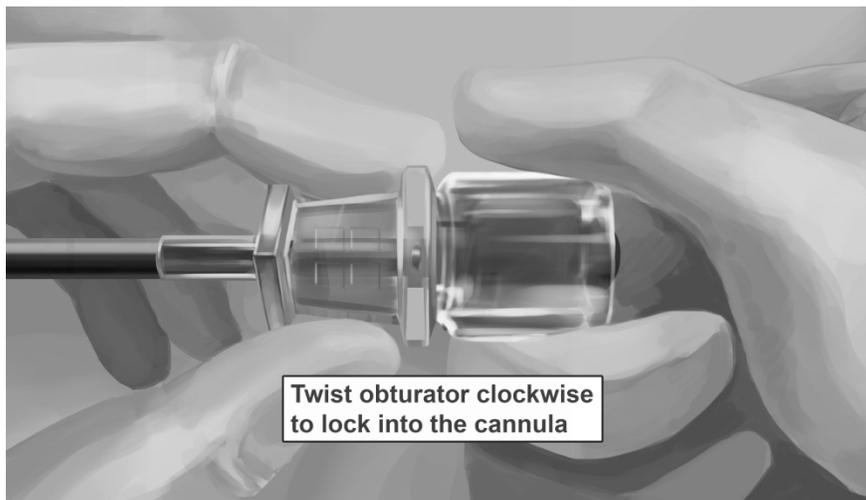
Step 15. While holding the obturator **fixed in place** on the arm, retract the cannula along the obturator, leaving the implant in place (Figure 10). **Note: do not push the obturator. By holding the obturator fixed in place on the arm and by retracting the cannula, the implant will be left in its correct subdermal position.**

**Figure 10**



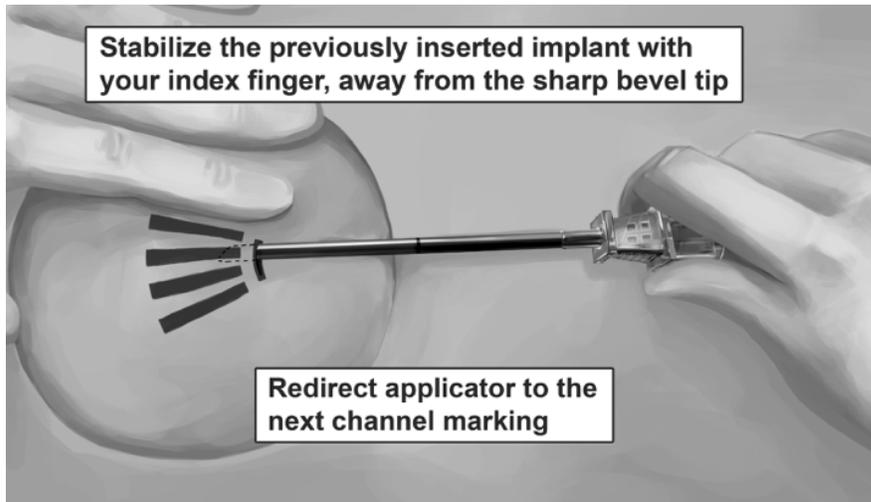
Step 16. Withdraw the cannula until the hub is flush with the obturator, and then **twist the obturator clockwise to lock onto the cannula** (Figure 11). Retract the applicator, **bevel up**, until the **distal marking** of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space).

Figure 11



Step 17. Redirect the applicator to the next channel marking **while stabilizing the previously inserted implant, with your index finger, away from the sharp tip** (Figure 12). Follow steps 13 through 16 for the insertion of the three remaining implants through the same incision, placing implants in a close fan-shaped distribution 4-6 mm apart at the top of the implant. The applicator can now be removed.

**Figure 12**



Step 18. Always verify the presence of each implant by palpation in the patient's arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant (Figure 13). If you cannot feel each of the four implants, or are in doubt of their presence, use other methods to confirm the presence of the implant. Suitable methods to locate are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Please note that the PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan. If ultrasound and MRI fail call **1-800-xxx-xxxx**.

**Figure 13**



Step 19. Apply pressure to the incision site for approximately five minutes if necessary.

Step 20. Clean the incision site. Apply liquid adhesive to the skin margins and allow to dry before closing the incision with the ¼ inch thin adhesive strip (butterfly strip) (for example Steri-strip skin closures).

Step 21. Place a small adhesive bandage over the insertion site.

Step 22. Apply a pressure bandage with sterile gauze to minimize bruising. The pressure bandage can be removed in 24 hours and the adhesive bandage can be removed in three to five days.

Step 23. Complete the PATIENT IDENTIFICATION CARD and give it to the patient to keep. Also, complete the PATIENT CHART LABEL and affix it to the patient medical record. Provide the patient with the Medication Guide and explain proper care of the insertion site.

Step 24. **The applicator is for single use only.** Dispose the applicator in accordance with the Centers for Disease Control and Prevention guidelines for hazardous waste.

Step 25. Instruct the patient to apply an ice pack on his/her arm for 40 minutes every two hours for first 24 hours and as needed.

Step 26. Complete the PROBUPHINE Patient Distribution Log.

### **Removal of PROBUPHINE**

#### **PROBUPHINE REMOVAL PROCEDURE**

**Before initiating the removal procedure, the healthcare provider should carefully read the instructions for removal and consult the PATIENT IDENTIFICATION CARD and/or THE PATIENT CHART LABEL for the location of the implants.** The exact location of all implants in the arm (patients will have four implants) should be verified by palpation. If all of the implants are not palpable, or you are in doubt of their presence, use other methods to confirm the presence of the implant(s). Non-palpable implants should always be first located prior to removal. Suitable methods to locate are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Please note that the PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan. If ultrasound and MRI fail call **1-800-xxx-xxxx**.

**After localization of a non-palpable implant, consider conducting removal with ultrasound guidance. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.**

#### **Preparation**

**Before removal of PROBUPHINE, the healthcare provider should confirm that:**

- The patient does not have allergies to the antiseptic or the anesthetic to be used.

**IMPLANTS SHOULD BE REMOVED UNDER ASEPTIC CONDITIONS.**

**THE FOLLOWING EQUIPMENT IS RECOMMENDED FOR IMPLANT REMOVAL:**

- An examination table for the patient to lie on
- Mayo instrument stand

- Sterile tray
- Adequate lighting (e.g. headlamp)
- Sterile fenestrated drapes
- Latex and talc-free sterile gloves
- EtOH prep
- Chlorhexidine (ChloroPrep®)
- Sterile marker
- Local anesthetic (1% lidocaine with epinephrine 1:100,000)
- 5 mL syringe with 1.5 inch 25g needle
- Adson single tooth tissue forceps
- Mosquito forceps
- Two X-plant clamps
- Iris scissors
- Needle driver
- #15 blade scalpel
- 4x4 sterile gauze
- Adhesive bandage
- 3-inch pressure bandage
- Sutures (4-0 Prolene™ with an FS-2 cutting needle)

### **Removal Procedure**

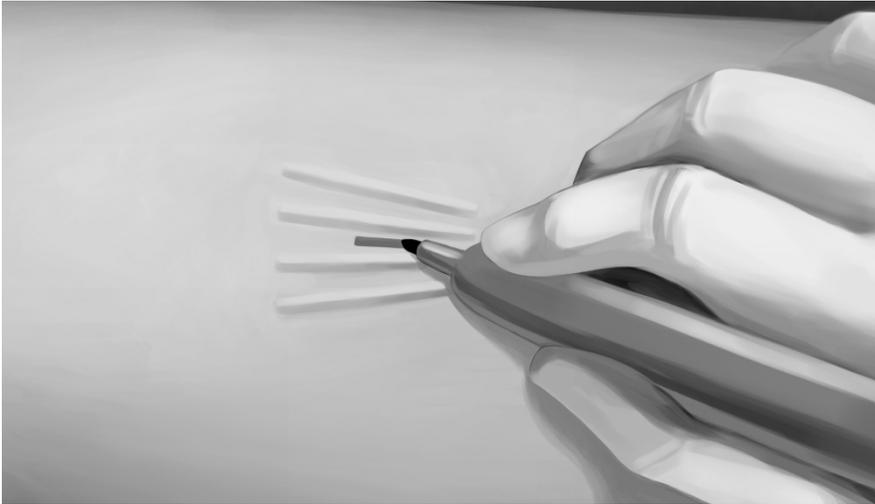
Step 1. Have the patient lie on his/her back, with the implant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head.

Step 2. Reconfirm the location of the implants by palpation.

Step 3. Clean removal site with alcohol prep pad prior to marking the skin.

Step 4. Mark the location of the implants with a sterile marker. In addition, mark the location of the incision, parallel to the axis of the arm, between the second and third implants (Figure 14).

**Figure 14**



Step 5. Using aseptic technique, place the sterile equipment on the sterile field of the mayo instrument stand.

Step 6. Clean the removal site with an antiseptic solution Chlorhexidine (ChloroPrep®) using gentle repeated back and forth strokes for 30 seconds. When using triple swabstick applicators, use each swabstick sequentially within the 30 seconds. Allow the area to air dry for approximately 30 seconds and do not blot or wipe away.

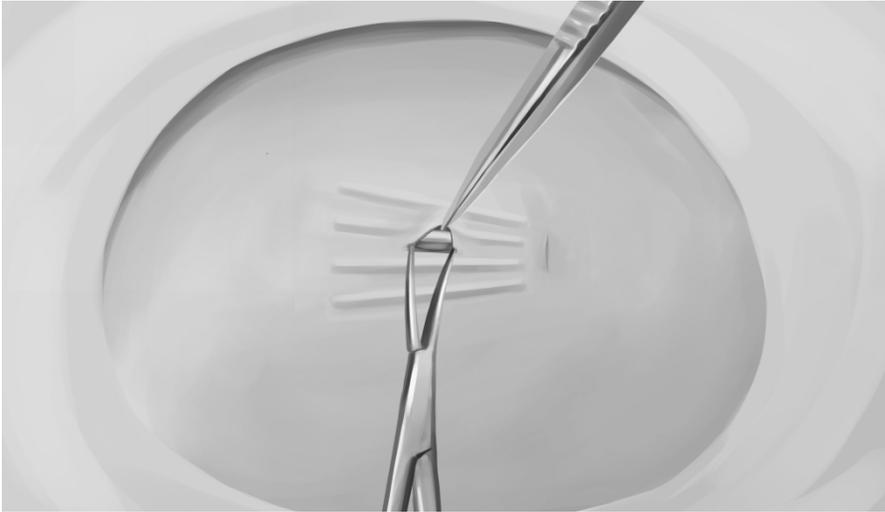
Step 7. Apply the sterile drape to the arm of the patient.

Step 8. Anesthetize the incision site and the subcutaneous space containing the implants (for example, by injecting 5-7 mL lidocaine 1% with epinephrine 1:100,000). Separate needles should be used for the incision site and the subcutaneous injections. NOTE: Be sure to inject the local anesthetic just beneath the implants; this will effectively lift the implants toward the skin, facilitating removal of the implants.

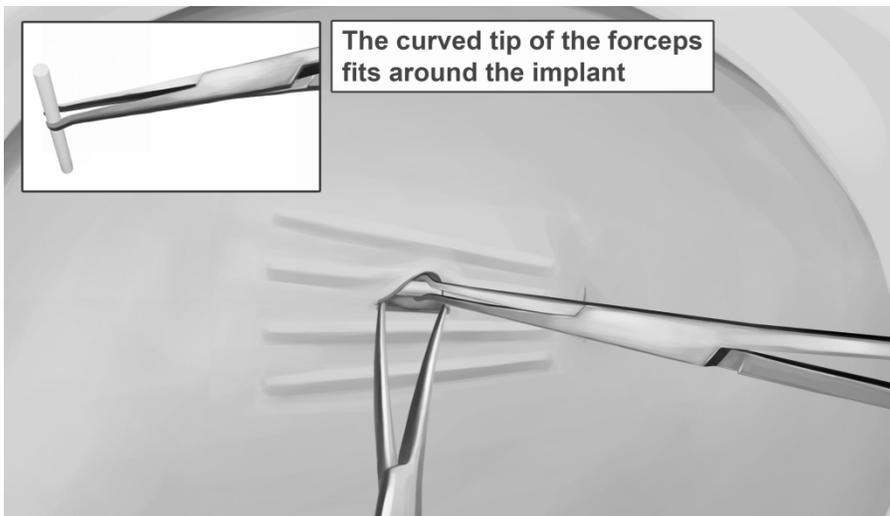
Step 9. After determining that anesthesia is adequate and effective, make a 7-10 mm incision with a scalpel, parallel to the axis of the arm, between the second and third implants.

Step 10. Pick up the skin edge with a toothed forceps and separate the tissues above and below the first visualized implant using an iris scissors or a curved mosquito forceps (Figure 15). Grasp the center of the implant with the X-plant clamp and apply gentle traction. Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue (Figure 16). If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed.

**Figure 15**



**Figure 16**



Step 11. Retract the next visible implant toward the incisional opening. You may see tenting of the skin at this point if the surrounding tissue is still adhering to the implant. Maintain gentle traction on the implant while you continue to dissect proximally and distally until the implant is free of all adhering tissue. At this point, you may require the use of your second X-plant clamp to remove the implant. If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed.

Step 12. After removal of each implant confirm that the entire implant, which is 26 mm long, has been removed by measuring its length. If a partial implant (less than 26 mm) is removed, the remaining piece should be removed by following the same removal instructions. Follow steps 10 through 12 for the removal of the remaining implants through the same incision.

Step 13. After removal of all four implants, clean the incision site.

Step 14. Close the incision with sutures.

Step 15. Place an adhesive bandage over the incision.

Step 16. Use the sterile gauze and apply gentle pressure for five minutes to the incision site to ensure hemostasis.

Step 17. Apply a pressure bandage with sterile gauze to minimize bruising. The pressure bandage can be removed in 24 hours and the adhesive bandage in three to five days.

Step 18. Counsel the patient on proper aseptic wound care. Instruct the patient to apply an ice pack to his/her arm for 40 minutes every two hours for first 24 hours and as needed.

Step 19. Schedule an appointment for the sutures to be removed.

Step 20. Dispose of PROBUPHINE implants in keeping with local, State and Federal regulations governing the disposal of pharmaceutical biohazardous waste.

Step 21. Complete the PROBUPHINE Distribution Log-Patient (PDL-P).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CELIA J WINCHELL  
02/13/2016